VOLUME 10 ISSUE 2 2024

ISSN 2454 – 3055

INTERNATIONAL JOURNAL OF ZOOLOGICAL INVESTIGATIONS

Forum for Biological and Environmental Sciences

Published by Saran Publications, India

International Journal of Zoological Investigations Vol. 10, No. 2, 1405-1416 (2024)

International Journal of Zoological Investigations
Contents available at Journals Home Page: www.ijzi.net
Editor-in-Chief: Prof. Ajai Kumar Srivastav
Published by: Saran Publications, Gorakhpur, India

ISSN: 2454-3055

A Comprehensive Review on *In Vitro* Models and Drugs Used for Lung Detoxification

Vasantha G.*, Alekya K., Soni Priya P., Vardhan B.J.Ch.S., Srujana Sri K. and Sowjanya B.N.

Department of Pharmacology, Vignan Institute of Pharmaceutical Technology, Duvvada, Visakhapatnam 530049, Andhra Pradesh, India

**Corresponding Author*

Received: 25th June, 2024; **Accepted:** 22nd November, 2024; **Published online:** 30th December, 2024

https://doi.org/10.33745/ijzi.2024.v10i02.141

Abstract: Lung detoxification, also referred to as Respiratory detoxification was developed based on traditional herbal medicine and the traditional herbal medicine's theoretical comprehension of the qualities of herbs. Lung detoxification has been demonstrated to have therapeutic effects for lung disease prevention and control. It is yet unknown, nevertheless, what the biochemically active ingredients in the polyherbal formulation for lung detoxification actually do and how they work. The current work aims to elucidate the molecular basis and mode of action of a polyherbal mixture used as a lung detoxifier.

Lungs, being vital organs constantly exposed to environmental toxins and pollutants, necessitate effective detoxification mechanisms for maintaining respiratory health. It encompasses the innate defense mechanisms, such as mucociliary clearance, antioxidant systems, and phase I and phase II metabolic pathways, elucidating their roles in neutralizing and eliminating airborne pollutants, particulate matter, and chemical agents. Insights into emerging research, therapeutic interventions, and challenges in enhancing lung detoxification mechanisms are also explored. Understanding and augmenting lung detoxification mechanisms holds promise in mitigating respiratory diseases and improving overall pulmonary health.

In recent years, the utilization of polyherbal formulations has gained attention for their potential in promoting lung detoxification and respiratory health. This review amalgamates current research insights into the multifaceted activity of polyherbal blends in supporting lung detoxification mechanisms. Polyherbal formulations composed of a synergistic combination of medicinal herbs, exhibit diverse bioactive compounds with antioxidative, anti-inflammatory, expectorant, and mucolytic properties. These compounds act synergistically to combat oxidative stress, neutralize free radicals, enhance mucociliary clearance, and alleviate airway inflammation, thus aiding in the expulsion of environmental pollutants and toxins. The review outlines select polyherbal formulations, elucidating their constituent herbs, active components, and documented effects on lung detoxification. Furthermore, it discusses the mechanisms underlying the synergistic actions of these herbal blends in fortifying the lungs' innate defense mechanisms against airborne toxins and particulate matter. Although the results are encouraging, more thorough research and clinical trials are necessary to confirm the effectiveness, safety, and dosage optimization of polyherbal formulations for lung detoxification. This review underscores the potential of integrating polyherbal therapies as adjunctive measures in respiratory health management, highlighting avenues for future research and therapeutic application.

Keywords: Lung detoxification, Polyherbal formulation, Mitigating respiratory diseases, Pulmonary health, Traditional herbal medicine

Citation: Vasantha G., Alekya K., Soni Priya P., Vardhan B.J.Ch.S., Srujana Sri K. and Sowjanya B.N.: A comprehensive review on *in vitro* models and drugs used for lung detoxification. Intern. J. Zool. Invest. 10(2): 1405-1416, 2024.

https://doi.org/10.33745/ijzi.2024.v10i02.141

Introduction

Polyherbal formulations are used in Ayurveda, the traditional Indian medical system that has been continuously practiced for hundreds of years. Pharmacognosy, chemistry, pharmacology, and clinical therapy have all conducted significant studies on Ayurvedic medicinal plants. Herb combinations as described in Ayurveda have been used to cure a broad spectrum of human illnesses. It is appropriate to take a scientific and rigorous approach to the production of innovative medication from plants when evaluating herbal formulations based on their use in conventional medical systems.

The subsequent properties of different polyherbal formulations, which have been demonstrated by multiple research efforts are illustrated in Table 1.

Clinical and Scientific Validation

The therapeutic application of polyherbal formulations is facilitated by traditional wisdom, although current scientific research aims to validate their efficacy through scientific studies and clinical trials. The empirical evidence compared to these investigations supports the role of polyherbal blends in respiratory health and lung detoxification.

Understanding the synergistic properties and potential mutually beneficial relationships among distinct herbs in polyherbal formulations discusses their value in increasing the procedure of lung cleansing. Polyherbal formulations encompassing a blend of diverse medicinal herbs have shown potential in supporting lung detoxification through various mechanisms:

Traditional Medicinal Wisdom

Traditional medical practices which include Ayurveda, Traditional Chinese Medicine (TCM), or other indigenous remedies are the origin of many polyherbal compositions. These configurations, that depend on centuries-old understanding of herbs and their synergistic effects, have been made use of historically for respiratory health and detoxification.

Combination Synergy

Compared to individual herbs, the combined benefits of multiple herbs in a polyherbal combination might bring more beneficial results. Combining multiple biologically active substances can target different pathways involved in lung detoxification, so supplying a broader approach to respiratory health by virtue of their combination effect.

