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Review Article

Literature Review on Small Molecules in Therapeutics for Lung Medicine

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Abstract

Lung diseases are a significant health burden globally caused by unending exposure of the respiratory system to environmental pollutants, pathogens and other dangerous chemicals. Standard treatments of chronic and progressive lung diseases like asthma, chronic obstructive pulmonary disease (COPD), pulmonary fibrosis, lung cancer, and infectious pulmonary diseases have little success in managing disease progression or in treating these conditions. In this regard, small-molecule therapeutics came to be an important platform of contemporary lung care because of their low molecular weight, strong cellular penetration, and the capability to be administered orally, and low costs of production.

This literature review critically discusses the role of small molecules in the treatment of lung therapy by emphasising their properties, action, therapeutic uses, benefits, and limitations. The major areas of disease, including inflammatory diseases of the lung, fibrotic diseases, malignancies, and respiratory infection, are discussed as key areas of enzyme inhibition and receptor modulation. Bronchodilators, phosphodiesterase inhibitors, tyrosine kinase inhibitors, antifibrotic agents, and antiviral drugs are clinically relevant agents that come into the limelight of the review. Although they have these advantages, some issues persist, including resistance to drugs, off-target toxicity and limitations on delivery. Prior development of artificial intelligence used to discover new drugs, drug delivery systems using nanotechnology, and combination therapy with biologics has a positive future direction. The development of small-molecule therapeutics remains central in the history of the lung as a medicine, and future developments in the product are leading to more customised and targeted respiratory therapy.

Keywords: *Small Molecule Therapeutics; Lung Medicine; Pulmonary Diseases; Drug Discovery; Enzyme Inhibition; Receptor Modulation; Targeted Therapy; Respiratory Pharmacology*

Introduction

Lungs are the key organs of the body that come into direct contact with the external environment continuously for gaseous exchange and to meet the body's needs for oxygen. In this whole process, these organs are exposed to smoke, microbes, pollens, pollutants, environmental chemicals, dust, and several other factors that increase the risks of developing various diseases and disorders [16]. In the context of discussing the diseases and disorders of the lungs, Cho and Stout-Delgado [8] stated that Pulmonary Function Impairment is one of the predictors of mortality and morbidity and promotes the development of various other diseases in the body. Some of the common lung diseases which are widely seen in the healthcare sector are asthma, Chronic Obstructive Pulmonary Disease (COPD), fibrosis, lung cancer, and others [36,39]. For treating all these diseases, the application of therapeutics is increasing in the global healthcare industry to treat several lung diseases both in the short term and the long term. Brewer., *et al*. [5] stated that the burden of chronic respiratory

diseases is increasing in the global market, and the conventional therapies, such as corticosteroids and bronchodilators, are not providing any benefits for disease progression. Thus, the development of new therapies and therapeutics is in need. Brewer., *et al*. [5] have discussed how small molecules are one of the emerging therapeutic innovations for targeting various specific fibrotic and inflammatory pathways.

As per the findings of Southey and Brunavs [34], more than 90% of the marketed drugs are produced with small molecules, consistent with low molecular weight organic compounds. Moreover, the development of small molecular drugs has been seen in the healthcare sector as these have low molecular weight, greater ability to penetrate the cells and tissues and higher oral bioavailability. The authors also provide examples of small-molecule drugs like penicillin as an antibiotic and paracetamol and analgesics. More specifically, from the study of Dailah [11], a smallest molecule drug named N-acetyl-L-cysteine is used to break down the mucous of the respiratory tract. For this context, a review of the literature on the use of small molecules in therapeutics for the development of lung medicine has been conducted. The review provides scope to know about the general mechanism of action of small-molecule drugs for lung diseases, along with the advantages and disadvantages of using small molecules for lung medicines. Some of the recent advancements and the future directions have also been reviewed in this section.

Background: Small molecules in drug discovery

Background and characteristics

Kamali., *et al*. [17] define small molecules as one of the organic compounds that have a low molecular weight of less than 900 Daltons and have recently been utilised for the development of therapeutics and drugs. Another information can be observed from the study of Ma., *et al*. [22] that small molecules are recently widely used for drug discovery as the small molecule drugs affect the molecular pathways by targeting low molecular weight proteins for easy penetration into cells. On the other hand, Southey and Brunavs [34] define small-molecule drugs as synthetic medicinal chemicals that are produced for enhancing, diminishing, and mimicking natural substances within the human body. However, there are some differences in the characteristics of the small molecules and biologics. In comparison to the small molecules, biologics are the large molecules having a size range between 1000 and 150000 Daltons [1,27]. Quraee., *et al*. [30] discussed that the small-molecule drugs and biologics are the two most commonly used for therapeutics, but both these compounds have different clinical applications and mechanisms of action. Biologics include recombinant proteins, monoclonal antibodies and other large molecules derived from living organisms. In turn, the small molecule drugs are synthesised from the chemical process and treat a broad spectrum of health conditions. However, the specific focus of the general mechanism of small molecules has not been covered in this literature.

