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Plant-Based Therapeutics for Chronic Obstructive Pulmonary Diseases: Nanoformulation Strategies to Overcome Delivery Challenges

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Abstract

Chronic obstructive pulmonary disease (COPD) is a widespread global health problem marked by increasing airflow limitation and chronic airway inflammation. Conventional treatments for COPD offer limited efficacy and have potentially undesirable effects, requiring the investigation of other therapeutic options. Because of their anti-inflammatory, antioxidant, and bronchodilatory effects, plant-based chemicals have emerged as viable candidates for COPD therapy. The successful delivery of these compounds to the respiratory system, on the other hand, remains an enormous challenge. This extensive review article explores the promising potential of plant-based therapies for COPD and investigates leading-edge nanoformulation technologies targeted at addressing the complex delivery challenges that accompany these natural compounds. We discuss multiple plant-derived compounds (polyphenols, flavonoids, and alkaloids) and their modes of action in reducing COPD-related indications and complications. Additionally, the function of nanotechnology in improving the bioavailability, stability, and targeted delivery of plant-based pharmaceuticals in COPD treatment is explored. Nanoformulation techniques, such as nanoparticles, liposomes, and micelles, are described, with an emphasis on their potential to precisely encapsulate and transport plant-derived bioactive to the afflicted parts of the lung. Furthermore, constraints in the development of plant-based nanoformulations for COPD are also highlighted, including safety, scalability, and regulatory issues. The current review aims to provide a thorough understanding of the promising future of COPD treatment by combining knowledge of plant-based therapies and novel nanoformulation technologies. The intersection of nature-inspired medicines and nanotechnology may hold the key to more effective, safer, and patient-centred therapeutic choices for people suffering from this chronic respiratory illness.

Keywords

Pulmonary Disorders, Lung Cancer, Drug Delivery, Nanoparticles, Inflammation, Antioxidants

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a multifactorial, progressive lung ailment characterized by chronic airflow restriction and respiratory symptoms such as dyspnoea, persistent cough, wheezing, and sputum production (G. Liu et al., 2022; Francesco Nucera et al., 2022). It is regarded as one of the top causes of illness and mortality worldwide, putting a significant strain on healthcare systems ((GOLD), 2021; Mehta, Dhanjal, Paudel, et al., 2020).

Chronic inflammation, increased airflow limitations, and pulmonary tissue remodelling are all associated with it and are primarily the result of long-term exposure to toxic substances (such as cigarette smoke, bushfire, and pollutants) (Barnes, 2016; De Rubis, Paudel, Manandhar, et al., 2023; Dharwal, Paudel, & Hansbro, 2020; I. Rahman & Adcock, 2006). Environmental factors, aberrant immune responses, and genetic predispositions all have an impact on the molecular processes that cause COPD. Understanding these pathways is critical for the development of tailored therapies and interventions. Due to its complex pathophysiology and the limited efficacy of traditional medications, managing COPD remains a substantial issue, even after several medical improvements in treatment alternatives (Shapiro & Ingenito, 2005). It affects millions of individuals worldwide, making it a serious global concern for practically all age groups (Sethi & Murphy, 2008). Furthermore, the key element driving COPD pathogenesis is an excessive and ongoing oxidative stress, inflammatory response, and senescence in the airways and lung tissue (F. Nucera et al., 2022; Paudel, Mehta, Shukla, et al., 2022). Prolonged exposure to hazardous substances, particularly cigarette smoke, attracts and activates neutrophils, macrophages, and T-lymphocytes. These cells emit reactive oxygen species (ROS), pro-inflammatory cytokines, and chemokines, causing tissue damage and increasing inflammation (Chellappan et al., 2021). Oxidative stress has a substantial impact on the progression of COPD (F. Nucera et al., 2022). Cigarette smoke and other environmental toxins disrupt the formation of ROS and the antioxidant defence mechanisms in the lungs. This causes oxidative damage to lipids, proteins, and DNA in cells, triggering inflammatory responses that aggravate tissue damage and remodelling. An imbalance between proteases and antiproteases in lung tissue is another factor that contributes to COPD. MMPs and neutrophil elastase, which are elevated in COPD, aid in the breakdown of lung tissue, particularly the elastin fibres in the alveoli (I. Rahman et al., 2006; Sethi et al., 2008). Additionally, endogenous antiproteases like alpha-1 antitrypsin (AAT) may suffer from inherent diseases such as AAT deficiency which impacts the lungs and/or liver. Furthermore, oxidative damage is often suffered reducing their effectiveness, making the harm done by proteases even worse. Epigenetic mechanisms such as DNA methylation, histone modifications, and non-coding RNA regulation have been linked to the start and progression of COPD (Giuditta Benincasa, 2020). These epigenetic changes, which can affect gene expression patterns, may have an impact on key pathways implicated in inflammation, oxidative stress, and tissue remodelling (Ridhima Wadhwa et al., 2020). Although bronchodilators, anti-inflammatory medications, lifestyle changes, and pulmonary rehabilitation are the mainstays of COPD treatment, research into novel therapeutic approaches is ongoing. In recent years, there has been an increase in

interest in researching the prospect of using bioactive compounds derived from plants as COPD supplementary therapies (Devkota, Adhikari-Devkota, et al., 2022). These bioactive compounds have numerous pharmacological activities, including anti-inflammatory, antioxidant, immunomodulatory, and bronchodilatory capabilities. They are derived from a variety of plants (Dirar et al., 2021; Jennifer, Mishra, Nigam, Devkota, Paudel, & Matsabisa, 2022; Kim, Paudel, & Kim, 2020; Manandhar, Paudel, Sharma, & Karki, 2018; Panth, Paudel, & Karki, 2016; Parham et al., 2020; Paudel & Panth, 2015; Ramanunny et al., 2022).

In recent years, there has been a growing interest in the possible therapeutic benefits of bioactive compounds derived from plants in the treatment of COPD. These naturally occurring compounds have a variety of pharmacological activities, including anti-inflammatory, antioxidant, immunomodulatory, and bronchodilatory effects (Capelli et al., 1999). Nonetheless, despite their obvious therapeutic potential, there are significant barriers to the practical application of plant-derived bioactive moieties in COPD. These include inadequate transport to the target location in the lungs, poor solubility due to inherent physicochemical features, degradation vulnerability, and limited systemic bioavailability (Sami, Salehi, Hashemi, & Atashi, 2021). To get over these limitations, researchers have resorted to nano-formulation techniques as a feasible strategy for increasing the pulmonary dispersion of these bioactive compounds (Clarence et al., 2022). The packaging of bioactive compounds in nanoscale carriers (Liposomes, Dendrimers, Polymeric nanoparticles, Solid lipid nanoparticles, Micro/Nanoemulsions, etc.) is included in the nanoformulation design (De Rubis, Paudel, Corrie, et al., 2023; Farokhzad & Langer, 2009; Mehta, Dhanjal, Satija, et al., 2020). In addition to being able to get past barriers like mucus and cell uptake, they are also more stable, soluble, controlled release, protect against enzyme degradation, increase bioavailability, and deliver these bioactive molecules to specific lung sites (Martínez-Ballesta, Gil-Izquierdo, García-Viguera, & Domínguez-Perles, 2018; J. K. Patra et al., 2018; P. Prasher et al., 2022) The goal of this review is to provide an overview of the use of natural compounds for the treatment and control of COPD, in addition to the existing pharmaceutical therapies accessible globally. Furthermore, it will delve into emerging methodologies, advantages, challenges, and aspects relevant to COPD and its therapeutic approaches.

2. Diseases majorly affecting the respiratory system

2.1 Chronic Obstructive Pulmonary Disease (COPD)

COPD is a significant and widespread respiratory disease that affects millions of people around the world. This chronic and progressive condition, which is predominantly caused by smoking

and environmental exposures, is marked by persistent airflow blockage, causing breathing difficulties and decreased lung function. COPD is a complex syndrome that includes a variety of disorders such as chronic bronchitis and emphysema. It is a major concern for global health, ranking as one of the main causes of illness and mortality worldwide (Rabe & Watz, 2017). It is inextricably related to the inhalation of toxic substances, principally cigarette smoke, but also air pollution, dust, and chemicals. The mechanisms taking place have been illustrated in figure 1 along with the most common irritants contributing to inflammation and oxidative stress. COPD is exacerbated by occupational hazards, genetic predisposition, and respiratory infections.

