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The definitive publisher version is available online at 10.1016/j.cbi.2018.12.009

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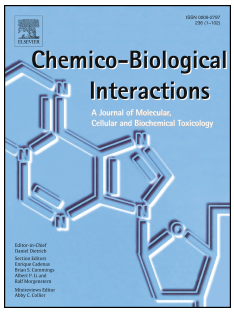

Increasing complexity and interactions of oxidative stress in chronic respiratory diseases: An emerging need for novel drug delivery systems

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PII: S0009-2797(18)31477-7

DOI: https://doi.org/10.1016/j.cbi.2018.12.009

Reference: CBI 8487

To appear in: *Chemico-Biological Interactions*

Received Date: 29 October 2018

Revised Date: 2 December 2018

Accepted Date: 12 December 2018

Please cite this article as: K. Dua, V. Malyla, G. Singhvi, R. Wadhwa, R.V. Krishna, S.D. Shukla, M.D. Shastri, D.K. Chellappan, P.K. Maurya, S. Satija, M. Mehta, M. Gulati, N. Hansbro, T. Collet, R. Awasthi, G. Gupta, A. Hsu, P.M. Hansbro, Increasing complexity and interactions of oxidative stress in chronic respiratory diseases: An emerging need for novel drug delivery systems, *Chemico-Biological Interactions* (2019), doi: https://doi.org/10.1016/j.cbi.2018.12.009.

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Increasing Complexity and Interactions of Oxidative stress in Chronic Respiratory Diseases: An Emerging Need forNovel Drug Delivery Systems

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Abstract

Oxidative stress is intensely involved in enhancing the severity of various chronic respiratory diseases (CRDs) including asthma, chronic obstructive pulmonary disease (COPD), infections and lung cancer. Even though there are various existing anti-inflammatory therapies, which are not enough to control the inflammation caused due to various contributing factors such as anti-inflammatory genes and antioxidant enzymes. This leads to an urgent need of novel drug delivery systems to combat the oxidative stress. This review gives a brief insight into the biological factors involved in causing oxidative stress, one of the emerging hallmark feature in CRDs and particularly, highlighting recent trends in various novel drug delivery carriers including microparticles, microemulsions, microspheres, nanoparticles, liposomes, dendrimers, solid lipid nanocarriers etc which can help in combating the oxidative stress in CRDs and ultimately reducing the disease burden and improving the quality of life with CRDs patients. These carriers improve the pharmacokinetics and bioavailability to the target site. However, there is an urgent need for translational studies to validate the drug delivery carriers for clinical administration in the pulmonary clinic.

Keywords

Asthma, COPD, drug delivery, lung cancer, respiratory diseases.

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List of Abbreviations

S.No.	Abbreviation	Explanation
1.	COPD	Chronic obstructive pulmonary disease
2.	CRD	Chronic respiratory diseases
3.	ROS	Reactive oxygen species
4.	RNI	Reactive nitrogen species
5.	NADPH	Nicotinamide adenine dinucleotide phosphate hydrogen
6.	VEGF	Vascular endothelial growth factor
7.	Nrf2	Nuclear erythroid 2 p45-related factor 2
8.	PDE	Phosphodiesterase type 4
9.	NF-κB	Nuclear transcription factor
10.	MAPK p38	P38 mitogen-activated protein kinases
11.	NTHi	Nontypeable *Haemophilus influenzae*
12.	3-NT	3-nitrotyrosine
13.	NSCLC	Non-small-cell lung cancer
14.	SCLC	Small-cell lung cancer
15.	AP-1	Activator protein
16.	LOX	Lipoxygenase
17.	iNOS	Inducible nitric oxide synthase
18.	COX2	Cyclooxygenase 2
19.	DNA	Deoxyribonucleic acid
20.	MMP	Matrix metalloproteins

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21.	PIG3	p53 inducible gene 3
22.	SLM	Solid lipid microparticles
23.	ERK	Extracellular signal-regulated kinase
24.	LMP	Lymphocyte-derived microparticles
25.	PLGA	Poly(lactic-co-glycolic acid)
26.	PVAX	Polymeric (vanillyl alcohol-containing copolyoxalate)
27.	TNF-α	Tumor necrosis factor-alpha
28	IL-6	Interleukin-6
29.	ME	Micro emulsion
30.	FP	Fluticasone propionate
31.	S-SMEDDS	Solid self-microemulsifying drug delivery system
32.	TPGS	Tocopheryl polyethylene glycol succinate
33.	ECGME	Etoposide, coix seed oil and ginsenoside Rh2 microemulsion
34.	G-Rh2	Ginesenoside Rh2
35.	IPM	Isopropyl myristate
36.	LTB4	Leukotriene B4
37.	NO	Nitric oxide
38.	PE	Pulmonary embolism
39.	TBA-RS	Thiobarbituric acid reactive species
40.	ICAM	Intracellular cell adhesion molecule
41.	PECAM	Platelet endothelial cell adhesion molecule
42.	NOX	NADPH oxidase inhibitors
43.	SOD	Superoxide dismutase

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44.	LPS	Lipopolysaccharide
45.	HSPC	Hydrogenated soy phosphatidylcholine
46.	SPC	Soy phosphatidylcholine
47.	FDA	Food and drug administration
48.	NAC	N-acetyl cystine
49.	Gold-PAMAM	Polyamidoamine
50.	Gold-PPI	Polypropyleneimine
51.	RNA	Ribonucleic Acid
52.	CFTR	Cystic fibrosis transmembrane conductance regulator
53.	SLN	Solid lipid nanocarriers
54.	NLC	Nanostructured lipid-based nanocarriers
55.	SLN-PTX	Solid lipid nanocarriers-paclitaxel
56.	AUD	Area under the curve
57.	PEG	Polyethylene glycol
58.	ARE	Antioxident response element
59.	GST	Glutathione S-transferases
60.	GPX	Glutathione Peroxidase
61.	DDS	Drug delivery systems
62.	CF	Cystic fibrosis
63.	TPs	Transdermal patches
64.	R_{aw}	Airway resistance
65.	C_{dyn}	Dynamic lung compliance
66.	LTRA	Leukotriene receptor antagonist

67.	FeNO	Fractional exhaled nitric oxide
68.	LABA	long-acting b2-agonists
69.	rhDNase	Recombinant human deoxyribonuclease

Introduction

An imbalance between increased oxidative agents and antioxidant defense mechanisms is known as oxidative stress, which plays a critical role in the pathogenesis of multiple disorders, especially chronic respiratory disease like asthma, COPD, respiratory infections and lung cancer [1]. There are various external and internal factors, which can increase the severity of respiratory diseases (Figure 1).

