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Review Article

Pharmacological screening of natural products for lung diseases: A comprehensive review

Anubhav Dubey[1], Sanyogita Shahi[2]*, Rajesh Mishra[3], Sribatsa Lanchhana Dash[4], Kumara Swamy Samanthula[5]

[1]Dept. of Pharmacology, Maharana Pratap College of Pharmacy, Kothi, Mandhana, Kanpur, Uttar Pradesh, India
[2]Dept. of Science (Chemistry), Kalinga University, Raipur, Chhattisgarh, India
[3]Dept. of Pharmacology, Swami Vivekanand College of Pharmacy Bhopal, Madhya Pradesh, India
[4]Dept. of Pharmachemistry, Maharana Pratap College of Pharmacy, Kothi, Mandhana, Kanpur, Uttar Pradesh, India
[5]Dept. of Pharmaceutics, Faculty of Pharmaceutical Science, Assam down town University, Guwahati, Assam, India

Abstract

Respiratory diseases like asthma, Chronic Obstructive Pulmonary Disease (COPD), and lung cancer pose a significant global health burden, with existing treatments often limited by side effects, drug resistance, and high costs. This comprehensive review explores the potential of natural products as a rich and diverse source for novel therapeutic agents. It begins by outlining the pathophysiology and unmet medical needs for major lung diseases, followed by a discussion of the historical use of natural remedies in traditional medicine, which has provided a valuable starting point for modern drug discovery. The review details the methodologies of pharmacological screening, including collection, extraction, bioassay-guided fractionation, and the use of both in vitro and in vivo models. After analyze promising natural compounds like quercetin and curcumin for their anti-inflammatory and antioxidant activities in asthma and COPD, and highlighting the anti-proliferative effects of agents such as paclitaxel in lung cancer. The discussion critically addresses the challenges facing this field, including issues of standardization, poor bioavailability, and regulatory hurdles. Finally, the review proposes future directions, such as exploring synergistic combinations, leveraging computational methods, and developing advanced delivery systems to overcome these limitations. This paper underscores the importance of continued research into natural products to develop more effective and sustainable therapies for lung diseases.

Keywords: Natural products, Pharmacological screening, Lung diseases, Quercetin, Curcumin, Bioavailability, Paclitaxel

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1. Introduction

1.1. The global burden of respiratory diseases and the need for novel therapies

Respiratory diseases like chronic obstructive pulmonary disease (COPD), asthma, and lung cancer represent a significant and escalating global health crisis.[1] These conditions affect hundreds of millions of people worldwide, imposing a heavy burden on individuals and healthcare systems.[2,3] While current treatments-such as bronchodilators, corticosteroids, and chemotherapy-have improved patient outcomes,[4] they come with notable drawbacks, including side effects, drug resistance, and high costs.[5,6] This creates an urgent and unmet need for discovering and developing new therapeutic agents that are more effective, safer, and affordable.[7]

1.2. Natural products as a source of bioactive compounds

For millennia, natural products from plants, microbes, and marine organisms have served as the foundation of traditional medicine and have been a primary source for drug discovery.[8] Many modern blockbuster drugs either have a natural origin or were inspired by the complex structures of natural compounds. The immense chemical diversity[9] and structural complexity of natural products allow them to interact with a wide range of biological targets with high specificity.[10] The vast, unexplored biodiversity on Earth offers a virtually limitless library of potential drug candidates, providing a

*Corresponding author: Sanyogita Shahi
Email: drsanyogitashahi@gmail.com

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promising avenue to find novel compounds with unique mechanisms of action that can overcome the limitations of conventional synthetic drugs.[11,12]

1.3. Rationale for pharmacological screening of natural products for lung diseases

The intricate pathophysiology of respiratory diseases involves a complex interplay of inflammation, oxidative stress, and immune dysregulation. This complexity often requires a multi-targeted therapeutic approach.[13,14] Natural products are uniquely suited for this purpose due to their pleiotropic effects, meaning a single compound can modulate multiple biological pathways simultaneously.[15] Pharmacological screening provides a systematic, evidence-based method to identify compounds with anti-inflammatory, antioxidant, bronchodilatory, and anti-proliferative properties.[16] This approach is especially valuable for lung diseases, where targeting multiple interconnected pathways—rather than a single target—may lead to more effective and holistic therapeutic outcomes.[17] By leveraging sophisticated in vitro and in vivo models, researchers can efficiently test a large number of natural compounds to identify those with the highest therapeutic potential.[18,19]

1.4. Scope of the review

This review provides a comprehensive analysis of the current landscape of pharmacological screening of natural products for lung diseases. The methodologies used for screening and isolating bioactive compounds and summarize key natural products that have shown promise for asthma, COPD, and lung cancer. The mechanisms of action for these compounds address the significant challenges facing this field, including standardization, bioavailability, and regulatory hurdles. Finally, we will propose future directions for research to overcome these limitations and advance natural product-based drug discovery.

2. Literature Review

*2.1. Overview of major lung diseases (**Table 1**)*

Respiratory diseases are a diverse group of conditions characterized by impaired lung function, often driven by chronic inflammation and tissue damage.[19] A comprehensive understanding of their pathophysiology is crucial for developing targeted therapies.

2.1.1. Asthma

Asthma is a chronic inflammatory disease of the airways, characterized by reversible airway obstruction, bronchospasm, and hyperresponsiveness.[20] The pathophysiology involves the activation of T-helper 2 (Th2) cells, leading to the release of inflammatory cytokines such as interleukin (IL)-4, IL-5, and IL-13, which promote eosinophilic inflammation and IgE production.[21] Current treatments primarily rely on long-term control medications like inhaled corticosteroids (e.g., fluticasone) and leukotriene modifiers (e.g., montelukast), as well as quick-relief bronchodilators such as short-acting beta-agonists (e.g., albuterol).[22] Despite these options, many patients, particularly those with severe asthma, remain symptomatic, highlighting a significant unmet need for more effective and personalized therapies that can target the underlying inflammatory pathways without the long-term side effects of corticosteroids.[23]

2.1.2. Chronic obstructive pulmonary disease (COPD)

COPD is a progressive disease characterized by persistent respiratory symptoms and airflow limitation, typically caused by exposure to noxious particles or gases, most commonly cigarette smoke.[23] The disease's pathophysiology involves a chronic inflammatory response in the airways and lung parenchyma, driven by macrophages, neutrophils, and T-lymphocytes, leading to oxidative stress and protease-mediated destruction of lung tissue (emphysema).[25] Current treatments include bronchodilators (e.g., tiotropium) and inhaled corticosteroids, but these therapies primarily manage symptoms and do not halt disease progression.[26] The complex, multi-faceted nature of COPD, including associated systemic inflammation and comorbidities like pulmonary hypertension, underscores the urgent need for new therapies that can modify the disease course.[27]

2.1.3. Lung cancer

Lung cancer remains a leading cause of cancer-related deaths worldwide.[28] Its development is closely linked to inflammation and oxidative stress, with cigarette smoke being the primary risk factor. The disease is characterized by uncontrolled cell proliferation, metastasis, and resistance to apoptosis.[29] While significant advancements have been made with targeted therapies and immunotherapy, many patients still face poor prognosis due to resistance mechanisms and the heterogeneity of tumours.[30] Novel agents with anti-proliferative, pro-apoptotic, and anti-metastatic properties are continuously sought to improve treatment outcomes.

Table 1: Overview of natural products for major lung diseases

Disease	Pathophysiology	Current Treatments	Promising Natural Product Compounds	Mechanisms of Action
Asthma	Chronic airway inflammation; reversible obstruction; T-helper 2	Inhaled corticosteroids (e.g., fluticasone),	**Ephedrine** from *Ephedra sinica*, **quercetin** from	**Ephedrine:** Bronchodilator and decongestant. **Quercetin:** Inhibits

	(Th2) cell activation; release of inflammatory cytokines (IL-4, IL-5, IL-13); eosinophilic inflammation; IgE production.	leukotriene modifiers (e.g., montelukast), short-acting beta-agonists (e.g., albuterol).	fruits/vegetables, **curcumin** from turmeric.	histamine release, suppresses inflammatory pathways. **Curcumin:** Downregulates NF-κB, inhibits smooth muscle proliferation and cytokine production.
Chronic Obstructive Pulmonary Disease (COPD)	Progressive airflow limitation; chronic inflammatory response from noxious particles (e.g., cigarette smoke); oxidative stress; protease-mediated tissue destruction (emphysema).	Bronchodilators (e.g., tiotropium), inhaled corticosteroids.	**Curcumin** from turmeric, **resveratrol** from grapes, **sulforaphane** from broccoli.	**Curcumin:** Antioxidant and anti-inflammatory effects by modulating NF-κB. **Resveratrol:** Activates SIRT1 to combat oxidative stress. **Sulforaphane:** Upregulates Nrf2 signaling pathway to enhance antioxidant and anti-inflammatory gene expression.
Lung Cancer	Uncontrolled cell proliferation, metastasis, and resistance to apoptosis, often linked to inflammation and oxidative stress from risk factors like cigarette smoke.	Targeted therapies, immunotherapy.	**Paclitaxel** from Pacific yew tree, **curcumin** from turmeric, **quercetin** from fruits/vegetables.	**Paclitaxel:** Anti-mitotic agent that stabilizes microtubules, preventing cell division. **Curcumin:** Anti-proliferative and pro-apoptotic effects by modulating pathways like NF-κB, STAT3, and Akt. **Quercetin:** Induces cell cycle arrest and apoptosis.

