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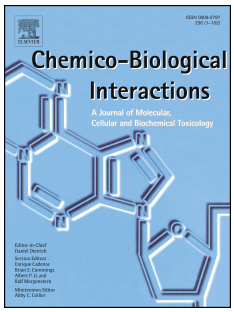

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Targeting Eosinophils in Chronic Respiratory Diseases using Nanotechnology-Based Drug Delivery

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Abstract

Asthma, COPD, COVID-19, EGPA, Lung cancer, and Pneumonia are major chronic respiratory diseases (or CRDs) affecting millions worldwide and account for substantial morbidity and mortality. These CRDs are irreversible diseases that affect different parts of the respiratory system, imposing a considerable burden on different socio-economic classes. All these CRDs have been linked to increased eosinophils in the lungs. Eosinophils are essential immune mediators that contribute to tissue homeostasis and the pathophysiology of various diseases. Interestingly, elevated eosinophil level is associated with cellular processes that regulate airway hyperresponsiveness, airway remodeling, mucus hypersecretion, and inflammation in the lung. Therefore, eosinophil is considered the therapeutic target in eosinophil-mediated lung diseases. Although, conventional medicines like antibiotics, anti-inflammatory drugs, and bronchodilators are available to prevent CRDs. But the development of resistance to these therapeutic agents after long-term usage remains a challenge. However, progressive development in nanotechnology has unveiled the targeted nanocarrier approach that can significantly improve the pharmacokinetics of a therapeutic drug. The potential of the nanocarrier system can be specifically targeted on eosinophils and their associated components to obtain promising results in the pharmacotherapy of CRDs. This review intends to provide knowledge about eosinophils and their role in CRDs. Moreover, it also discusses nanocarrier drug delivery systems for the targeted treatment of CRDs.

Keywords: Chronic Respiratory Diseases (CRDs), Eosinophils, Inflammation, Nano-carriers, Target drug delivery.

1. Introduction

Chronic respiratory diseases (CRDs) are affect the lungs and other parts of the respiratory system. Some of the lethal CRDs are Asthma, Chronic Obstructive Pulmonary Disease (COPD), COVID-19, Eosinophilic granulomatosis with polyangiitis (EGPA), Lung Cancer, and Pneumonia [1,2]. Some of these CRDs are claimed to be irreparable, which means they cannot regain normal functioning; therefore, they are stated as fatal diseases. According to World Health Organization (WHO), 334 million people have asthma, and 65 million have COPD, out of which 3 million die yearly. Concerning the current pandemic situation, WHO has stated that approximately 1 million people out of 28.9 million are prone to COVID-19, and this number is increasing exponentially [3–5].

Moreover, lung cancer often expressed as the lethal killer, has been responsible for 1.6 million deaths worldwide [6–8]. Apart from these fatal diseases, a few other respiratory diseases like Eosinophilic granulomatosis with polyangiitis (EGPA), Loffler's syndrome, and Pneumonia [5] also showed an elevated level of eosinophils in both the blood and the lungs. This makes eosinophil the viable target because it is an immune-mediator, performing diverse functions with inflammatory cells like maintaining homeostasis and indicating disease conditions in different tissues and cells of the body [9]. Additionally, elevated eosinophil count in the lungs causes the secretion of various chemokines, cytokines, proteins, and growth factors, leading to unceasing inflammation. Sometimes, it leads to permanent damage to lung tissues [10,11].

The first line of treatment for CRDs has always been traditional pharmacotherapy, which involves prescribed doses of several medicines, primarily antibiotics, anti-inflammatory, bronchodilators, and corticosteroids [12,13]. But these conventional approaches are not effective in curing these CRDs solely. For example, the therapies used to treat asthma, COPD, and other

respiratory diseases primarily focus on treating the symptoms and reducing the chances of exacerbations. The foremost reasons for the onset of CRDs include exposure to allergens, chemical dust, fume, and cigarette smoke. Although available pharmacotherapy suppresses immunological symptoms, it is frequently ineffective in treating these multifactorial CRDs such as EGPA, pneumonia, and lung cancer. [14]. Even though pharmacotherapy approaches play an important role in treating and managing patients throughout their lives, their limitations have encouraged us to discover novel therapeutic options. Recent advancements in nanotechnology have revealed the significance of nano-drug delivery systems, which have shown promising results in pharmacotherapy [15,16].

Additionally, these nanocarriers can target the desired site, significantly improving the therapeutic drug's pharmacokinetics. Eosinophils are now the most effective target for the treatment of CRDs. In the line of interest, targeting eosinophils via nanocarriers drug delivery systems can unlock the unseen potentials of therapeutic importance [17,18]. Hence, this review aims to provide insight into the role of eosinophils in the treatment of CRDs with the help of the nanocarrier drug delivery system.

1.1. Global Prevalence of Chronic Respiratory Disease

Chronic Respiratory Diseases (CRDs) have become the most prominent health hazard among all the socioeconomic classes and a significant factor in morbidity and mortality worldwide [19,20]. Therefore, global assessment of CRD patients, the World Health Organization (WHO) introduced the Global Alliance against Respiratory Diseases (GARD) in 2016. The role of GARD is to provide a comprehensive report of CRD patients' burden among 195 countries/territories. Moreover, about 7.63 million (66.7%) people have died of these CRDs due to tobacco consumption, in/outdoor pollution, allergens, diet, physical inactivity, obesity, and

95 occupational and environmental exposures [21,22]. Some of the common CRDs with associated
96 complications are depicted in **Figure 1**.