Studies involving asthmatics have demonstrated increased levels of reactive oxygen species (ROS) [2] and reactive nitrogen intermediates (RNI). These primarily include superoxide anions (O_2^-), hydrogen peroxide (H_2O_2) and hydroxyl radicals (OH). The major external sources of oxidative stress in asthma include air pollution, pollens, cigarette smoke and the influx of inflammatory cells into airways post allergen exposure. Whereas, internal factors include mitochondrial dysfunction and metabolic factors such as obesity/metabolic syndrome [2, 3]. In addition, asthma patients also have depleted antioxidant defenses, including superoxide dismutase, glutathioneand catalase .An increase in the levels of oxidative stress, either exogenous (smoking, air pollution etc.) or endogenous (generated by immune cells such as macrophages, neutrophils and eosinophils) is linked to more severe asthma [4]. Whilst NADPH oxidase-dependent complex and the cytosolic xanthine oxidase system is involved in the generation of ROS, the interaction of nitrite and myeloperoxidase or eosinophil peroxidase–

derived ROS results in RNI burden [4, 5]. The crucial triggers of asthma exacerbations include respiratory infections, environmental pollutants and certain drugs (e.g., aspirin) [6]. These activate differential inflammatory profiles and in turn, differential oxidative burden during exacerbations [7]. Moreover, increased levels of oxidative stress markers (plasma lipid peroxides) have been reported in asthma patients experiencing exacerbations [8].

Low levels of oxidative stress initiate the release of antioxidant and anti-inflammatory genes via the activation of nuclear erythroid 2 p45-related factor 2 (Nrf2). In nucleus, Nrf2 binds to and activates antioxidant response element (ARE) leadingupregulation of genes encoding antioxidant-detoxifying proteins, including antioxidants (GPx), thiol metabolism-associated detoxifying enzymes (GSTs) and stress-response genes (HO-1) [9]. Evidently, Nrf2 seems to be protective against cigarette smoke-induced COPD, as Nrf2-deficient mice exposed to cigarette smoke exhibited greater bronchoalveolar inflammation, enhanced alveolar expression of 8-oxo-7,8-dihydro-2'-deoxyguanosine, increased apoptosis of endothelial and type II epithelial cells and most importantly, greater degree of emphysema when compared to control mice [10]. However, high intensities of oxidative stress trigger the activation of pro-inflammatory intracellular signaling leading to the expression of inflammatory cytokines, chemokines and adhesion molecules [11] resulting in increased airway inflammation and airway hyper-responsiveness.

Although glucocorticosteroids remain the mainstay therapy for the management of asthma, they are not adequate to control oxidative stress-induced airway inflammation due to their ability to interfere with the expression of anti-inflammatory genes as well as antioxidant enzymes [12]. Hence, there is an urgent need to develop new strategies targeting oxidative stress to control or prevent airway inflammation. One potential approach could be the use of nanotechnology to improve antioxidant activity and lung function [13, 14].

COPD is a multi-factorial disease that is primarily caused by the external factors such as, cigarette smoking and/or exposures to biomass smoke, air pollution and a variety of occupational exposures to chemical dust and fumes. All these risk factors are also frequently implicated in the increases in the oxidative burden and ROS/RNI in the lungs, as well as systemically [15]. For example, airway smooth muscle cells from COPD patients exhibited increased ROS levels compared to healthy individuals [16]. Likewise, the neutrophils harvested from the peripheral blood of COPD patients have been shown to produce more ROS compared to healthy individuals [17]. Increased levels of ROS can then initiate myriad of biochemical reactions, leading to damaged cellular components (proteins, lipids, and nucleic acids). Moreover, ROS also initiates inflammatory cascades via multiple mechanisms, such as protein kinase pathways, transcription factors, and genomic expression of pro-inflammatory regulators. All these factors result into an 'over-activated' immune system. Notably, the higher oxidative burden may lead to significant reductions in the VEGF levels in the lungs, which has been associated with the development of emphysema [17]. Inhalation of air pollutants results in the induction of oxidative stress in the lungs. For instance, inhalation of carbon particles present in air pollution, are retained by the lung tissues and induces oxidative stress [18]. Moreover, exposure to particulate matter from biomass/fossil fuels depletes anti-oxidants in cultured cells [19]. Occupational exposure (such as exposure to welding fumes) has been linked to significantly increased oxidative burden in the lung [20].

Even though there arevarious options available for the treatment of COPD like PDE4 inhibitors, NF-κB inhibitors, MAPK p38 inhibitors, β_2-agonistsand corticosteroids. However, none of them reduces the progression and inflammation of COPD. This indicates the need

forinvestigationsfocusing on delivering such potential therapeutics directly to the small airways in reducing thedisease features and pathology of the disease.

Respiratory infections, especially with *Mycobacterium tuberculosis* results in increased oxidative burden and inflammation in the lungs [21]. In addition, tuberculosis is also linked to increased risk of developing COPD [22]. Similarly, pulmonary infection with *Streptococcus pneumoniae* (common bacterial pathogen in CRDs) also induces oxidative stress that is depended on the pneumococcal auo lysin LytA, and independent of bacterial-derived H_2O_2 and pneumolysin [23]. Non-typeable *Haemophilus influenzae* (NTHi), also a major bacterial pathogen in CRDs, has been shown to induce ROS formation in human-derived primary cell lines (alveolar macrophages, human-lung fibroblast, and epithelial cell lines and blood-derived neutrophils) [24]. Moreover, mice infected with NTHi showed overproduction of oxidant, 3-nitrotyrosine (3-NT) in the lungs [24]. Furthermore, respiratory viral infections also affect redox homeostasis, which has been reviewed by Khomich *et.al* .[25].

Lung cancer is the leading cause of death amongst all cancers especially in men all over the world [26]. Lung cancer can be classified as Non-small-cell lung cancer (NSCLC) and small-cell lung cancer (SCLC). NSCLC contributes to 85% of all the lung cancers [27]. The causes of lung cancer are attributed to smoking, inhalation of polluted air, noxious gases like ozone (O3), sulphur dioxide (SO2), nitrogen dioxide (NO2) and micro-organisms. Cigarette smoke accounts for 90% of lung cancer deaths [28]. It has carcinogens including nitrosamines, acrolein, and poly- hydrocarbons. Along with, ROS/RNI produced from smoke contributes to cancer development. ROS initiates signaling cascades by activating the production of chemokines and cytokines thereby, causes chronic inflammation which up regulates nuclear transcription factor (NFκB), activator protein (AP-1), lipoxygenase (LOX), nitric oxide synthetase (iNOS) and

cyclooxygenase (COX2) [29]. It also activates oncogenes such as c-jun, c-myc and c-fos, further induces over-expression of c-jun has been reported to conciliate growth factors for NSCLC [30]. ROS/RNI also oxidizes protein and lipid moieties by carbonyl groups introduction in amino acids, the formation of protein-centered alkyls, malondialdehyde production etc. which eventually brings about the loss of histidine residues, oxidative scission, elevates mutagenesis and genotoxic products. Furthermore, these interact with DNA and modify polymerases, repair enzymes causing DNA- damage [31]. The most common DNA modification is 8-OH-G and is found to be 10 folds elevated in the urine of smokers [32]. In situations of inflammation in lungs, matrix metalloproteins (MMPs) interacts with growth factor, cytokines, chemokines, cell adhesion factors, apoptotic ligands, and angiogenic factors but over expression of MMPs induces tumor progression and metastasis [33]. During lung cancer, p53 is mutated causing defective apoptosis. p53 intervenes mitochondrial apoptotic signal by up-regulation of ROS [30]. The PIG3 protein responsible for oxidation-reduction, which is over-expressed in the tumor, thus fails to initiate apoptosis [34]. However, anti-oxidant therapy would contribute to balance oxidant levels in the body such as Thioredoxin (MOL-294) has been used against lung cancer, dietary supplements (Ascorbic acid, Vitamin E, β-carotene, Selenium etc.) reduce oxidative stress to some extent [35]. MMPs are an important component of the inflammatory cascade in lungs [33], therefore nano-formulation based targeted drug delivery or gene therapy has the potential to control disease progression and provide us with a better understanding.