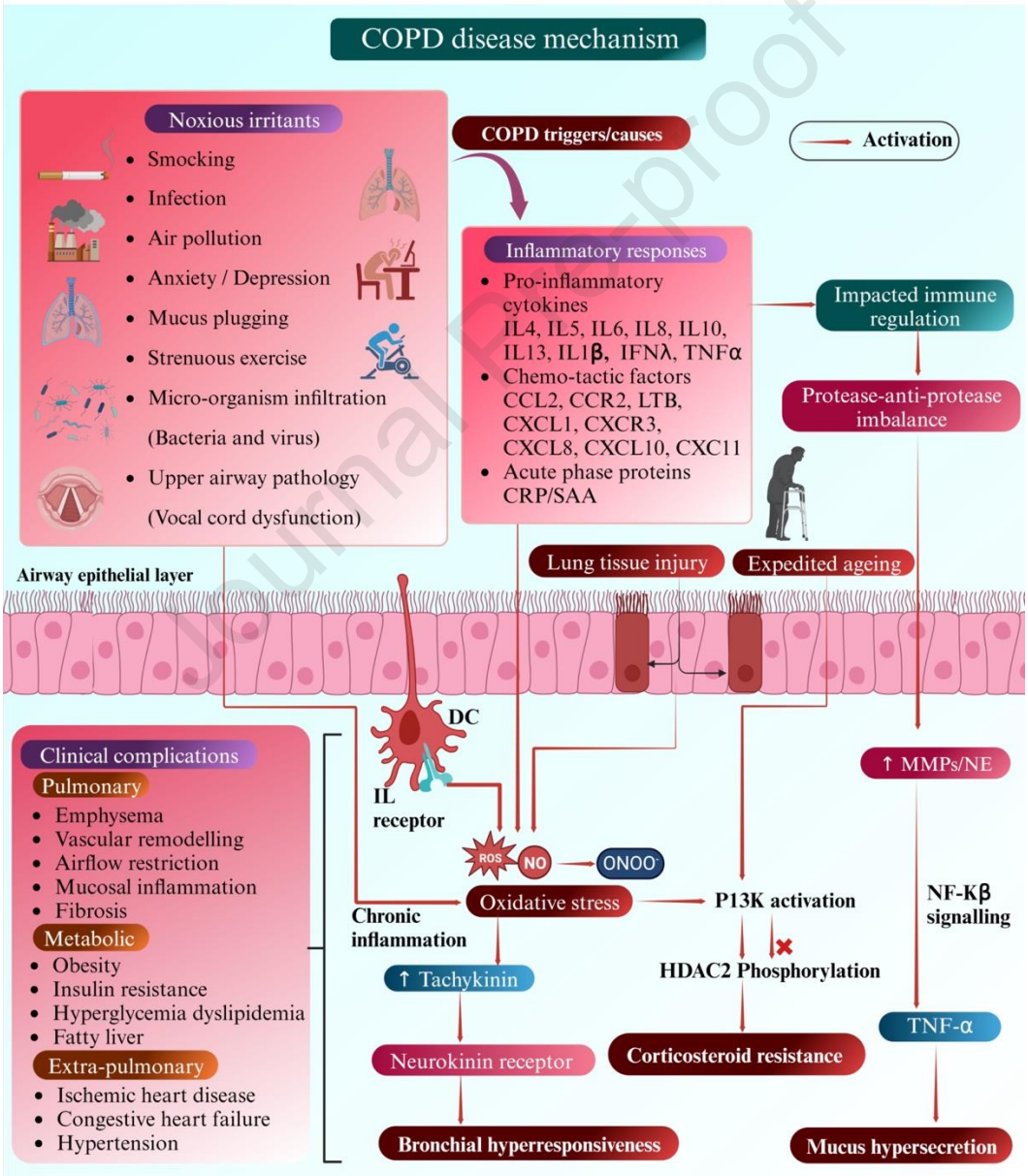


Figure 1 – Representative figure displaying the mechanisms of COPD

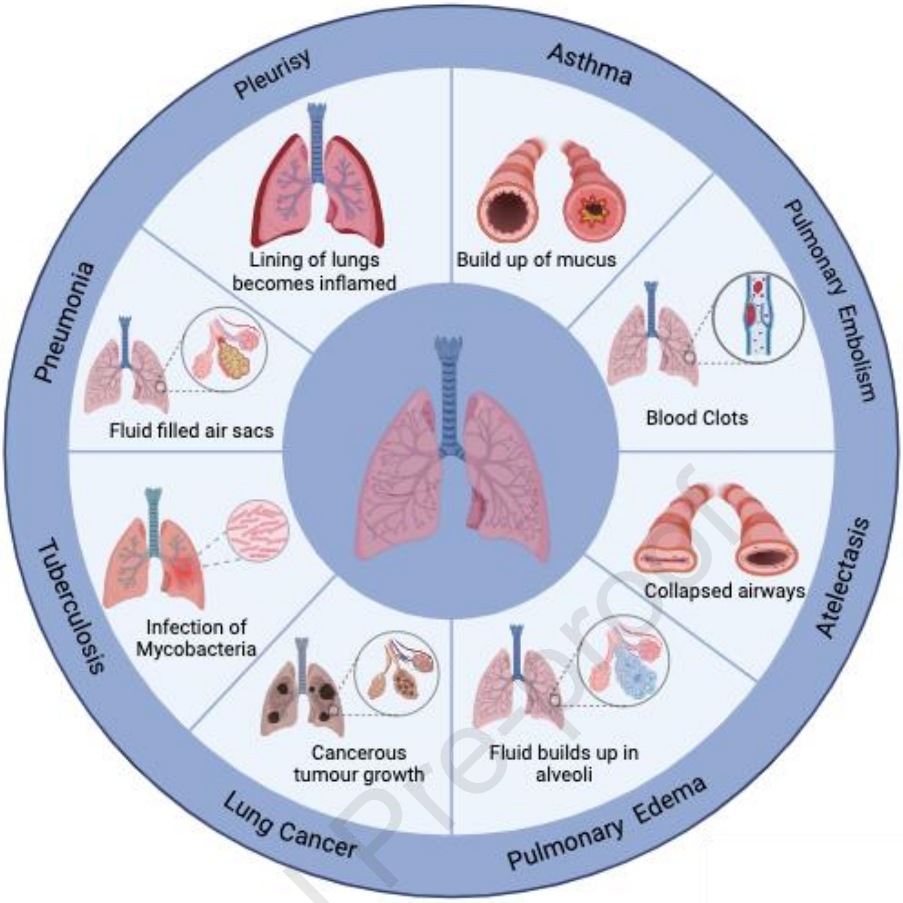
It is distinguished by the progressive damage it causes to the airways and lung tissue. COPD can also be caused by a genetic abnormality on rare occasions (Vestbo et al., 2013). Alpha-1 antitrypsin (AAT) insufficiency is one of the few genetic categories with a particular treatment for COPD. Furthermore, chronic irritant exposure causes chronic inflammation and remodelling of the airway walls, resulting in narrower airways and decreased lung elasticity. It promotes goblet cell hyperplasia, mucus gland hyperplasia, and fibrosis, which obstructs the airways and reduces airflow (Decramer, Janssens, & Miravitlles, 2012). As a result of the inflammation, the wall lining starts to degrade and thicken. An excess of mucus is also produced which is unable to move through the lungs, producing more obstructions and limiting an individual's ability to breathe. Symptoms include a chronic cough, sputum production, and trouble breathing, particularly during strenuous exertion. COPD is classified according to the degree of airflow limitation. While there is no cure for COPD, care focuses on symptom relief, slowing disease progression, and improving quality of life. Smoking cessation, medication (bronchodilators, corticosteroids), pulmonary rehabilitation, oxygen therapy, and lifestyle changes are all part of the treatment plan (Buist et al., 2007). Preventing COPD is dependent on limiting exposure to risk factors, with smoking cessation being the primary focus. To prevent future cases, public health campaigns, education activities, and legislation targeted at reducing tobacco smoking and environmental contaminants are critical. It is a complicated respiratory illness that has a considerable impact on patients and healthcare systems. Its avoidable character, combined with its chronic and progressive history, emphasises the necessity of thorough prevention, early diagnosis, and appropriate management strategies (Agusti & Soriano, 2008).

2.2 Lung Cancer and its connections to COPD

Lung cancer (LC) is one of the most serious and concerning diseases affecting the respiratory system. It is a formidable opponent, distinguished by its prevalence, intensity, and the complex challenges it brings to patients and medical personnel. LC is characterised by the uncontrolled growth of abnormal cells within the lungs, resulting in the production of tumours that impede the pulmonary system and can potentially spread to other areas of the body (Herbst, Morgensztern, & Boshoff, 2018; Siegel, Miller, & Jemal, 2020).

Its prevalence is highlighted by the link between long-term exposure to environmental and lifestyle risk factors. Heavy smoking, as well as passive smoking, has been suggested to be the leading cause of LC (Samet, 2005). Exposure to environmental pollutants (radon and asbestos), genetic predisposition, and occupational hazards are also eminent risk factors. Given the

prevalence of smoking in society, LC has been designated as the major cause of cancer death in the twenty-first century(Peto, Darby, Deo, Silcocks, Whitley, & Doll, 2000). Non-small cell lung cancer (NSCLC) accounts for 80%-85% of LC diagnoses, making it one of the most common types of LC, followed closely by small cell lung cancer (SCLC), which is less common but is distinguished by its rapid growth and strong spreading potential (Molina, Yang, Cassivi, Schild, & Adjei, 2008). Squamous cell carcinoma, big cell carcinoma, and adenocarcinoma are the three most common kinds of NSCLC identified in patients. In the early stages of LC, a patient usually has few or unnoticeable symptoms; however, scans, such as low-dose computed tomography (LD-CT), can reveal 'black patches' on the lungs that represent any abnormalities (Alberg, Brock, & Samet, 2005; Shi et al., 2014). A summary of respiratory diseases impacting the lungs have been illustrated in figure 2.The lack of symptoms in the early stages of LC makes it difficult to detect; often, when it is detected, the patient is already in chronic or terminal phases (Gridelli et al., 2015). due to its complicated aetiology, multiple subtypes, and propensity for late-stage diagnosis, LC poses numerous challenges. Studies in research have aimed at clarifying the molecular mechanisms underlying LC development, in addition to seeking novel biomarkers for early-stage diagnosis and developing novel therapeutic strategies (Travis et al., 2015; Youlden, Cramb, & Baade, 2008).



199

200 *Figure 2: This figure illustrates a comprehensive overview of diseases primarily affecting the*
201 *respiratory system. Each disease is represented by an icon or symbol for easy identification.*

202 **3. Current Pharmacological interventions in COPD and its relative limitations**

203 The lack of efficacious drugs is the most significant barrier to treating COPD. Its clinical
204 treatments include Antibiotics, bronchodilators, glucocorticoids etc. While these medications
205 provide some therapeutic benefits, they lack specificity, and long-term use, frequently
206 resulting with serious side effects in patients. Furthermore, conventional medicines have major
207 shortcomings due to COPD-induced pulmonary inflammation, which causes airway
208 constriction, coughing, and mucus secretion, prominently establishing a drug delivery barrier.
209 At the same time, this milieu promotes bacterial colonisation, resulting in persistent bacterial
210 biofilms that are resistant to therapeutic interventions (F. L. Ramos, Krahnke, & Kim, 2014).

211

212 Therefore, to address this complex pathology, COPD management entails the use of several
213 medications to relieve symptoms, minimize exacerbations, and enhance total lung function. In
214 recent years, there has been a surge of interest in using nano-formulation techniques to deliver

plant-derived bioactive moieties as prospective COPD therapies (Tan et al., 2022). There are many types of medications routinely used to treat COPD, and their suitability for pulmonary delivery via nano-formulation techniques. Medication used to treat COPD can help improve symptoms and slow down the progression of the disease. Each has its own limitations and potential negative effects that must be carefully assessed.

***3.1 Bronchodilators*:** Bronchodilators are an important part of COPD therapy because they relieve bronchoconstriction and enhance airflow. **β**-agonists and anticholinergics are the two primary types of bronchodilators used in COPD treatment. **β**-agonists, such as salbutamol and formoterol, cause bronchodilation by relaxing the smooth muscles surrounding the airways (Paudel et al., 2021). Tiotropium and glycopyronium are anticholinergic drugs that stop acetylcholine (Ach) from doing its job. This makes the airways revert to their original shape, paving the way for mucus clearance. Nano-formulation techniques have the potential to improve the targeted transport of these bronchodilators to the lungs, resulting in a more lasting and efficient therapeutic effect while minimizing systemic side effects (Miravitlles, Anzueto, & Jardim, 2017). Short-acting bronchodilators, on the other hand, provide relief for a limited time, necessitating repeated administration, whereas long-acting bronchodilators may have a longer beginning of action and may not be suited for immediate relief during acute exacerbations. Beta-agonists can also produce tremors, an increase in heart rate, and palpitations, whilst anticholinergics can cause dry mouth, constipation, and urine retention (Almadhoun & Sharma, 2023).

***3.2 Corticosteroids*:** Inhaled corticosteroids (ICS) are routinely recommended to COPD patients to manage airway inflammation, lower exacerbations, and improve lung function. The 2023 GOLD updated guidelines found there was an increased amount of attention on ICS for treatment/management plans(Terry & Dhand, 2023). COPD patients can be grouped based on their level of dyspnea using the GOLD ABCD phenotype to determine the appropriate initial pharmacological treatment. The 2023 report has recently purified this by addition of Group E (a combination of Group C and D)(Terry et al., 2023) containing the use of triple therapy of ICS, LAMA and LABA. Fluticasone and budesonide are widely used in conjunction with long-acting beta-agonists (LABA) to improve therapeutic benefits (Agusti et al., 2018; Tashkin & Strange, 2018). Furthermore, GOLD has stated that when using ICS at a fixed dose combined with LABA patients are benefited with a higher quality of life, reduced hospitalisations and decreased exacerbations(Wilkie, Finch, & Schembri, 2015). Nano-formulations can assist in

optimizing corticosteroid distribution to the lungs, enhancing local anti-inflammatory action, and lowering the risk of systemic adverse effects that are frequently linked with long-term corticosteroid treatment (Singh, Biswas, Shukla, & Maiti, 2019).

In COPD, ICS are frequently used to manage airway inflammation and minimize exacerbations. Long-term usage of ICS, however, may raise the risk of acquiring pneumonia and oral thrush (Suissa, Patenaude, Lapi, & Ernst, 2013). Some individuals may not respond satisfactorily to ICS therapy, and systemic adverse effects such as osteoporosis, skin thinning, and adrenal suppression are possible with high doses or long-term use (Mkorombindo & Dransfield, 2020).

Combination treatments, such as ICS/LABA or LABA/LAMA, are frequently used in COPD to improve symptom control and lung function. Combining numerous medications, on the other hand, may raise the chance of side effects and drug interactions. Unfortunately, for some patients, due to unique sensitivities as such, some people may be unable to handle certain combinations (Hizawa, 2015). In particular, it has been seen that COPD patients have an increased chance of greater exacerbations along with steroid sensitivity (Hizawa, 2015). ICS/LABA has been found to have various side effects a major one being an increased incidence of pneumonia (Wilkie et al., 2015). Dose related reasons are one of the most common reasons for the presence of side effects, resulting in things such as tuberculosis, bone fracture, skin thinning, cataracts, diabetes or oropharyngeal candidiasis (Price, Yawn, Brusselle, & Rossi, 2013).