Common mechanisms of action

From the research of Li and Kang [19], it is known that drug discovery of small molecules requires diverse techniques and various expertise, as this is considered one of the complicated processes. The presented Figure 1 shows the process of obtaining small molecules with the help of phenotypic screening with cell-based assays, by which the identification of novel targets can be done.

Moreover, there are two common mechanisms of action of the small molecules, which are enzyme inhibition and receptor modulation [44]. There are many different medicines developed with small molecules used for treating different lung diseases with different mechanisms of action. Bondarev., *et al*. [4] have stated that Roflumilast works as a phosphodiesterase inhibitor to treat inflammation in COPD. Salbutamol works as a beta agonist for bronchodilation to treat asthma [37]. Rifampin, Isoniazid, and Levofloxacin are mostly used as antibiotics to treat pulmonary infections like Pneumonia and Tuberculosis [15]. Besides these, some drugs were discovered in early 2000 for treating lung cancer, which include Gefitinib, Erlotinib, Entrectinib and many others [2,9].

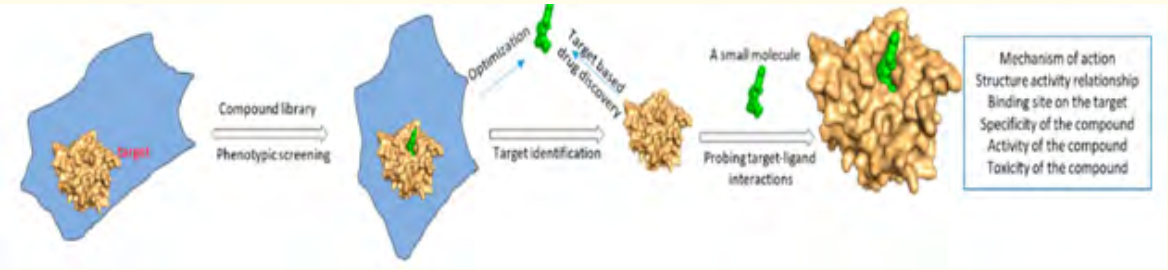

Figure 1: *The process of obtaining small molecules to affect a protein's function (Source: Li, Q. and Kang, C., (2020).*

Therapeutic areas in lung medicine

Asthma and COPD

The application of lung medicines is done differently for various types of lung diseases. Dey., *et al*. [13] mentioned both asthma and COPD in the category of inflammatory lung diseases, in which to treat these diseases, the bronchodilator mechanism and use of anti-inflammatory agents are used. According to the study of Tanwar., *et al*. [37], the beta-2-agonist uses the receptor binding mechanism for bronchodilation and to treat both asthma and COPD. Along with this, the study of Bondarev., *et al*. [4] showed the phosphodiesterase inhibition activities of the small molecules to treat COPD. Besides the use of these procedures, there are many anti-inflammatory agents which are used for the treatment of lung inflammation. For example, Frank., *et al*. [14] have stated that patients with inflammatory lung diseases can inhale corticosteroids, in which the small molecules bind with the glucocorticoid receptors to alter gene transcription. In these areas, some of the notable small molecule drugs have been identified, which are used for bronchodilation, receptor modulation and as anti-inflammatory agents. Salbutamol and Salmeterol are the short and long-acting beta agonists [6]. On the other hand, budesonide and fluticasone are known as inhaled corticosteroids [12]. The drug called Roflumilast has been found in the study of Bondarev., *et al*. [4] to be a phosphodiesterase inhibitor for bronchodilation.