A variety of anti-oxidant therapies have been proposed for CRDs [36], however, their targeted delivery and efficacy remains a challenge for managing patients with CRDs. Targeting oxidative stress and associated lung/systemic inflammation by utilizing modern drug delivery strategies

could indeed improve disease progression, survival and most importantly, quality of life in patients with chronic respiratory diseases.

There is an emerging need of new therapeutic interventions, pharmaceutical agents, and drug delivery to target the oxidative stress, an important hallmark feature in various chronic respiratory diseases such as asthma, COPD, respiratory infections and lung cancer. Various natural and synthetic active moieties have been proposed with potent anti-oxidant and anti-inflammatory properties in such diseases. The revolution in the area of drug delivery systems particularly the emerging concept of advanced controlled release drug delivery approaches such asmicroparticles, microemulsions, microspheres, nanoparticles, liposomes, dendrimers, lipid nanocarriers, solidlipidnanocarriers, nanostructured lipid carriers, are gaining massive attention and can help in combating the state of oxidative stress in CRDs. The various novel drug delivery systems and approaches with their applications in targeting oxidative stress are detailed below (Figure 1):

1. Microparticles

During the past decade, more attention has been given to the development of micro-particulate drug delivery carriers as these systems have better delivery of therapeutics to disease sites,particularly in treating pulmonary diseases [37, 38]. Particle size plays an important role in the delivery of drugs to the target site without affecting the non-target sites. It has been reported that the particle <0.5 μm cannot be retained in the airway for a prolonged time period due to the easy exhalation of such particles. On the other side particles with >10 μm diameter is suitable for deposition in the oropharynx. The microparticle in 1–5 μm size range is considered asanideal to achieve efficacious pulmonary deposition [39, 40].

Amore *et al.* described alginate and chitosan-basedmucoadhesive solid lipid microparticles (SLMs) for the effective delivery of fluticasone propionate to treat chronic obstructive pulmonary diseases (COPDs). The developed SLMs were more effective in controlling oxidative stress-induced lung inflammation including ERK1/2 pathway activation and cigarette smoke extract-inducedsurvivin expression [39]. Lymphocyte-derivedmicroparticles (LMPs) stimulate oxidative stress in endothelial cells [41]. Qiu*et al*.(2014) identified that LMPs cause apoptosis of alveolar epithelial and bronchial cells by the activation of p38 mitogen-activated protein kinase signaling with an increase in cellular oxidative stress and arachidonic acid production [42].

The first report on the expression of lung vascular endothelial growth factor in benzo(a)pyrenefed mouse model ofa lungtumour was published by Bandi and co-workers. PLGA microparticles released budesonide in a sustained manner for over 21 days. Microparticles have also showed potential of inhibiting the angiogenic factors in lung cancer on local delivery with a sustained release in benzo(a)pyrene-fed mice. This inhibtion resulting is attributed to the reduced malondialdehyde accumulation, glutathione depletion, vascular leakage, and vascular endothelial growth factor and c-myc expression.Inhibition of oxidative stress by the developed microparticles is especially beneficial in treating tumours [43].

In a study, Yoo*et al*. fabricated porous poly(lactide-co-glycolide) microparticles by water-in-oil-in-water multi-emulsion method for effective pulmonary delivery of anthocyanin. Ammonium bicarbonate and starch were used as a porogen and viscous additive, respectively. Prolonged residence (up to 20 days) of anthocyanin was recorded in lung epithelium of BALB/c mice. The microparticles showed a sustained *in-vitro* release profile of anthocyanin and antioxidant activity for 2,2-diphenyl-1-pikryl-hydrazyl radicals for a period of 5 days. Developed microparticles

have been recommended as a potential drug delivery carrier for effective relief of oxidative stress in pulmonary diseases like COPD [44].

Porous polymeric (vanillyl alcohol-containing copolyoxalate - PVAX) microparticles containing dexamethasone as a therapeutic agent to treat airway inflammatory diseases have been reported by Jeong*et al*. The drug-loadedmicroparticles significantly reduced oxidative stress level and inhibited expression of pro-inflammatory tumor necrosis factor-alpha (TNF-α) and inducible nitric oxide synthase in the lungs of ovalbumin-challenged asthmatic mouse models. The results suggested the potential applicability of PVAX based porous microparticles as therapeutic systems in treating asthma [45].

It has been established that *in-vitro* exposure of human alveolar cells to hydrogen peroxide causes microparticle generation by p38 activation. Neri *et al.* reported inhibition of p38 phosphorylation-dependenthydrogen peroxide-induced microparticlesin alveolar cells by pirfenidone. Pirfenidone inhibited hydrogen peroxide induced microparticle generation in both flow cytometry and solid phase thrombin generation methods. Inhibition of p38 mediated procoagulant microparticle generation by pirfenidone has been disclosed first time by these researchers [46].

The fundamental mechanism of tungsten oxide microparticle and nanoparticle toxicity has been reported in human lungcarcinoma (A549) cells. The average size of synthesized microparticles and nanoparticles was 3.88 μm and 53.84 nm, respectively. Nanoparticles reduced cell viability and membrane damage in a dose-dependent manner. A significant gain in tail DNA and micronuclei formation was observed after 24 h. The DNA damage induced by tungsten oxide nanoparticles could be due to the increased level of inflammation and oxidative stress, which is correlated with an increase in malondialdehyde levels and depletion of reduced glutathione

content, catalase. Nanoparticles inhibited G2/M phase of the cell cycle. The results showed that themicroparticles did not instigate toxic effects [46].

Spray driedresveratrol and budesonide inhalable microparticles have been reported for effective therapy of chronic lung diseases. Cytotoxicity studies of the microparticles were carried outin rat alveolar macrophages. The formulations were further tested to access the biological response of alveolar macrophages in terms of cytokine expressions, free radical scavengingand nitric oxide production. The results showed that the alveolar macrophages toleratedresveratrol and budesonide. The microparticles decreased interleukin-6 (IL-6) and (TNF-α) levels in lipopolysaccharide-induced alveolar macrophages [47].