Table 2: Natural product sources and compound classes

Source	Compound Class	Description	Examples
Plants	**Alkaloids**	Nitrogen-containing compounds with significant pharmacological activity.	**Ephedrine** (*Ephedra sinica*), **berberine**.
	Flavonoids	Polyphenolic compounds are known for their strong antioxidant and anti-inflammatory effects.	**Quercetin**.
	Terpenoids	Diverse class of compounds found in essential oils and resins.	**Curcumin**.
Marine Organisms		A largely untapped source of chemical diversity, producing unique compounds for competitive environments.	Marine alkaloids and polyketides with cytotoxic activity.
Microorganisms		A prolific source of natural products, including fungi and bacteria.	**Penicillin** and **cyclosporin** from fungi.

2.2. The historical and cultural context of natural products in respiratory medicine

The use of natural remedies for respiratory ailments is deeply rooted in the history of human civilization. Traditional systems of medicine, such as Traditional Chinese Medicine (TCM) and Ayurveda, have long utilized specific herbs and plant formulations to treat conditions ranging from coughs and bronchitis to more severe lung ailments.[31] In Ayurveda, plants like Tulsi (*Ocimum sanctum*), turmeric (*Curcuma longa*), and Pippali (*Piper longum*) are traditionally used for their anti-inflammatory and immune-modulating properties to support respiratory health.[32] Similarly, TCM has an extensive pharmacopoeia of herbs, including *Ginkgo biloba* and *Ephedra sinica*, used for centuries to manage asthma and other lung conditions.[33]

This historical precedent has not only provided a rich source of traditional knowledge but has also directly influenced modern drug discovery. The extraction of salicylic acid from willow bark, which led to the development of aspirin, is a classic example.[34] Another notable case is artemisinin, a powerful antimalarial drug derived from the sweet wormwood plant (*Artemisia annua*), which won a Nobel Prize for its discovery.[35] These examples underscore the validity of natural products as a source for potent

therapeutic agents and establish a strong precedent for their continued exploration in the context of respiratory medicine.

*2.3. Key natural product sources for drug discovery (**Table 2**)*

The vast biodiversity of the planet offers a diverse array of natural product sources, each with unique chemical libraries waiting to be explored for their therapeutic potential.

2.3.1. Plants

Plants are the most extensively studied source of natural products due to their long history of medicinal use. They produce a wide variety of secondary metabolites, which are the basis for their therapeutic properties. These compounds are typically classified into major groups:

1. Alkaloids: Nitrogen-containing compounds with significant pharmacological activity. Examples include ephedrine from *Ephedra sinica*, which acts as a bronchodilator and decongestant, and berberine, an alkaloid with potent anti-inflammatory properties.[36,37]
2. Flavonoids: A large group of polyphenolic compounds known for their strong antioxidant and anti-inflammatory effects. Quercetin, found in many fruits and vegetables, has been shown to inhibit histamine release and suppress inflammatory pathways, making it a promising candidate for asthma and allergic lung diseases.[38]
3. Terpenoids: A diverse class of compounds, including mono- and diterpenes, found in essential oils and resins. Curcumin, the active compound in turmeric, is a well-studied terpenoid with a wide range of anti-inflammatory and antioxidant activities that show promise for treating both COPD and lung cancer by modulating key signaling pathways like NF-κB.[39]

2.3.2. Marine organisms

The oceans are a largely untapped reservoir of chemical diversity, with marine organisms producing unique compounds to adapt to their competitive and often extreme environments.[40] Sponges, tunicates, and marine microorganisms have yielded novel compounds with promising anti-inflammatory and anti-cancer properties. For instance, some marine alkaloids and polyketides have shown potent cytotoxic activity against lung cancer cell lines, presenting new scaffolds for drug development.[41]

2.3.3. Microorganisms

Microbes, including fungi and bacteria, are a prolific source of natural products. Many of the antibiotics and immunosuppressants currently in clinical use, such as penicillin and cyclosporin, were originally discovered from fungi.[42] These organisms produce a wide range of secondary metabolites to compete with other microbes, many of which have powerful biological activities. The screening of soil and marine microorganisms has led to the discovery of compounds with novel antibacterial and anti-inflammatory properties, which could be particularly relevant for treating pneumonia and cystic fibrosis-associated infections.[43]

2.4. Ethnobotanical studies as a starting point

Ethnobotany, the study of the relationship between people and plants, provides a crucial and logical starting point for modern pharmacological screening.[44] Traditional healers and indigenous communities possess a wealth of knowledge passed down through generations regarding the medicinal uses of local flora. This traditional knowledge can significantly expedite the drug discovery process by directing researchers to plants that are already known to have specific therapeutic effects.[45] For example, the knowledge that Native Americans used the bark of the Pacific yew tree led to the isolation of paclitaxel, a highly effective anti-cancer drug.[46] By systematically documenting and scientifically validating these traditional uses, ethnobotanical studies can provide a focused and efficient pathway for identifying promising candidates, thereby reducing the time and resources required for the random screening of numerous plant species.[47] Some of the historical use of plants in traditional medicine are

2.4.1. Curcumin (from Turmeric)

Clinical trials have explored the use of curcumin for various inflammatory lung diseases. Studies have shown its potential to reduce inflammation and improve lung function in patients with asthma and chronic obstructive pulmonary disease (COPD) due to its anti-inflammatory and antioxidant properties.[48]

2.4.2. Baicalin (from Scutellaria baicalensis)

This flavonoid has been studied in clinical trials for its effects on COPD. Research has indicated that baicalin can improve lung function and reduce the levels of pro-inflammatory cytokines, which are key markers of inflammation in the disease.[49]

2.4.3. Hedera helix (Ivy Leaf Extract)

Used traditionally as an expectorant, ivy leaf extract has been shown in clinical trials to improve respiratory symptoms and lung function in patients with bronchitis and asthma. It is often found in over-the-counter cough syrups and is one of the most well-documented herbal remedies in clinical use for respiratory ailments.[50,51]

2.4.4. Nigella sativa (Black Seed)

Traditional use of black seed for respiratory issues has led to modern clinical investigations. Studies on asthmatic patients have shown that extracts from this plant can have a bronchodilatory effect, helping to relax the airways and improve breathing.[52,53]

3. Methodology

3.1. Collection, identification, and extraction of natural products

The initial and a foundational step in the pharmacological screening of natural products is the systematic collection and preparation of samples.[54] Plant materials, marine organisms, or microbial strains are collected from their native habitats or established repositories. Meticulous care is taken to ensure proper taxonomic identification by a qualified botanist, marine biologist, or microbiologist to avoid misidentification and to ensure reproducibility of results.[55] Samples are then prepared for extraction, which typically involves drying, grinding, and maceration.[56]

The extraction process aims to isolate a wide range of compounds from the raw material. This is commonly achieved through solvent extraction, utilizing solvents of varying polarities to isolate different classes of compounds.[57] For instance, non-polar solvents like hexane or chloroform are used to extract lipids and terpenoids, while more polar solvents like ethanol, methanol, or water are used to obtain alkaloids, flavonoids, and other polyphenols.[58] Modern techniques, such as solid-phase extraction (SPE) and supercritical fluid extraction, are also employed to enhance the efficiency and selectivity of the extraction process, yielding more concentrated and purer crude extracts for initial screening.[59]

3.2. Bioassay-guided fractionation and isolation

Following the initial extraction, the complex mixture of compounds in the crude extract is screened for its desired biological activity. This is where bioassay-guided fractionation becomes a crucial and iterative process.[60] If an extract shows promising activity in a preliminary screen, it is then subjected to a series of fractionation steps using chromatographic techniques, such as column chromatography, thin-layer chromatography (TLC), and high-performance liquid chromatography (HPLC).[61] Each fraction is re-tested in the same bioassay. The fraction that retains the activity is further purified, and this cycle of purification and biological testing continues until a single, pure, active compound is isolated.[62] Once isolated, the chemical structure of the compound is elucidated using spectroscopic methods, including Nuclear Magnetic Resonance (NMR) and Mass Spectrometry (MS).[63]

3.3. In vitro screening models for lung diseases (**Table 3**)

The development of various *in vitro* models has been instrumental in rapidly and cost-effectively screening natural products for their potential therapeutic effects on lung diseases.[64]

3.3.1. Anti-inflammatory assays

To identify compounds with anti-inflammatory properties, cell-based assays are commonly used. Assays measuring the release of pro-inflammatory cytokines are critical. Macrophage or epithelial cell lines (e.g., A549 cells) are stimulated with pro-inflammatory agents like lipopolysaccharide (LPS) or tumor necrosis factor-alpha (TNF-α) to mimic an inflammatory state.[65] The test compounds are then added, and the levels of inflammatory markers, such as IL-6, TNF-α, and IL-1β, are quantified using techniques like enzyme-linked immunosorbent assay (ELISA).[66]

3.3.2. Antioxidant assays

Oxidative stress is a key driver of lung diseases like COPD and pulmonary fibrosis. Antioxidant activity can be evaluated through both chemical and cellular assays. The 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging assay is a common chemical method to assess a compound's ability to neutralize free radicals.[67] In cell-based models, lung cells are exposed to oxidative stress inducers (e.g., hydrogen peroxide), and the production of reactive oxygen species (ROS) is measured using fluorescent probes like DCF-DA (2',7'-dichlorofluorescin diacetate).[68]

3.3.3. Bronchodilatory assays

For asthma, bronchodilation is a critical therapeutic target. The potential of a compound to relax airway smooth muscle is often evaluated using isolated tracheal smooth muscle rings from animal models.[69] The rings are pre-contracted with a constricting agent (e.g., carbachol or histamine), and the test compound is added. The subsequent relaxation of the muscle tissue is measured isometrically, providing a direct assessment of its bronchodilatory activity.[70]

3.3.4. Anti-cancer assays

The anti-cancer potential of natural products is screened using various lung cancer cell lines. The MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay is a widely used colorimetric method to measure cell viability and proliferation.[71] Other assays, such as those measuring apoptosis (e.g., flow cytometry with annexin V staining), can determine if a compound induces programmed cell death, a key mechanism for a successful anti-cancer drug.[72]

3.4. In Vivo models for efficacy confirmation

Once a natural compound demonstrates promising activity *in vitro*, its efficacy is further validated in relevant animal models that mimic human lung diseases.[73] These *in vivo* studies are essential for assessing the compound's safety, pharmacokinetics, and therapeutic effects in a complex biological system.

3.4.1. Asthma models

Ovalbumin (OVA)-induced allergic asthma in mice is a well-established model. Mice are sensitized and challenged with OVA to induce airway inflammation, hyperresponsiveness, and eosinophilia, and the effect of the test compound is evaluated by measuring parameters like inflammatory cell

counts in bronchoalveolar lavage fluid (BALF) and lung function.[74]

3.4.2. COPD models

Chronic exposure to cigarette smoke in mice or rats is used to induce emphysema, airway inflammation, and irreversible airflow limitation, mimicking human COPD.[75] The effects of a test compound on lung tissue damage, inflammatory markers, and lung function are then assessed.

3.5. High-throughput screening (HTS)

High-Throughput Screening (HTS) has revolutionized natural product drug discovery by enabling the rapid evaluation of vast libraries of compounds.[76] HTS utilizes automation, robotics, and miniaturized assays (e.g., in 96- or 384-well plates) to screen thousands of extracts or pure compounds in a short period.[77] This technology significantly accelerates the initial discovery phase, allowing researchers to quickly identify "hits" that can then be subjected to more detailed bioassay-guided fractionation and *in vivo* studies. Modern HTS platforms are capable of simultaneously measuring multiple parameters, such as cytotoxicity, anti-inflammatory effects, and specific enzyme inhibition, providing a comprehensive profile of a compound's activity.[78]

Table 3: Pharmacological screening methods for lung diseases

Screening Category	Disease Focus	Assay/Model	Description & Key Metrics
In Vitro Assays	Anti-inflammatory	Cell-based cytokine assays	Macrophage or epithelial cell lines (e.g., A549) are stimulated with agents like LPS or TNF-α. Test compounds are added, and levels of inflammatory markers (IL-6, TNF-α, IL-1β) are measured using ELISA.
In Vivo Models	Antioxidant	DPPH radical scavenging assay & cell-based ROS assays	**Chemical assay:** DPPH assay measures a compound's ability to neutralize free radicals. **Cellular assay:** Lung cells are exposed to oxidative stress (e.g., hydrogen peroxide), and the production of reactive oxygen species (ROS) is measured using fluorescent probes like DCF-DA.
	Bronchodilatory	Isolated tracheal smooth muscle rings	Tracheal rings from animal models are pre-contracted with a constricting agent (e.g., carbachol or histamine). The test compound is then added, and its ability to relax the muscle tissue is measured.
	Anti-cancer	MTT assay & apoptosis assays	**MTT assay:** Measures cell viability and proliferation in lung cancer cell lines. **Apoptosis assays:** Techniques like flow cytometry with Annexin V staining are used to determine if a compound induces programmed cell death.
	Asthma	Ovalbumin (OVA)-induced allergic asthma in mice	Mice are sensitized and challenged with OVA to induce airway inflammation and hyperresponsiveness. The effects of the test compound are assessed by measuring inflammatory cell counts in bronchoalveolar lavage fluid (BALF) and lung function.
	COPD	Chronic cigarette smoke exposure in rodents	Mice or rats are exposed to cigarette smoke to induce emphysema and airway inflammation. The effects of a test compound are evaluated by assessing lung tissue damage, inflammatory markers, and lung function.
High-Throughput Screening (HTS)	All diseases	Automated, miniaturized assays	Uses robotics and miniaturized plates (e.g., 96- or 384-well) to rapidly screen thousands of compounds. Measures multiple parameters simultaneously, such as cytotoxicity, anti-inflammatory effects, and enzyme inhibition, to quickly identify "hits."

4. Results and Discussion

The pharmacological screening of natural products has yielded a wealth of promising compounds with therapeutic potential for a range of lung diseases. These discoveries highlight the ability of natural compounds to modulate complex pathological pathways.

*4.1. Promising natural products for asthma (**Figure 1** & **2**)*

Asthma, a disease driven by chronic airway inflammation and hyperresponsiveness, has been a significant focus of natural product research. Several compounds have shown potential to address the underlying inflammatory cascades.

4.1.1. Quercetin

A flavonoid found in various plants, has demonstrated potent anti-inflammatory and anti-allergic properties.[79,80] Studies have shown that quercetin can inhibit the release of pro-inflammatory cytokines, such as TNF-α and IL-6, and suppress the activity of NF-κB, a key transcription factor involved in the inflammatory response.[81] Quercetin has been found to stabilize mast cells, thereby preventing the release of histamine and other mediators that trigger bronchoconstriction.[82] In animal models of asthma, quercetin treatment has been shown to reduce eosinophil infiltration and airway hyperresponsiveness, providing a strong rationale for its therapeutic use.[83]

4.1.2. Curcumin

The active component of turmeric has emerged as a multi-targeted compound for asthma. Its anti-inflammatory effects are attributed to its ability to downregulate NF-κB, a central player in the Th2-mediated immune response that characterizes asthma.[84] Curcumin has also been shown to inhibit smooth muscle proliferation and cytokine production, suggesting it could address both inflammation and airway remodeling in asthmatic patients.[85]

4.1.3. Promising natural products for COPD

COPD is characterized by chronic inflammation and oxidative stress, which lead to irreversible lung damage. Natural products with strong antioxidant and anti-inflammatory activities are therefore of particular interest.

4.1.4. Resveratrol

A polyphenol found in grapes and other plants, has been extensively studied for its antioxidant and anti-inflammatory properties. Resveratrol can activate sirtuin 1 (SIRT1), a protein that plays a crucial role in cellular defense against oxidative stress, and has been shown to reduce inflammatory cytokine production in COPD models.[86] Its ability to protect against cigarette smoke-induced oxidative damage makes it a strong candidate for a disease where this is a primary driver.[87]

4.1.5. Sulforaphane

An isothiocyanate found in cruciferous vegetables like broccoli, has been shown to upregulate the Nrf2 signaling pathway, a master regulator of antioxidant and anti-inflammatory gene expression.[88] By activating Nrf2, sulforaphane enhances the production of protective enzymes and reduces oxidative damage in lung cells, offering a promising strategy to mitigate the effects of cigarette smoke and other environmental pollutants in COPD patients.[89]

4.2. Promising natural products for lung cancer

The search for new anti-cancer agents from natural sources has a long and successful history, with several natural product-derived drugs already in clinical use.

4.2.1. Paclitaxel

Isolated from the bark of the Pacific yew tree (*Taxus brevifolia*), is a prime example of a successful natural product drug.[90] It is a potent anti-mitotic agent that stabilizes microtubules, thereby preventing cell division and leading to apoptosis in rapidly dividing cancer cells.[91] Paclitaxel is a cornerstone of chemotherapy for various cancers, including non-small cell lung cancer (NSCLC).

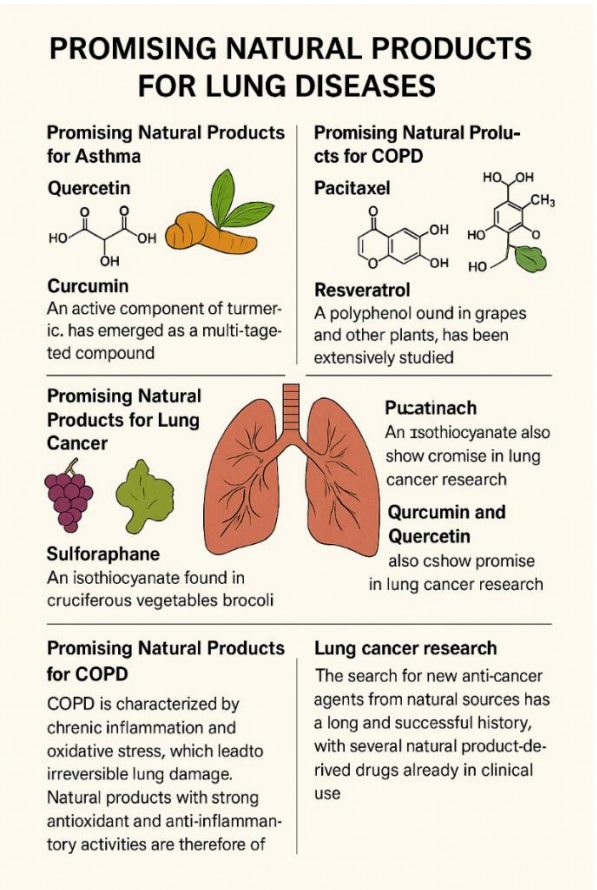

Figure 1: Promising natural products for lung disease

4.2.2. Curcumin and quercetin

These compounds also show promise in lung cancer research. Curcumin has demonstrated anti-proliferative and pro-apoptotic effects in lung cancer cell lines by modulating a variety of signaling pathways, including NF-κB, STAT3, and Akt.[92] Quercetin has been shown to induce cell cycle arrest and apoptosis, and it may also sensitize cancer cells to conventional chemotherapy drugs, suggesting its potential as an adjunct therapy.[93]

4.3. Challenges and limitations in natural product drug discovery

Despite the promising findings, the path from a natural product "hit" to a clinically approved drug is fraught with challenges. A critical analysis of these limitations is essential for guiding future research.

4.3.1. Standardization and variability

A major obstacle in the development of natural products as pharmaceuticals is their inherent variability. The concentration and profile of bioactive compounds can fluctuate significantly depending on the plant's species, geographical location, season of harvest, and extraction methods.[94] This lack of standardization makes it difficult to ensure consistent efficacy and safety, which is a fundamental requirement for regulatory approval.[95] To address this challenge, recent advancements in quality control systems and analytical techniques are crucial. These innovations go beyond traditional methods like High-Performance Liquid Chromatography (HPLC-MS) to provide a more comprehensive "fingerprint" of the natural product.[96]

1. Genomic and Proteomic Analysis: Techniques such as DNA barcoding are now used to authenticate the plant species, preventing misidentification or adulteration. This ensures that the raw material is the correct one, which is the first step in quality control.[97]
2. Metabolomics: This cutting-edge approach analyzes the entire set of metabolites within a natural product extract. By creating a metabolic profile, researchers can identify subtle variations in chemical composition that might affect the product's therapeutic effect. This provides a detailed "snapshot" of the compound mixture, ensuring batch-to-batch consistency.[98]
3. Chemometrics**:** Statistical tools are applied to the data from these advanced analytical techniques to build models that predict quality and efficacy, allowing for a more robust and objective quality control process.[99,100]
2. By integrating these innovative technologies, the natural products industry can move towards a more scientific and evidence-based approach, strengthening the case for regulatory approval and bridging the gap between traditional medicine and modern pharmacology.

4.3.2. Poor bioavailability

Many potent natural compounds exhibit poor bioavailability, meaning they are poorly absorbed, rapidly metabolized, or quickly eliminated from the body.[101] This limits their therapeutic efficacy and often necessitates high doses, which can increase the risk of toxicity. For example, curcumin and quercetin, despite their strong *in vitro* activity, suffers from poor systemic absorption. Research efforts are now focused on developing novel drug delivery systems, such as nanoparticles, liposomes, and microemulsions, to enhance the solubility and bioavailability of these compounds.[102,103]

4.3.3. Potential for toxicity

While often perceived as safe due to their natural origin, many plant-derived compounds can be toxic at high concentrations or through long-term use. For instance, some alkaloids can have neurotoxic or cardiotoxic effects.[104,105] Rigorous toxicological screening, including both *in vitro* and *in vivo* studies, is therefore mandatory to determine the therapeutic window of a compound and to ensure its safety before it can be considered for clinical trials.[106]

4.3.4. Regulatory hurdles and intellectual property

The complex and often undefined nature of natural products poses significant challenges for regulatory bodies like the FDA.[107,108] The lack of a single, well-defined active ingredient in a crude extract makes it difficult to prove efficacy and safety according to current pharmaceutical standards. Furthermore, protecting intellectual property is challenging, as the source material is often not a novel invention.[109] This can deter pharmaceutical companies from investing the substantial resources required for drug development, leaving this field of research often relegated to academic institutions and smaller biotech firms,[110] which further emphasizes the high cost and resource requirements that larger companies are unwilling to undertake. Novel approaches to patenting, such as defining specific extraction processes or unique formulations, are being explored to overcome this barrier.[111]

4.3.5. Clinical application and data

Preclinical studies provide a strong scientific foundation, the true test of a compound's therapeutic potential lies in human clinical trials. A critical gap in the literature is the scarcity of robust clinical data for many promising natural products.

1. Quercetin: Despite extensive preclinical evidence for its anti-inflammatory effects in asthma models, human studies on quercetin as a monotherapy for asthma are still very limited.[112] The focus remains largely on laboratory and animal studies, highlighting the need for more clinical investigation to confirm its efficacy and safety in human patients.
2. Resveratrol: The translation of promising antioxidant effects of resveratrol into clinical benefits for COPD has faced challenges. A randomized controlled trial on

COPD patients found no significant improvement in muscle mitochondrial function and, in fact, reported an unexpected decline in lean mass, demonstrating the complexity of its effects in human physiology.[113]

3. Sulforaphane: Clinical trials have begun to explore the potential of sulforaphane in respiratory health. A completed randomized, placebo-controlled trial investigated whether ingesting a broccoli sprout extract rich in sulforaphane could enhance the Nrf2 pathway in the lungs of COPD patients, providing a critical "proof-of-principle" for future larger-scale efficacy studies.[114]
4. Paclitaxel: In contrast to the other compounds, paclitaxel has a well-established and successful history in the clinic. Its efficacy in treating lung cancer has been confirmed in numerous large-scale clinical trials. For instance, a phase II study has explored its combination with immunotherapy in non-small cell lung cancer, confirming its role as a cornerstone of chemotherapy in various combination therapies.[115] The success of paclitaxel in clinical settings serves as a powerful example of what is possible when a natural product navigates the entire drug development pipeline.

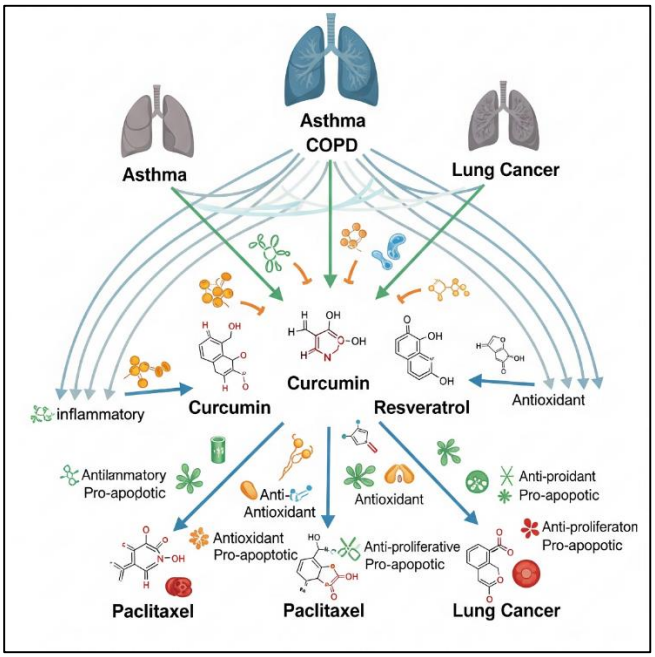

Figure 2: Chemical constituents for the treatment of lung diseases

5. Conclusion

The pharmacological screening of natural products presents a compelling and essential strategy for addressing the global health burden of respiratory diseases. As this review has demonstrated, a diverse array of compounds derived from plants, marine organisms, and microorganisms has shown significant therapeutic potential against diseases such as asthma, COPD, and lung cancer. From flavonoids like quercetin, which modulate inflammatory pathways in asthma, to the antioxidant-rich compounds like resveratrol and sulforaphane that combat oxidative stress in COPD, the evidence strongly supports the value of natural products as a source of novel drug leads. The success of drugs like paclitaxel underscores the fact that nature's chemical diversity can provide unique solutions to complex medical challenges that current synthetic drugs may not be able to overcome.

5.1. Future directions

To fully realize the therapeutic potential of natural products, several critical research avenues must be pursued.

5.1.1. Synergistic combinations of compounds

A key future direction involves moving beyond single-compound therapies. Many natural products, particularly in traditional medicine, are used in complex mixtures. Future research should focus on understanding the synergistic effects of multiple compounds found in a single plant extract. Utilising advanced statistical and pharmacological models, researchers can identify optimal combinations that enhance efficacy while reducing side effects at lower individual doses, thereby mimicking the holistic approach of traditional remedies.

5.1.2. Utilizing modern computational methods

The drug discovery process can be significantly accelerated by integrating modern computational methods. Techniques such as molecular docking, quantitative structure-activity relationship (QSAR) analysis, and machine learning can be used to predict the biological activity of compounds, identify potential targets, and filter vast chemical libraries of natural products more efficiently. This *in silico* approach can provide a focused and rational starting point for laboratory-based screening, reducing the time and resources required for random experimentation.

5.1.3. Developing advanced delivery systems

A major limitation of many natural compounds is their poor bioavailability. Future research should prioritise the development of advanced delivery systems specifically designed for pulmonary administration. Nanotechnology offers a promising solution, with the development of nanoparticles, liposomes, and microemulsions that can encapsulate bioactive compounds. These systems can enhance solubility, protect the compound from degradation, and ensure its targeted delivery to the lungs, thereby maximizing therapeutic efficacy while minimizing systemic side effects.

5.1.4. Conducting more clinical trials

Despite a wealth of *in vitro* and *in vivo* data, there remains a significant gap in the number of rigorous clinical trials for natural product-based therapies. A concerted effort is needed to transition promising candidates from the laboratory to human studies, with a focus on well-designed, placebo-controlled trials to validate their safety and efficacy. This will

build the robust body of evidence necessary for regulatory approval and widespread clinical use.

The exploration of natural products for lung diseases is not merely an academic exercise but a critical endeavour in the global fight against respiratory illnesses. By embracing the rich history of traditional medicine, leveraging advanced scientific methodologies, and addressing the persistent challenges of standardization and bioavailability, we can unlock the full potential of nature's pharmacy. Continued, innovative research in this field is essential to discover and develop the next generation of effective and sustainable therapies that will ultimately improve the lives of millions of people affected by lung diseases worldwide.

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None.

7. Conflict of Interest

None.

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