Pulmonary fibrosis

Besides inflammatory lung diseases, Pulmonary Fibrosis (PF) is another type of disease, and this refers to the progressive scarring of lung tissue. The pathophysiological steps include the injury in the epithelial layer, abnormal healing of the wound, and proliferation and differentiation of fibroblasts [10]. The use of small molecules for treating the PF has been reviewed from various literature sources. Zhou., *et al*. [45] found Nintedanib, which worked as a Tyrosine Kinase Inhibitor and inhibits the growth factor receptors. The small molecule specifically inhibits the keloid fibroblast functions by blocking the phosphorylation. However, the study has focused on the treatment of various types of cancers and has gaps in showing the treatment for PF. The gap can be mitigated by the findings of Ma., *et al*. [21], where the mechanism of action of Nintedanib can be seen to treat PF. Another key small molecule used for the treatment of PF is Pirfenidone. The molecule is recognised as an anti-fibrotic as well as anti-inflammatory molecule, which inhibits the synthesis of collagen with the influence of TGF-β [33]. Findings from the clinical trials can enhance the benefits of using both of these molecules. Lamb [18] has discussed the results of IMPULSIS-1 and IMPULSIS-2 clinical trials of Nintedanib and stated that there is a 50% decline in the annual rate of Forced Vital Capacity (FVC) that delays the time of first exacerbation. In this study, randomised, double-blind, placebo-controlled trials have been done. Patients get the oral Nintedanib for 52 weeks, and the decline in FVC is seen after 52 weeks. On the other hand, Behr., *et al*. [3] did the post-hoc analysis of six clinical trial studies, and in the case of Ascend or Capacity trials, the annual average rate of FVC has also declined from the baseline with the use of Pirfenidone. The studies show the positive clinical trial results for Nintedanib and Pirfenidone increase their importance for the treatment of PF.

Lung cancer

Szalontai., *et al*. [36] found that COPD is a frequently fatal pathology for the respiratory tract of humans, and there is a connection between COPD and the development of lung cancer. Similar findings have been seen in the study of Uliński., *et al*. [39], and the authors have mentioned that COPD is one of the risk factors for the development of lung cancer, with the influence of tobacco smoking. For the treatment of lung cancer, some of the targeted therapies are Epidermal Growth Factor Receptor (EGFR) inhibition mechanisms, in which erlotinib, gefitinib, and Osimertinib use EGFR Inhibition [46]. Along with this, the Anaplastic lymphoma kinase (ALK) inhibitors are also used, which are alectinib and crizotinib, that treat the ALK-rearranged non-small cell lung cancer (NSCLC) [7]. From the findings of the study of other researchers, some other mechanisms of action have also been found, which are MET inhibitors like capmatinib, tepotinib, KRAS inhibitors like sotorasib, which target the KRAS G12C mutation and others [35]. The advancement is seen in the lung cancer treatment with this process, but several times, the issue with the emerging resistance to the mechanism has been found. In many cases, tumours are not responsive or initially respond, but after that, the progression is seen. Mansour., *et al*. [23] have mentioned some of the resistance mutations for EGFR inhibitors, such as T790M, MET amplification and C797S.

Infectious lung diseases

There are infectious lung diseases such as Pneumonia, tuberculosis (TB), Covid-19 COVID-19-related ARDS and for these diseases, the therapy with the small molecules is different. The causative agent for TB is Mycobacterium tuberculosis, and to treat this bacterium, the use of Rifampin, Bedaquiline, Ethambutol, and Isoniazid is done [38]. From this same study, some of the small molecule medicines have been found that are applied for the treatment of Pneumonia. The small molecule therapeutic medicines are Tetracyclines, Macrolides, Fluoroquinolones, and others. Additionally, for the COVID-related ARDS and pneumonia, some of the small molecule medicines are used, such as Molnupiravir, Remdesivir, Favipiravir and others [43]. A case example of the use of Remdesivir for the treatment of COVID-19-induced Pneumonia can be seen from the research of Marocco., *et al*. [24]. A comparative study has been done between two groups of patients, in which one group has been treated with Remdesivir. The result shows that the medicine has reduced the mortality by 21.7% and reduced the progression of pneumonia to ARDS.

Mechanisms of action of small molecules in lung therapeutics

Enzyme Inhibition

Enzyme inhibition is the most common mechanism of action of small molecules. In this process, small molecules bind to the active site or allosteric site of enzymes or create a covalent bond to block their catalytic activities. Li and Kang [19] also showed the enzyme inhibition process of small molecules with an example enzyme, flavivirus protease.

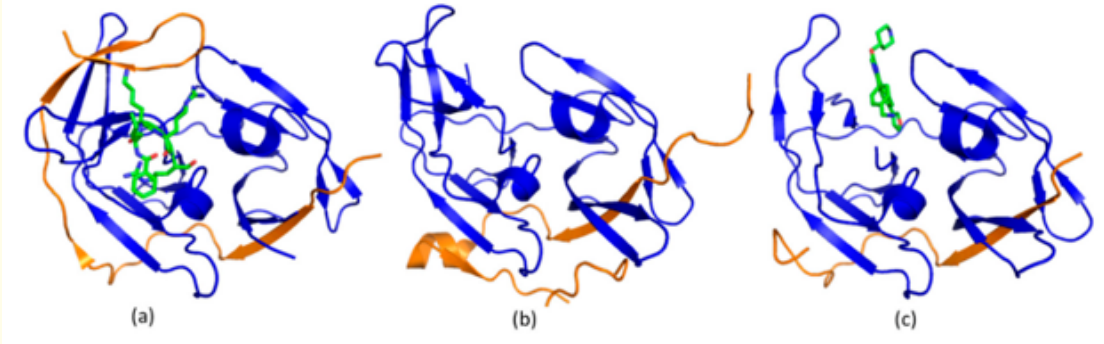

Figure 2: *Enzyme inhibition mechanism of small molecule drugs (Source: Li, Q. and Kang, C., (2020)).*

Figure 2a shows the structure of the actual flavivirus protease in the absence of any inhibitors. The NS2B and NS3 have been shown in orange and blue, respectively, and the green sticks are shown as the inhibitor for the enzyme. In this stage, the protease is in a closed conformation, and the peptide inhibitor is in the micromolar stage. After that, figure 2b shows the open conformation of the protease in which the C-terminal region of NS2B is away from the active site. Figure 2c shows an allosteric inhibitor for a protease. This is effective for stabilising the inactive conformation of the protease. However, the other types of small molecule inhibitors can bind with the active site of the enzymes, making them inactive. However, this study has gaps in discussing the enzyme inhibitors for lung disease. Whereas the review of the study of Bondarev., *et al*. [4] has mitigated the gap, and knowledge about the phosphodiesterase inhibitors has been gained, which facilitates the treatment of several conditions of the lungs, such as erectile dysfunction, COPD, and Pulmonary Arterial Hypertension (PAH). Roflumilast is one of the small-molecule medicines that work as phosphodiesterase inhibitors to treat lung diseases.

Receptor modulation

Receptor modulation is another mechanism of action of the small molecules that uses agonists, antagonists, and allosteric modulators. Agonists activate receptors by mimicking the process of a natural ligand. Tanwar., *et al*. [37] have studied the beta-2-agonist, which binds with the β2-adrenergic receptor for the treatment of both COPD and asthma. From figure 3, the mechanism of action of β2-Agonists can be seen, in which the β2-Agonists exert their effect after binding to the active site of β2-adrenergic receptors (2AR), which are located on airway smooth muscle (ASM). The mechanism of action involves a canonical signalling pathway through the activation of adenylyl cyclase (AC) and by generating intracellular cAMP. The pathway then activates the effector molecules of cAMP-dependent protein kinase A (PKA) as well as Epac, which is a Rap1 guanine nucleotide exchange factor. After that, a key regulator protein named PKA Phosphorylates, increasing the control of the ASM tone, and Epac increases the process of ASM relaxation. The authors have provided a drug example named Salbutamol, which works in the same pathway for treating lung diseases [37].

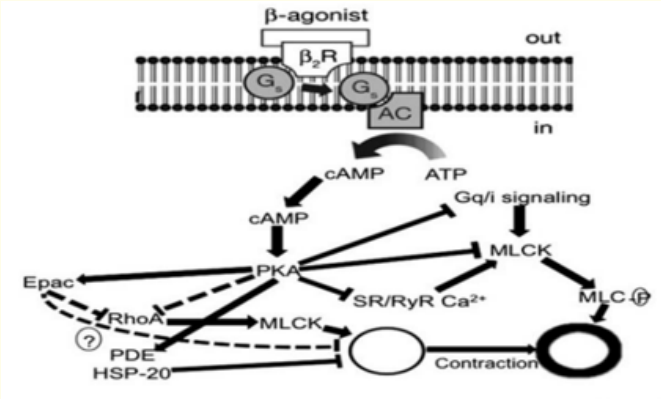

Figure 3: *Mechanism of action of a beta 2 antagonist with the receptor modulation process (Source: Tanwar, S., Dhingra, G., Goyal, S., Chaturvedi, V. and Tanwar, K., (2022)).*

Moreover, Tanwar., *et al*. [37] have researched the actions of antagonists, which also block the activation of the endogenous ligands. Some examples have been found, such as Muscarinic antagonists, Leukotriene antagonists, Beta-1 selective antagonists that include the bisoprolol, metoprolol and others, Carvedilol as a non-selective beta antagonist and many others. Even after the literature has the strengths in discussing different agonists and antagonists, the literature lacks discussion of other mechanisms.