Bot *et al.* investigated the applicability of lipid-based hollow and porous spray dried microparticles (PulmoSpheres™) for the effective delivery of human immunoglobulin. An improved release profile of immunoglobulinwasobservedfrom the synthesized microspheres once added to an aqueous environment. The results show systemic bio-distribution of microparticlesinupperand lower respiratory tract of BALB/c mice .Also, the receptor-mediated loading of alveolar macrophages relates to the enhanced immune responses against xenotypic epitopes was observed. The formulation approach is compatible with local and systemic delivery via there respiratory mucosa [48]. Vehring *et al.* reportedformoterol fumarate dihydrate, mometasonefuroate or glycol pyrrolate, containing porous phospholipid microparticles delivered using 1,1,1,2-tetrafluoroethane as a propellant. The formulation containing drug microcrystals associated with porous particles improved suspension stability than the suspensions without porous particles [49].

2. Microemulsions

Microemulsions are gaining popularity due to their unique propertiessuch as ease of preparation, stability, clarity, increased bioavailability *etc.* [50]. Akhuemokhan *et al.* formulated microemulsion (ME) of fluticasone propionate (FP) for pulmonary delivery using mesh or jet nebulizers and compared with the marketed nebuliser suspension of the same drug (Flixotide®nebules). Jet nebuliser effectively delivered the drug, while the mesh nebuliser failed to deliver the microemulsion. The delivery of microemulsion from the nebulizer was controlled by the viscosity, particle sizeand aerodynamic particle size distribution. The aerodynamic particle size distributions produced by microemulsions using a jet nebuliser showed these to be promising results [51].

Effective pulmonary delivery of atorvastatin from solid self-microemulsifying drug delivery system (S-SMEDDS) has been reported. The attempt for prepare microemulsion (ME) was firstly done using isopropyl myristate (IPM). The microemulsion was examined for physicochemical characterization, phase diagram, and stability studies. The microemulsion was spray dried to obtain solid S-SMEDDS using a combination of sugars and leucine with or without polyethylene glycol 6000. *In-vitro* cytotoxicity studies were carried out for both the formulations (microemulsion and S-SMEDDS) using a lung cancer cell line. Lecithin/TPGS (1:3), lecithin/oil (1:1) and surfactant/co-surfactant (1:1) were identified as optimized ratios for the formulation of the microemulsion. The improved cytotoxic activity on lung cancer cells was observed when the atorvastatin was deliveried with d-α-tocopheryl polyethylene glycol succinate in S-SMEDDS [52].

Mikhail *et al.* reported improved and more consistent absorption of Neoral and Sandimmun (cyclosporin) from microemulsion in patients with lung transplants for cystic fibrosis. The results of respiratory function tests remained stable [53]. Penninga *et al* investigated the comparative

immunosuppression effect of microemulsions containing tacrolimus and cyclosporin in 413 adult lung transplant recipients. Tacrolimus was found to be superior to cyclosporinwith respect to the incidence of lymphocytic bronchitis score, bronchiolitis obliterans syndrome, arterial hypertension, and treatment withdrawal. More frequent diabetes mellitus was reported in patients who received tacrolimus when compared with the patient's received cyclosporin. No significant difference was observed in mortality between tested groups [54].

The applicability of etoposide, coix seed oil, and ginsenoside Rh2 containing microemulsion (ECGME) in lung cancer treatment has been validated and the mechanism underlying the enhanced antitumor efficacy has been explored. Ginsenoside Rh2 (G-Rh2) (3% w/w) was selected as optimum concentration to formulate microemulsion with small particle and high drug encapsulation efficiency. The intracellular fluorescence of human non-small cell lung cancer cells treated with fluorescein isothiocyanate-labeled microemulsion was significantly higher. *In vivo* anticancer study results showed significant inhibition non-small cell lung cancer tumor xenograft growth and induced tumor cells apoptosis in mice treated with microemulsion [55].

Oral bioavailability of the quercetin, a plant-derived anti-oxidan tand anti-inflammatory agenthas significantly improved frommicroemulsionwhen compared tothe suspension in an experimental mousemodel of airways allergic inflammation. After immunization with ovalbumin, the animals received daily oral doses of microemulsion (3 or 10 mg/kg body weight in an oil-in-water microemulsion content 0.02:0.2:1 of lecithin:castoroil:Solutol HS15®), suspension (10 mg/kg body weight in carboxymethylcellulose 0.5% in water)or vehicle for a period of 22 days. The control group received dexamethasoneasa positive control drug. Orally administered suspension failed to interfere with leukocytes, while microemulsion inhibited leukocytes in a dose-dependent manner. A significant decrease in IL-5 and IL-4 levels were recorded in animals

treated with microemulsion. However, it failed to interfere with chemokine (CCL11), cytokines (IFN-γandlipid (LTB_4) levels. Microemulsion also inhibited the activation of nuclear transcription factor kappa B, P-selectin expression and the production of mucus in lungs [56].

3. Microspheres

Microspheres are small and spherical particles with 1–1000 μm diameters [57]. The influence of the reactive oxygen species (ROS) scavenger Tempol on pulmonary hypertension has been described by Mizera *et al*. They described NO synthase activity and production of NO oxidative products (NOx) after pulmonary embolism (PE). When Sephadex microspheres suspended in PSS were applied in right jugular vein as the pulmonary microembolism, thechanges in perfusion pressure in isolated salt solution-perfused lungs, the activity of NO synthase and NOx plasma concentration were measured in rats. Tempol was applied intraperitoneally before pulmonary embolism which demonstrates the significant reduction in the basal perfusion pressure [58].

The selective pulmonary vasodilation effect of soluble guanylate cyclase and a low dose of 5-Cyclopropyl-2-[1-(2-fluoro-benzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-pyrimidin-4-ylamine (BAY 41-2272) has been reported in dogs with an acute pulmonary embolism. Evaluation of arterial blood gas and hemodynamic were carried out in non-embolized vehicle treated dogs and in embolized dogs treated with intravenous injections of BAY 41-2272 microspheres. Thiobarbituric acid reactive substances and plasma cyclic guanosine 3',5'-monophosphate concentrations were determined byafluorometricand a commercial enzyme immunoassay method, respectively. A decrease in pulmonary artery pressure and pulmonary vascular resistance was recorded in animals treated with BAY 41-2272 [59].

The effects of sildenafil on the hemodynamic changes caused by acute pulmonary embolism have been examined in anesthetized dogs and rat isolated perfused lung preparation. Acute

pulmonary embolism was induced by intravenous injections microspheres (300 μm) to increase mean pulmonary artery pressures by 20mmHg. Plasma thiobarbituric acid reactive species were determined to measure oxidative stress. Sildenafil was found toreduce mean pulmonary artery pressures in dogs and attenuated the increase in oxidative stress after acute pulmonary embolism. Similar results were recorded in rat isolated perfused lung preparation [60].