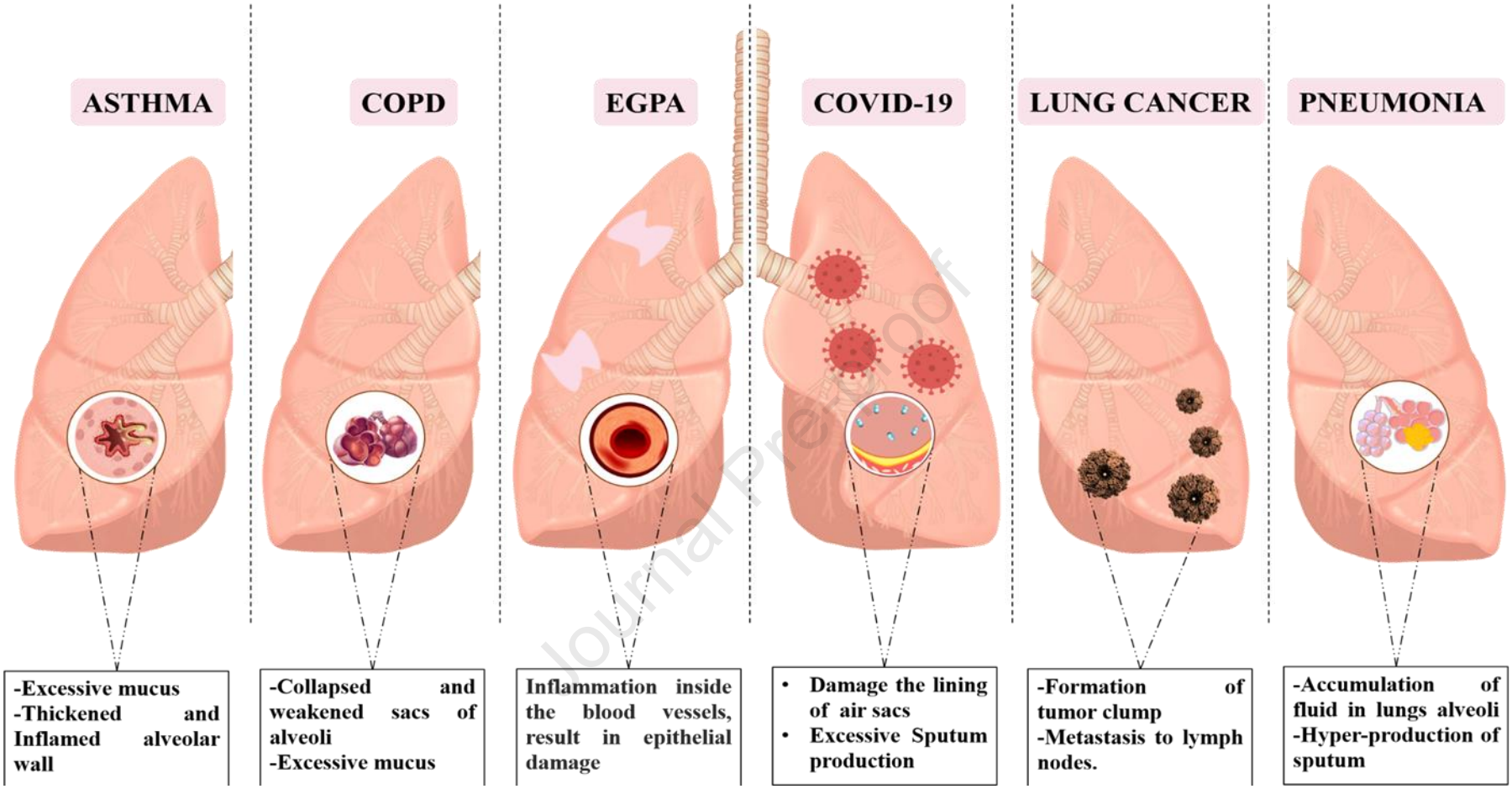

Figure-1 Diagrammatic Representation of Common Chronic Respiratory Diseases with its Associated Complications

Asthma is a long-lasting, inflammatory disease of the upper airways which usually occurs in the early stage of life. In this disease, the airways get inflamed, narrowed, thickened, and filled with mucus, restricting airflow [23]. This is the reason for wheezing sounds produced while coughing. The asthma symptoms include tightness in the chest, shortness of breath, coughing, fatigue, wheezing, and conjunctivitis. In 2020, nearly 3.39 million asthma cases globally and about 4.1 million deaths had been recorded for asthma [24]. Moreover, more than 80% of asthma-related mortality has been reported in middle/low-income countries. The prevalence of asthma is usually high in nations like Great Britain, Australia, Canada, Peru, Brazil, and the United States, whereas China, Russia, and India have a low prevalence rate [25].

Even though most respiratory disorders share similarities, asthma has unique clinical features that distinguish it from COPD and other pulmonary diseases [26,27]. The pathogenesis of asthma includes hyper-responsiveness of the non-ciliated epithelium in the upper airways, including bronchi, bronchioles, and trachea. This hyper-response of airway epithelial is generally triggered by allergens (pollens, dust particles) or environmental stimuli. This hyperresponsiveness leads to airway remodeling of smooth muscles and goblet cells, which causes constriction, inflammation in the bronchioles, and hyper-secretion of mucus [28–30]. Eosinophils play a crucial role in hyperresponsive reactions and are often associated with significant complications [31].

COPD, commonly referred to as Chronic Obstructive Pulmonary Disease, is a progressive pulmonary condition involving chronic bronchitis and emphysema[7]. During the early stages of COPD, emphysema gradually deteriorates the air-sacs of the lungs, obstructing the airflow. In contrast, bronchitis causes narrowing and thickening of bronchioles and is also responsible for producing mucus plugs [32,33]. Globally, around 65 million people have suffered from COPD, and about 3.19 million people die annually [34,35]. COPD mortality/morbidity rates

were significantly higher in 2015 than in 2010, corresponding to 2.8-3.0 million people. Hence, it is proclaimed the 3rd leading cause of death globally. COPD is expected to be the leading cause of high mortality and morbidity rates in the next 15 years [36]. Countries such as Austria, Canada, Australia, Brazil, South Africa, Italy, Uganda, and the U.S.A have recorded a high number of COPD patients compared to countries like Peru, Abu Dhabi, India, Singapore, Thailand, etc. [37].

COPD is mainly caused by cigarette/tobacco smoking, toxic particulates, and chemical irritants in the polluted air [38]. It is also caused due to some genetic factors like deficiency of α-1-antitrypsin, which leads to lung deterioration [39]. COPD pathological effect is also observed in bronchioles at the terminal end, as augmentation in air spaces wrecks the alveolar wall of bronchioles. Further, activation of eosinophils, structural amendment, and inflammation in small airways also enhance the severity of the disease [40]. Symptoms of COPD include cough with or without mucus, weight loss, wheezing sound, chest tightness, and flu [41].

COVID-19 is a viral infectious disease caused by a new strain of coronavirus that was not previously discovered in humans and named "novel-Coronavirus (nCOV-19)". Coronavirus is species of virus that is associated with different pulmonary diseases, such as common cold, Severe Acute Respiratory Syndrome (SARS-CoV), and Middle East Respiratory Syndrome (MERS-CoV) [42]. Till 24th November 2020, around 59.1 million people had been infected by a coronavirus, and about 1.4 million people had died globally. Worldwide, the most COVID-19 cases are reported in the U.S.A., India, Brazil, Russia, and France, contributing approximately 60% of the total cases [43].

COVID-19 is a zoonotic virus spreading among different animals and humans. Detailed studies showed that SARS-CoV was transferred from civet cats, and MERS-CoV was

transferred from dromedary camels to humans. Similarly, in the case of nCOV-19, there is a high level of genomic similarity with the bat-coronavirus. However, there is no evidence yet, confirming that it has emerged from a bat-borne virus [44]. The pathogenesis of this disease includes bilateral pneumonia and pleural effusion. Bilateral pneumonia causes the inflammation of alveoli which later get filled with pus.

In contrast, pleural effusion leads to fluid accumulation in the pleural cavity, restricting lung expansion. The common symptoms of COVID-19 include breathlessness, fever, dry cough/cough with mucus, and loss of taste and smell sensation. In severe cases, the persistent viral infection causes the onset of other ailments like influenza, Acute Respiratory Distress Syndrome (ARDS), and organ failure, which often leads to death [45–47].

Eosinophilic Granulomatosis with Polyangiitis (EGPA), also known as Churg-Strauss Syndrome, is a rare auto-immune pulmonary disease that primarily affects the upper airways**.** The estimated prevalence of EGPA is around 10-14 million people globally, corresponding to 2.5 cases over 10,00,00 people every year. The high majority of EGPA is recorded in Australia, Canada, Brazil, United States, and low in Asian (India and China) and Europe (Russia) countries [48,49]. It involves three stages, *viz*. allergic, eosinophilic, and vasculitis [50,51]. The allergic stage is characterized by an allergy/asthma or rhinitis, followed by the eosinophilic stage, distinguished by high eosinophil levels that last for months or a year. At this stage, the hyper-eosinophilic condition affects the lungs and the digestive tract, causing night sweating, weight loss, asthma, abdominal pain, cough, fever, malaise, gastro-intestinal bleeding, etc. Vasculitis is the final stage and a defining feature of this chronic disease. It usually occurs after hyper-eosinophilia. During systemic small-vessel vasculitis disease, arterioles/venules are inflamed (thickened, narrowed), restricting blood flow to tissues and body organs [52–54]. The pathogenesis of this disease is multifactorial, as it can be triggered by medication, allergens, or genetic factors, particularly HLA-DRB4, which has been

identified as a genetic risk factor involved in complex pathophysiology. The clinical signs of EGPA include chest pain, shortness of breath, skin lesions, sinusitis, blood in stools, and muscle/joint pain [55,56].