Anti-oxidant Defense

Combining antioxidant-rich herbs like tulsi and turmeric works as a team to scavenge free radicals and reduce oxidative stress in the lungs. By working together, we can protect lung tissues from the adverse effects that pollutants and toxins in the environment might cause.

Anti-inflammatory Support

Herbs possessing anti-inflammatory properties, such manjistha and liquorice, tend to reduce airway inflammation, which is a vital component of lung detoxification. These herbs assist in restoring the condition of the lungs by reducing inflammatory responses brought on by pollution.

Mucociliary Clearance Enhancement

Mulethi and certain herbs in polyherbal mucociliary clearance blends help release toxins and impurities that have become clogged in the respiratory tract, it has expectorant properties that help clear the airways of mucus.

Table 1: Properties of different polyherbal formulations

Plant Name	Plant Part	Forms	Traditional Use
Abies pindrow	Bark	Powder	Cough, chronic asthma
Abrus precatorius	Leaves	Decoction	Asthma bronchitis, cough, tuberculosis
Acalypha indica	Whole plant	Juice	Asthma
Aconitum ferox	Root	Dried root juice	Cough
Acorus calamus	Root	Juice small piece	Bronchitis, to clear the throat and open the voice
Allium fasciculatum	Whole plant	Paste	Sore throat
Bombax ceiba	Root	Decoction	Bronchitis
Bothriocline longipes	Leaves	Juice	Cough
Calotropis gigantea	Root and leaves	Decoction	Shortness of breath
Chromolaena odorata	Whole plant	Juice	Cough
Coriandrum sativum	Fresh leaves and dried fruits	Decoction	Bronchitis
Curcuma Longa	Stem	Powder	Bronchodilation Anti-inflammatory Anti-cancer Lung damage
Cymbopogon citratis	Leaves	Tea	Cough
Dicarnopteris linearis	Fronds	Decoction	Throat pain
Embelia ribes	Root	Juice	Cough
Euphorbia hirta	Leaves	Dried/soaked	Against Covid-19
Gentianodes tianschanica	Leaves	Infusion	Pneumonia, bronchitis, cough
Glycyrrhiza glabra	Root	Powder	Asthma
Hydrocotyl verdicillta	Whole plant	Decotion	Asthma
Malva parviflora	Leaves	Powder	Pneumonia
Oxalis debilis	Leaves	Powder	Asthma
Piper Nigrum	Seeds	Decotion	Antioxidant, Anti inflammatory
Rubia cordifolia	Leaves	Juice	Pneumonia
Saccharum officinarum	Stem	Maceration	Asthma, respiratory diseases in children
Solanecio cydoniifolius	Root	Boiled	Cough
Sonchus wightianus	Root	Raw root	Tonsillitis
Trifolium alexandrium	Stem, leaves	Decoction, juice, vegetable, and paste	Respiratory tract infection
Verbascum thapsus	Timber	Root paste	Asthma
Zingiber officinale	Rhizome	Juice	Cough

A broad spectrum of biologically active substances can be identified in polyherbal preparations, which are made from a synergistic combination of medicinal herbs and may offer a complete approach to alleviating bronchial constriction. Because several herbs are combined to create these formulations, they contain a variety of bioactive chemicals, including broncho dilatory, anti-inflammatory, and smooth muscle relaxant properties. The unique properties of each herb in these polyherbal combinations combine to produce a synergistic effect that suggests broncho-spasm alleviation and bronchial smooth muscle relaxation as a potential therapy option. The

combination of these bioactive compounds highlights the potential to reduce acute broncho-constriction and address underlying inflammatory pathways, which will facilitate bronchial relaxation and enhance respiratory efficiency.

The rising recognition of natural medicine has driven research into polyherbal formulations as potential medicines to support lung cleansing and improve respiratory health. The ability of these polyherbal preparations, which combine many types of medicinal herbs, to enhance the lungs' detoxifying processes has drawn attention to their wide range of bioactive chemicals. Using medicinal plants, each of which has unique bioactive components, offers a thorough method of lung detoxification. Polyherbal compositions are created via the combination of various herbs in a way that optimizes their combined antioxidative, anti-inflammatory, expectorant, and mucolytic properties. Collectively, these components provide a potent barrier against oxidative stress, scavenge free radicals, improve mucociliary clearance, minimize airway inflammation, and aid the lungs expel dust and other airborne pollutants. It aims to clarify the processes that underlie the combined effects of polyherbal mixtures in strengthening the lungs' natural defenses against environmental toxins. The focus will be on talking about individual polyherbal remedies, including knowledge regarding the plants that make up them, their active ingredients, and their proven benefits on lung detoxification processes. Although preliminary data is encouraging, more investigations in the form of comprehensive preclinical and clinical studies are required to validate the safety, effectiveness, and appropriate dosages of polyherbal formulations for respiratory health. The goal of this review is to clarify the possible role of polyherbal therapies as supplemental tactics in promoting lung health and detoxification processes by compiling existing knowledge and viewpoints.

Role of poly herbal formulation for lung detoxification

In Ayurveda, a historical Indian medicinal system that has been continuously practiced for hundreds of years, polyherbal formulations are used. A large amount of study on Ayurvedic medicinal plants has been carried out in the fields of pharmacognosy, chemistry, pharmacology, and clinical therapies. Many human ailments have been treated using combinations of herbs as described in Ayurveda. Choosing a scientific and rigorous methodology for the assessment of herbal formulations based on their application in conventional medical systems is a suitable approach to the development of innovative drugs from plants.