Souza-Costa *et al.* analyzed the hypothesis that L-arginine would reduce the strength of oxidative stress and pulmonary hypertension during acute pulmonary embolism. The study involved isolated lung perfusion rat models of acute pulmonary embolism. Sephadex microspheres were injected into the pulmonary artery. The oxidative stress and NO production were recorded based on the results of thiobarbituric acid reactive species (TBA-RS) and nitrite/ nitrate (NO*x*) concentrations obtained. L-Arginine reduces the strength ofacute pulmonary embolism-induced pulmonary hypertension by about 50% through antioxidant mechanisms with increased NO synthesis [61].

4. Nanoparticles

These are the particles having a size range of 1-100nm and are the new approach for targeted delivery of the drugs [62]. Nanoparticles due to its small size have a tendency to behave as vessels for drugs, which in turn can reach any region of the humanbody [63]. The Intracellular cell adhesion molecule-1 (ICAM-1) and platelet endothelial cell adhesion molecule (PECAM) receptors present over the endothelial cells of pulmonary airways are targeted by these nanoparticles. Therefore, these can be used as carriers for NADPH oxidase (NOX) inhibitors, superoxide dismutase (SOD) and catalase in order to prevent oxidative stress in the respiratory system [64]. Muro *et al.* demonstrated that delayed the intracellular accumulation of anti-ICAM-1 nanoparticles incorporated with catalase helps to prevent oxidative stress in the endothelial

cells of the airways. These nanoparticles are uptaken by the endothelial cells and remain there for 1hr and then delivered to lysosomes after 2-3hrs for degradation. Due to this delayed delivery to lysosomes, the antioxidant activity of catalase is extended and thus is able to prevent any oxidative injury to the lungs [65]. Pu and co-workers discovered the potential of curcumin-loaded nanoparticles in treating oxidative stress and inflammation. Upon release, curcumin decreases the surplus amount of oxidants formed by lipopolysaccharide (LPS)-stimulated macrophages (Figure 2). Thus, these have the capability of targeting disorders associated with oxidative stress [65]. Chen *et al* developed nanoparticles encapsulated with Cerium oxide, also known as nanoceria and determined their potential as an antioxidant. As it contains both $Ce^{3+}$and Ce^{4+} ions, it causes redox reactions that are responsible for reducing the level of ROS [66] (Figure 2).

5. Liposomes

Liposomes are the drug delivery system suitable for encapsulation of both hydrophilic and lipophilic drugs. Liposomes are attracted towards pulmonary delivery, following inhalation local drug effect is observed in the lungs with prolonged duration of action [67, 68]. Liposomal constituents phospholipids, cholesterol used in liposomes preparation are typically analogous to pulmonary surfactants in mammals [69, 70]. Many reports suggest liposomal constituents are found to compatible with alveolar macrophages, hydrogenated soy phosphatidylcholine (HSPC) and soy phosphatidylcholine (SPC) liposome exposure for prolonged nebulization (concentrations up to 150mg/mL) has no effect on the lungs of sheep. Liposomes found to be safe for inhalation in studies performed on human volunteers. Studies reveal liposomes are suitable for delivery of genes, antimicrobial agents and antidiabetic drugs [71].The delivery of

liposomal formulation containing amikacin by Insmed's (Arikace®) in nebulized form is one of the FDA approved formulation [72].

Chennakesavulu and co-workers investigated the delivery of colchicine and budesonide encapsulated in liposomes for Idiopathic Pulmonary Fibrosis. Thin layer film hydration method was used for preparation, optimized formulation means particle size was 100 nm. The formulation is lyophilized by addition of mannitol as cryoprotectant and carrier. *In-vivo* efficacy studies were performed in adult male Wistar rats. Liposomal dry powder for inhalation prolonged drug retention in lungs with reduced systemic absorption. The liposomal lyophilized powder was stable for 6 months at 25 ± 2°C 60% ± 5% RH and refrigerated conditions (2 - 8 °C) [73].

These are the drug delivery systems used for distribution of both hydrophilic and lipophilic anti-oxidants for the management of diseases related to oxidative stress. Suntres showed the potential of Glutathione-loaded liposomes as an antioxidant for the treatment of hypoxia-associated lung damage or paraquat-induced lung injury. During pre-clinical trials, it was found that 10% of the dose of liposomes was retained in the lungs for 24-48 hours following treatment and pulmonary retention was enhanced by 18%. Thus, prolonged retention causes decreased discharge of glutathione from liposomes. He also proved that liposomes encapsulated with N-acetyl cysteine (NAC) showed the anti-oxidant property. As a result of NOS-induced lung damage, NAC initiates MAPK (Mitogen-activated protein kinase) pathway and decreases inflammatory responses (Figure 3). When these liposomes are taken via IV route, their half-life was increased from 6min to 30 min. Thus, these enhance the duration time of the drug in the target organ [69].

Glavao *et al.* prepared cationic liposomes encapsulated with ceftriaxone and three antioxidants i.e. NAC, Vitamin C and Vitamin E using the method of hydration of lipid film. They decrease

the lung damage caused by sepsis and improves survival rate in rats. They also decrease nitrates/nitrites level and increases the life of alveolar macrophages [74] (Figure 3).

6. Dendrimers

These are the branched systems containing a center area surrounded by star-shaped branches. Various ligands could be attached at the surface for targeted release [75]. Esumi and co-workers developed Gold-PAMAM (Polyamidoamine) dendrimers and Gold-PPI (Polypropyleneimine) dendrimers by reduction of $HAuCl_4$ with sodium borohydride and compared their antioxidant action. These dendrimers act by terminating the oxidative action of hydroxyl radicals. The catalytic activity of these dendrimers depends on the type of terminal group present over them. Gold-PAMAM dendrimers were found to have more antioxidant activity than that of Gold-PPI dendrimers. When their activity was compared with ascorbic acid, the rate constant of Gold-PAMAM dendrimers was 85 times more than ascorbic acid. Thus, these have the potential of being used as a drug delivery system for targeting oxidative stress [76]. Feliu *et al.* prepared cationic poly (amidoamine) dendrimers (PAMAM-NH_2) using RNA sequencing and computational approaches. These cause down-regulation of genes related to cell cycle at low doses and is uptaken by lung cells and resides in lysosomes. Thus, biological methods help for the prediction of cellular responses to these delivery systems [77]. Brockman *et al* developed dendrimers containing cysteamine i.e. an autophagy-inducing drug having bactericidal activity. These prevent ΔF508 mutation in Cystic fibrosis transmembrane conductance regulator (CFTR) gene which is involved in causing cystic fibrosis. It also reduces *Pseudomonas aeruginosa* development and causes breakdown of the mucus. This system enhances bioavailability and provides targeted delivery of cysteamine [78].

7. Lipid Nanocarriers:

Lipid-basednanocarriers are the drug delivery system widely used for lipophilic drug delivery. Solid lipid nanocarriers (SLN), nanostructured lipid-based nanocarriers (NLC), liposomes are widely used nanocarriers in drug delivery. Lipid-based nanocarriers have several advantages in comparison to polymeric nanocarriers, lipid used in nanocarriers are non-toxic, free from organic solvents, exhibit good tolerability in air-ways and lipids used are of biodegradable [79].

The nanosize of the lipid particles are easily aerosolized, they exhibit adhesion, accumulation, and retention in the lungs as well as prolong the drug release. These are ideal properties of the lipid nanocarriers make advantage in case of pulmonary drug delivery [37]. Lipid nanocarriers are more prone to adsorption on to the epithelium which helps to escape from mucociliary transport [80].

8. Solid Lipid Nanocarriers:

Solid lipid nanocarriers are next-generation lipid nanocarriers of emulsion-based formulations where liquid oil is replaced with solid lipid. Solidnanocarriersprotect encapsulated drug, provide controlled release of the drug, with enhanced physical stability. Large-scale batches can be formulated in case of SLN using high shear homogenizer Solid lipid nanocarriers can overcome the limitations of liposomal drug delivery systems [37]. Liposomes cannot withstand the shear force exerted by nebulizer, physical stress gets applied on to the liposomal bilayer when aqueous dispersion is converted into the respirable aerosol formulation. This leads to loss of originally entrapped drug, this can be overcome by SLN based formulations [81].

Han and his co-workers encapsulated green fluorescence protein plasmid (pEGFP) and doxorubicin in solid lipid nanocarriers (SLN). Surface modification of SLN was done by

transferrin-containing ligands for targeted delivery of drug and gene in lung cancer. *In-vitro* efficiency was evaluated in human alveolar adenocarcinoma cell line (A549 cells) whereas in vivo transfection efficiency was evaluated in mice bearing with A549 tumors. The particle size of optimized nanoformulation was 267 nm whereas the surface charge of nanocarriers was +42mV. There was a remarkable therapeutic effect both in the delivery of plasmid (gene) and drug doxorubicin. Ligand coating of nanocarriers improved therapeutic efficiency of the carriers targeting lung cancer cells in combination delivery of gene and a chemotherapeutic agent [82].

Videira and colleagues formulated solid lipid nanocarriers (SLN) of paclitaxel to enhance solubility and delivery to lungs. The SLN based formulation increased the accumulation of drug at the target site (in lung cancer) which resulted in augmentation of paclitaxel therapeutic index. Compared with marketed formulation Taxol®, SLN loaded paclitaxel was found 20 folds higher cytotoxic effect. Lipid content of SLN based nanoparticulate systems improves permeation through the cell wall, which leads to an escalation in cellular internalization of drug loaded in SLN. Increase in cellular internalization is expected for enhanced cytotoxicity response of SLN based particles. SLN loaded paclitaxel inhalation exhibited improved efficacy in comparison to intravenous administration of Taxol® in experimental metastasis stage of tumor model. Pulmonary administration of SLN-PTX by inhalation has high therapeutic efficacy within 2-weeks, metastases in the lung surface were reduced to a substantial level. On the extension of a treatment, the tumor was completely disappeared [83].

Wang *et al.* developed curcumin loaded SLN by the solvent-injection method and its efficacy was tested in ovalbumin (OVA)-induced asthma models. The size of optimized nanoparticles based formulation was 190 nm, with -20.7mV zeta potential, entrapment of curcumin was found to be 75%. Pharmacokinetic studies performed in ovalbumin-induced asthma allergic model

developed in the rat, a high concentration of curcumin was observed in lungs and liver in case of SLN formulations. *In-vivo* administration of curcumin loaded SLNs shown prominent inhibition of T-helper-2 type cytokines interleukin-4 and interleukin-13. In comparison to curcumin alone, SLN based formulations exhibited active suppression of hyper responsiveness and infiltration of inflammatory cells. The study reveals SLN based formulations as better delivery system strategies for the treatment of asthma [84].

Hu *et al.* prepared SLN of epirubicin inhalable formulation for lung cancer. *In-vitro* studies revealed formulations remains stable while nebulization and the respirable fraction was improved compared to the solution. There was no cytotoxicity of blank SLN on A549 alveolar epithelial cells. *In-vivo* studies revealed increased drug concentrations in lungs in case of SLN compared to epirubicin solution for treatment of lung cancer [85].

9. Nanostructured Lipid Carriers:

Solid lipid nanocarriers exhibit limitations such as low potential drug loading and on storage,low ordered lipid modification is transformed to highly ordered β-modification. This leads to few imperfections in by perfect crystal lattice which leads to drug expulsion on storage. Nanostructured lipid carriers are next generation to SLN in which solid lipid is mixed with liquid lipid at the ratio of 70:30 to 99.9:0.1. By the addition of the liquid lipid to the solid lipid matrix, it maintains lipid in a less ordered form which improves drug loading and stability of nanocarriers (decrease drug expulsion) [86].

Moreno-Sastre and co-workers worked on nanostructured lipid carriers (NLC) for pulmonary delivery of tobramycin. Hot melt homogenization technique was utilized for preparation of NLC

and particle size of optimized formulation was 250 nm with 93% encapsulation efficiency. Lipid-based nanoparticles labeled with infrared dye were used for *in-vivo* administration studies in BALB/c mice. Formulations labeled using infrared dye were administered using MicroSprayer™ aerosolizer after suspending in phosphate buffer saline. It was instilled by spraying into lungs with help of syringe plunger. After immediate administration nanoparticles dispersed in entire lungs, after 2 hours drug administration was found to systemic and detected in kidney and liver and it was less intense in the spleen. After 48 hours drug was disappeared in other organs and remained in lungs were as free drug cleared faster to other organs and there was no presence of the drug in lungs. Apart from the improved sustained release of drug from NLC formulations,*in-vitro* studies revealed there was no effect on cell viability. The *in-vitro* study was performed to check the effect of mucus on nanocarriers by application of artificial mucus layer, which revealed the mucus layer has no effect on SLNs [87].

Patil-Gadhe *et al.* formulated montelukast loaded NLC for pulmonary applications. The optimized formulation with particle size 184.6±2.7 nm with >95% encapsulation was subjected to lyophilization for inhalable dry powder by adding 3% mannitol. The lyophilized powder density was 0.051±0.002 g/cc with a mass median mean diameter of 15.1 ± 1.4 µm. The *in-vivo* studies in Wistar rat revealed amplified bioavailability, with longer residence and targeting factor 11.76 times in comparison to montelukast aqueous solution. This suggested NLC based dry powder for inhalation improve efficacy with reduced toxicity [88].

Pardeike and colleagues developed NLC based formulations of itraconazole, optimized formulation exhibited 98.78% entrapment. Tonicity of the formulation was adjusted with glycerol and subjected to sterilization which did not affect size are zeta of the formulation. There

was burst release of drug from the optimized formulation. Using jet stream and an ultrasonic nebulizer there was no effect on size and entrapment of nanocarriers [89].

Patlolla and co-workers developed NLC of celecoxib by high-pressure homogenization. The particle size of the optimized formulation was 217±20 nm and >90 % entrapment. Fine particle fraction and median mass aerodynamic diameter were found to be 75.6+/-4.6 and 1.6+/-0.13µ in in-vitro aerosolization studies. *In-vivo* studies were performed in Balb/c mice, celecoxib NLC formulations showed 4 fold increase in AUC(t)/D in lung tissue compared to celecoxib solution. The systemic clearance of celecoxib solution was 20.03 liter/hour were as celecoxib NLC clearance was 0.93 liters/hour. The study reveals improved bioavailability with minimal dosing interval [83].

Miscellaneous

Mucoadhesive drug delivery system

Mucoadhesive drug delivery is mediated by the interaction between the mucus layer over the mucosal epithelial, mucin moieties and polymer/co-polymer with increased dosage residence time to the site of absorption [90]. This system is beneficial over other srug delivery systems (DDS) including oral controlled drug release as it has increased residence time in the gastrointestinal tract, better targeting at the specific site and elevated flux of drug at the target site. The nasal cavity has a mucosal layer of 150-200 cm^2 allowing a residence time of 15-30 min to particulate matter. Increased residence time elevates the mucociliary activity due to the existence of foreign particulate matter. The phenomenon of the mucoadhesive system is,

polymer/copolymer absorbs water from the mucosal layer followed by penetration into the mucus for localization of drug in the nasal cavity, forming a gradient across the membrane for controlled drug release [91, 92]. Co-polymers are used for nasal based mucoadhesive DDS such as poly (amidoamine) dendrimer, methylcellulose, hydroxyl ethyl cellulose, poloxamer, poly (vinyl pyrrolidone), thiolated poly (acrylic acid), poly (dimethyl siloxane) etc [93-96].

In a study by Zhang Lan *et al*. fabricated mucoadhesive DDS based budesonide in chitosan microparticle and characterized drug release and the features of theallergic asthma using mice model. The therapeutic action was identified by measuring the IL-4 and IL-5 in bronchoalveolar lavage and mRNA. From this study, it is evident that drug release lasted for 12 or 18 hr depending on the molecular weight of chitosan. It is also reported that after consecutive seven days of treatment, eosinophil number and IL-4 & IL-5 in mRNA was found to be decreased. Mucoadhesive DDS chitosan-budesonide decreases the drug dose by 50% for effective treatment [97, 98].

Anotherstudy by Suk *et al*. reported the use of mucolytic adjuvant including N-acetylcysteine (NAC) and recombinant human deoxyribonuclease (rhDNase) to deliver highly compact DNA nanoparticle in the treatment of cystic fibrosis (CF). Furthermore, it was reported that PEGylated NAC and combination of NAC with rhDNase nanoparticles penetration increased by 3 and 6-folds repectively [99, 100]. Another strategy of mucoadhesion phenomenon is by coating mucolytic agents over the surface of nanoparticles such as the use of DNase which cleaves the accumulated DNA in the mucus of CF, non-specifically [101].

Montelukast loaded xyloglucan microspheres have been considered ideal lung delivery as DPI due to entrapment efficacy, mucoadhesion, flowability and controlled drug release from

microspheres. It has been suggested that the residence time of Montelukast-xyloglucan microsphere is 6 h and has a low frequency of drug administration. It has been reported as an ideal system for antihistamine delivery via pulmonary route [102, 103]. Ruge *et al.* reported that mucoadherent particles do not disintegrate in static condition while it only occurs when particles are bound to mucus. Therefore, mucociliary clearance forces play role in particle disintegration, thus such a combination can be utilized for pulmonary gene therapy [104, 105].

Transdermal patches:

The largest organ in the human body by mass is skin with a surface area of 16.1-21.5 sq. ft. transdermal patches (TPs) has various advantages over conventional drug delivery such as a potential alternative to hypodermic injection and oral drug delivery systems that can also be used for drugs which undergo rapid first-pass metabolism with better patient compliance[106] .

Kim and *et.al.* Studied the effective use of adrenergic β2 receptor agonist tulobuterol TPs for prophylactic treatment in asthma and COPD, the application of TPs has shown decreased airway resistance (R_{aw}) and increased dynamic lung compliance (C_{dyn}) in clinical study. Katsunuma T *et al* proved that TPs can be used for continues and short-term therapy for pediatric asthma [107], especially which are undergoing leukotriene receptor antagonist (LTRA) therapy, and the results showed a tremendous rise in volume of peak expiratory flow (% PEF) without intensifying fractional exhaled nitric oxide (FeNO) [108]. Another study by Mochizuki *et al* involved testing the effectiveness of TPs in elderly people (H)have proved that elderly people with COPD when treated with TPs and inhaled long-acting b2-agonists (LABA) salbutamol, showed an adherence rate of 90.3 1 1.6% for TPs whereas 75.5 1 2.9% for LABA. Such studies clearly demonstrate the potential of TPs indifferent age group of people with chronic respiratory diseases [109].

Conclusions

Investigating the role of oxidative stress in CRDs like asthma, COPD, respiratory infections and lung cancer can help in designing potential and better therapy for CRDs. The concept of novel drug delivery systems and approaches such as microparticles, microemulsions, microspheres, nanoparticles, liposomes, dendrimers, lipid nanocarriers, solid lipid nanocarriers, nanostructured lipid carriers has shown a tremendous revolution in the recent times with an emerging potential for CRDs when blended with the biological discoveries to target oxidative stress and ultimately reducing the diseases pathology. The discussed delivery methods such as nebulization and dry powder inhalation of the nanoparticle and microparticle drugs are advantageous as they escape mucociliary clearance and can encounter the deep target sites. There are various future challenges, whichstill warrant attention in combating the oxidative stress in CRDs using drug delivery, which is underway. Rigorous studies are being done to maximize drug delivery and minimize the toxicity, which includes modification of surface by PEG, mucolytic agents, osmotic pressure gradient for improved penetration through mucus by using mannitol and optimization of the formulation to upgrade the stability, deep lung deposition, and distribution. Several physiochemical characteristics of the drug formulation influence the pulmonary drug delivery including the size of particle, charge, morphology, and biodegradability. However, the concept of drug delivery targeting at the cellular and molecular level using the novel drug delivery concepts are providing a new direction to the pulmonary clinic providing better treatment, maximal patient compliance with minimum side effects.

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Figure Ligands:

1. **Fig. 1.** Various internal and external factors which enhance oxidative stress in the lungs, eventually increasing the severity of CRDs.
2. **Fig 2.**The action of Curcumin over NADPH oxidase
3. **Fig. 3** Mechanism of N-acetyl cysteine in the management of oxidative stress.