Lung cancer is a severe pulmonary disorder characterized by genetic material (DNA) alteration. This disruption of cell growth and proliferation system eventually leads to cell mass formation, termed a tumor. Tumors are classified as "benign" or "malignant" based on their ability to spread, i.e., metastasis [24,57]. In 2020, about 2.29 million cases (1.25 million females and 1.16 million males, respectively) and 1.35 million deaths (63,220 females and 72,500 males, respectively) had been recorded for lung cancer [58,59]. Therefore, lung cancer is the most common cancer in men and women, accounting for 25% of cancer-related deaths worldwide. The nations like Greece, Belgium, Denmark, Guam, Serbia, Hungary, Turkey, India, and Montenegro have been accorded the increasing trend of lung cancer [60].

Contributing factors in lung cancer include cigarette smoking, asbestos exposure, radon, biomass fuel, passive inhalation of cigarette smoke, etc. [61,62]. Lung cancer can develop in any part of the lungs; however, 90-95 percent of lung cancer develops in the airway epithelial cells. Symptoms of lung cancer include lack of appetite, fatigue, respiratory illness, coughing, clubbing of fingers, recurrent chest inflammation, thrombocytosis, and weight loss [63].

Pneumonia is an infectious lung disease that causes the inflammation of air sacs within one or both lungs. In this disease, the air-sacs become clogged with purulent fluid or pus, which decreases the surface area for gaseous exchange [64]. Pneumonia is caused by different bacterial species like *Mycoplasma pneumoniae, Haemophilus influenzae, Staphylococcus aureus,* etc. [65]. However, various fungi such as *Aspergillus spp., Coccidioides immitis, Coccidioides posadasii, and some viral moieties act as causative organisms* [66,67]. Pneumonia is the most common pulmonary disorder globally, affecting approximately 450

million people yearly. In 2017, about 2.56 million people died as a result of pneumonia all over the world. [68]. Out of which, more than 0.8 million deaths were of children (under the age of 5 years). Household air pollution was responsible for 45 percent of these children's deaths. [69]. The most frequent death cases have been reported in Southeast Asia and Sub-Saharan Africa, including India, Afghanistan, Democratic Republic of Congo, Ethiopia, Indonesia, Pakistan, Philippines, and Nigeria, due to the poor hygienic conditions, malnutrition, and air pollution. In contrast, fewer pneumonia deaths have been reported in North Korea, China, Peru, and Mexico [70]. The pathogenesis of pneumonia patients involves the inflammation in the lining of the pulmonary pleura resulting in extreme pain while coughing and breathing [71,72]. Pneumonia involves chest pain, shortness of breath, sputum in cough, fever, diarrhea, and fatigue [73,74].

Characteristics and different quantification methods of Eosinophils in Chronic Respiratory Diseases

Eosinophils are a vital immune-mediator that performs various cellular functions and plays an essential role in disease pathology and homeostasis across multiple body tissues. [75]. These are generally derived from the pro-genitor stem cells found in the bone marrow, which enter the bloodstream during maturation. In the blood circulation, IL-3 and IL-5 are the central cytokines that promote eosinophils' rolling, adhesion, trafficking, and survival. Under healthy conditions, eosinophil count and activity are low in the blood. However, during the disease conditions, eosinophils become highly active in response to pro-inflammatory mediators like IL-3, IL-5, and GM-CSF and start migrating towards the site of inflammation [76,77]. After reaching the targeted site, eosinophils trigger different eosinophil-mediated inflammatory responses. Certain chemotactic factors, such as CCL-5, CCL-7, CCL-11, CCL-13, CCL-15, CCL-24, and CCL-26, regulate eosinophil migration towards the site of inflammation in the lungs. These chemotactic factors act on the CCR-3, CRTH-2 receptors (expressed on T-

helper-2 (Th2) cells), and its ligand prostaglandin D-2 (PGD2) [78,79]. Various pro-inflammatory mediators, such as basic proteins (eosinophil-cationic protein, eosinophil-derived neurotoxin, and eosinophil-peroxidase), chemokines (CCL-5, CCL-7, CCL-26), cytokines (IL-3, IL-5, IL-10, IL-13, IL-25), and specific growth factors like Transforming Growth Factor (TGFα & β), Tumor Necrosis Factor (TNF); are also released by the eosinophils which play a significant role in various cell signaling pathways associated with different pulmonary diseases [80]. Although eosinophils play an immune-modulatory role, they are recruited inside the airway epithelium by the influence of other immune-mediator cells (ILC-2, basophils), resulting in necrosis and sustained inflammation within the lungs, as depicted in **Figure 2**.

Various studies have revealed that hyperactivation of eosinophils permanently damages the lung. Therefore, determining eosinophils may serve as a practical element for determining the onset of CRDs. Eosinophils count can be determined through blood, sputum, or Broncho-alveolar lavage (BAL) fluid, either as a percentage of total leukocytes or as an absolute concentration (cell/μl). The quantification of eosinophils can also be done via a lung tissue biopsy. Moreover, eosinophils concentration only provides information about the overall eosinophil levels but does not provide any information regarding its activation [81,82]. Furthermore, eosinophil concentration in blood is a good predictor of its concentration in the airways compared to the concentration of sputum/bronchial sub-mucosal samples. Because the blood-eosinophil count is simple, inconsistent, and samples are easily obtained, it is preferred over other clinical methods [83]. However, it may be noted that the blood eosinophil count is only a surrogate biomarker for airway eosinophilia in COPD and the eosinophilia of the sputum is seen in only a third of stabilized COPD patients, if not the exacerbated ones. Negewo et al. reported a statistically significant correlation between the eosinophil count in the peripheral blood and sputum samples [84].

In recent studies, a wide range of blood samples from CRD patients were found to have a high eosinophil count. For instance, a study of 491 asthmatic patients found that patients with a high eosinophilic count, i.e., ≥300 cells/µl, have significantly higher mean eosinophil concentration in induced sputa than patients with mean blood eosinophils count <300 cells/µl [85]. A recent study on COPD patients reported the high eosinophil concentration, i.e.,≥250 cells/µl, in BAL fluid, bronchial mucosa, and sputum in contrast to low eosinophil concentrations, i.e., <150 cells/µL in blood [82,86]. Similarly, high eosinophil concentrations are recorded in patients suffering from COVID-19, EGPA, lung cancer, and Pneumonia.