Other mechanisms

Additionally, ion channel modulation and blockage are other mechanisms in which the small molecules bind to ion channels and affect their flow across the membranes [41]. Moreover, from the study of Nicklisch and Hamdoun [28], the transporter inhibition process can be seen. In this process, the small molecules block the transport proteins from moving across the membrane. Moreover, the small molecules use the gene expression regulation mechanism as well, with epigenetics and transcription factors [40].

Advantages and limitations

The advancement of the use of small molecules has been seen in the therapeutics for lung medicine, as this has several advantages. Mehrotra., *et al.* [25] suggested that the oral availability, higher cellular penetration, and rapid actions are the reasons. Rinderknecht., *et al.* [32] have indeed some other benefits, such as lower manufacturing cost, chemical stability, higher flexibility to design the drugs and the specific targeting process. However, the studies lack a discussion of the limitations of using small molecules in lung medicine for lung therapeutics. From the findings of Mansour., *et al.* [23], the issue of drug resistance has been found in lung cancer treatment with small-molecule medicines. Besides this, Li., *et al.* [20] have opposed the benefit mentioned by Rinderknecht., *et al.* [32], that even after the molecules use a specific target process, there are some toxicity and off-target effects. For example, EGFR inhibitors can develop skin rash, and the patients can face diarrhoea as well. Moreover, the off-target effects can be severe in conditions such as pregnancy, patients with kidney or liver dysfunctions or for children as well. Moreover, there are issues in delivering the small molecule medicine to the cells of the lungs as well [26]. However, even after having the limitations of using the small molecules in lung therapeutics, there are some recent advances which offer a positive future direction for using small molecules in lung medicines.

Recent advances and future directions

With the help of technical advancement and with a better understanding of the disease biology, lung therapeutics are evolving rapidly with the integration of small molecules. As per Qureshi., *et al.* [31], the acceleration in the design of small molecules is happening with the AI and drug discovery platforms. With this process, the resistance mutation of the NSCLC can be overcome by the healthcare industry by designing different EGFR inhibitors. This can help the healthcare sector to mitigate the limitations of using small molecules found in the study of Rinderknecht., *et al.* [32]. Additionally, the use of nanotechnology can be done to reduce the challenges of small-molecule delivery for lung diseases. Mitchell., *et al.* [26] have suggested from their finding that the use of nanocarriers like polymeric nanoparticles and liposomes can be used to deliver small-molecule drugs to the lung cells. There is another alternative for using the small molecules in the therapeutics of lung diseases, which is combination therapy. In this case, the combination of the small molecules and biologics is seen to treat lung diseases. Yamasaki., *et al.* [42] have given an example of using the PDE4 inhibitors, which are small-molecule medicines with anti-IL-5antibodies to treat severe asthma or COPD among patients. All these advances in using small molecules in lung therapeutics indicate a future direction for personalised and precision medicine approaches. Patel and Patel [29] discussed that in the future the integration of the digital health platforms can be seen with the help of wearable devices, AI, ML, and others which can enable the healthcare providers to monitor the effect of the small molecule medicine for the lung therapeutics and this can further help in personalisation of the treatment process as per the needs of the patients.

Conclusion

This can be summarised from the findings of different previous literature that lung diseases are divided into different categories, and for these different categories, different mechanisms of action of the small molecule medicines. Among several other mechanisms of action, enzyme inhibition and receptor modulation are the two common mechanisms. As there are some limitations still present for using the small molecules in the therapeutics of lung medicines, some of the alternative paths and future directions have also been observed. The advancements of AI and technologies, combination therapy process, and use of nanoparticles are increasing the clinical significance of the use of small molecules in lung therapeutics, as these are helpful for the reduction of the side effects and reducing the challenges of

the drug delivery to the lung cells. It has been seen that in the future, wearables can be used for monitoring the effect of small molecule medicines for lung disease, and personalised treatment approaches can be developed to increase the efficacy of the use of small molecules in lung medicine.

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