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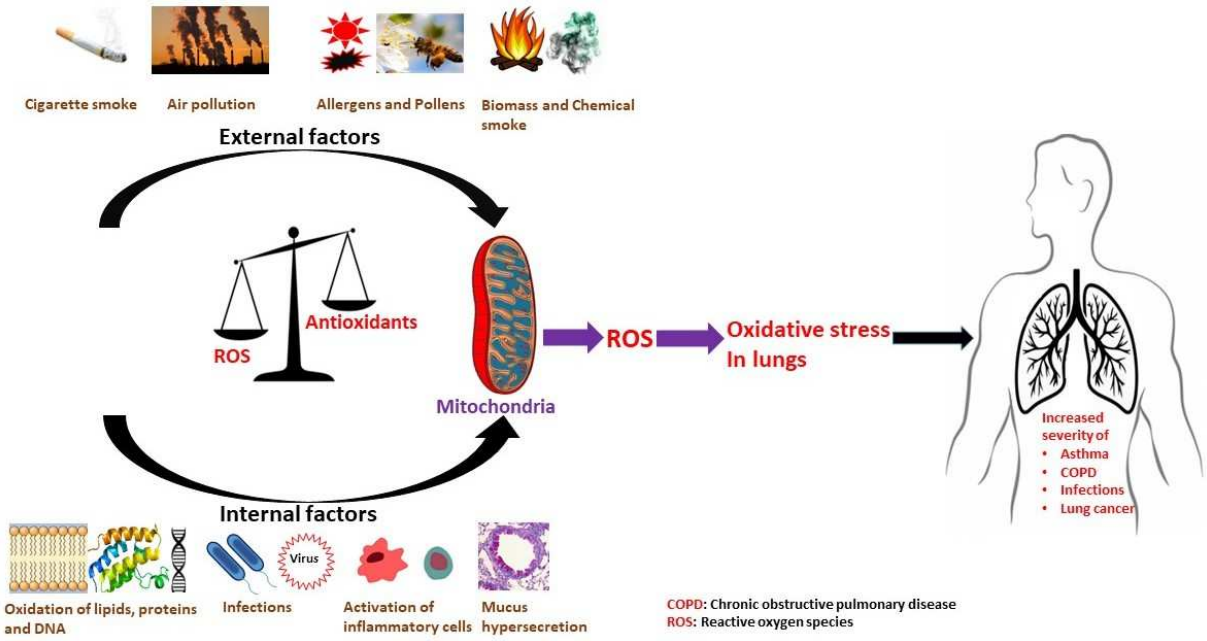

Fig. 1. Various internal and external factors which enhance oxidative stress in the lungs, eventually increasing the severity of CRDs.

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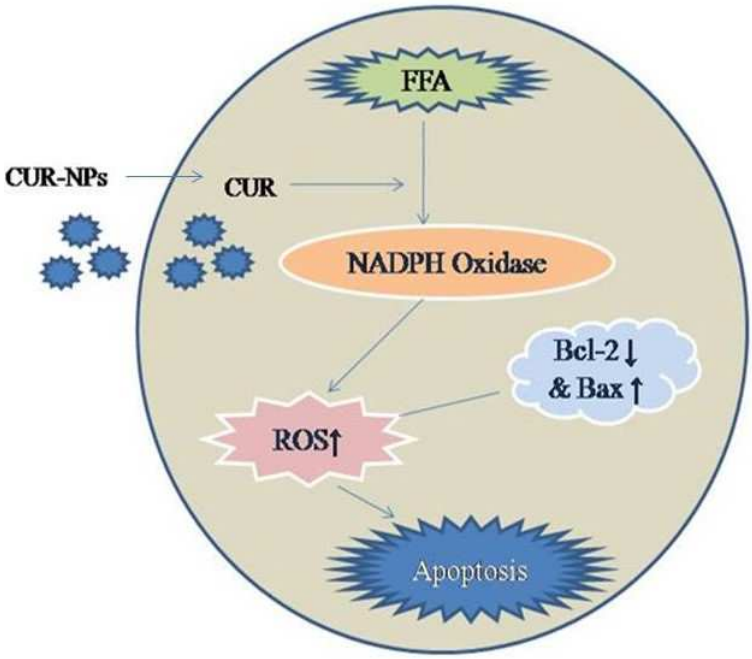

Fig. 2. The action of Curcumin over NADPH oxidase

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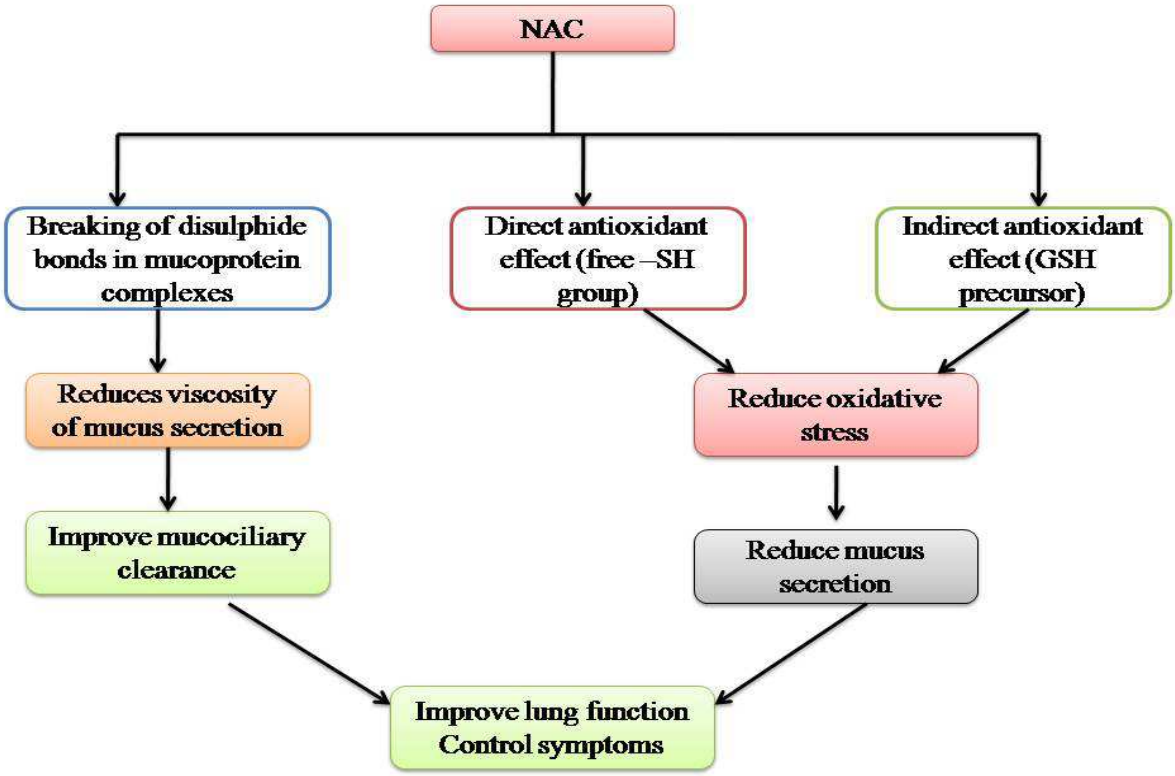

Fig. 3. Mechanism of N-acetyl cysteine in the management of oxidative stress.

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HIGHLIGHTS

1. Oxidative stress level contributes to severity of chronic respiratory diseases.
2. Delivery of new antioxidant therapies via novel drug delivery is urgently needed.
3. Novel vesicular drug delivery systems are gaining attention in targeting oxidative stress.
4. Vesicular drug delivery provides improved patient compliance and fewer side effects.

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