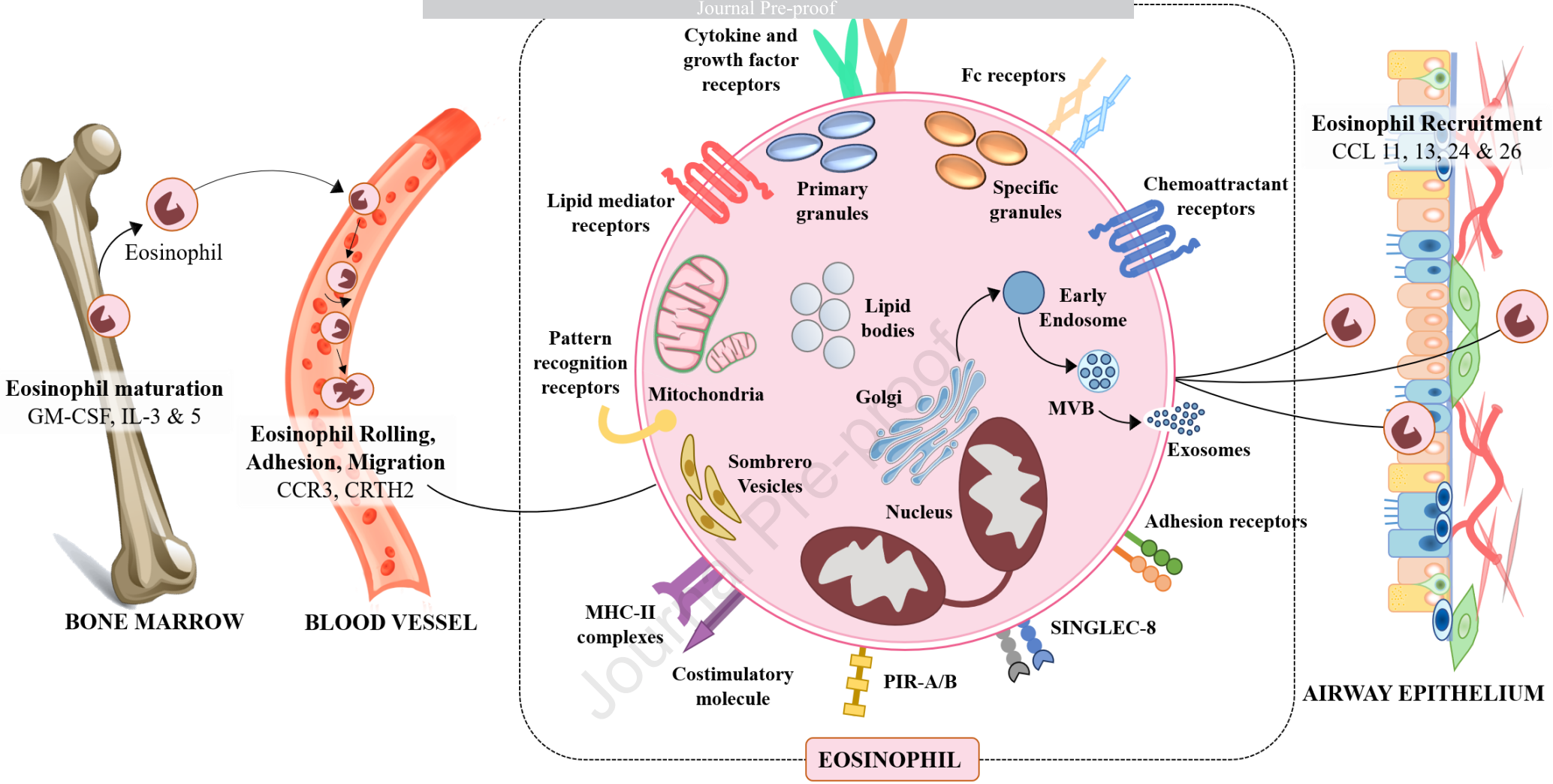

Figure-2 Diagrammatic Representation of Characteristics of Eosinophil and Its Interrelation with the Lung Diseases

2. Synergism between Eosinophils and Cell Signaling pathway involved in Chronic Respiratory Diseases

Eosinophils are granulocytic white blood cells with distinct phenotypical characteristics such as bi-lobed nuclei and acidic cytoplasmic granules. The pathogenesis of eosinophils mainly occurs inside the tissues and is associated with different mechanisms involving eosinophilic recruitment, as illustrated in **Figure 3**. Eosinophils are synthesized from pluripotent CD-34 stem cells in the bone marrow [76]. Eosinophils differentiate in response to the stimuli Granulocyte Monocyte Colony Stimulating Factor (GM-CSF) and IL-3,5. Upon maturation, these eosinophils are released from the bone marrow into the bloodstream under the influence of IL-5 and start migrating towards the bronchial endothelium. They begin rolling and adhering to the bronchiole endothelial layer once they reach the endothelial layer. Then, eosinophils begin transmigrating across the endothelial layer to complete the infiltration process [87–89]. This preferential eosinophilic adhesion from the blood onto various body tissues is regulated by interactions among different adhesion receptors (PSGL-1, VCAM-1 ligand) and integrins (eosinophilic surface) present on the endothelial layer. IL-4 and IL-13 have been discovered to enhance the expression of PSGL-1 and VCAM-1 ligand in IL-4,13 cell-signaling pathway, which is common in asthma, EGPA, and pneumonia patients. Chemokines such as CCL-5,7,11,13,15,24 and 26, along with cognate receptor CCR-3, regulate the recruitment of eosinophils to the airways in CRDs [90,91]. Certain proteins are found in the secondary granules of eosinophils, such as Eosinophil Cationic Protein (ECP), Eosinophil-derived neurotoxin (EDN), Eosinophil Peroxidase (EPO), and Major Basic Protein (MBP), have been found to contribute to complications associated with CRDs. Major Basic Protein (MBP) has been reported for the lysis of alveolar epithelium, escalating inhaled allergen penetration in asthmatic patients. Furthermore,

Eosinophil Cationic Protein (ECP) has been essential in altering epithelial permeability and increasing ROS production in both COPD and lung cancer [92–94]. Additionally, all these granular proteins are cytotoxic and often involved in disrupting the protective barrier around the pulmonary epithelium, which elicits additional inflammatory responses [77,95,96]. There is a debate over whether the biomarkers like ECP are eosinophil-selective, which warrants research into novel eosinophil-specific biomarkers. One of the reasons for such observations is the deficiency of information about the interpretation of the total blood eosinophil counts in connection with the levels of eosinophil-derived proteins. Research on the soluble Siglec-8 (sialic acid-binding immunoglobulin-like lectin 8) has revealed that it could be a potential eosinophil-selective serum biomarker [97]. Although, Siglec-8 is uniquely found on the surfaces of eosinophils, basophils (at low levels) and mast cells [98]. As such, a promising and exclusive eosinophil-specific biomarker is still awaited and there is a need for more research at the transcriptomic and proteomic level for establishing a specific biomarker for eosinophil activation.

Prostaglandin D-2 (PGD-2) receptor signaling pathway is a pro-inflammatory mediator usually derived from the arachidonic acid via the Cyclo-oxygenase-2 (COX-2) pathway. Phospholipids are converted to arachidonic acid by Phospholipase A-2 (PLA-2) and then to prostaglandins (PGs) by the Cyclo-oxygenase (COXs) enzyme activity [99–102]. Then, PGs penetrate the airway epithelium and differentiate into PGD-2, PGE-2, and other prostaglandins involved in different inflammatory reactions. PGD-2 interacts with DP-1, DP-2, and G-Protein-Coupled-Receptors and stimulates the thromboxane receptors that improve the vascular permeability of bradykinin, histamine, and leukotrienes during inflammatory response [103–105]. DP-2 receptor is homologous to the CRTH-2 receptor, which is generally expressed on the surface of

eosinophils, T-helper-2 (Th-2) cells, and mast cells. The activation of DP-2 receptors on Th-2 cells via PGD-2 stimulates the expression of IL-4,5 and 13, which upregulates the pro-inflammatory signaling pathways and terminate the eosinophils activation [106,107]. IL-4 is mainly responsible for the Airway Hyper-Responsiveness (AHR), whereas IL-13 induces the hyperplasia of goblet cells, resulting in hypersecretion of mucus. These are the main pathological characteristics associated with asthma, EGPA, and pneumonia which get triggered due to the activation of IL-4 and 13 cell-signaling pathways [91,108,109].

Further, IL-5 activation causes eosinophil infiltration into the lungs and is generally recognized as a key mediator of the IL-5 pathway in lung cancer. The activated eosinophils induce the up-regulation of mast cells aided by MBP and EPO granular proteins, increasing histamine production and eliciting the hyper-responsiveness of smooth muscles. Furthermore, MBP and EPO proteins are also involved in damaging of epithelial layer [110,111]. Eosinophils are also involved in activating Th-2 and fibroblasts, responsible for the airway remodeling and structural damage of the respiratory tract. Therefore, PGD-2 plays an essential role in the complications of CRDs like asthma, COPD, COVID-19, EGPA, and pneumonia. Hence, antagonists molecules can be used to target the PGD-2 signaling pathway for managing these conditions [112–115].