In Vitro Studies

2D ALI culture

Conventional cell culture techniques typically use surface of 2D from tissue culture plates, trans well inserts, or flasks, where lung cell mono-or- co-cultures are generated and kept submerged. (Hermanns *et al*., 2004) The inability of the lung epithelium to produce ciliated cells that have undergone differentiation in a liquid culture medium however, serves as an example of how the epithelium cannot correctly and when submerged completely differentiate into a functional, physiological-like barrier because of its constant, direct contact with air present in the atmosphere. (De Jong *et al*., 1994; Gerovac *et al*., 2014). Alternatively, removing cell medium from the apical compartment and seeding epithelial cell in trans well inserts or specialized devices successfully replicates the pulmonary environ-ment exposed to air of cell monolayer and simulating the ALI barrier *in vitro* (Hittinger *et al*., 2016; Cao *et al*., 2021). A lot of research has also been done and ALI platform, that sold commercially, available such as Epi Airway (Mat Tek, Ashland, Massachusetts) (Neilson *et al*., 2015; Zavala *et al*., 2016) and MucilAir (Huang *et al*., 2013; Balogh Sivars *et al*., 2018). In this kind of arrangement, cells can establish apical-basolateral polarity and can reach culture media from the insert membrane in basolateral side (Acosta *et al*., 2016; Jiang *et al*., 2018; Chen and Schoen, 2019).

Many studies comparing the responses of cells in both 2D and 3D environments have shown the surface of 2D cells often exhibit behavior that is physiologically irrelevant (Mirbagheri *et al*., 2019; Jensen and Teng, 2020). Significant differences between 2D and 3D have been noted, particularly in lung cells. In 2D, there was a reduce trans epithelial electrical resistance (TEER), less tight junction protein expression, and an increased susceptibility to bacterial infection In 3D, these differences were not as pronounced. (Carterson *et al*., 2005; Bhowmick and Gappa-Fahlenkamp 2016). However, because of its scalability, affordability, and ease of interpreting experimental data, 2D culture has some useful and logistical advantages that pose serious challenges when working with 3D culture models. These advantages are primarily related to its suitability for large-scale studies and cell imaging (Mirbagheri *et al*., 2019; Jensen and Teng, 2020). To enhance the simulation of native tissue *microenvironment*, 2D culture techniques can be improved by incorporating dynamic culture conditions (Chandorkar *et al*., 2017) or surface modifications that incorporate suitable physical micropatterns that can recognize cells and sense their movements (Sacchi *et al*., 2020). The application of specialized structures such as micro- or nanogrooves, pillars, or pits on such micropatterned surfaces has demonstrated a great deal of capacity to control cell shape, adhesion, and movement, leading to the development of 2.5D cell culture (Mirbagheri *et al*., 2019). As a result, 2.5D cell culture may offer a useful middle ground between reproducibility and scalability, as well as being a reasonably easy way to obtain cellular responses that are consistent and physiologically meaningful. As a result, 2.5D cell culture may offer a useful middle ground between reproducibility and scalability, as well as being a reasonably easy way to obtain cellular responses that are consistent and physiologically meaningful. This 3D tetra culture system is built on cell culture inserts, just as the other ALI models (Klein *et al*., 2013).

Spheroids/Organoids

To assess the safety and efficiency of pharmaceuticals, human lung organoids are three-dimensional culture systems with tissue engineering. That can replicate key anatomical features of the airways (Shin *et al*., 2019; Liu *et al*., 2020). Respiratory organoids, as opposed to ALI monoculture models, physiologically replicate the three-dimensional lumen, the environment of the respiratory airways by promoting the growth and development of distinct cell types to mimic the diverse structural branching present in airways (Barkauskas *et al*., 2017; van der Vaart and Clevers, 2021). Human lung organoids are made up of pluripotent stem cells or primary lung cells. These cells self-repair to form spheroids, which are subsequently embedded in an intricate combination of extra-cellular matrix proteins (fibronectin, laminin, and collagens) (Barkauskas *et al*., 2017; Chen *et al*., 2017; Jacob *et al*., 2017). In order to promote the proper spatial organization of heterogeneous cell counts (epithelial, alveolar, and mesenchymal cells) and produce luminal development inside the organoid, exposure to extracellular matrix (ECM) proteins furnishes the physiological and structural foundation for the long-term proliferation, differentiation, and signaling pathways between cells and between cells and matrices (Jacob *et al*., 2017; Tan *et al*., 2017; Miller *et al*., 2019). The organoid lumen is directly microinjected with medicinal chemicals to create a physiologically appropriate platform for *in vitro* drug screening (Shin *et al*., 2019). Furthermore, organoids are included in microfluidic apparatuses (Hill *et al*., 2017) or embedded within *in vivo* models (Miller *et al*., 2019; Berkers *et al*., 2019; Kim *et al*., 2019; Takahashi *et al*., 2019). The unique traits and physiological features of many respiratory illnesses, including cystic fibrosis (Dekkers *et al*., 2013; Berkers *et al*., 2019,), fibrosis (Strikoudis *et al*., 2019), bacterial and viral infections (Chen *et al*., 2017; Hill *et al*., 2017; Kondo *et al*., 2019), and

lung cancer (Shin *et al*., 2019; Kim *et al*., 2019; Takahashi *et al*., 2019), have been modelled by respiratory organoids. Drug distribution in flow circumstances that resemble the respiratory system has been made possible by the integration of organoids into microfluidic devices (Shin *et al*., 2019). By applying flow conditions, the organoid receives a steady supply of nutrients and oxygen as well as a drug-containing media, simulating the systemically administered drug's diffusion absorption process. To enable clinically realistic chemotherapeutic sensitivity under flow conditions that are physiologically relevant and to establish safe treatment dosages at the preclinical stage, the work by (Shin *et al*., 2019) generated lung cancer organoids from patients that were placed onto a microfluidic chip device. Furthermore, respiratory organoid models have been created to offer personalized treatment. These models are very helpful for conditions such as cystic fibrosis. (Paolicelli *et al*., 2019; Berkers *et al*., 2019) and lung cancer (Kim *et al*., 2019; Kondo *et al*., 2019), which have considerable phenotypic and genetic heterogeneity. Developed lung organoids of cancer derived from tumour tissues of 36 patients represented 5 distinct histological subtypes to ascertain the individual sensitivity of each patient. In several instances, previously unidentified resistance to chemotherapeutics was discovered. Directly implanting organoids *in vivo* mice, typically replicates the structural characteristics of cancer tissue while preserving the disease's genetic and histological characteristics (also known as PDX models). At the moment, direct medication administration to the organoid's luminal region is not possible using these PDX models; rather, medications can be injected intraperitoneally, and the organoid can subsequently be extracted for additional pharmacodynamic and bio-pharmacokinetic investigations. Organoids with different genetic defects causing cystic fibrosis have been grown from individuals, and treatment plans have been developed to better anticipate the therapeutic outcomes of individual patients (Dekkers *et al*., 2013; Berkers *et al*., 2019). Personalized medicine strategies can be used by using patient-derived cystic fibrosis organoids' culture media as the most reliable indicator of treatment results and patient reactions to single- and combination-drug treatment regimens (Dekkers *et al*., 2013).

Scaffold-based cell culture

The extracellular matrix (ECM) in the native lung is complex and multifaceted; it shapes the cell microenvironment by providing structural cues, regulating cell adhesion and migration, and regulating access to soluble growth factors. This is true even though isolated human lung cells can survive in 2D on plastic and in 3D Matrigel or collagen environments (McGowan, 1992; Vorotnikova *et al*., 2010; White, 2015; Patel *et al*., 2017). In disease states like emphysema and lung fibrosis, the ECM undergoes substantial remodeling. Researchers have developed techniques for decellularizing rodent and human lungs or lung sections, and reseeding human lung cells onto the matrix. These techniques are motivated by the desire to model cell-ECM interactions in order to gain a better understanding of disease and the possibility of producing a new lung for patients with end-stage lung disease. There are numerous methods available for decellularizing the lungs (Ott *et al*., 2010; Petersen *et al*., 2010; Booth *et al*., 2012; Guyette *et al*., 2014; Wagner *et al*., 2014; Gilpin and Ott, 2015). Though, the success rate of decellularizing human lungs surpasses that of recellularizing them to produce fully grown, operational types of cell found in the natural lung. Recellularizing scaffolds was initially accomplished by seeding them with primary mesenchymal stem cells (Bonvillain *et al*., 2012), which can engraft and multiply within the scaffold. In a more recent development, decellularized rat lungs were seeded with basal stem cells that were obtained from donated human lungs and grown in culture (Gilpin *et al*., 2016). The rat lungs retained their basal cell identity. While decellularized scaffolds have made significant strides towards creation, much more work needs to be done to

Table 2: Drugs, their route of administration, therapeutic uses and adverse effects

Drugs	Mode of action	Route of administration	Therapeutic uses	Adverse effects
Salbutamol (beta 2 sympathomimetics) The first selective short-acting β2-agonist (SABA) utilized as an alternate asthma medication is salbutamol.	Its strong smooth muscle relaxant qualities, which enable the suppression of bronchial smooth muscle contraction and consequent bronchodilation, are the basis for its therapeutic action (Marques and Vale, 2022).	Can be administered orally, intravenously (IV), intramuscularly (IM), subcutaneously, or by inhalation (Marques and Vale, 2022).	Treatment of asthma, bronchospasm and COPD	Tachycardia peripheral cardiac vasodilation-induced reflex (Neville *et al*., 1982, Corris *et al*., 1982) Trembling in the hands. Nervous tension. Headaches. Suddenly noticeable palpitations Muscle cramps.
Ipratropium bromide An anticholinergic drug class that opens the lungs' medium and large airways.	It is a muscarinic acetylcholine receptor antagonist. (Rehder, 2017) Consequently, the airways' parasympathetic neural system is suppressed, which stops the airways from operating normally. The production of bronchial secretions and constriction in the airway is attributed to the parasympathetic nervous system; blocking this activity may lead to bronchodilation and a reduction in secretions. (Almadhoun *et al*., 2023) Acetylcholine, which causes muscle cells to restrict and produce a small airway, controlling the airway's diameter at the cellular level. Consequently, administering ipratropium results in the smooth muscle's acetylcholine ceasing to function, thereby halting contraction and causing relaxed airways (Upfal, 2007).	Breathing Through the Mouth The oral formulation can be administered as a nebulization solution or as an aerosol inhalation (Patel *et al*., 2023) Breathing in Aerosols In the event that the patient has trouble breathing in the medication after it has been triggered, they may utilize a spacer or a valved holding chamber (Patel *et al*., 2023) A patient can select between a mouthpiece and a face mask alongside a spacer or VHC, depending on which is more comfortable for them. (Summers and Tarala, 1990)	Prevent the symptoms of chronic obstructive pulmonary disease (COPD), which includes bronchitis and emphysema, such as wheezing and shortness of breath.	Most common adverse reactions: Bronchitis, nausea, dryness of mouth, Flush skin, Dyspnea (Patel *et al*., 2023) Intranasal Ipratropium Most common adverse reactions: Infections in upper respiratory system. Epistaxis pharyngitis Headache (Patel *et al*., 2023) Severe adverse reactions (Kopsaftis *et al*., 2018): Hypersensitivity reaction Anaphylaxis
Omalizumab Recombinant humanized immunoglobulin G1 (IgG1) monoclonal anti-IgE antibody omalizumab is used to treat chronic urticaria and allergic asthma.	The body's antigen-presenting cells (APCs) absorb environmental allergens when they initially enter the body. Then, T and B immune cells are shown after it has been digested. Next comes the generation of IgE that is specific to allergens and the activation of B lymphocytes. After then, plasma cells (reformed B lymphocytes) release this IgE, which is then free to attach to IgE receptors on a variety of different cells. (Patel *et al*., 2023). IgE attaches itself to both low-affinity (Fc€RII) and high-affinity (Fc€RI) receptors on a variety of immune system cells. After being exposed to more	Omalizumab injectable solution, 75 mg/0.5ml, prefilled syringe for single dose. Omalizumab injectable solution at 150 mg/ml in a prefilled, single-dose syringe. Omalizumab lyophilized powder, 150 mg, intended for single-dose reconstitution vial. (Plosker *et al*.,2008) Over Europe, the recommended range for the total serum IgE level for adults and children aged 12 or older should be between levels of 30 to 1500 IU/ml, especially for children between the ages of 6 to 12, it	Those with moderate to severe persistent asthma who are 6 years of age and older, whose symptoms are not adequately controlled by inhaled corticosteroids, and who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen are prescribed this anti-IgE antibody medicine.	An omalizumab is generally considered to have an excellent safety profile, there are some significant concerns regarding the potential adverse effects of the drug. The following four classes comprise the significant side effects of omalizumab: systemic reactions, potential effects on malignancy, risk of parasite disease, and immunological effects, including serum sickness and Churg-Strauss vasculitis. (Godse *et al*., 2015). The most reported adverse events during omalizumab clinical trials were injection-

	antigens, multiple FcRI-bound IgE molecules on the surface of mast cells and basophils cross-link the antigen. This results in the release of histamine and the activation of mast cells, causing urticaria symptoms such as wheezing. (Patel *et al*., 2023).	should be under 1300 IU/ml (Kumar and Zito, 2023)		site reactions (45%), viral infection (23%), upper respiratory tract infection (20%), sinusitis (16%), headache (15%), and pharyngitis (11%). (Ledford, 2009).
Montelukast Due to their capacity to induce bronchoconstriction, mucus secretion, and increased vascular permeability, leukotrienes are significant mediators of asthma. Due to their capacity to induce bronchoconstriction, mucus secretion, and increased vascular permeability, leukotrienes are significant mediators of asthma (Thomson and Chaudhuri, 2012)	Montelukast is a member of the pharmacological class of leukotriene receptor antagonists. (Brynjolf *et al*.,1998) It works by stopping the lungs' natural production of leukotriene D4, which lowers inflammation and relaxes smooth muscle. (Knorr *et al*.,1998)	It is an orally dosed drug (available as a film-coated tablet, chewable tablet, or oral granules) (Montelukast sodium monograph for professionals, 2018)	asthma bronchospasm allergic rhinitis urticaria (Wermuth *et al*., 2023) mastocytosis treatment (Montelukast sodium, 2019)	Common side effects Diarrhea, nausea, vomiting, mild rashes, fever Severe side effects Angioedema, erythema multiforme, and liver problems. (Cardet *et al*., 2013, Singular 10mg film coated tablets, 2018)

improve cell survival, differentiation, and maturation on the scaffolds to create functionally restored lungs for use in organ transplantation. A possible explanation for the challenge of reseeding scaffolds is a deficiency of vascular networks and other supporting cells and structures. Research has documented the effective repopulation of endothelial cells in human lung scaffolds (Ren *et al*., 2015) and decellularized rat lung scaffolds (Stabler *et al*., 2016), resulting in a partial restoration of barrier function in both scenarios. In the future, successful recellularization of entire organs may depend on the inclusion of several supportive cell types, such as endothelial cells, neuronal cells, and mesenchymal cells that are reseeded in the appropriate niche.

Decellularized extracellular matrix (*ECM*)

The ECM is a three-dimensional framework for all bodily tissues and organs. The extracellular matrix (ECM) is crucial for morphogenesis, differentiation, and homeostasis in addition to functioning as a physical framework (Frantz *et al*., 2010). Remarkably, the inclusion of an *in situ*-like extracellular matrix is essential for simulating cell-to-cell and cell-ECM interactions (Bhowmick *et al*., 2016), it also applies for remodeling events in conditions like emphysema (Kulkarni *et al*., 2016; Burgstaller *et al*., 2017). The ECM promotes the movement of oxygen gradients, nutrients, metabolites, among other things (Tibbitt *et al*., 2009); these are essential features for determining the effectiveness of a drug in the end. Collagen is much of the protein in the extracellular matrix (ECM), comprising about 30 per cent of the tissue's total protein content, in addition to elastin and laminin. It stimulates chemotaxis and cell motility, controls cellular adherence and gives tensile strength (Rozario *et al*., 2010; Burgstaller *et al*., 2017). Even though hydrogel scaffolds rich with collagen have been increasingly employed in grafts and other tissue engineering applications (e.g., bone, cardiovascular, skin, etc.) (Sears *et al*., 2016; Duan, 2017), most of the applications of as of now, the only available Extracellular matrix (ECM) proteins, such as the collagen layer, are coated onto the apical and basal surfaces of the porous membranes that act as the cell substrate in ALI-based *in vitro* lung models.

Considering that a very thin basement membrane (~50 nm) must separate the epithelial and endothelial cell layers *in vivo* for effective gas exchange from air into capillary blood, the average thickness of the ACB is only approximately 1 µm overall (Doryab *et al*., 2019). Though custom-

designed artificial membranes using materials like PDMS can be even thicker (~50-100 µm), currently used ALI-based assays typically use commercially available polycarbonate (PC) and polyethylene terephthalate (PET) membranes, which are typically ~10-20 µm thick and result in additional resistance to respiratory gas and macromolecular exchange (Guenat and Berthiaume, 2018). While Limits are being pushed toward thinner frameworks by recent advancements in biomaterials, in vitro plans to accurately imitate transfer qualities across the ACB remain difficult due to the disparity with the in-situ environment (Sakagami, 2020). Additionally, a novel design has been demonstrated that consists of a biodegradable, flexible membrane that is generated using the drop-casting of a collagen-elastin solution onto a gold mesh (Zamprogno *et al*., 2021).

Drugs Introduction

The common inflammatory lung disease is asthma. Asthma is becoming more common worldwide, and research indicates the number individuals with the disease will increase in the upcoming years for a number of reasons, most notably the risky lifestyles we are embracing (Marques and Vale, 2022). Table 2 illustrates the drugs, their route of administration, therapeutic uses and adverse effects.

Conflict of Interest

The authors declare no conflicts of interest.

References

Acosta MF, Muralidharan P, Meenach SA, Hayes D, M-Black S and Mansour HM. (2016) *In vitro* pulmonary cell culture in pharmaceutical inhalation aerosol delivery: 2-D, 3-D, and *in situ* bioimpactor models. Curr Pharm Des. 22(17): 2522-2531.

Almadhoun K and Sharma S. (2023) Bronchodilators. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing. PMID: 30085570.

Balogh Sivars K, Sivars U, Hornberg E, Zhang H, Brändén L, Bonfante R, Huang S, Constant S, Robinson I, Betts CJ and Åberg PM.(2018) A 3D human airway model enables prediction of respiratory toxicity of inhaled drugs *in vitro*. Toxicol Sci. 162(1):301-308.

Barkauskas CE, Chung MI, Fioret B, Gao X, Katsura H and Hogan BL. (2017) Lung organoids: Current uses and future promise. Development 144(6): 986-997.

Berkers G, van Mourik P, Vonk AM, Kruisselbrink E, Dekkers JF, de Winter-de Groot KM, Arets HG, Marck-van der Wilt RE, Dijkema JS, Vanderschuren MM and Houwen RH. (2019) Rectal organoids enable personalized treatment of cystic fibrosis. Cell reports 26(7): 1701-1708.

Bhowmick R and Gappa-Fahlenkamp H. (2016) Cells and culture systems used to model the small airway epithelium. Lung 94: 419-428.

Bonvillain RW, Danchuk S, Sullivan DE, Betancourt AM, Semon JA, Eagle ME and Bunnell BA. (2012) A nonhuman primate model of lung regeneration: detergent-mediated decellularization and initial in vitro recellularization with mesenchymal stem cells. Tissue Engineering Part A 18(23-24): 2437-2452.

Booth AJ, Hadley R, Cornett AM, Dreffs AA, Matthes SA, Tsui JL and White ES. (2012) Acellular normal and fibrotic human lung matrices as a culture system for *in vitro* investigation. American J Respiratory Crit Care Med. 186(9): 866-876.

Burgstaller G, Oehrle B, Gerckens M, White ES, Schiller HB and Eickelberg O. (2017) The instructive extracellular matrix of the lung: basic composition and alterations in chronic lung disease. Eur Respir J. 50(1): 1601805.

Cao X, Coyle JP, Xiong R, Wang Y, Heflich RH, Ren B, Gwinn WM, Hayden P and Rojanasakul L. (2021) Human air-liquid-interface organotypic airway tissue models derived from primary tracheobronchial epithelial cells-- overview and perspectives. *In Vitro* Cellular Develop Biol Anim. 57: 104-132.

Cardet JC, Akin C and Lee MJ. (2013) Mastocytosis: update on pharmacotherapy and future directions. Expert Opin Pharmacother. 14(15): 2033-2045

Carterson AJ, Honer zu Bentrup K, Ott CM, Clarke MS, Pierson DL, Vanderburg CR, Buchanan KL, Nickerson CA and Schurr MJ. (2005) A549 lung epithelial cells grown as three-dimensional aggregates: alternative tissue culture model for *Pseudomonas aeruginosa* pathogenesis. Infection Immunity 73(2):1129-1140.

Chandorkar P, Posch W, Zaderer V, Blatzer M, Steger M, Ammann CG, Binder U, Hermann M, Hörtnagl P, Lass-Flörl C and Wilflingseder D. (2017) Fast-track development of an in vitro 3D lung/immune cell model to study *Aspergillus infections*. Sci Rep. 7(1): 11644.

Chen S and Schoen J. (2019) Air-liquid interface cell culture: From airway epithelium to the female

reproductive tract. Reproduction Domestic Anim. 54: 38-45.

Chen YW, Huang SX, De Carvalho AL, Ho SH, Islam MN, Volpi S, Notarangelo LD, Ciancanelli M, Casanova JL, Bhattacharya J and Liang AF. (2017) A three-dimensional model of human lung development and disease from pluripotent stem cells. Nature Cell Biol.19(5): 542-549.

de Jong PM, van Sterkenburg MA, Hesseling SC, Kempenaar JA, Mulder AA, Mommaas AM, Dijkman JH. and Ponec M. (1994) Ciliogenesis in human bronchial epithelial cells cultured at the air-liquid interface. American J Respiratory Cell Molec Biol. 10(3): 271-277.

Dekkers JF, Wiegerinck CL, De Jonge HR, Bronsveld I, Janssens HM, De Winter-de Groot KM and Beekman JM. (2013) A functional CFTR assay using primary cystic fibrosis intestinal organoids. Nature Med. 19(7): 939-945.

Doryab A, Tas S, Taskin MB, Yang L, Hilgendorff A, Groll J and Schmid O. (2019) Evolution of bioengineered lung models: recent advances and challenges in tissue mimicry for studying the role of mechanical forces in cell biology. Adv Functional Materials 29(39): 1903114.

Duan B. (2017) State-of-the-art review of 3D bioprinting for cardiovascular tissue engineering. Annals Biomed Engineer. 45: 195-209.

Frantz C, Stewart KM and Weaver VM. (2010) The extracellular matrix at a glance. J Cell Sci. 123(24): 4195-4200.

Gerovac BJ, Valencia M, Baumli N, Salathe M, Conner GE and Fregien NL. (2014) Submersion and hypoxia inhibit ciliated cell differentiation in a notch-dependent manner. American J Respiratory Cell Molec Biol. 51(4): 516-525.

Gilpin SE, Charest JM, Ren X and Ott HC. (2016) Bioengineering lungs for transplantation. Thoracic Surgery Clin. 26(2): 163-171.

Gilpin SE and Ott HC. (2015) Using nature's platform to engineer bio-artificial lungs. Annals American Thoracic Soc. 12(Supplement 1): S45-S49.

Godse K, Mehta A, Patil S, Gautam M and Nadkarni N. (2015) Omalizumab- A review. Indian J Dermatol. 60(4): 381-384.

Guenat OT and Berthiaume F. (2018) Incorporating mechanical strain in organs-on-a-chip: Lung and skin. Biomicrofluidics 12(4): 042207.

Guyette JP, Gilpin SE, Charest JM, Tapias LF, Ren X and Ott HC. (2014) Perfusion decellularization of whole organs. Nature Protocols 9(6): 1451-1468.

Hermanns MI, Unger RE, Kehe K, Peters K and Kirkpatrick CJ. (2004)Lung epithelial cell in coculture with human pulmonary microvascular endothelial cells: Development of an alveolo-capillary barrier *in vitro*. Lab Investig. 84(6): 736-752.

Hittinger M, Janke J, Huwer H, Scherließ R, Schneider-Daum N and Lehr CM. (2016) Autologous co-culture of primary human alveolar macrophages and epithelial cells for investigating aerosol medicines. Part I: model characterisation. Alternatives Lab Anim. 44(4): 337-347.

Huang S, Wiszniewski L, Constant S and Roggen E. (2013) Potential of *in vitro* reconstituted 3D human airway epithelia (MucilAir™) to assess respiratory sensitizers. Toxicology in Vitro 27(3): 1151-1156.

Jacob A, Morley M, Hawkins F, McCauley KB, Jean JC, Heins H, Na CL, Weaver TE, Vedaie M, Hurley K and Hinds A. (2017) Differentiation of human pluripotent stem cells into functional lung alveolar epithelial cells. Cell Stem Cell 21(4): 472-488.

Jensen C and Teng Y. (2020) Is it time to start transitioning from 2D to 3D cell culture?. Front Molec Biosci. 6(7): 33.

Jiang D, Schaefer N and Chu HW. (2018) Methods in Molecular Biology, Humana Press Inc, New Jersey.

Kim M, Mun H, Sung CO, Cho EJ, Jeon HJ, Chun SM and Jang SJ. (2019) Patient-derived lung cancer organoids as *in vitro* cancer models for therapeutic screening. Nature communications 10(1): 3991.

Klein SG, Serchi T, Hoffmann L, Blömeke B and Gutleb AC. (2013) An improved 3D tetraculture system mimicking the cellular organisation at the alveolar barrier to study the potential toxic effects of particles on the lung. Particle Fibre Toxicol. 10(1): 1-8.

Knorr B, Matz J, Bernstein JA, Nguyen H, Seidenberg BC, Reiss TF, Becker A. (1998) Montelukast for chronic asthma in 6- to 14-year-old children: a randomized, double-blind trial. Pediatric Montelukast Study Group. JAMA 279(15): 1181-1186.

Kondo J and Inoue M. (2019) Application of cancer organoid model for drug screening and personalized therapy. Cells 8: 470.

Kopsaftis ZA, Sulaiman NS, Mountain OD, Carson-Chahhoud KV, Phillips PA, Smith BJ. (2018) Short-acting bronchodilators for the management of acute exacerbations of chronic obstructive pulmonary disease in the hospital setting: systematic review. Syst Rev. 7(1): 213.

Kulkarni T, O'Reilly P, Antony VB, Gaggar A and Thannickal VJ. (2016) Matrix remodeling in pulmonary fibrosis and emphysema. American J Respiratory Cell Molec Biol. 54(6): 751-760.

Kumar C and Zito PM. (2023) Omalizumab: In StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing.

Ledford DK. (2009) Omalizumab: overview of pharmacology and efficacy in asthma. Expert Opin Biol Ther. 9(7): 933-943.

Liu Z, Anderson JD, Deng L, Mackay S, Bailey J, Kersh L, Rowe SM and Guimbellot JS. (2020) Human nasal epithelial organoids for therapeutic development in cystic fibrosis. Genes 11(6): 603.

Marques L and Vale N. (2022) Salbutamol in the management of asthma: A review. Int J Mol Sci. 123(22): 14207.

McGowan SE. (1992) Extracellular matrix and the regulation of lung development and repair. FASEB J 6: 2895-2904.

Miller AJ, Dye BR, Ferrer-Torres D, Hill DR, Overeem AW, Shea LD and Spence JR. (2019) Generation of lung organoids from human pluripotent stem cells in vitro. Nature Protocols 14(2): 518-540.

Mirbagheri M, Adibnia V, Hughes BR, Waldman SD, Banquy X and Hwang DK. (2019) Advanced cell culture platforms: a growing quest for emulating natural tissues. Materials Horizons 6(1): 45-71.

Montelukast Sodium Monograph for Professionals (2019) Drugs.com. AHFS.

Neilson L, Mankus C, Thorne D, Jackson G, DeBay J and Meredith C. (2015) Development of an *in vitro* cytotoxicity model for aerosol exposure using 3D reconstructed human airway tissue; application for assessment of e-cigarette aerosol. Toxicology in Vitro 29(7): 1952-1962.

Neville E, Corris P, Vivian J, Nariman S and Gibson G. (1982) Salbutamol aerosol causes a tachycardia due to the inhaled rather than the swallowed fraction. Br J Clin Pharmacol. 9: 273-274.

Ott HC, Clippinger B, Conrad C, Schuetz C, Pomerantseva I, Ikonomou L and Vacanti JP. (2010) Regeneration and orthotopic transplantation of a bioartificial lung. Nature Med.16(8): 927-933.

Paolicelli G, Luca A, Jose SS, Antonini M, Teloni I, Fric J and Zelante T. (2019) Using lung organoids to investigate epithelial barrier complexity and IL-17 signaling during respiratory infection. Front Immunol. 10: 323.

Patel P, Saab H and Aboeed A. (2023) Ipratropium: In StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing.

Patel VN, Pineda DL, Hoffman MP. The function of heparan sulfate during branching morphogenesis. Matrix Biol. 57-58: 311-323.

Petersen TH, Calle EA, Zhao L, Lee EJ, Gui L, Raredon MB and Niklason LE. (2010) Tissue-engineered lungs for *in vivo* implantation. Science 329(5991): 538-541.

Plosker GL and Keam SJ. (2008) Omalizumab: a review of its use in the treatment of allergic asthma. BioDrugs 22(3): 189-204.

Rehder KJ. (2017) Adjunct therapies for refractory status asthmaticus in children. Respir Care 62(6): 849-865.

Ren X, Moser PT, Gilpin SE, Okamoto T, Wu T, Tapias LF and Ott HC. (2015) Engineering pulmonary vasculature in decellularized rat and human lungs. Nature Biotechnol. 33(10): 1097-1102.

Rozario T and DeSimone DW. (2010) The extracellular matrix in development and morphogenesis: a dynamic view. Develop Biol. 341(1): 126-140.

Sacchi M, Bansal R and Rouwkema J. (2020) Bioengineered 3D models to recapitulate tissue fibrosis. Trends Biotechnol. 38(6): 623-636.

Sakagami M. (2020) *In vitro, ex vivo* and *in vivo* methods of lung absorption for inhaled drugs. Advanced Drug Delivery Rev. 161: 63-74.

Sears NA, Seshadri DR, Dhavalikar PS and Cosgriff-Hernandez E. (2016) A review of three-dimensional printing in tissue engineering. Tissue Engineer Part B Rev. 22(4): 298-310.

Shin TH, Kim M, Sung CO, Jang SJ and Jeong GS. (2019) A one-stop microfluidic-based lung cancer organoid culture platform for testing drug sensitivity. Lab Chip 19(17): 2854-2865.

Stabler CT, Caires Jr LC, Mondrinos MJ, Marcinkiewicz C, Lazarovici P, Wolfson MR and Lelkes PI. (2016) Enhanced re-endothelialization of decellularized rat lungs. Tissue Engineer Part C Methods 22(5): 439-450.

Strikoudis A, Cieślak A, Loffredo L, Chen YW, Patel N, Saqi A, Lederer DJ and Snoeck HW. (2019) Modeling of fibrotic lung disease using 3D organoids derived from human pluripotent stem cells. Cell Rep. 27(12): 3709-3723.

Summers QA and Tarala RA. (1990) Nebulized ipratropium in the treatment of acute asthma. Chest 97(2): 425-429.

Takahashi N, Hoshi H, Higa A, Hiyama G, Tamura H, Ogawa M and Takagi M. (2019) An *in vitro* system for evaluating molecular targeted drugs using lung patient-derived tumor organoids. Cells 8(5): 481.

Tan Q, Choi KM, Sicard D and Tschumperlin DJ. (2017) Human airway organoid engineering as a step toward lung regeneration and disease modeling. Biomaterials 113: 118-132. Thomson NC and Chaudhuri R. (2012) Omalizumab: clinical use for

the management of asthma. Clin Med Insights Circ Respir Pulm Med. 6: 27-40.

Tibbitt MW and Anseth KS. (2009) Hydrogels as extracellular matrix mimics for 3D cell culture. Biotechnol Bioengineer. 103(4): 655-663.

Upfal J. (2007) The Australian Drug Guide. Melbourne, Vic.: Black Inc.. ISBN: 9781863951746

van der Vaart J and Clevers H. (2021) Airway organoids as models of human disease. J Intern Med. 289(5): 604-613.

Vorotnikova E, McIntosh D, Dewilde A, Zhang J, Reing JE, Zhang L, Cordero K, Bedelbaeva K, Gourevitch D, Heber-Katz E, Badylak SF and Braunhut SJ. (2010) Extracellular matrix-derived products modulate endothelial and progenitor cell migration and proliferation *in vitro* and stimulate regenerative healing *in vivo*. Matrix Biol. 29: 690-700.

Wagner DE, Bonenfant NR, Parsons CS, Sokocevic D, Brooks EM, Borg ZD and Weiss DJ. (2014) Comparative decellularization and recellularization of normal versus emphysematous human lungs. Biomaterials 35(10): 3281-3297.

Wermuth HR, Badri T and Takov V. (2023) Montelukast. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing.

White ES. (2015) Lung extracellular matrix and fibroblast function. Annals American Thoracic Soc. 12(Supplement 1): S30-S33.

Zamprogno P, Wüthrich S, Achenbach S, Thoma G, Stucki JD, Hobi N and Guenat OT. (2021) Second-generation lung-on-a-chip with an array of stretchable alveoli made with a biological membrane. Communications Biol. 4(1): 168.

Zavala J, O'Brien B, Lichtveld K, Sexton KG, Rusyn I, Jaspers I and Vizuete W. (2016) Assessment of biological responses of EpiAirway 3-D cell constructs versus A549 cells for determining toxicity of ambient air pollution. Inhalation Toxicol. 28(6): 251-259.