Phosphodiesterase-4 (PDE-4) inhibitors, such as roflumilast, are another type of medicine used to treat COPD. These inhibitors may be ineffective in some COPD patients, and nausea is a common adverse effect that may lead to medication withdrawal in some circumstances. PDE-4 inhibitors frequently cause gastrointestinal disturbances such as nausea, diarrhoea, and abdominal pain (Crocetti, Floresta, Cilibrizzi, & Giovannoni, 2022; Rhee & Kim, 2020).

3.3 Anti-inflammatory Agents: In addition to corticosteroids, various plant-derived bioactive moieties have demonstrated promising anti-inflammatory activities, which may be useful in the management of COPD. Preclinical research has shown that compounds including curcumin, quercetin, and resveratrol have anti-inflammatory properties. Strategies for nano-formulation can keep these sensitive bioactive components from breaking down, help them get

to the inflamed lung tissue faster, and make COPD treatments work better (L. Y. Li et al., 2022; Timalsina, Pokhrel, & Bhusal, 2021).

***3.4 Antioxidants*:** Oxidative stress is a major factor in the aetiology of COPD, causing tissue damage and inflammation. Endogenous and exogenous antioxidants can both neutralize free radicals and minimize oxidative damage (Miklós & Horváth, 2023). Several plant-derived antioxidants, such as epigallocatechin gallate (EGCG) from green tea and quercetin from fruits and vegetables, have shown promise in reducing oxidative stress associated with COPD. Nano-formulations can improve the antioxidants' stability and bioavailability, allowing for more effective delivery to the lungs and improving their protective effects (Gonçalves, Sodero, & Cordeiro, 2021).

3.5 Mucolytics: Mucolytic medicines are used to break down and reduce the viscosity of mucus in the airways, allowing it to be cleared more easily and improving breathing. N-acetylcysteine (NAC) is a well-known mucolytic agent used in COPD treatment. Nano-formulations can improve the localized distribution of mucolytic drugs to the airways, resulting in greater treatment outcomes while reducing the risk of side effects (R. Gupta & Wadhwa, 2023). NAC is used to break down and lower the viscosity of mucus in the airways, allowing it to be cleared more easily. Mucolytics, on the other hand, may not be beneficial for all patients, particularly those with limited mucus production. In some people, NAC might produce nausea, vomiting, and bad breath. Lastly, using nano-formulation techniques to deliver bioactive molecules from medicinal plants to the lungs is an efficient way to improve COPD treatment (Paudel, De Rubis, et al., 2022; Rubin, 2002). These novel techniques can increase therapeutic efficacy, eliminate systemic adverse effects, and pave the way for more effective COPD care by directing specific therapies to the lungs.

A summary of the mentioned therapeutics has been tabulated below in Table 1, reflecting the mechanisms taking place. Additionally, COPD patients with severe hypoxemia may require oxygen therapy. While oxygen therapy can save lives, long-term oxygen therapy can be difficult and may impair mobility and quality of life. It can also cause nasal dryness, nosebleeds, and skin irritation.

Table 1: Representing detailed compounds used in COPD treatment, their mechanisms of action, and common medications within each category.

Anti-Inflammatory Compound	**Mechanism of Action**	**Common Medications**
Inhaled Corticosteroids (ICS)	Suppress inflammation in the airways and reduce exacerbations	Fluticasone Budesonide Beclomethasone
Phosphodiesterase-4 (PDE-4)	Inhibits PDE-4 enzyme, reducing inflammation and improving lung function	Roflumilast
Plant-derived anti-inflammatory compounds	Compounds such as curcumin, quercetin and resveratrol all demonstrate anti-inflammatory properties	Curcumin Quercetin Resveratrol
Systemic corticosteroids	Used in severe COPD exacerbations as well as the management of systemic inflammation	Prednisone Methylprednisolone Dexamethasone
Pharmacologic interventions	Intermediate outcomes such as reduced symptom scores Reduce exacerbations and inflammation	Beta-adrenergic agonists Anticholinergic agents Antibiotics Mucolytics Opioids
Non-pharmacologic interventions	Resolution of exacerbations, mortality, quality of life	Oxygen therapy Early pulmonary rehabilitation Nutritional support Neuromuscular electrical stimulation

4. Plant-derived bioactive moieties with potential in COPD

Plant-derived bioactive moieties appear intriguing as a potential therapy for COPD by addressing its pathogenesis's complexities with a multi-targeted approach. Polyphenols, flavonoids, terpenoids, alkaloids, and other plant-derived bioactive moieties are highly desired compounds due to their immense antioxidant, anti-inflammatory, and immunomodulatory properties (Alharbi et al., 2023; Allam et al., 2022; Y. Chan et al., 2023). These characteristics minimise the oxidative stress, inflammation, and immune system dysregulation associated with COPD. The plant derived bioactives to be explored has been surmaised and tabulated below (Table 2). From this data, the associated groups and mechanisms of the phytoceuticals can easily be compared.

328

329 *Table 2 – Summary of various plant-derived bioactive moieties that have shown potential*
330 *benefits in COPD.*

331

Bio logical activity	Plant derived bioactive moiety	Phytocompounds /associated groups	Responsible recovery mechanism in COPD	References
Anti -Inflammatory Properties	Curcumin	Curcuminoids	Neutralizes reactive oxygen species (superoxide anions, hydrogen peroxide, and nitrite radicals)	**(Amalraj, Pius, Gopi, & Gopi, 2017; Joe, Vijaykumar, & Lokesh, 2004)**
	Quercetin	3,3',4',5,7-pentahydroxyflavone (Flavonoid – Flavanol)	Effective quorum sensing inhibiting agent in P. aeruginosa, antiviral action, antioxidant property and chemo preventive activity	**(Baksi, Singh, Borse, Rana, Sharma, & Nivsarkar, 2018; M. A. Rahman, Shorobi, Uddin, Saha, & Hossain, 2022; Tran & Hadinoto, 2021)**
	Resveratrol	Polyphenol Pleiotropic	Metabolic and cardioprotective potential, improve skeletal and respiratory muscle impairment, improved mitochondrial oxidative metabolism	**(Beijers, Gosker, & Schols, 2018)**
	Eucalyptus (Eucalyptus globulus)	Eucalyptol Limonene Terpineol	Bronchodilator, antibacterial, antiviral, analgesic and anti-pyretic effects, down-regulation of pro-inflammatory biomarkers	**(Arooj et al., 2023)**
	Ginseng (*panax ginseng*)	Phytosterol Ginsenosides triterpene saponins	Alleviate pro-inflammatory chemokines and cytokines, enhanced overall pulmonary function	**(Alsayari, Muhsinah, Almaghaslah, Annadurai,**

				& Wahab, 2021)
	Boswellic Acid	Oleo gum resin, Tetracylic triterpenes, phenylpropanoids	Limiting NF-κB regulated gene expression, protection against acute lung injury, immunomodulatory effect	**(Gomaa, Mohamed, Abd-Ellatief, & Gomaa, 2021)**
	Berberine	berberrubine, thalifendine, demethylene berberine, and jatrorrhizine,	inhibiting the activation of NF-κB and caspase-1 signalling pathways, anti-protozoal and anti-microbial activities	**(Tew et al., 2020)**
	Zerumbone	Sesquiterpene from ginger	In mice macrophage induced by cigarette smoke extract, Zerumbone inhibited the gene expression of IL-1β, TNF-α, IL-6 In human bronchopeithelail cells induced by cigarerte smoke xtract, Zerumbone inhibited the gene expression of IL-1β, IL-6, PGST2	**(Hari Prasad Devkota, Keshav Raj Paudel, et al., 2021; Paudel et al., 2023)**
	Naringenin	predominant flavonone in grapefrui	Anti-inflammatory potential of Naringenin was revealed by decreased gene expression of *IL-6, IL-8, IL-1β*, and *TNF-α* in lipopolysaccharide-induced human bronchoepithelial cells (BCi-NS1.1).	**(Chin et al., 2020; R. Wadhwa et al., 2021)**
	18-β Glycerritinic acid	Triterpenoids (Glycyrrhiza species), 18β-glycyrrhetinic acid (18βGA)	antiasthmatic, pulmonary arterial hypertension, antiviral, antibacterial	**(Shinu et al., 2023)**
	Serratio peptidase	Protease Enzyme/Proteolytic (*Bacterium Serratia marcescens*)	Biocatalyst, anti-biofilm, anti-endemic and analgesic effects, fibrinolytic properties	**(Tiwari, 2017)**
Anti-Oxidant Properties	Epigallocatechin gallate (EGCG)	Polyphenolic Catechins, Amino acids	Antioxidant and immunomodulatory properties Potential reduction of oxidative stress, limits pro-inflammatory cytokines production	**(Y. Liang, Liu, Yeung, Li, Ip, & Mak, 2017)**
	Andrographis Paniculata	Diterpene lactone; Andrographolide	Antipyretic and analgesic, anti-inflammatory, antibacterial, antiviral, immune regulatory,	**(X. Li, Yuan, Wu, Zhen, Sun,**

			anti-tumor and reduce mitochondrial dysfunction	**& Yu, 2022)**
	Lutein	Flavonoids Carotenoid	Limits oxidative (ROS) damage and hyperresponsiveness of airway, Anti allergic, decreases airway inflammation	**(Islam et al., 2022)**
	Apigenin	5,7-trihydroxyflavone Flavonoids	Anti-inflammatory and liver-protecting effects	**(B. S. Li, Zhu, Lim, Seo, & Choi, 2021)**
	Ascorbic Acid	Vitamins	Potential to restore lung function and decrease damage caused by oxidative stress	**(Kolniak-Ostek, Oszmiański, & Wojdyło, 2013)**
	Tocopherols	Tocotrienols (Vitamin E) Lipophilic phenolic	Averts macrophage and ROS infiltration, limits cytokine secretions	**(Z. Liu et al., 2023)**
	Alpha-lipoic acid	I-5-(1,2-Dithiolan-3-yl) pentanoic acid, Organosulphur	Anticancer, anti-inflammatory, anti-viral, pro-oxidants regulates NRF2 pathway	**(Guo et al., 2023)**
	Glutathione	Tripeptide (Glutamic Acid, Cysteine, Glycine)	Ability to reduce oxidative stress	**(Hariharan & Dharmaraj, 2020; Packer, Witt, & Tritschler, 1995; Sanguinetti, 2016)**
Mucolytic Properties	Ambroxyl	Mucolytics	Prevention of acute exacerbations	**(Ge et al., 2016; Z. Li, 2021)**
	Bromhexine	Expectorants	Ability to reduce excessive mucus	**(Murali et al., 2006)**
	Carbocisteine	Mucolytics	Clears breathing pathways, Reduces excessive mucus production, modulate mucins and ciliary functions	**(Pace et al., 2022)**
	Erdosteine	Thiol derivative	Reduces systemic inflammation, recurrence of exacerbation Potential Anti-oxidant, modulates bacterial adherence	**(Mario Cazzola, Calzetta, Page, Rogliani, & Matera, 2018; M.**

				Cazzola, Page, Rogliani, Calzetta, & Matera, 2020)
	N-acetylcysteine (NAC)	Amino Acid Cysteine	Clears airway pathways, Mucolytic, Prevents bacterial stimulation	**(Rushworth & Megson, 2014; Šalamon, Kramar, Marolt, Poljšak, & Milisav, 2019)**

4.1 Anti-Inflammatory Compounds

4.1.1. Curcumin: Curcumin, which is produced from turmeric or Curcuma longa extract, is categorised as an Active Pharmaceutical Ingredient (API) and has been demonstrated to significantly reduce inflammation markers. It is known to have very poor bioavailability but it has efficient polyphenols, leading it to have a high anticancer, antioxidant and anti-inflammatory activities (Hardwick et al., 2021). These qualities have made curcumin an excellent molecule for treating and reducing airway inflammation and associated symptoms (Sharifi-Rad et al., 2020). Since, COPD is related to increased oxidative damage to lung cells, antioxidants such as curcumin may have a protective function. Some research suggests that curcumin may help reduce excessive mucus formation in the airways, which is a common symptom in COPD patients and can contribute to airflow restriction (Moghaddam et al., 2009; Safari et al., 2023). While there are promising preclinical and *in vitro* studies on curcumin's potential advantages in COPD, there is a dearth of large-scale clinical trials with human patients to demonstrate its effectiveness in treating COPD. Researchers are experimenting with alternative formulations and delivery strategies to boost curcumin bioavailability (Peng et al., 2021) [NCT04687449].

4.1.2 Quercetin: Quercetin is a flavonoid, which is a type of plant compound found in a variety of fruits, vegetables, and grains (Panthi, Imran, Chaudhary, Paudel, & Mohammed, 2023). It has been researched for potential health advantages, including its role in managing COPD. By delivering quercetin with propylene glycol, IL-8 levels were shown to decrease in COPD *in*

vitro models. The potential of quercetin to suppress inflammation and oxidative stress aids in alleviating symptoms and further preventing disease development. Based on its anti-inflammatory, antioxidant, bronchodilatory, and possible mucus-reducing qualities, quercetin has shown promise in preclinical trials and animal models as a potential supplementary method to controlling COPD. More study, including human clinical trials, is needed to understand its exact role and effectiveness in COPD treatment (Ganesan et al., 2013).

4.1.3 Resveratrol: Resveratrol, a natural polyphenol found in a variety of plants, most notably the skin of red grapes, has sparked interest in its possible therapeutic benefits in the context of respiratory illnesses (Devkota, Paudel, Lall, Tomczyk, & Atanasov, 2022). It has the ability to inhibit pro-inflammatory molecules (IL-6 and IL-8) synthesis and alter the immunological response in the respiratory system (Xiao-Li, Li, Ji-Hong, Shu-Ying, & Xian-Zhong, 2017). It has also been studied for its ability to prevent airway remodelling (Lee, Kim, Yoon, Kwon, Rhee, & Lee, 2017). In preclinical studies and animal models, research on the effects of resveratrol on asthma control has yielded promising results. It may aid in the reduction of airway inflammation and the improvement of lung function. Resveratrol has also been shown to be able to induce all stages of carcinogenesis in both *in vitro* and *in vivo* models of cancer (Salehi et al., 2018).

4.1.4 Epigallocatechin gallate (EGCG): The natural polyphenol epigallocatechin gallate (EGCG) present in green tea has been researched for its possible usefulness in the treatment of many diseases, including respiratory disorders (Hari Prasad Devkota, Anjana Adhikari-Devkota, et al., 2021; Hari Prasad Devkota, Bhakta Prasad Gaire, et al., 2021). In respiratory disorders such as asthma, chronic obstructive pulmonary disease (COPD), and interstitial lung diseases, EGCG has been demonstrated to have considerable anti-inflammatory and antioxidant activities with a prime ability to reduce oxidative stress and neutralise damaging free radicals, potentially protecting the lungs from further damage. EGCG has been examined for its ability to suppress the growth of some viruses and bacteria, which is especially important in situations of respiratory infections. Some studies have also exhibited its ability to suppress fibrosis by limiting the production of scar tissue in the lungs (Interstitial lung disease, ILD). Similarly, it was observed that there was a potential decrease in active oxygen species in cigarette smoke extract (CSE) induced oxidative stress (Lakshmi, Reddy, Kodidhela, & Varadacharyulu, 2020). The potential advantages of EGCG in respiratory conditions are more complemented when combined with other bioactive chemicals that have similar effects,

such as quercetin or resveratrol. These combinations may provide a more complete approach to respiratory disease management. Besides this, due to quick metabolism and poor absorption, the bioavailability of EGCG, particularly when administered orally, can be reduced (Sethi et al., 2008).

4.1.5 Boswellic acid: Boswellic acid is a triterpene derived from the resin of the *Boswellia serrata* tree, which is native to India and other areas of Asia. It has been studied for its possible involvement in the treatment of respiratory illnesses, particularly those connected with inflammation and oxidative stress (Solanki et al., 2023; Solanki et al., 2020). Boswellic acids are derived from the oleogum resin of numerous boswellic species and have been shown to reduce inflammation markers in chronic inflammatory disorders. Besides having potential bronchodilatory and immunomodulatory mucolytic actions, it is well known for its powerful anti-inflammatory properties. It prevents the synthesis of inflammatory chemicals such as leukotrienes and cytokines. According to Clarence et al, 2022 (Clarence et al., 2022), Boswellic acid reduced inflammation in a mouse model of acute lung injury, implying its potential application in inflammatory respiratory disorders. Chronic inflammation plays a critical role in worsening symptoms in respiratory illnesses such as asthma, COPD, and bronchitis. Boswellic acid has been shown to help reduce inflammation, mucus production, airway hyperreactivity, and enhance lung function in the airways, potentially alleviating symptoms such as wheezing and shortness of breath. Another study released in 2021 by Gomaa et al (Gomaa et al., 2021) investigated the efficacy of Boswellia serrata extract in acute respiratory distress syndrome (ARDS). According to the findings, *Boswellia serrata* extract may have anti-inflammatory and antioxidant characteristics that could help reduce lung injury and inflammation associated with ARDS.

4.1.6 Andrographolide: Andrographolide is a bioactive molecule produced from *Andrographis paniculata*, commonly referred to as the "King of Bitters." Due to its diverse pharmacological characteristics, it has attracted interest for its possible function in respiratory illnesses. The herb is frequently used in traditional Chinese and Indian remedies and possesses immense anti-inflammatory characteristics that have been proven to enhance the formation of Nrf2, inhibiting neutrophils and macrophages from infiltrating the lungs (Guan et al., 2013). According to certain research, andrographolide has antiviral capabilities. It may aid in the inhibition of respiratory viral reproduction, such as influenza and common cold viruses. This is especially

important during viral epidemics since it can lower the severity and duration of respiratory illnesses.

It has also exhibited bronchodilatory properties Li et al explored the anti-inflammatory effects of andrographolide in a rat model of allergic asthma in 2022 (X. Li et al., 2022) Andrographolide was observed to lower airway inflammation and hyperresponsiveness in the trial, showing its potential as an anti-inflammatory drug in asthma. Another study published in 2022 investigated andrographolide's antiviral efficacy against respiratory syncytial virus (RSV). The results showed that andrographolide suppressed RSV replication *in vitro*, implying that it could be used to treat respiratory viral infections (Che, Xie, Lin, Liu, Xie, & Liu, 2022). In a 2013 study, researchers looked at the effects of andrographolide on lipopolysaccharide (LPS)-induced acute lung damage in mice. The study discovered that andrographolide reduced lung inflammation and injury, showing its potential for lung damage mitigation (Zhu et al., 2013).

4.1.7 Cannabidiol (CBD): By extracting CBD from Cannabis sativa L, the psycho-active THC can be prevented, making it an ideal active for COPD patients due to its anti-inflammatory and analgesic effects (Porter, Barbara St, Milavetz, & Herr, 2021). High doses of CBD can be administered via prescription as an oil extract or ingestible gelatine capsule. The use of CBD has become increasing popular for a variety of diseases from Parkinson's, seizures, cancer, anxiety, insomnia and many other chronic pains.

Various clinical studies have been conducted over the years, reflecting the beneficial effects of using CBD for chronic pain inflammation by reducing pro-inflammatory cytokines (Atalay, Jarocka-Karpowicz, & Skrzydlewska, 2019).

4.1.8 Flavonoids: luteolin and apigenin: Flavonoids are polyphenolic structures that are naturally occurring in plants to help with growth. They have gained recent popularity due to their beneficial effects on health as a result of their antioxidant, anti-inflammatory and anti-mutagenic properties. Luteolin and apigenin are two common flavonoids apart of the subclass flavones which have both been shown to have anticancer effects (Panche, Diwan, & Chandra, 2016). Flavones can be found in fruits, flora and glucosides An *in vivo* study using cigarette smoke induced mice found treating with flavonoids isolated from loquat supressed the histological changes in the lungs. This evidence was backed up by the reduction of pro-inflammatory cytokines (IL-6 and IL-1β)(Germain et al., 2020).

4.1.9 Berberine, an alkaloid, offers many anti-inflammatory properties similar to those of curcumin. Berberine is a naturally occurring chemical most commonly derived from goldenseal although it can be found in various other stems, barks and roots (Alnuqaydan et al., 2022; De Rubis, Paudel, Liu, et al., 2023; Malyla et al., 2023; M. Mehta et al., 2021; Paudel, Mehta, Yin, et al., 2022). Its strong natural colour made the compound quite popular as fabric dye and still is used to this day. Although berberine is more commonly used as an anti-inflammatory drug and typically administered to patients whom experience high blood pressure or are diabetic. Unfortunately, there are some difficulties with using berberine in pharmaceuticals due to its poor bioavailability and low gastrointestinal absorption (Chakraborty et al., 2023; Spinozzi et al., 2014). By taking advantage of the nature of liquid crystalline nanoparticles, berberine was encapsulated and tested on both human broncho-epithelial cells (16HBE) and mouse macrophages (RAW264.7). It was seen to have substantial impacts on the inflammation and oxidative stress caused as a side effect of COPD, as well as reducing the gene expression of p21(Paudel, Panth, et al., 2022).

4.1.10 18-β-glycyrrhetinic acid: (18BGA), the bioactive chemical 18-β-glycyrrhetinic acid (GA) is found in liquorice root (*Glycyrrhiza glabra*). Its anti-inflammatory, antimicrobial and antioxidant effects have long been employed in traditional medicine (Mohamad et al., 2023). Scientific study has focused on GA's potential benefits in a variety of health disorders, including COPD (Kowalska & Kalinowska-Lis, 2019). Anti-inflammatory activities of 18BGA have been demonstrated by decreasing the activation of nuclear factor-kappa *B* (NF-kB), a transcription factor involved in the production of pro-inflammatory genes. This inhibition may aid in the reduction of the inflammatory response found in COPD.GA works as an antioxidant, scavenging free radicals and preventing oxidative damage to lung tissue thus, helping in slowing the onset of COPD and its accompanying consequences. According to certain research, GA may impact mucus synthesis and viscosity, potentially enhancing mucus clearance and decreasing airway blockage. Recent studies have shown how 18BGA also possesses anti-cancer properties and its role in inducing apoptosis in A549 lung cancer cells (Shinu et al., 2023).

4.2 Antioxidant Compounds

Antioxidants are important in COPD since they reduce oxidative stress and neutralize free radicals, which can help decrease inflammation and oxidative damage in the lungs. Among the notable antioxidant bioactive substances researched or used in COPD therapy are:

4.2.1 Vitamin C (Ascorbic acid): The naturally occurring compound, Vitamin C, is easily derived from citrus fruits such as lemons and oranges (Kolniak-Ostek et al., 2013). Vitamin C is an antioxidant and vital nutrient which can be ingested as well as used topically for skin care. It is known to be a quite versatile vitamin and helps the body with bone growth and development, blood vessels and skin. Additionally, vitamin C has found a part in skincare and can be applied topically to; boost collagen production reducing wrinkles, helping slow early signs of skin aging as well as preventing sun damage and reduce dark spots caused by sun exposure. When it comes to the role that Ascorbic acid plays in the role of managing COPD, a meta-analysis conducted underlined that administrating more than 400 mg a day generally improved the forced expiratory volume in a second (FEV1) (Lei et al., 2022).

4.2.2 Vitamin E (Tocopherols and Tocotrienols): Vitamin E naturally derives from various plant oils as well as a range of nuts, seeds, and vegetables (Q. Jiang, 2014). More specifically tocopherols and tocotrienols are known for their antioxidative properties and have been shown to help maintain an individual's immune system as well as aiding the formation of red blood cells to prevent blood clots. Tocopherols are fat-soluble allowing for the active to pass through the stomach lining into the bloodstream. Meanwhile, tocotrienols play a similar role to tocopherols but also are used for heart health.

There are four main types of tocotrienols; alpha, beta, gamma and delta. Each plays a different antioxidative role although gamma and delta are typically the most potent due to their longer chain structure. Vitamin E is typically prescribed and/or administered in a very low dose although can be up to 1000 mg a day depending on the circumstances. Studies have shown that one of vitamin E's major key functions is to prevent lipid molecule peroxidation due to its antioxidant nature. Furthermore, because oxidative stress is a prominent characteristic of COPD, vitamin E may have an effect on COPD prevention (Z. Liu et al., 2023).

4.2.3 Selenium and selenium-based compounds: Selenium is a trace element that can be found in soil, water, and many foods. It is essential for many physiological functions in the body, including antioxidant defence systems and immune system function. It is an essential component of selenoproteins, a group of enzymes that prevent cells from oxidative injury and control an array of physiological functions (Hariharan et al., 2020). Ebselen is a synthetic organoselenium, its anti-

inflammatory and antioxidant propertied make it a great solution for respiratory diseases. By mimicking glutathione peroxidase (GPx), ebselen is able to reduce oxidative stress typically caused by COPD(Sies, 1993; Vlahos & Bozinovski, 2013). Recent studies have found how ebselen has been able to assist in the inducing cell cycle arrest and cell death in lung cancer cells (W. H. Park, 2023). Selenium is a component of the selenoprotein family, which includes glutathione peroxidases, that are essential parts of the body's antioxidant defence mechanism. Enzymes such as these aid in the scavenging of free radicals and the reduction of oxidative damage in lung tissues. Selenium has been demonstrated to have anti-inflammatory qualities via altering immunological responses and controlling the expression of pro-inflammatory cytokines so, helps attenuate COPD exacerbations by lowering chronic inflammation in the airways and lungs. It promotes the formation and activation of immune cells and aids in the maintenance of respiratory mucosal barriers (Avery & Hoffmann, 2018).

4.2.4 Alpha-lipoic acid: Alpha-lipoic acid (ALA) can be derived from caprylic acid (Nguyen & Gupta, 2023)however it is also a naturally occurring antioxidant in the body. ALA is commonly used for the treatment and management of chronic diseases, in particular those with oxidative stress. This is due to the fact that ALA has the ability to inhibit nuclear factor kappa B (NF-kB) as well as the quenching of reactive oxygen species (ROS) (Packer et al., 1995). A clinical trial consisting of 10 COPD patients revealed that when using an antioxidant cocktail of vitamin C, Vitamin E and ALA the concentration of resting plasma free radicals was decreased (Rossman, Groot, Reese, Zhao, Amann, & Richardson, 2013). This suggests that the combination of vitamins and ALA has the potential to reduce oxidative stress if further tested.

4.2.5 Glutathione: Glutathione can be derived from a range of vegetables such as spinach, asparagus, and avocados and is made up of three key amino acids; glycine, glutamic acid and cysteine. Glutathione is naturally produced by the liver although taking supplements is also beneficial. Its antioxidant properties allow for the active to take part in a variety of process within the body most importantly tissue and cell growth as well as contributing to the immune system. The combination of amino acids are able to combat free radicals which are known for damaging ones cells. As previously mentioned, a decrease in free radicals will prevent further oxidative stress. In a study, the compound has shown to increase overall antioxidant capacities for patients with COPD who experience increased levels of oxidative stress (Sanguinetti, 2016). Various other clinical trials found elevated levels of glutathione in COPD patients compared to non-smokers as well as evidence of oxidative stress (Packer et al., 1995).

4.2.6 Carotenoids: Carotenoids are naturally derived from plant-based species such as algae and fungi (Metibemu & Ogungbe, 2022). Their strong pigmentation makes them suitable for natural colourings. As for their effect on the body, carotenoids have a strong antioxidant nature enabling them to play a major role in maintaining health by reducing the risk of various diseases. lutein, lycopene, b-carotene and zeaxanthin are the most common occurring types of carotenoids and have numerous studies reflecting their oxidative properties on a variety of diseases.

Carotenoids have shown to be able to prevent oxidative reactions from occurring in individuals with COPD (Kentson, Leanderson, Jacobson, & Persson, 2018). A group of 66 individuals including 28 whom rely on long term oxygen therapy underwent a range of blood tests and health, diet, and lifestyle questionnaires. It was seen that the COPD group had significantly lower levels of carotenoids, which was concluded to be a result of their diets further contributing to their higher levels of inflammation seen in markers IL-6 (Kentson et al., 2018).

4.2.7 Polyphenols: Polyphenols are a part of a group of metabolites and are a type of compound that can be derived from an extremely wide range of products from fruits to oil and wine (Bertelli, Biagi, Corsini, Baini, Cappellucci, & Miraldi, 2021). Polyphenols behave in a similar way to vitamin E and carotenoids as they are all antioxidative compounds. They encompass a large group of phenols including flavonoids. As polyphenols are reducing agents they are helpful for the protection from oxidative stress in patients that are exposed to cigarette smoke (Rudrapal et al., 2022). Diets rich in polyphenols often experience reduced oxidative stress and a decreased change of chronic health conditions.

4.2.8 Coenzyme Q10 (Ubiquinone): Coenzyme Q10 (CoQ10) also known as ubiquinone is known to be naturally derived from various sources such as oily fish and whole grains (Saini, 2011). CoQ10 is naturally made in the body and helps convert food into energy. The strong antioxidant is typically produced in the heart, kidney and liver reflecting its high potency in the body. Although CoQ10 can be taken as a supplement and is often prescribed to patients with heart failure but is also recommended for general heart health along with blood sugar. It has been found to successfully decrease inflammation within the respiratory tract by increasing cellular activity (Zozina, Covantev, Kukes, & Corlateanu, 2021).

4.2.9 Melatonin: The hormone melatonin is naturally produced in the pineal gland of the body however it can also be produced from serotonin (tryptophan) (Masters, Pandi-Perumal, Seixas, Girardin, & McFarlane, 2014). When it is dark the brain releases an excess of melatonin to help

one go to sleep. Being exposed to light at night can prevent this production from occurring making it difficult to go to sleep. Melatonin can be prescribed/administered to aid patients experiencing insomnia, this is a common side effect COPD patients experience. When used as a treatment for COPD patients it was seen to reduce lung oxidative stress (determined by 8-isoprostane levels) as well as improve dyspnoea (de Matos Cavalcante et al., 2012). However, melatonin was shown to have no significant impact on lung function.

4.3 Mucolytic Agents

Mucolytic drugs are used in COPD to break down and lower the viscosity of mucus in the airways, allowing it to be cleared with greater efficiency and improving breathing. Some of the bioactive mucolytic drugs that are routinely used in COPD are as follows:

4.3.1 N-acetylcysteine (NAC): NAC is known as a precursor to a compound called glutathione, the natural compound of N-acetylcysteine is a powerful antioxidant that is found in onions (Šalamon et al., 2019). This compound has played a role in the decreasing rate of exacerbations for COPD patients administered high doses of NAC (Sanguinetti, 2016). NAC can also be classed as a mucolytic drug which has been utilised on the global market for the past 50 years for a range of indications including COPD (Calverley, Rogliani, & Papi, 2021). NAC mechanism of action involves delivering sulfhydryl moieties to target sites. There have been some potential benefits of utilising NACs in COPD in the management of chronic mucous production. However, the long term benefits of using NACs are unknown but may be more cost effective for patients with severe COPD who experience frequent exacerbations (Rushworth et al., 2014).

4.3.2 Erdosteine, (N-(carboxymethylthioacetyl)-homocysteine thiolactone) is a thiol-based mucolytic agent which changes the physical properties of mucous glycoproteins by interrupting their disulfide bonds (Mario Cazzola et al., 2018). This action results in an increased clearance of mucous.

In 1996, Erdosteine had a few clinical studies which concluded that it was an effective and tolerable mucolytic which could be used for symptomatic management of COPD namely, its ability to significantly reduce the severity of COPD exacerbations (M. Cazzola et al., 2020).

4.3.3 Ambroxol, (Amb, 2-amino-3,5-dibromo-N-[trans-4-hydroxycyclohexyl] benzylamine) is an active metabolite of bromhexine, a common active ingredient in expectorant cough syrups including Bisolvon (Ge et al., 2016). Ambroxol has been shown to initiate phospholipid

synthesis which stimulates the production of pulmonary surfactants to dissolve sputum and reduce inflammation within lung tissue cells. Thus, suggesting Ambroxol may be a desirable clinical therapy in patients presenting with COPD however, further research is required to establish the extent of its clinical effectiveness (Z. Li, 2021). Within the scope of drug delivery, Ambroxol has historically been administered orally or via injections however, research conducted by Ge et.al. 2016 has demonstrated that mucous hypersecretion could be reduced by inhaling Ambroxol in mouse models that were exposed to whole-body cigarette smoke exposure.

4.3.4 Bromhexine, is a plant-based treatment derived from the *Adhatoda Vascia* plant. COPD is distinguished by increased mucus production and poor mucus clearance. This extra mucus can clog the airways, aggravating COPD symptoms. Bromhexine aids in the removal of mucus by increasing its quality, making it less adherent and easy to expel. This can lead to better airway clearance and less coughing, which is a typical and distressing symptom of COPD. It is an oral mucolytic and administered for COPD management. Bromhexine may help minimise the likelihood of exacerbations caused by mucus buildup in the airways by facilitating mucus clearance. Clinical studies have shown how the use of bromhexine can improve FEV_1 as well as the quality of life of COPD patients (Murali et al., 2006).

Bromhexine can help with the management of COPD, especially in people who have high mucus production and airway clearance problems. It has the potential to improve symptom control and quality of life for people suffering from this chronic respiratory illness.

4.3.5 Carbocisteine: (SCMC) is a generally well tolerated and effacious mucolytic agent utilised to prevent acute COPD exacerbations (Song et al., 2019). SCMC was first developed in in the 1930's and became available on the market for consumer use during the 1960's as a mucoregulator for respiratory illnesses. However, there has been inconsistency in clinical efficacy which has caused the agent to be 'blacklisted' from the National health system in the 1980's. There has been a greater understanding to mucoactive drugs and their role in reducing the exacerbations for COPD patients, which has resulted in the NHS making prescriptions available for Carbocisteine in 2003 (Hooper & Calvert, 2008). Carbocisteine acts on the balance of fucose and sialic acid within secretory mucins, Mucin 5B and mucin 5AC to improve mucous clearance and reduce bacteria adhesion within the airways (Song et al., 2019).

4.3.6 Serratiopeptidase is a therapeutic, anti-inflammatory enzyme which can also exert mucolytic effects within the lungs. It has the ability to decrease mucosal viscosity and improves mucocilary clearance for patients with respiratory illnesses by reducing the presence of neutrophils (Nair & C, 2022). Whilst, this mucolytic agent has been submitted to clinical trials, Serratiopeptidase has not being prioritised as there are other drugs available which have higher levels of potency and safety (Allegra, 2005).

5. Nano-formulation strategies for Pulmonary Drug Delivery of Bioactives

Nano-based products and nanotechnology have covered almost all the realms of human discoveries in today's time and has emerged as one of the most suitable research tools for theranostic purpose in the field of biomedical sciences (Chellappan et al., 2020; Jayanta Kumar Patra et al., 2018). The nanomaterials used in nanotechnology-based products, now have enormous options available ranging from polymeric nanoparticles, metallic nanoparticles to graphene, and quantum dots to carbon nanotubes (Khursheed, Dua, et al., 2022; Khursheed, Paudel, et al., 2022; Parteek Prasher et al., 2022; Schmidt & Storsberg, 2015). Their suitability and wide application are not only based on their nanometric size range, rather they also encompass the unique physicochemical properties that come with these nanomaterials (Weiss et al., 2020). All the more the best attribute it offers is its dimensional resemblance with biomolecules (Proteins, Carbohydrates, Lipids, DNA, RNA etc.) present in the human system laying the trail to be effectively used in the field of biomedicine for various purposes (M. Gupta et al., 2022; Imran, Jha, et al., 2022; Imran, Paudel, Jha, Hansbro, Dua, & Mohammed, 2022; Kaur et al., 2022; Prasher et al., 2021). In comparison to bulk material, nanomaterials often possess some unique properties of their own likely catalytic activity, their electronic or magnetic properties, photonic properties and many more. Therefore, this connection between biomolecules as a complementary recognition element to nanomaterials encouraged the interest and imagination of many scientists and researchers in developing nanotechnology-based approaches in treatment therapies and diagnosis (Gnach, Lipinski, Bednarkiewicz, Rybka, & Capobianco, 2015; Mansoori & Soelaiman, 2005).

5.1 Types of Nano-formulations Used in COPD Therapy

Drug delivery systems have constantly been further developed and explored since the 1950s (H. P. Devkota et al., 2021; Mehta, Satija, et al., 2020; H. Park, Otte, & Park, 2022). These advanced systems have enabled the distribution of drugs into and throughout the body and are commonly used for vaccines and medication within today's society. A delivery system can range from anywhere between a capsule you ingest to a vaccine you take to a nanoparticle such as micelles to remove make up. Regardless of the system, the active is protected from degradation and can withstand harsh conditions. Nanoparticles (NPs) can be defined as particles within the range of 1 to 100 nm and have a variety of different naturally occurring shapes, making them ideal for many different situations as displayed in figure 3. The surface area of these NPs is greater than the volume as a result of the small scale, allowing for the structures to have different chemical properties (Khan, Saeed, & Khan, 2019). The low toxicity as well as other characteristics provide NPs with endless applications from pharmaceutical to industrial uses.

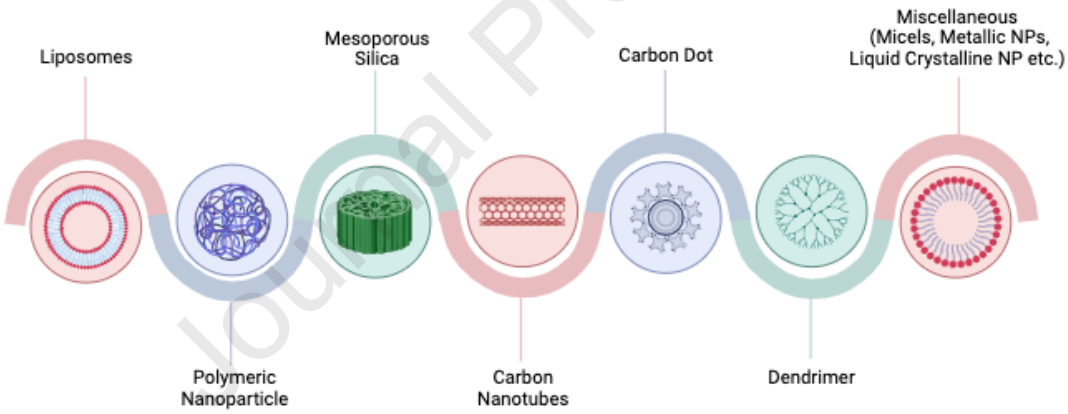


Figure 3: Representing the associated strategies involved in developing and utilizing nano-formulation strategies for pulmonary drug delivery of Bioactives

5.1.1 Lipid-Based Nanocarriers for Pulmonary Delivery

Lipid based nanoparticles (LNP) use lipids vesicles to transfer drugs through the body. During the mid 1960's liposomes were first discovered by Alec D. Bangham, and consisted of single or multiple concentric lipid bilayers. Lipids are commonly defined as sphere-shaped vesicles consisting of one or more phospholipid bilayers. Liposomes, a form of LNP, are an emerging technology used to deliver Active pharmaceutical ingredients (API) into the body. Liposomes

have provided many benefits to society especially amongst the medicinal industry for vaccines and administration of anti-cancer drugs. The API is encapsulated, protecting them from damage or degradation when entering a patient's body. LPNs typically use phospholipids, cholesterol, polyethylene glycol (PEG) or ionisable cationic lipids to coat the API (Leong & Ge, 2022).

Using LNPs have been increasingly popular due to the delivery systems ability to reduce toxicity of drugs allowing for a higher loading. Additionally administering drugs via inhalation prevents drug degradation from the gastrointestinal tract (GI) along with first-pass metabolism (Leong et al., 2022).COPD Treatments often utilise LNPs to improve the local concentration and retention time of drugs in the lungs.

There are two main methods for the preparation of liposomes passive and active loading techniques. Within passive loading techniques there are three methods which liposomes are most commonly made by, mechanical dispersion (sonication, pressure cell, etc.), solvent dispersion (reverse phase dispersion, ethanol injection etc) and detergent removal (dialysis and gel-permeation chromatography)(Akbarzadeh et al., 2013). The method focused on in this report uses mechanical dispersion, with probe sonication. In general, this method is one of the most common for the preparation of small unilamellar vesicles (SUV) from multilamellar vesicles (MLV).

5.1.2 Polymer-Based Nanoparticles and Their Applications

Polymer based NP's are known to have a good biocompatibility, biodegradability and also allow for surface modifications (Passi, Shahid, Chockalingam, Sundar, & Packirisamy, 2020). Controlled drug administration is able to be made by utilising polymer NP's as the outer part of the NP degrades slowly allowing the drug to gradually be released into the system. Poly lactic-co-glycolic Acid or PLGA is one of the most common polymer-based NP which is typically used for drug delivery. PLGA's high biocompatibility, low toxicity and adaptable degradation (Saxena et al., 2022) all contribute to its versatility and high demand within the pharmaceutical industry.

5.2 Advantages of Nano-Formulation in Drug Delivery

The ability of nanoformulation techniques to increase the pharmacokinetics and bioavailability of bioactive substances has gained popularity (Yinghan Chan et al., 2021). Nanoformulations that improve the stability and targeted delivery of plant-derived chemicals to the lungs include

nanostructured lipid carriers (NLCs), liposomes, and solid lipid nanoparticles (SLNs) (Sabine, Thomas, & Silke, 2014). These strategies aid in the removal of challenges such as fast clearance and enzymatic degradation, allowing for extended release and long-term therapeutic benefits (Passi et al., 2020).

Nanoformulations allow for the targeted distribution of bioactive substances to the lungs, hence reducing systemic exposure and any negative effects. Nanoformulations can improve deposition in the bronchoalveolar regions by optimising particle size and surface characteristics, precisely targeting the locations of inflammation and tissue damage associated with COPD (Xu, Liu, & Song, 2020).

The inclusion of plant-derived chemicals into nanoformulations not only protects their bioactivity but also provides sustained release over long periods of time, adding to the prolongation of therapeutic benefits.

6. Challenges and Considerations in Nano-Formulation for COPD Treatment

Nano-formulations, that encapsulate therapeutic compounds in nanoscale carriers, have various advantages, including improved drug solubility, targeted delivery, and fewer adverse effects. However, developing and implementing nano-formulations for COPD treatment has special challenges and constraints. A vital goal in COPD treatment is to achieve targeted medicine delivery to the lungs (Vij, 2011). Although nano-formulations can improve lung deposition but ensuring that nanoparticles reach the intended region of action can be difficult. Therefore, to optimise pulmonary targeting, variables such as particle size, surface characteristics, and breathing technique must be carefully studied (Roy & Vij, 2010).

Additionally, controlled drug release from nano-carriers serves as an essential factor for sustaining therapeutic medication levels over an extended period at the targeted site. Achieving the desired release kinetics that match the disease progression and patient needs is a complex task.

Furthermore, nano-formulations must be inhalable as well as biocompatible with lung tissues thus to ensure that it does not cause inflammation, cytotoxicity, or undesirable immunological reactions is also essential. To establish the long-term safety of nano-formulations, extensive toxicological investigations are required (Sahoo, Panyam, Prabha, & Labhasetwar, 2002). Drug stability within nano-carriers system is a concern particularly with biologics and peptides. Maintaining therapeutic efficacy requires ensuring drug stability during formulation, storage, and aerosolization. Moreover, the regulatory landscape for nanoformulations in COPD

778 treatment is changing hence to understand the regulatory restrictions and obtain clinical
779 approval is necessary. Also, nano-formulations may necessitate the use of specialised
780 inhalation devices and it becomes difficult to ensure patient adherence and proper use of these
781 devices. COPD is a complex condition, and individual patient responses to therapies can vary
782 greatly. So, tailoring nano-formulations to particular patient demands, such as disease severity
783 and specific symptoms, is a challenge in personalised medicine (Passi et al., 2020).
784 To summarise, while nano-formulations show potential for improving COPD treatment,
785 various obstacles and issues must be addressed. Lung targeting, drug release kinetics, safety,
786 regulatory approval, patient adherence, and cost-effectiveness are just a few of the difficult
787 concerns that researchers and healthcare practitioners must confront (Zhong, Zhang, Zeng, Lin,
788 & Wu, 2021). Despite these obstacles, the potential benefits of nano-formulations in improving
789 COPD treatment outcomes make further study and development in this field important.
790
791 ***6.1 Biocompatibility and Safety of Nano-Formulations***
792 As discussed through this review, nano-formulations represent a revolutionary avenue for
793 enhancing the treatment of COPD, a debilitating lung disorder characterised by progressive
794 airflow limitation and respiratory symptoms. These formulations involve the manipulation and
795 utilisation of materials at the nanoscale, allowing for improved drug delivery precision,
796 enhanced targeting of specific lung regions, and increased overall treatment efficacy (Passi et
797 al., 2020). By capitalising on nanotechnology, nano-formulations offer the potential to address
798 some of the longstanding challenges associated with conventional COPD therapies. However,
799 the successful development and deployment of these innovative formulations require a
800 comprehensive understanding of the intricacies involved.
801
802 ***6.2 Targeting Strategies for Efficient Drug Delivery to the Lungs***
803 A primary challenge in developing nano-formulations for COPD treatment lies in ensuring
804 effective drug delivery and precise targeting within the complex and heterogeneous
805 environment of the lungs. The intricate network of airways, mucus accumulation, and varying
806 levels of inflammation in COPD patients can impede the distribution of therapeutic agents (Xu
807 et al., 2020). Overcoming these barriers is crucial to ensure that nanoparticles encapsulating
808 drugs can reach the intended sites of action. Researchers must engineer nano-carriers with
809 surface modifications that enable them to navigate through the mucus barrier, evade immune
810 responses, and effectively deliver drugs to inflamed airway regions (Passi et al., 2020). By

optimising the physicochemical properties of nanoparticles, such as size, surface charge, and coating, researchers aim to achieve controlled and targeted drug delivery (Xu et al., 2020).

The safety and potential toxicity of nanoformulations present another critical consideration. The unique physicochemical properties of nanoparticles can lead to interactions with biological systems that are distinct from those observed with larger materials (Nasim, Sandeep, & Mohanty, 2022). Concerns arise regarding the potential induction of inflammatory responses or the accumulation of nanoparticles in unintended tissues, which could result in adverse effects. To address these concerns, comprehensive preclinical studies are essential to evaluating the long-term safety of nanoformulations (Prasher et al., 2020). Moreover, innovative techniques such as advanced imaging technologies and biomarker analyses are employed to monitor the behaviour of nanoparticles within the lungs and assess any potential systemic effects (Z. Liang, Ni, Zhou, & Mao, 2015).

6.3 Combination Therapies and Synergistic Effects

In the quest for innovative efficient COPD therapies, experts have progressively investigated combination therapies which make use of the potential synergistic effects of plant-derived bioactive compounds when delivered through nanoformulation techniques. COPD is a multifaceted disease with a variety of pathophysiological pathways and alteration of lung microbiome that are contributing to its advancement (Paudel et al., 2020). Single-agent therapy frequently fails to address the disease's complex character (Donohue, 2005). Additionally, by targeting numerous pathways at the same time, combination therapy can reduce the development of drug resistance, making it harder for the disease to adapt. Many bioactive chemicals originating from plants have distinct/complementary modes of action. Combining compounds with complimentary attributes can result in synergistic effects that increase the total therapeutic potential (Tashkin & Ferguson, 2013). Similarly, anti-inflammatory and antioxidant interactions with Plant substances with anti-inflammatory and antioxidant effects include quercetin and curcumin. Their combination can treat both chronic inflammation and oxidative stress, both of which are frequent in COPD.

Another example is the combination of curcumin, produced from turmeric, and resveratrol, found in red grapes and some berries, which has showed promise in the treatment of COPD (Cione, La Torre, Cannataro, Caroleo, Plastina, & Gallelli, 2019). These chemicals have anti-inflammatory, antioxidant, and antifibrotic actions when combined. Epigallocatechin Gallate

(EGCG) with Quercetin (Aftab & Vieira, 2010): Quercetin, a flavonoid found in apples and onions, has anti-inflammatory and bronchodilatory properties when coupled with EGCG from green tea. This combination has the potential to reduce airway inflammation while also improving lung function. Similarly, Nanoformulation Strategies for Combination Therapies can be created, such as Co-Encapsulation in Nanoparticles, which allows for the co-encapsulation of various plant-derived chemicals within the same nanoparticles, assuring their simultaneous delivery to the target site. Nanoformulations can improve chemical absorption, allowing for lower doses while preserving therapeutic efficacy, which is especially useful in combination medicines (Zhang, Virgous, & Si, 2019).

However, this strategy has significant disadvantages, such as It might be difficult to determine the optimal dosage and ratio of substances in combination therapy. This necessitates substantial preclinical and clinical research. To avoid negative consequences, it is critical to evaluate the safety and potential interactions of numerous medications.

Finally, when given utilising nanoformulation techniques, combination medicines that harness the synergistic effects of plant-derived bioactive chemicals represent an interesting prospect in COPD therapy. These methods have the potential to give more comprehensive and personalised therapy for COPD patients, providing hope for better disease control and quality of life. However, further research and clinical trials are required to fully realise the potential of combination treatments in the fight against COPD.

6.4 Stability and Sustained Release of Bioactive Moieties

Maintaining the stability and shelf life of nanoformulations is imperative for their successful clinical application. The intricate nature of these formulations, often involving complex structures and combinations of materials, can render them sensitive to environmental factors such as temperature, humidity, and light. Ensuring the structural integrity of nano-carriers and preventing issues like aggregation or drug degradation during storage and administration is vital to guarantee consistent therapeutic performance over extended periods. Researchers focus on optimising formulation parameters, encapsulation techniques, and storage conditions to enhance stability and prolong shelf life. In Figure 4, A flow diagram reflecting the key principles for nanoformulations that are considered by researchers is represented along with the anticipated outcomes.

Navigating the regulatory landscape is a complex challenge in the development of nano-formulations for COPD treatment. Regulatory agencies typically require comprehensive data on the safety, efficacy, quality, and manufacturing processes of novel therapies (Tofiño-Rivera, Castro-Amaris, & Casierra-Posada, 2020). Due to the unique characteristics of nano-formulations, developers must provide detailed information on particle size distribution, surface modifications, and potential interactions with biological systems (Wang et al., 2020). This necessitates a close partnership between researchers, clinicians, and regulatory authorities to ensure that the necessary data are collected and that the formulations meet the rigorous standards required for approval.

Patient acceptance and compliance are pivotal factors that contribute to the success of nano-formulations in clinical practice. Ensuring that patients are well informed about the benefits and potential risks of these innovative therapies is essential for fostering trust and acceptance (X. Jiang et al., 2020). Moreover, researchers strive to optimise the administration methods and dosing regimens of nano-formulations to enhance patient convenience and adherence (Jian et al., 2020). By minimising the complexity of administration and dosing, nano-formulations can improve patients' overall experience and willingness to comply with treatment plans.

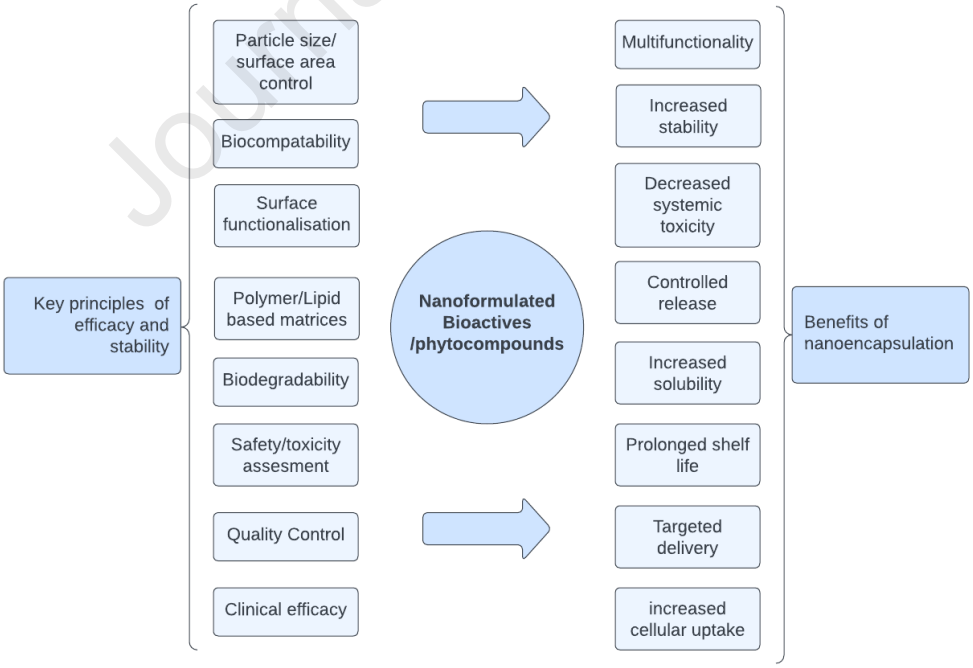


Figure 4: This figure represents the key principles of stability and sustained release, crucial for the successful delivery of bioactive moieties in nano-formulations designed for the treatment of respiratory conditions such as COPD.

7. Preclinical Studies and Experimental Evidence: Therapeutic Efficacy in COPD

Preclinical and experimental research has accelerated the examination of plant-derived bioactive chemicals for the treatment of COPD. These investigations have provided valuable insights into the potential therapeutic efficacy of several bioactive compounds in the treatment of COPD-related diseases (Woodcock et al., 2018). Furthermore, the incorporation of improved nanoformulation technologies has emerged as a promising strategy for improving the pulmonary transport and bioavailability of these drugs, thereby maximizing their therapeutic impact (Calzetta et al., 2022). Experimental evidence from *in vitro* studies has shed light on the mechanistic pathways through which plant-derived compounds exert their therapeutic effects. Compounds like epigallocatechin gallate (EGCG) have been shown to change the signalling pathways involved in inflammation and oxidative stress. This makes the release of pro-inflammatory cytokines less likely to happen and reduces the damage caused by ROS (Shanmugam, Selvaraj, & Poomalai, 2016). Additionally, these compounds may regulate immune cell functions, contributing to the overall immune homeostasis in the lung microenvironment (Mokra, Joskova, & Mokry, 2023). Emerging *in vivo* evidence has demonstrated the feasibility and efficacy of nano formulated plant-derived compounds. These studies showcase enhanced therapeutic outcomes, including improved lung function, reduced airway inflammation, and enhanced antioxidant defence mechanisms. Preclinical studies utilizing animal models of COPD have shown promising results; for instance, animal models exposed to cigarette smoke or environmental pollutants and subsequently treated with compounds like curcumin, resveratrol, and quercetin exhibited reduced lung inflammation, oxidative stress, and improved lung function. These findings underscore the potential of these compounds to ameliorate COPD-related lung impairments (L. Y. Li et al., 2022; I. Rahman, 2008)

When given *via* nanoparticles (NPs), amikacin (AM), a widely used antibacterial agent for treating COPD in cases involving gram-negative bacilli lung infections [132, 133], shown increased lung drug concentrations and reduced systemic adverse effects. Considering the strategy to enhance its therapeutic index, researchers used an ion crosslinking approach to combine chitosan with black phosphorus quantum dots (BPQDs), then modified the surface using PEG (Z. Li et al., 2020; Z. Liu et al., 2021). This effort concluded in the successful development of a nanodrug controlled-release carrier system efficiently crossing the pulmonary mucus barrier, considerably enhancing medication delivery, and having a

933 synergistic effect on COPD treatment. This study proposes a unique therapy strategy to address
934 the drug-treatment problems provided by mucus barriers associated with respiratory diseases.
935 Similarly, targeting ROS, plays an important role in the onset and development of
936 COPD causing a decrease in histone deacetylase 2 (HDAC2) levels and eventually leading to
937 glucocorticoid resistance (Zwinderman, de Weerd, & Dekker, 2019). The researchers
938 developed core-shell lipid-polymer nanoparticles (LPNs) made of polylactic acid (PLA) and
939 containing an efficient antioxidant called Mn porphyrin dimer (MnPD)(Ma, Xu, Ying, Li, &
940 Jin, 2015). The LPN core contains the cationic lipid DOTAP as well as plasmid DNA encoding
941 HDAC2 (pHDAC2). Transfection of pHDAC2 increases HDAC2 expression and reduces ROS
942 levels via MnPD. Furthermore, LPN therapy was shown to lower interleukin-8 levels,
943 indicating successful hormone resistance mitigation in COPD mice. This method, which
944 capitalises on the collaborative influence of HDAC2 expression and ROS management,
945 provides a new path towards increasing glucocorticoid resistance in COPD patients (Chikuma
946 et al., 2020).
947 The NPs based carrier systems were also designed for MicroRNAs (miRNAs) and decoy
948 deoxyoligonucleotides, which are investigated for their potential as viable alternatives for
949 COPD and lung cancer treatment in recent years (Datsyuk et al., 2023; Meenu Mehta, Keshav
950 Raj Paudel, et al., 2021; Meenu Mehta, Saurabh Satija, et al., 2021). To reduce the expression
951 of the interleukin-1 receptor-associated kinase-1 (IRAK1) gene in COPD patients, researchers
952 created nanoparticles containing the cationic lipid DOTAP (Singer, Fleischman, Al-Fayoumi,
953 Mascarenhas, Yu, & Agarwal, 2018; Sun et al., 2022). These nanoparticles exhibited effective
954 aggregation within lung cancer cells as well as long-term release. Notably, at appropriate
955 concentrations, miR-146a contained in these nanoparticles can significantly lower IRAK1
956 expression. These findings highlight the potential of poly (glycerol adipate-co—penta
957 decalactone) nanoparticles as a COPD therapeutic strategy, notably in the therapy of miR-146a
958 (Mohamed, Pekoz, Ross, Hutcheon, & Saleem, 2019).
959
960 Numerous studies on selective medication and gene delivery based on PLGA nano systems for
961 COPD treatment have been conducted. However, when the emulsifier polyvinyl alcohol
962 (PVA) is utilised in their production, PLGA nanoparticles have some disadvantages, including
963 a highly negative charge on the nanoparticle surface. Researchers used PEGylation to improve
964 the characteristics of PLGA nanoparticles, which not only aids in airway defence but also
965 allows for efficient mucus prevention. PEGylated PLGA increases nanoparticle retention,

increasing accumulation in target cells while decreasing molecular load (Puricelli et al., 2023). Furthermore, nanoparticle-mediated medication or gene delivery enables targeted therapy.