Other PGs like PGE-2 is also involved in the production of various pro-inflammatory cytokines such as RhoA (Ras Homolog Gene-A), ERK (Extracellular-signal Regulated Kinase), PI3K (Phosphatidylinositol-3-Kinase), cAMP (cyclic-Adenosine Mono-Phosphate), Ca^{2+} (Calcium ion), which play a significant role in the pathophysiology of different CRDs [116,117]. The RhoA pathway promotes eosinophil recruitment, whereas the ERK pathway regulates eosinophil activation and migration within the lungs. The cAMP pathway is responsible for eosinophil survival and apoptosis because it regulates persistent hyperresponsiveness in the lungs.

Moreover, Ca^{2+} is involved in chemotaxis and polarization of eosinophils, and PI3K-pathway regulates the cell-angiogenesis, growth, metabolism, proliferation, and survival in COPD and lung cancer patients [118–120].

The activated form of PI3K (Phosphatidylinositol-3,4,5- Triphosphate) induces conformational changes in the Akt signaling pathway, also known as the serine/threonine kinase signaling pathway [121,122]. The Akt signaling pathway is involved in several cellular processes and has been linked to COPD and lung cancer [123,124]. The Akt signaling pathway regulates the eosinophil activation, airway remodeling, and release of different immune-mediators [125,126]. The comprehended literature shows the involvement of eosinophils in different cell signaling pathways and chronic respiratory diseases. Hence, eosinophils can be targeted as they could pave the way for new therapeutic drugs and aid in preventing respiratory and other disorders [127,128].

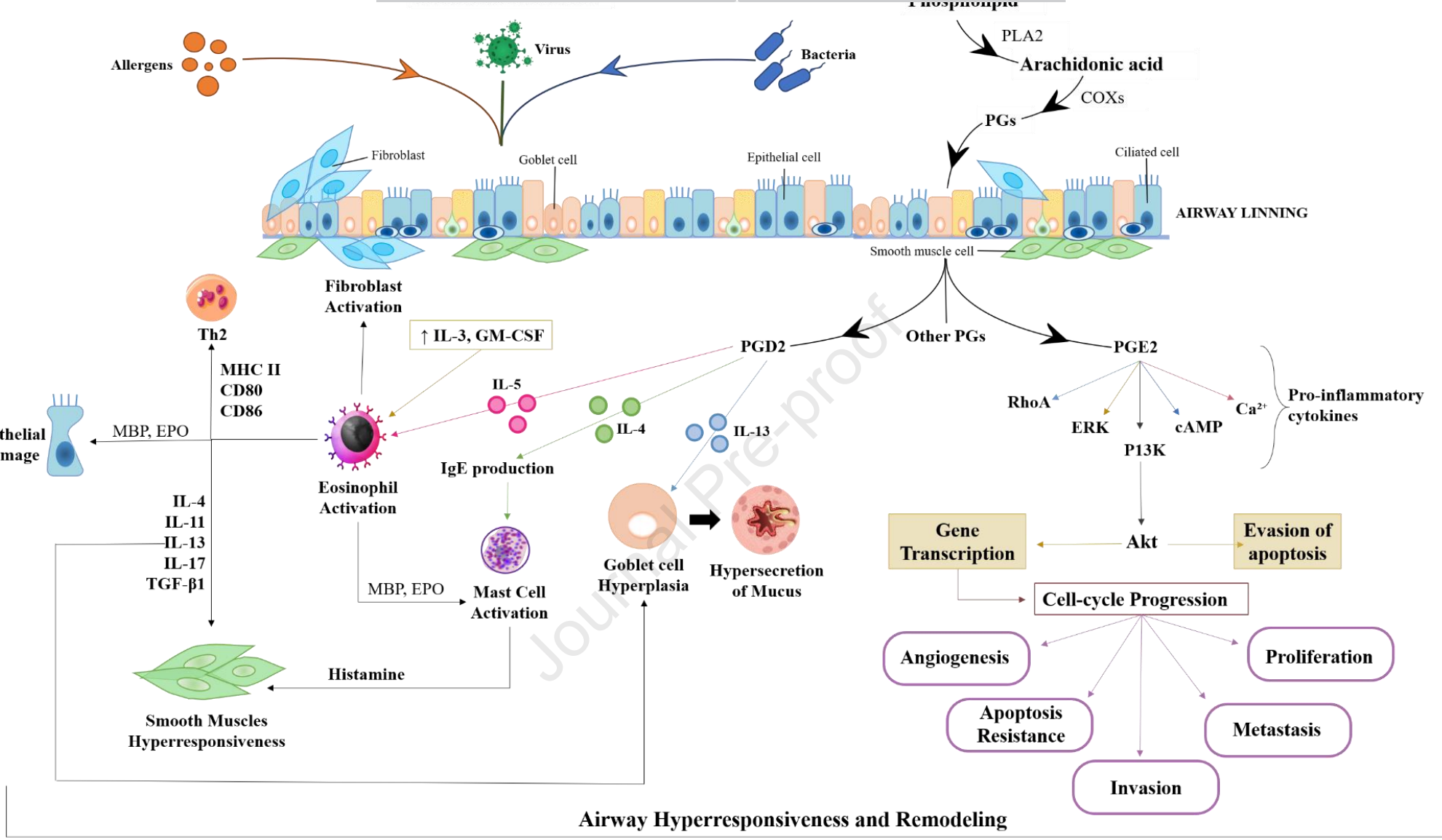

Figure-3 Diagrammatic Representation of Synergism between Eosinophils, Cell-Signaling Pathways, and CRDs

3. Current Treatments Available for treating Chronic Respiratory Diseases

Although CRDs are incurable, different chemotherapeutic agents are used to curb the clinical symptoms, reduce mortality/morbidity, and improve the quality of life. Presently, progressive advancement has been made to improve drug efficacy and drug delivery. However, effective management of CRDs remains a challenge [129]. The current treatment involving different therapeutic regimens for CRDs have been discussed below:

3.1. Antibiotics

Antimicrobial agents used explicitly for treating different bacterial infections are known as antibiotics. Antibiotics are primarily used to treat asthma, and COPD, due to their effective anti-inflammatory and pro-kinetic properties [130]. In chronic respiratory diseases, antibiotics are administered either through nebulizers or oral routes. Azithromycin, oleandomycin, clarithromycin, theophylline erythromycin, and roxithromycin are some macrolide antibiotics that have been clinically certified and are specifically used to treat asthma [131]. Similarly, macrolides have shown promising effects in COPD patients in reducing exacerbation like inflammation of alveoli, expression of Macrophage Mannose Receptors (MMR), and phagocytosis of macrophages [132]. For lung cancer, antibiotics such as amoxicillin, cephalexin, amoxicillin-clavulanic acid, floxacillin, penicillin V, erythromycin, oxytetracycline, and trimethoprim are commonly used [133]. Additionally, macrolide monotherapy is the recommended treatment for community-acquired pneumonia out-patients [134,135]. For patients with severe pneumonia (exacerbated cases with admission into a hospital), firstly, the sputum and blood cultures are drawn and then the antibiotics are administered based on the identified pathogen [136]. Although these antibiotics effectively treat CRDs, their continuous usage leads to resistance or other side effects such as hearing loss and alteration in QTc [137].

3.2. Anti-inflammatory

Anti-inflammatory drugs are chemical entities that have the potential to reduce inflammation within the body [138]. They are classified as steroidal or non-steroidal (NSAIDS) anti-inflammatory drugs based on their chemical structure. This medication usually involves inhibiting Cyclo-oxygenase enzymes (COX-1 & 2) responsible for thromboxane and prostaglandins production inside the cells. Thromboxane is the primary biological mediator, accountable for the blood-clotting pathway, whereas prostaglandins are involved in inflammation, following the PGD-2 pathway, which results in eosinophil activation [139]. Therefore, inhaling corticosteroids (beclomethasone, furoate, or fluticasone), systemic corticosteroids (prednisone, prednisolone, and methyl prednisolone), mast cell stabilizers (Cromolyn sodium), leukotriene modifiers (montelukast, zileuton) are used in the treatment of asthma to prevent the hyperactivation of eosinophils [140,141]. A physician generally prescribes inhaled and oral corticosteroids to avoid symptoms of COPD [142,143]. In COVID-19, NSAIDs like aspirin, diclofenac, ibuprofen, and naproxen are prescribed during the acute phase to control respiratory inflammation [144,145]. In EGPA patients, combination therapy of prednisone with cytotoxic agents (cyclophosphamide), methotrexate azathioprine, or mycophenolate mofetil is given to circumvent the vasculitis stage [146]. In the case of lung cancer, different anti-inflammatory drugs like celecoxib, ibuprofen and ketorolac are mainly prescribed for overcoming the clinical symptoms [147]. Moreover, a different combination of NSAIDs (ibuprofen and acetaminophen) is given to pneumonia patients [148,149]. Although anti-inflammatory drugs are the mainstream medication for CRDs, long-term usage of these medications lead to severe side-effects such as hypertension, osteoporosis, loss of appetite, mood swings etc [150,151].

3.3. Bronchodilators

Bronchodilators are therapeutic agents that are specifically used to dilate the bronchi. They treat air resistance and breathing difficulties and improve airflow within the lungs [152]. Bronchodilators are broadly categorized into three categories, i.e., β-2/Adrenoceptor (AR) agonists (formoterol, salmeterol), anti-muscarinic/anticholinergics drugs (aclidinium, ipratropium) and methylxanthines (caffeine, theophylline). A β-2 agonist is an adrenergic drug that binds onto adrenergic receptors of smooth muscles of bronchioles and aid in bronchodilation [153]. Anti-cholinergic drugs block the neurotransmitter acetylcholine's function and prevent involuntary muscle constriction[154]. These sub-categories of bronchodilators are either administered alone or in combination to ease the complications of CRDs. Short-acting-β-2 agonists like Albuterol, Levalbuterol, or a combination of Albuterol and ipratropium bromide are used [155,156]. COVID-19 patients are generally prescribed a nebulizer (Aeroneb Solo) containing the albuterol.

Furthermore, theophylline, a methylxanthine, has a high bioavailability and anti-inflammatory potential, which aids in regulating and inhibiting eosinophil infiltration in COPD, asthma, and COVID-19 [155,157]. For EGPA and lung cancer, dual bronchodilator therapy is used. Despite this, these bronchodilators have a therapeutic effect and are widely used in CRD patients; long-term use of these bronchodilators causes drug toxicity and the development of drug resistance [158,159]. Hence, there is an urgent need to develop novel bronchodilators that can be used long-term and have good clinical efficacy.

4. Challenges associated with Conventional Treatment of Chronic Respiratory Diseases

These CRDs have complex pathophysiology, and severe clinical symptoms managed using traditional methods such as long-term antibiotics, bronchodilators, or anti-inflammatory drugs. Furthermore, the continued use of these conventional medications creates additional challenges that have already been discussed [160]. Antibiotics are the primary remedies that are used to treat respiratory infections. But continuous use of these drugs, especially macrolides, cause impairment in phagocytosis and autophagy of macrophages, resulting in bacterial infection. Extensive use of penicillin resulted in abdominal cramps, nausea, and vomiting. Additionally, improper and long-term usage of these antibiotics also increases the drug tolerance and often leads to antibiotic-resistant bacteria development [137,161].

On the other hand, anti-inflammatory drugs possess various therapeutic benefits for treating inflammation in different CRDs. Despite that, oral and systemic administration of these drugs increases the risk of bone fracture and osteoporosis [162]. Long-term use of corticosteroids is associated with hyperglycemia because it promotes gluconeogenesis in the liver, while inhaled corticosteroids have fewer side effects. Moreover, the presence of corticosteroids in the bloodstream has been associated with retardation of cellular growth in children [163]. Other risks associated with the extensive use of anti-inflammatory drugs include glaucoma, sodium retention, cataract, gastrointestinal bleeding, and skin atrophy [164]. The administration of β-2 agonists causes side effects in the cardiovascular system, such as ischemia and arrhythmia.

Furthermore, these agonists impair the disease control system's functioning, leading to osteoporosis and increasing the probability of developing tolerance to these drugs [165]. Long-term use of muscarinic agents leads to glaucoma, mouth dryness, cognitive dysfunction, and tachycardia [166]. Thus, these challenges have prompted us to improve the available therapeutic interventions and developed novel therapeutic agents for effective treatment.

5. Advantages of Novel Drug Delivery System

There is a need to explore a novel and improved drug delivery approach to circumvent the limitations associated with the conventional therapeutic approach. The new approach should increase the residence time of the drug and can be quickly cleared from the body [167,168]. In light of the abovementioned requirements, a novel drug delivery system based on nanoparticles has emerged as an effective approach for treating various CRDs. [169]. Nanoparticles Drug Delivery System (NDDS) has an advantage over traditional therapy as it is a targeted approach that avoids and reduces the chances of side effects and complications. Moreover, a novel drug delivery approach effectively evades the pulmonary barriers like lung clearance, mucus barrier, and residence time as the drug is incorporated inside the nanocarrier system [170,171]. Due to their small size, these nanoparticles can easily cross the mucus barrier and reach the alveolar space. In a few cases, polymers such as hydroxypropyl methyl cellulose (HPMC) and hydroxyethyl cellulose (HEC) are used to coat the nanocarriers to increase their residence time by enhancing their interaction with the mucus layer [172]. Furthermore, these nano-carriers increase the drug's stability, reduce toxicity, and deliver the therapeutic agent at a specific or target site in the lungs. Some advantages of these NDDS are: 1) They are site-specific, biodegradable, non-toxic, and can be stored for up to a year 2) They can be easily amended via matrix selection for controlled release of therapeutic agents 3) They are inert and have the tendency to cross the barriers associated with the target site 4) They have the potential to enhance the performance and pharmacological response of the therapeutic agent 5) They can be administered via oral, nasal, parenteral and intraocular routes.

5.1. Novel Drug Delivery System for Treating Chronic Respiratory Disease

In past decades, different NDDS have been developed for targeted drug delivery for treating CRDs, as illustrated in **Figure 4**. Detailed information on different NDDS explicitly designed for targeting eosinophils and their associated intermediates have been discussed below.