In conclusion, preclinical studies and experimental evidence support the exploration of plant-derived bioactive compounds as COPD therapeutics. The integration of nanoformulation strategies further amplifies the potential of these compounds by enhancing their pulmonary delivery and targeted action. While more research is needed to establish their clinical applicability, the combination of plant-derived bioactive compounds and advanced nanoformulations holds promise as a groundbreaking approach for managing COPD and improving the quality of life for affected individuals.

8. Clinical Perspectives and Translational Potential

Nanotechnology has emerged as a viable area in the treatment of respiratory conditions such as COPD in recent years. This review explores the clinical implications and translational potential of nanoformulations in the context of plant-derived bioactive compounds for COPD treatments. In the same pretext, nanoformulations enable precise drug distribution to afflicted lung regions, maximising therapeutic impact while minimising systemic side effects. This customised approach is especially important in COPD, as specific lung regions may be impacted more severely (Ibarra-Sánchez et al., 2022). It has been reported in many studies that the plant-derived bioactive compounds utilised in COPD treatment have low water or physiological fluid solubility. Nanoformulations can address this issue by increasing drug solubility and promising improved drug dispersion during inhalation (Malamatari, Charisi, Malamataris, Kachrimanis, & Nikolakakis, 2020). It also aids in the attainment of regulated release kinetics, which give maintained medication levels in the lungs throughout time, assuring long-term therapeutic effects (Sharma et al., 2023). On the contrary, it is critical to ensure the safety and biocompatibility of nanoformulations (Taghavizadeh Yazdi, Qayoomian, Beigoli, & Boskabady, 2023). Plant-derived chemicals may have diverse interactions with lung tissues, and extensive toxicological studies are required to establish their safety profiles when administered by nano-carriers.

Finally, nanoformulations of plant-derived bioactive chemicals present exciting potential for the advancement of COPD therapies. Their ability to increase targeted drug administration, solubility, and controlled release kinetics provides a considerable clinical advantage. However, addressing safety, patient adherence, regulatory barriers, and economic concerns is critical for moving these promising methods from the lab to the clinic. As research in this subject advance,

it has the potential to revolutionise the care of COPD and other respiratory ailments, ultimately enhancing the quality of life for those who suffer from them.

8.1 Current Status of Nano-Formulated COPD Therapies in Clinical Trials

As the clinical trial landscape globally is dynamic and changing at a rapid scale. The nanoformulations like - Liposomes, nanoparticles, and micelles have been studied as nano-sized drug carriers for delivering various COPD treatments, including bronchodilators and anti-inflammatory drugs (group, 2012). The goal of these nano-formulations is to optimise drug delivery to the lungs, boost therapeutic efficacy, and reduce systemic side effects. Some of these formulations may have advanced to early-stage clinical trials to evaluate safety and efficacy (Y. Liu et al., 2023).

Anti-inflammatory drug nano-formulations, such as corticosteroids, have been studied to reduce lung inflammation in COPD patients. These formulations may provide targeted and long-term medication delivery. Furthermore, oxidative stress is implicated in the pathophysiology of COPD (Passi et al., 2020). N-acetylcysteine (NAC) encapsulated in liposomes, for example, has been studied for its ability to minimise oxidative damage and enhance lung function in COPD patients (Passi et al., 2020). Nanoparticle-based vaccinations for COPD are currently being researched. These vaccinations are designed to stimulate the immune system into producing a protective response against microorganisms that are typically associated with COPD exacerbations, such as respiratory viruses (Ji, Jareño-Esteban, & de Miguel-Díez, 2022; Simon, Joean, Welte, & Rademacher, 2023).

Some nano-formulated mucolytic drugs aim to break down and thin mucus in the airways, hence improving mucus clearance and alleviating symptoms such as coughing and shortness of breath. Clinical trials to assess their safety and efficacy in COPD patients is still pending (R. Gupta et al., 2023; Miller & Rumack, 1983).

Nano-formulated gene treatments are being researched in order to target specific genetic variables linked to COPD. These treatments try to change or fix genes that are involved in the illness process. Clinical investigations in this field are still in the planning stages (Chen, Kim, Ryter, & Choi, 2008; Silverman, 2020).

Early COPD diagnosis improves prognosis greatly. Vital capacity measures are currently the gold standard for COPD diagnosis and monitoring. However, in the early stages of the disease, when individuals are asymptomatic, standard spirometry frequently fails to accurately reflect the disease's true condition. According to research, an electronic nose based on nano sensors

can be a potential diagnostic tool for COPD, as well as discriminating between asthma, COPD, and lung cancer. Clinical experiments have shown that the electronic nose may be used to analyse pathogen colonisation in COPD patients, providing a simple, non-invasive, and reliable diagnostic approach for bacterial colonisation in these patients (de Heer et al., 2013; Dragonieri et al., 2009).

It is critical to highlight those clinical studies for new medicines utilising nanotechnology, can take many years to advance from early-phase trials (Phase I and II) to larger-scale Phase III trials and ultimately regulatory approval. Furthermore, the effectiveness of these medicines is determined by aspects such as safety, efficacy, patient adherence, and regulatory considerations (Shafiek et al., 2015).

8.2 Regulatory Considerations and Hurdles for Clinical Translation

Nanoformulation techniques for the research and clinical translation of plant-derived bioactive chemicals for COPD therapy present a viable route for enhanced treatment outcomes. The journey from laboratory research to actual patient treatment, on the other hand, has its share of regulatory complexity and hurdles. There are differences in Regulations for Natural Health Products across multiple regions, including the United States, Canada, and the European Union. Natural health products, which may contain plant-derived chemicals, are subject to special regulatory frameworks set by regulatory bodies (Ajazuddin & Saraf, 2012; WHO, 2004).

Also, determining whether a plant-derived component fits under the category of a drug, dietary supplement, or traditional herbal medicine can be quite complex. This categorization has the potential to greatly transform the regulatory pathway as well as the need for clinical trials and approval (Thakkar et al., 2020).

Apart from the Safety and Efficacy Assessment, the Toxicological Evaluation, in particular, requires detailed toxicological analyses of the nano formulated plant-derived substances (Zielińska et al., 2020). This includes identifying probable adverse effects, establishing dose-response correlations, and developing long-term safety profiles (Tirumala, Anchi, Raja, Rachamalla, & Godugu, 2021). Regulatory organisations want substantial evidence of therapeutic efficacy. Clinical studies are planned to meet these criteria, which frequently include rigorous research design, endpoints, and statistical analyses. It is critical for regulatory approval to maintain consistency in the composition of plant-derived nanoformulations. It is

critical to have strong quality control measures and documentation to assure batch-to-batch uniformity (Souto et al., 2020).

The most significant aspect is the standardisation of plant extracts. It is critical to ensure that plant extracts used in nanoformulations meet recognised quality and purity criteria. Variability in plant composition can have an impact on the end product's effectiveness and safety (T. I. Ramos et al., 2022).

It can be difficult to navigate the complexities of intellectual property regulations and ensure that patent claims are thorough.

Conducting clinical studies with plant-derived medicines requires ethical considerations, particularly with plant material sourcing and potential implications on local ecosystems. Finding appropriate patient groups for clinical trials can be difficult, especially for rare or specialised illnesses such as COPD. It is critical to ensure varied patient recruitment while adhering to ethical norms. Following regulatory approval and commercialization, continued pharmacovigilance is required to monitor the product's safety and effectiveness in real-world situations.

It is critical to navigate these regulatory issues and roadblocks in order to promote the clinical translation of plant-derived bioactive molecules for COPD therapies. Researchers, industry partners, and regulatory authorities must work closely together to assure the safe and successful use of nanoformulation techniques in COPD care, giving patients with this severe respiratory ailment new hope.

9. Future Directions and Opportunities

The use of nanotechnology for targeted drug delivery is one of the most promising discoveries in the field of COPD and this treatment approach will guide the pulmonary therapeutics in future. It was always known that the plant-derived bioactive compounds are enormously efficacious, but they have limited therapeutic utility due to their poor solubility and stability. By increasing the solubility of these phytocompounds and preventing them from enzymatic breakdown in the intestinal tract needs a resolution which has been circumvented by applying varied nanoformulation methods and strategies. For delivering plant-derived bioactive chemicals to the lungs, nanoformulations such as nanoparticles, liposomes, and nanofibers have various advantages. These nanocarrier systems can prevent bioactive substances from degradation while additionally allowing for regulated release, consistent drug levels, and enhanced lung uptake. Furthermore, nanocarriers are capable of being customised to increase

their affinity for particular target cells in the pulmonary system, thereby enhancing compounds efficiency while limiting systemic side effects.

Subsequently, improved bioavailability is crucial in enhancing the therapeutic potential of plant-derived medicines for COPD and it has been exhibited in many studies that when many plant-derived compounds are combined, they have synergistic effects. Nanoformulations provide a platform for co-encapsulating several bioactive chemicals, allowing for the benefits of synergism to be realised. This technique offers the potential to provide potent and personalised COPD therapies that target many elements of the disease, including inflammation, oxidative stress, and bronchial constriction altogether. Nanotechnology and personalised medicine advancements are allowing for the customising of COPD therapy to patient characteristics. Researchers can build nanoformulations that are optimised for each patient by using patient-specific data such as genetics, biomarkers, and illness severity. This technique may result in more effective and accurate medicines, with fewer side effects and better therapeutic outcomes. Combination medicines may pave the door for personalised therapy regimens suited to COPD patients' specific needs, thereby enhancing overall therapeutic outcomes. Also, lowering individual drug doses in combination therapy may result in fewer side effects, improving patient adherence and comfort. Future studies could look for biomarkers that predict patient responses to specific combination medicines, allowing for a more focused approach. To evaluate the safety and efficacy of combination treatments in COPD, rigorous clinical trials in collaboration between academia, industry, and regulatory authorities are required.

10. Conclusion

In conclusion, the utilisation of plant-derived bioactive compounds as possible COPD therapeutics is a promising avenue for better controlling this debilitating pulmonary disorder. Although these phytocompounds have shown considerable anti-inflammatory, antioxidant, and bronchodilatory activities, their clinical relevance has been restricted due to their limited bioavailability, stability, and targeted delivery challenges. The development of nanoformulation methods has brought in an entirely novel phase of COPD solutions. We can overcome the barriers that have impeded the effective utilisation of plant-derived bioactive chemicals by using the potential of nanotechnology. As they provide improved bioavailability, controlled release, and the potential for personalised medicine, thus transforming COPD treatment effectively. Looking ahead, more research and development in this field will be required for fully recognise the therapeutic value of plant-derived bioactive compounds in

COPD therapy. Natural compound synergy paired with nanoformulation precision holds the possibility of highly efficient, personalised, and targeted pharmaceuticals. Also, the capacity to adapt treatments to individual patient profiles while taking genetic and biomarker data into consideration gives an interesting opportunity to improve outcomes while reducing negative effects. Although regulatory approval, clinical validation, and large-scale production remain constraints, the trajectory is obvious. When plant-derived bioactive chemicals are used in nanoformulation processes, they have the potential to improve the lives of COPD patients by providing safer, more effective, and personalised treatments. We believe that continuing research efforts will continue to refine and broaden the applications of nanotechnology in COPD treatments in the coming years. The combination between nature's pharmacy and cutting-edge science will pave the way for creative and transformative COPD therapies, ultimately improving the quality of life for millions of people suffering by this chronic respiratory condition.

Conflict of interest statement

There is no conflict of interest in this review.

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