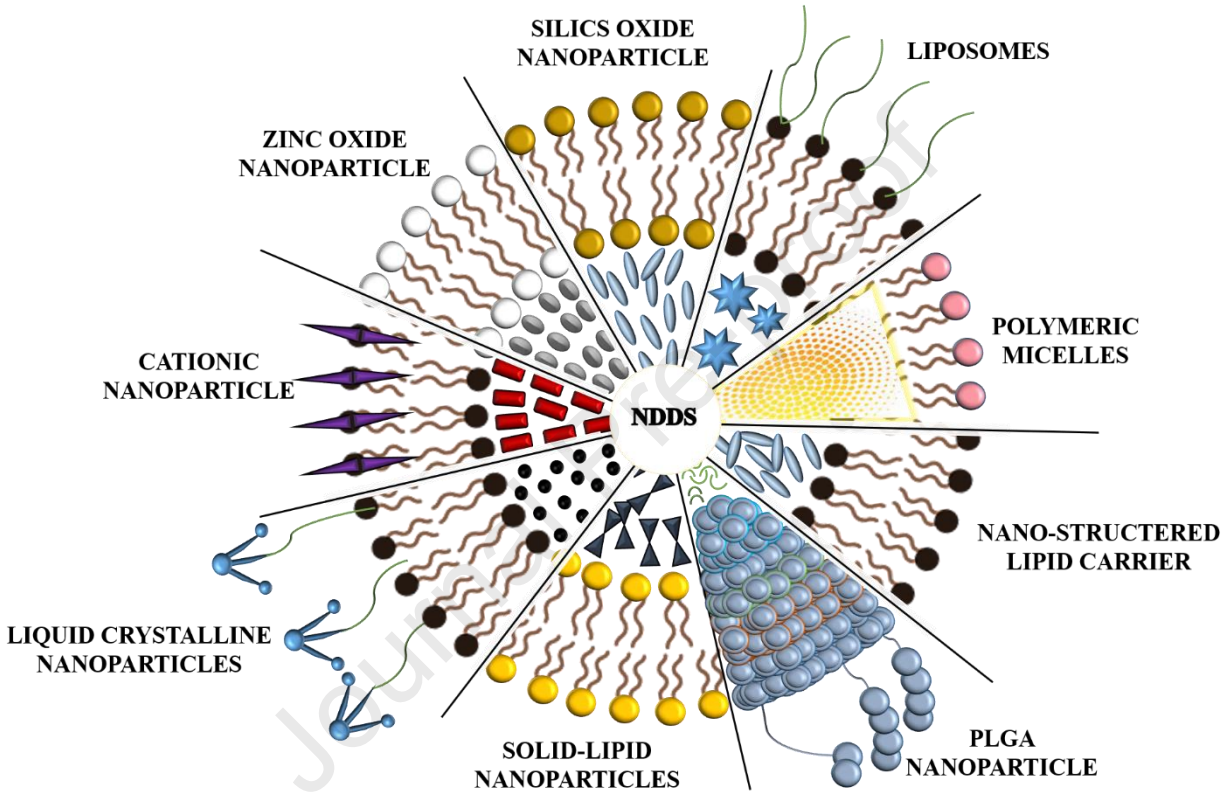

Figure-4 Diagrammatic Representation of Different Nanoparticle-Based Drug Delivery Systems

5.1.1. Liposomes

Liposomes are spherical nano-scaled vesicles that can incorporate hydrophobic and hydrophilic drugs into the aqueous core and resemble biological membranes [173]. Distinct characteristics of liposomes, such as their non-toxic nature, easy-to-modify surface via external stimuli, physical resilience, high retention time, and high vascular density, make them unique from other

nanocarrier systems [174]. Cholesterol, phospholipids, and an aqueous core are the major components of a liposome. The liposomes generally possess sizes ranging from 0.05–5μm [175,176]. Liposomes effectively deliver the therapeutic agent through targeted strategies such as active/passive targeting, pH, and magnetic-responsive targeting. These targeting strategies increase the pharmacodynamic and pharmacokinetic profiles of the therapeutic agent, controls the release of the therapeutic agent, and reduce the toxicity in contrast to a conventional drug solution [177]. Furthermore, targeting induced by external stimuli and ligands has significant advantages in drug delivery systems, particularly in eosinophil-mediated inflammation. This method improves drug bioavailability, reduces toxic effects, and improves overall therapeutic response at the target site [178]. The lack of eosinophil-specific biomarkers is one of the concerns. A lack of such a biomarker also implies that there is a corresponding short fall of a druggable target to tackle eosinophilic activation. Therefore, it may also be suggested that the nanotechnology-based delivery systems be developed for targeting the mucosal surfaces of the lower airway. Using these systems, enough concentration of the drugs can be delivered at the site of inflammation.

Chen *et al.* (2012) developed salbutamol sulphate (SBS) encapsulated liposome formulation and conducted a study to assess the potential of liposomes for prolonging the therapeutic effect of an anti-asthmatic therapeutic agent through pulmonary delivery. The encapsulated SBS showed an encapsulation efficiency of 70%. In an *in-vitro* study conducted on Asian toads, the liposomes showed a slower transport rate than a free solution of SBS. Pulmonary delivery of SBS via liposome showed an effective result in both rat and guinea pig models. The overall result of the study showed a positive outcome related to concentration and retention time of SBS, which attributed to prolonged therapeutic effect [179]. Yin Ng et al. (2018) also conducted a study to

assess the potential of curcumin-loaded liposomes as a therapeutic approach for treating asthma. In this, curcumin-loaded liposomes were evaluated for their anti-inflammatory potential in BCi-NS1.1 cell line.

Additionally, pro-inflammatory markers like IL-6, IL-8, IL-1β, and TNF-α were studied. The results showed that curcumin-loaded liposomes effectively lowered the expression of pro-inflammatory markers, making it a promising intervention in asthma therapy [180]. Serrano and colleagues conducted the study on COVID-19 positive patients confirmed by rapid test using liposomal bovine lactoferrin (LLF) nutritional syrup food supplement. During the investigation, patients were orally administered 4-6 doses of liposomal formulation per day for ten days. LF is known to possess anti-inflammatory, antiviral, and immunomodulatory potential, due to which it was considered that it could be effective in treating the symptoms of COVID-19. The result concluded in the study stated that LLF can be a potential preventive measure for curing COVID-19 infection [181]. Another study assessed the improved potential of liposomes targeting the IL-4 receptor on tumor endothelial cells. This study used the potential of IL-4R-binding peptide-1 (IL4RPep-1), a CRKRLDRNC peptide, to target the lung tumor. Liposomes labeled with IL4RPep-1 containing doxorubicin showed the effective delivery of doxorubicin in H226 cells. In addition, an *in-vivo* study on naked mice xenotransplant with H226 tumor cells revealed that liposomes labeled with IL4RPep-1 were more effective at targeting the tumor.

Furthermore, they effectively inhibited tumor growth when compared to unlabeled liposomes. This finding suggests that using an IL-4R targeting nanocarrier to improve drug delivery to both tumor endothelial cells and tumor cells could be an effective strategy [182]. Li and his teammates developed liposomal Andrographolide (AG) dry powder inhalers (LADPIs) for treating *Staphylococcus aureus*-induced pneumonia. The *in-vivo* result of the study revealed that

the LADPIs approach is more effective in comparison to AG alone, as it showed a more substantial anti-pneumonic effect. The result obtained from this study indicates that the LADPIs approach will be an effective method for treating bacterial pneumonia [183].

5.1.2. Solid Lipid Nanoparticles (SLNs)

Another nanocarrier system that has emerged as an alternative to the conventional colloidal delivery system is solid lipid nanoparticles (SLNs) [184]. These nanocarriers are spherical and range between 50-1000 nm. The biocompatible lipids used for synthesizing these nanocarrier makes them compatible and safe for use. Hence, this nanocarrier system is strongly recommended for delivering pulmonary drugs in dry or suspension form as it doesn't induce any inflammatory response [185,186]. Generally, SLNs are composed of solid lipid 0.1–30% (w/w) that quickly gets mixed in an aqueous solution.

Additionally, 0.5-5% surfactant is added to the aqueous solution mixture during the formation of SLNs to improve their stability. The SLNs are unique as lipids used for their synthesis remain solid at room temperature. The advantage of this nanocarriers system is that it can easily be modified, has a biocompatible nature with lipophilic drugs, delivers the medicine at the target site, is less toxic, and improves the stability of drug [187,188]. This nanocarrier combines the characteristics of liposomes, fat emulsion carriers, and polymeric nanoparticles, making it a unique drug delivery system. The easily modifiable nature of this nanocarrier system via ligands transforms it into an active delivery system with improved target efficiency [189].

In 2008, Choi and his colleagues formulated cationic SLNs for targeted delivery of the p53 gene in lung cancer. The transfection by SLNs carrying the p53 gene resulted in high expression of wild-type p53 mRNA and protein in H1299 cells. Reestablishing the p53 gene (wild-type) in

lung cancer cells causes the restoration of the apoptotic pathway. The result indicates that the cationic SLNs-mediated p53 gene delivery system could serve as a non-viral vector-mediated lung cancer therapy as it is effective in inhibiting tumor growth and inducing apoptosis [190]. Another study was conducted in which hyaluronic acid-coated SLNs were evaluated for targeted delivery of paclitaxel (PTX) to CD44-overexpressing B16F10 tumor cells. The result obtained from the study showed a significant antitumor effect at a relatively low dosage of PTX. It indicated that this targeting system could serve as a promising tool in cancer therapy [191,192].

Wang et al. (2012) developed curcumin-loaded SLNs to enhance the therapeutic potential of curcumin in an ovalbumin (OVA)- induced allergic asthmatic rat model. In this study, the pharmacodynamic and pharmacokinetics of the formulation were assessed. The *in-vivo* results revealed that curcumin-loaded SLNs effectively suppressed the inflammatory cell infiltration and hyperresponsiveness of airways. It also effectively inhibited the expression of cytokines like IL-4 and IL-13 of Th2 cells in BAL fluid in the asthmatic rat model [193]. Kalhapure and his colleagues developed SLNs of clotrimazole silver complex for improved antibacterial potential against *S. aureus* and methicillin-resistant *S. aureus* (MRSA). The result obtained from the study showed the MIC value of 104 and 208 g/mL against both *S. aureus* and MRSA, respectively. This nanocarrier system was also stated as an effective nano-antibiotic [194].

5.1.3. Polymeric micelles

Polymeric micelles are extensively used for controlled release and targeted delivery of hydrophobic drugs [195]. This nanocarrier system is composed of a hydrophobic copolymer core for entrapment of hydrophobic drugs and a hydrophilic shell for entrapping hydrophilic drugs [196,197]. Moreover, the hydrophilic shell provides the additional advantage of high stability to these polymeric micelles. These polymeric micelles range from 20 to 100 nm, making them a

reliable carrier system for delivering hydrophobic drugs due to their high permeability, high payload capacity, and long retention time in blood [198,199]. Furthermore, modifying the surface of polymeric micelles improves their efficiency for targeted drug delivery. The most significant advantage of this nanocarrier system is its biodegradability, which makes it an ideal drug delivery system [200].

Onoue *et al.* (2012) reported on the development of a water-soluble formulation of Chafuroside A (CFA) with the help of a self-assembling micellar (SAM) system. This formulation was developed to improve the dissolution behavior as well as the anti-inflammatory potential of CFA. During dissolution evaluation, CFA/SAM complex showed apparent improvement in dissolution behavior. The effective result obtained for the therapeutic potential of the CFA/SAM complex indicates that it could be an effective approach for treating inflammatory diseases like asthma and COPD [201]. Another study reported integrin-coupled polymeric micelles that effectively targeted tumor cells. The advantage of this complex is its biodegradable nature. Hence it can be employed for ocular and cancer drug delivery [202]. Gao *et al.* (2015) developed paclitaxel and itraconazole encapsulated polymeric micelles and revealed that they effectively decreased toxicity in non-small cell lung carcinoma (NSCLC).

Moreover, α-Conotoxin ImI coated polymeric micelles have also emerged as a potent nanocarrier for targeted delivery of docetaxel in the A549 cell line [203]. Zahedipour and his colleagues reviewed curcumin-loaded polymeric micelles, which effectively inhibit the effects of NF-κB and various pro-inflammatory cytokines. They aim to provide the prospect for curcumin application in treating covid-19 [204].

5.1.4. Nano-structured lipid carriers

Another nanocarrier developed to overcome limitations like drug expulsion during storage, formation of crystals under different conditions and low payload capacity of SLNs is Nano-structured lipid carriers (NLCs) [205,206]. This nanocarrier system is a blend of solid and liquid lipids that improves the payload capacity and reduces the chances of drug expulsion during storage [207].

Shao and his colleagues developed transferrin (Tf) coated NLCs for co-delivery of DNA and paclitaxel (PTX) at the targeted site in lung cancer with high efficacy. The result obtained from the study revealed high gene transfection efficacy, low cytotoxicity, and improved antitumor potential in both *in vitro* as well as *in vivo* studies. These effective results indicate that this drug delivery system could be a promising approach for treating lung cancer [208]. Chikuma *et al*. (2019) developed a nano-structured lipid co-delivery system composed of a poly(lactic acid) (PLA) core encapsulating antioxidant Mn-porphyrin dimer (MnPD) and cationic lipid (DOTAP) shell with affinity to bind HDAC2-encoding plasmid DNA (pHDAC2) as a novel therapeutic approach for treating COPD. The obtained results demonstrated an effective result, revealing the multi-antioxidative potential of this nanocarrier system. In-vitro studies also provide evidence for lowering IL-8 expression levels [209]. Zai *et al*. (2019) reported the development of NLC containing all-trans retinoic acid (ATRA) for oral administration. NLC-RA was administered through macrophages, which triggered an anti-inflammatory response by increasing the production of anti-inflammatory cytokines and suppressing NF-B signaling. The study's findings suggest that this approach could be used as an alternative therapy for inflammatory diseases. [210].

5.1.5. Other Nanocarrier Systems

Yong *et al*. reported that quercetin-loaded liquid crystalline nanoparticles (LCNs) can be used to treat asthma's clinical symptoms by suppressing the activity of pro-inflammatory biomarkers like IL-1β, IL-6, and IL-8. Additionally, this nanocarrier system also improved the anti-inflammatory activity of the drug. Moreover, the improved anti-inflammatory activity of quercetin substantially enhances the permeability of broncho-epithelial cell membranes resulting in increased cellular uptake and drug absorption [211]. Another recent study has reported that silica dioxide and zinc oxide nanoparticles have negative impacts on asthma exacerbation as they substantially elevate the expression level of mRNA encoding for inflammatory cytokines, followed by the elevation in the expression of inflammatory 3- like NOD pyrin domain (NLRP3), IL-1β-proteins and thioredoxin- interacting protein (TXNIP). Various other studies have reported that nanoparticles-based delivery of drugs like andrographolide, budesonide, and dexamethasone have an effective inhibitory effect on Th2 cytokines, primarily IL-4 and IL-13, due to improved bioavailability, lung deposition, and persistent release of drug [212]. Luo *et al*. conducted a study to assess the implications of nanovaccine with poly(lactic-co-glycolic) acid (PLGA-ovalbumin (OVA) + A20 (ubiquitin E3 ligases) in an asthmatic murine model. The results showed a significant increase in the Treg cell and IL-10 generation, which ultimately curbed allergic response in the airway of sensitized mice [213].

6. Conclusion

Eosinophils are an essential immune mediator that performs various cellular functions and plays a vital role in disease pathology and homeostasis across multiple body tissues. It also plays a role in regulating the functional homeostasis of various non-immunocompetent tissues. A complex eosinophil-containing cell signaling pathway involves B cells, Th-2 lymphocytes, mast cells, and circulating platelets activated by inflammatory stimuli at the inflammation site to protect the host

from various infections caused by bacteria, fungi, and viruses. Furthermore, the same mechanism is involved in tissue damage caused by clonal disease, infection, hypersensitive response, or autoimmune disease. Because of eosinophil's involvement in various complications, it should be targeted for relieving and controlling the complications of various diseases. Recent development has provided insight into pathogenic events. Although the nanocarrier system approach is in its infancy stage, various eosinophil targeting nanocarriers systems are being developed and believed to offer promising results in treating eosinophil-mediated respiratory diseases.

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Highlights

- Eosinophils are important immune mediators in respiratory diseases.
- Targeting of eosinophils can effectively be achieved by nanotechnology.
- These nanocarriers can target desired site and improves the drug's pharmacokinetics.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: