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Pharmacologic Activities of Plant-Derived Natural Products on Respiratory Diseases and Inflammations

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Abstract

Respiratory inflammation is caused by an air-mediated disease induced by polluted air, smoke, bacteria, and viruses. The COVID-19 pandemic is also a kind of respiratory disease, induced by a virus causing a serious effect on the lungs, bronchioles, and pharynges that results in oxygen deficiency. Extensive research has been conducted to find out the potent natural products that help to prevent, treat, and manage respiratory diseases. Traditionally, wider floras were reported to be used, such as *Morus alba*, *Artemisia indica*, *Azadirachta indica*, *Calotropis gigantea*, but only some of the potent compounds from some of the plants have been scientifically validated. Plant-derived natural products such as colchicine, zingerone, forsythiaside A, mangiferin, glycyrrhizin, curcumin, and many other compounds are found to have a promising effect on treating and managing respiratory inflammation. In this review, current clinically approved drugs along with the efficacy and side effects have been studied. The study also focuses on the traditional uses of medicinal plants on reducing respiratory complications and their bioactive phytoconstituents. The pharmacological evidence of lowering respiratory complications by plant-derived natural products has been critically studied with detailed mechanism and action. However, the scientific validation of such compounds requires clinical study and evidence on animal and human models to replace modern commercial medicine.

1. Introduction

Respiratory inflammatory disorders comprise several air-mediated diseases such as chronic bronchitis, pulmonary diseases, and asthma. Chronic obstructive pulmonary disease (COPD) is a lung inflammatory disease that is the 5th leading cause of death worldwide [1]. Respiratory inflammation is mainly caused by airway disease, characterized by several complications such as coughing, sneezing, and shortness of breath [2]. The disease can act on both upper and lower airways and worsens the other diseases including rhinosinusitis and tightness of the chest [3]. There are multiple problems associated with respiratory inflammation. The upper inflammation is associated with the common cold, pharyngitis, sinusitis, laryngotracheitis, and epiglottitis, and lower inflammation is associated with bronchiolitis, bronchitis, and pneumonia [4]. The inflammation is also induced by a respiratory virus that infects the epithelial lining of the airways and replicates in it [5]. This inflammation normally leads to type 1 inflammation. Inflammation in the healthy airway results in the activation of antiviral state and clearance of viral infection [6, 7], but in chronically inflamed airways, the response against the virus may impair resulting in sustained inflammation [8, 9] and reduced ability of viral clearance [10, 11]. The acute exacerbations may be triggered by several allergens, pollutants, cold and dry air, smoke inhalations, and several pathogenic bacteria in the airways [12]. Asthma is one of the chronic respiratory diseases marked by reversible airway constriction, eosinophil infiltration, increased mucus production, and nonspecific hyperresponsiveness of the airways [13].

There are several treatment methods for reducing complications of respiratory inflammation that include oxygen therapy, steam therapy, draining mucus from the lungs, and taking antihistamines and bronchodilators. Several steroidal and nonsteroidal drugs are used to lessen down inflammation. Inhaled corticosteroids (ICS) in combination with long-acting beta-agonist (LABA) are recommended in many countries. Long-acting bronchodilators such as salmeterol and formoterol can be used in asthma according to the rate of intrinsic activity. Some ultraclass drugs such as β-2 agents [14], olodaterol [15], vilanterol [16], carmoterol, PF-610355, LAS100977, and AZD3199 are recommended for therapy against respiratory diseases. Many of the plants such as *Adiantum capillus-veneris*, *Aegle marmelos*, *Aerva javanica var. javanica* [17], *Albizia lebbeck*, *Alhagi maurorum*, and *Alhagi maurorum* were used in respiratory disorders by traditional healers and indigenous people [18]. There are many plant-derived compounds of different classes such as alkaloids, flavonoids, glycosides, lignans, polyphenols, and saponins that are studied for their activities against respiratory disease and inflammation. Some compounds like mangiferin, zingerone, glycyrrhizin, piperine, and forsythiaside A are promising and have evidence of positive results in an animal study. Despite the promising effect of plant-derived natural products, the extensive study of clinical evidence and their toxicological aspect is still lacking. Only some of the compounds have been isolated, and a lesser number of experiments have been done in the human model. This review is aimed at collecting and analyzing the traditional approach, reported natural products, and their pharmacological evidence on respiratory diseases and inflammations with sufficient research gaps and recommendations.

2. Methodology

The information on respiratory diseases and inflammations had been retrieved from an extensive literature survey. Systematic literature had been searched by using an online database such as Google Scholar, PubMed, SciFinder, ScienceDirect, Mendeley, and Scopus. Literatures were searched in the online database using keywords such as "Respiratory inflammation", "Ethnomedicine and respiratory diseases", "Bioactive compounds and respiratory disease", and "Respiratory drugs". The cross-referenced articles were also retrieved. Various books, thesis, proceedings, and news articles were secondary sources of information.

3. Current Clinical Practice and Approved Drugs

Respiratory inflammatory diseases like asthma and chronic obstructive pulmonary disease (COPD) are usually treated with effective modern medicines of different classes. Nonsteroidal anti-inflammatory drugs (NSAIDs) is a class of drug that has been used efficiently and commonly in the inhibition of the cyclooxygenase enzyme. The past study showed the prescription of triple therapy for the treatment of pulmonary diseases [19] which suggested the use of a long-acting beta-agonist (LABA) and long-acting muscarinic antagonist (LAMA) in combination with inhaled corticosteroid (ICS) [20]. There is a major development in treating COPD and asthma by the ICS-LABA-LAMA therapy. The most common prescriptions nowadays are LABA and ICS discovered by the physician in Europe [21]. The common uses of 22% ICS and 39% bronchodilators are for lower symptoms and 46% ICS and 67% bronchodilators are for greater symptoms. Due to the limited effect of this medication, a trial for triple therapy is tried in every patient [22]. NSAIDs, bronchodilators (β_2-adrenoreceptor (AR) agonists, muscarinic receptor antagonists, and xanthines) [23], and corticosteroids [24] are a highly recommended initial therapy for most patients individually or in combination with one of the other classes [25]. Nonselective COX inhibitors for reducing respiratory inflammation include aspirin, ibuprofen, naproxen, and diclofenac, and selective COX inhibitors include celecoxib, lumiracoxib, etoricoxib, valdecoxib, and rofecoxib [26]. Among different bronchodilators, fast-acting and short-acting albuterol, terbutaline, and fenoterol are efficiently used, yet long-acting agonists salmeterol and formoterol are best for therapy. Some drugs of class ultra-long-acting β_2 agents indacaterol [14], olodaterol [15], vilanterol [16], carmoterol, PF-610355, LAS100977, AZD3199, etc. had been prescribed for achieving one dose daily [27]. The use of a combination of drugs using β_2 long-acting and antimuscarinic controls the transforming growth factor (TGF)-β^1-mediated inflammation in COPD. The novel antimuscarinic agents such as QAT370, glycopyrronium (NVA237), aclidinium, GSK573719, CHF5407, BEA2180BR, TD4208, PF452297, RBx343E48F0, trospium, and dexpirronium are generally used at a high dose for a prolonged duration of action [27]. Anti-inflammatory and bronchodilator action of xanthines such as bamiphylline, enprofylline, isbufylline, and doxophylline is reported to be used in the treatment of asthma and COPD. The safer use of xanthines inhibits the family of phosphodiesterase (PDE3 and 4) enzymes for long-term improvement in lung function [28]. Different NSAIDs like ibuprofen are used in COVID-19 infection,

but there is a lack of studies that shows the association between the use of NSAID and COVID-19 severity. Currently, known antiviral agents like lopinavir/ritonavir and remdesivir have a high affinity to the viral enzyme and could inhibit the synthesis of the nitrogenous base resulting in the inhibition of RNA replication through premature termination of the virus [29]. Anti-inflammatory drugs like corticosteroids had a role in the significant reduction of in-hospital mortality by COVID-19 [30]. During this pandemic of COVID-19, several pulmonary complications from this disease were reported such as mucormycosis and pulmonary aspergillosis [31]. These are life-threatening fungal infections and have a role in complicating pulmonary conditions like asthma, bronchiectasis, and COPD. These pulmonary infections are found to attack patients with low immunity. Many researchers and health personnel assumed it was due to the excessive use of corticosteroids. Corticosteroids are used for the treatment of COVID-19 patients which in turn reduces immunity due to which the patients are prone to be infected by mucormycosis and aspergillosis [32]. Losmapimod, p38, a subfamily of mitogen-activated protein kinase (MAPK) inhibitor, is widely studied and used safely as a single IV infusion of 1 to 3 mg doses. There are no severe effects reported except headache, nausea, and fatigue ([33]). Various reports suggested that this can be appropriate in treating COVID-19 patients [34]. The recent trial in the mouse model supported a similar result [35]. Besides this, p38 was able to cause a pathogenic role in asthma and COPD. The adverse factors causing these diseases activate the p38 which in turn amplifies lung inflammation. The clinically trialed anti-interleukins like benralizumab, daclizumab, reslizumab, MEDI-528, mepolizumab, and lebrikizumab showed improvement in patients by decreasing eosinophils and other exacerbations [36]. The clinical trial of benralizumab revealed the effects in reducing eosinophil and improved lung function but with some headache and nausea effects [37]. Number of trials had been conducted for treating upper airway disorders such as allergic rhinitis, nasal polyps, and chronic rhinosinusitis for which several therapeutics such as omalizumab, mepolizumab, dupilumab, a monoclonal antibody targeted toward IgE, an anti-IL-5 agent, anti-IL-4, and IL-3 had been used. The outcomes of the trials were positive [38].

Several other modern drugs have been discovered and synthesized in the laboratory with promising results. However, the success of low-molecular-weight drugs remains low as respiratory inflammation diseases are complex in etiology. The critical target molecule that is directly associated with the disease process has not been found yet. The plant can be the potent source of such medicine as plants have diverse compositions and complex molecular associations. Recently available techniques are effective but associated with several complications such as cost, demand, and availability. Thus, a new kind of efficient and easily available therapeutics should be introduced for developing new kinds of drugs against respiratory inflammation.

4. Ethnomedicinal Practice on Treating Respiratory Complications

Several plants were reported to be used for their anti-inflammatory properties that can be used in acute as well as chronic bronchitis. Ethnomedicinally, the number of plants had been reported based on indigenous knowledge of people and the practice of traditional healers. Plants such as *Morus alba* [39],

Dicliptera bupleuroides, *Adiantum capillus-veneris*, *Trichodesma indicum*, and *Viburnum grandiflorum* were reported to be traditionally used in Pakistan and Korea for treating whooping cough and the common cold. The decoction of leaves of *Dicliptera bupleuroides* was known to apply externally in the throat for managing the cough by the local people of Kashmir of Pakistan [40]. The milky latex and flower paste of *Calotropis gigantea* found in the Terai forest of western Nepal were reported to be taken orally for the management of cough and bronchitis [41]. Some of the reported plants acting against respiratory disorders, based on traditional knowledge and practices, have been listed in Table 1.

Table 1

Traditionally used plants in different countries and localities against respiratory disorder.

S.N.	Plant names (local name if available)	Country (locality if available)	Plant parts used	Forms	Mode of application	Traditional use	Refe
1.	*Abies pindrow*	Pakistan (Kashmir)	Bark	Powder	Internal	Cough, chronic asthma	[
2.	*Abies pindrow* (partal)	Pakistan (Kashmir)	Root	Decoction	Internal	Cough, bronchitis	[
3.	*Abrus precatorius* (omisinmisin)	Nigeria (Osun State)	Leaves	Decoction	Oral	Asthma bronchitis, cough, tuberculosis	[
4.	*Acalypha indica*	Myanmar (Mon)	Whole plant	Juice	Oral	Asthma	[
5.	*Acanthus pubescens* (Amatojo)	Uganda	Root	Boiled	Oral	Cough	[
6.	*Achyranthes aspera* (Puthkanda)	Pakistan(Gujranwala)	Leaves	Decoction	Oral	Pneumonia	[
7.	*Achyranthes aspera* (Puthkanda)	Pakistan (Soan Valley)	Root	Decoction, juice	Oral	Pneumonia	[
8.	*Aconitum ferox* (Seto bikhma)	Nepal	Root	Dried root juice	Oral	Cough	[
9.	*Aconitum heterophyllum*	Nepal (Rasuwa)	Root	Powder	Oral	Cough	[

5. Plant-Derived Compounds on Treating Respiratory Complications

The number of compounds (Table 2) derived from plants was reported for the prominent therapeutics against respiratory inflammation. The flavonoids such as kuwanone E, kuwanone G, and norartocarpanone from *Morus alba* [61], sakuranetin from *Baccharis retusa* [62], and pinocembrin (5,7-dihydroxyflavanone) from *Alpinia katsumadai* have been reported to act against respiratory inflammation. The polyphenols such as curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) from *Curcuma longa* rhizome[63, 64], resveratrol from grapes [65], and luteolin from *Lonicera japonica* [66] were reported to act against respiratory inflammation. The other classes of plant-derived compounds such as alkaloids [67], coumarins [68], and triterpenoids, saponins, and steroids [69–72] were reported to be effective against several kinds of inflammations. Colchicine is a plant alkaloid derivative that could be used as a substitute for commercial colchicine. Colchicine concentrations differ from organ to organ, and colchicine content was demonstrated to be influenced by plant age, seasonality, and location. Colchicine was found to reduce neutrophil elastase concentration in bronchoalveolar lavage fluid in ex-smokers with COPD [73]. Some of the structures of the potent bioactive compounds are given in Figures 1 and 2.

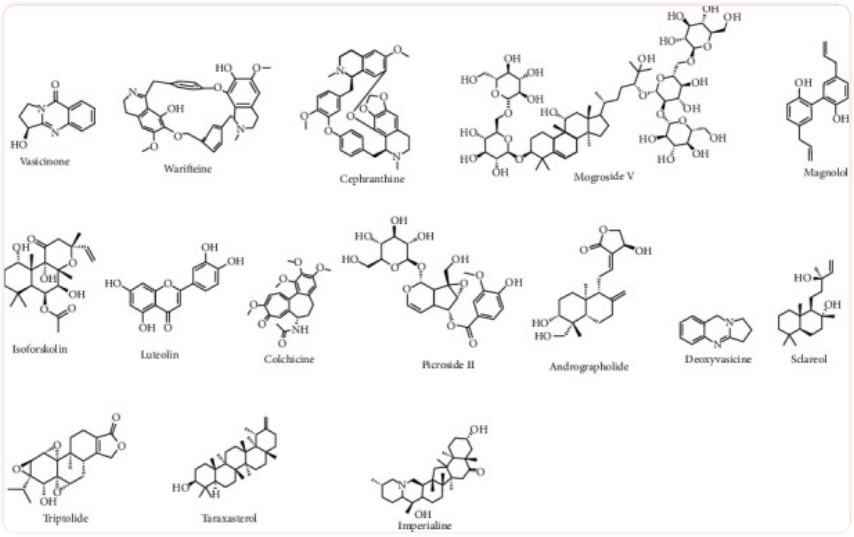

Figure 1

Some major bioactive compounds for respiratory disease.

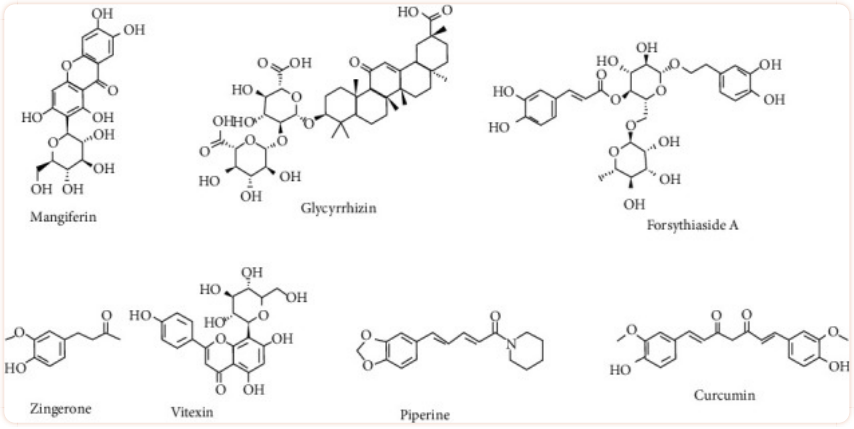

Figure 2

Some promising bioactive compounds for respiratory disease.

Table 2

Plant-derived compounds associated with respiratory inflammation.

S.N.	Constituents	Plant origin	Doses	Inflammagen used	References
Alkaloids					
1.	Warifteine	*Cissampelos sympodialis*	2 mg/kg	OVA-induced	[74]
2.	Colchicine	*Colchicum autumnale*	0.25-0.5 mg/kg	Idiopathetic pulmonary fibrosis	[73]
3.	Imperialine	*Fritillaria cirrhosa*	3.5-7 mg/kg	Cigarette smoke or LPS	[75]
4.	Piperine	*Piper longum*	2.25-4.5 mg/kg	Ovalbumin	[67]
5.	Cepharanthine	*Stephania cepharantha*	5 mg/kg	LPS	[76]
6.	Nimbandiol	*Azadirachta indica*	(*in silico*)	—	[77]
7.	Vasicine	*Peganum harmala*	45 mg/kg	Ammonia liquor, capsaicin, and citric acid	[78]
8.	Vasicinone				
9.	Deoxyvasicine				
Cannabinoids					
10.	Cannabidiol	*Cannabis sativa*	20 mg/kg	LPS	[79, 80]
Flavonoids					
11.	Pinocembrin (5,7-dihydroxyflavanone)	*Alpinia katsumadai*	20-50 mg/kg	LPS	[81]
12.	Naringenin	*Prunus persica*	15-100 mg/kg	LPS, *Staphylococcus aureus*	[82, 83]

The reported compounds are mostly tested in mice *invivo*, and the inflammation is mainly induced by LPS. The study on the human model and its clinical evidence is still lacking. The possible therapeutics from this promising compound is yet to be studied. The compounds with lower doses and higher activi-

ties should be taken into the clinical trial in a sample population.

6. Mechanism of Action of Plant-Based Natural Product

The lung inflammation involves the activation of inflammatory cells such as eosinophils, lymphocytes, macrophages, and neutrophils, which serve as the source of different inflammatory mediators such as tumor necrosis factor (TNF-α), interleukins (IL-4, IL-1β, IL-6, and IL-5), histamine, prostaglandins, nitric oxide, and leukotriene. The release of these inflammatory mediators causes several abnormalities in the lungs and their function [156]. Natural products target the epithelial-mesenchymal transition (EMT), oxidative stress, fibroblast activation, inflammatory injury, metabolic regulation, and extracellular matrix accumulation. The basic mechanisms involved are the NF-κB, TGF-β1/Smad, PI3K/Akt, p38 MAPK, Nrf2-Nox4, and AMPK signaling pathways [157]. The plant flavonoid such as eriodictyol was reported to serve as the anti-inflammatory agent in the lungs which regulates the Nrf2 pathway and inhibited the expression of inflammatory cytokines IL-6, TNF-α, IL-1β, etc. [86]. The flavonoids kaempferol and luteolin reduced the LPS-induced activation of the MAPK and NF-κB pathways and also reported to inhibit the ICAM-1, TNF-α, SOD, KC, and neutrophil inflammation. This compound was also found to involve in the reduction of the activity of superoxide dismutase and catalase and further reduces the lipid peroxidation and oxidative damage in the lung tissue [158, 159]. A natural product such as sakuranetin was also reported to reduce the TNF-α, eosinophils, M-CSF, RANTES, IL-5, and IL-1β and inhibited the NF-κB, MMP-12-positive, and MMP-9-positive cells and also increased the TIMP-1 expression to serve as anti-inflammatory activities in the lungs of the elastase-treated animals [62]. Several compounds such as epigallocatechin, gallocatechin gallate, berberine, berbamine, coptisine, and dicentrine were reported to involve in the inhibition of viral replication, by inhibiting the viral life cycle in the host and act against the viral-induced respiratory inflammations [160]. The 1,8-cineol isolated from the essential oil of *Eucalyptus globulus* leaves was studied for its ability to reduce the expression of NF-κB target gene MUC2 [161]. The 3-methoxy-catalposide had been studied for its ability to inhibit the expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase (COX)-2 in RAW264.7 cells stimulated by LPS. This compound also suppressed the release of nitric oxide (NO) and prostaglandin E2 (PGE2). This compound significantly reduced the activation of inflammatory genes such as interleukins IL-1β, IL-6, and TNF-α and inhibited the activation of nuclear translocation of NF-κB and AP-1 [162]. Nepitrin, matte flavonoside G, rutin, etc. were reported to inhibit the influenza virus by damaging the viral membrane, by blocking the viral penetration into the cells, and by suppressing neuraminidase in both bacterial and viral infections [163]. Thus, the possible mechanism of action of natural products to reduce the inflammation and diseases in the respiratory system could be by the inhibition of bacteria and viruses and also by the protease-antiprotease balance, NF-κB activation, oxidative stress, and MAPK pathways. The simple flowchart of the mechanism involved is in Figure 3.

Figure 3

Mechanism of action of a natural product in respiratory inflammation.

7. Some Promising Natural Products and Their Pharmacology

Based on the *in vitro* and *in vivo* study, the number of plants based natural products has been studied. Some of them are discussed in detail.

7.1. Piperine

Piperine is a major compound and is a class of alkaloid found in the *Piper nigrum* fruits. Piperine was reported to be used in pain management, fever, influenza, hypotension, vascular cell modulation, salivation, stimulation of appetite, antimicrobial, insecticidal, and chills ([164]). This compound was found to enhance the bioavailability of different drugs. Cosupplementation of piperine with resveratrol was reported to increase its efficacy by enhancing bioavailability [165]. Piperine was reported for its dose-dependent activities in reducing the allergic responses, involving sneezing, nasal rubbing, redness of the nose, etc. [166]. This compound was reported to act as an immunomodulatory and antiallergic effect on ova-albumin-induced rhinitis in the rat, by significantly ameliorating the sneezing, coughing, and redness induced by sensitizing. The histopathological section of nasal mucosa showed the attenuation of redness and disruption of alveoli and bronchioles [167]. The antitussive activities of plant extracts containing piperine showed the good enhancement of the antitussive effect [168]. The inhibition of tumor growth in the lungs (B16F-10 melanoma cells) was observed after administration of piperine in the mice. The piperine was found to be 100% cytotoxic to melanoma cells shown by histopathology of lungs, resulted in a significant decrease in tumor mass. The alveolar passage and pleura were tumor-free in the piperine-treated mice [169]. The investigation of the efficacy of curcuminoids co-administered with piperine was measured by measuring the serum level of glutathione (GSH) and malondialdehyde (MDA) in sulfur-mustard-induced chronic pulmonary complications and showed the significant increase in GSH and decrease in MDA indicating improvement in COPD status and health-related quality of life (HRQoL) [170]. There are several other pharmacological activities of piperine that can add to the management of several diseases including respiratory inflammation.

7.2. Forsythiaside A

Forsythiaside A is the pharmacologically active monomer of phenylethanoid glycoside. It is the main active ingredient isolated from the fruit and leaves of *Forsythia suspensa.* This compound was reported as a potent component that controls inflammation caused by influenza A virus infection by the molecular mechanism through receptor downregulation of the RLRs signaling pathway. It was reported for anti-inflammatory, antioxidant, and anti-infective activities that explained major biological activities [171]. In a recent study, the anti-inflammatory activity in the lungs of mice had been demonstrated well. Forsythiaside was reported to suppress the inflammatory action of cytokines involving (TNF-α, IL-6, and IL-1β) via activating Nrf2 and inhibiting the NF-κB signaling pathway in a dose-dependent manner. The number of neutrophils as mediators of inflammation and macrophages was reduced which typically reduced inflammations in the lungs of cigarette and smoke-induced mice [154]. It was reported to act as an immunomodulatory agent which showed an increment in anti-inflammatory cytokines after treatment and restrained the activation of T cell immune response [172]. Forsythiaside A could be developed as a possible therapeutic candidate against respiratory complications.

7.3. Mangiferin

Mangiferin, a C-glucosyl xanthone, is a natural polyphenolic compound found in *Mangifera persiciformis*, *Mangifera indica*, *Anemarrhena asphodeloides*, *Salacia hainanensis*, and *Mangifera persiciformis*, along with other plant species [173]. The major source of mangiferin was reported from bark, fruits, roots, and leaves of the papaya tree, peels and kernels of mango fruits, and the leaves, heartwood, and bark of the mango tree [174]. It was reported to reduce the pathological condition that occurred due to inflammation and was effective in inhibiting inflammatory signaling and treating sepsis with acute lung injury (ALI). Mangiferin suppressed respiratory burst and dramatically reduced the expression of NF-$\kappa\beta$ and proinflammatory cytokines like IL-1, IL-6, and TNF-α [175, 176]. An *in vivo* experiment in sepsis-induced mice showed the dose-dependent action of mangiferin upregulated the action of HO-1 (heme oxygenase-1) and mediated the inflammation [177]. Mangiferin had a functional effect on the contraction of tracheal rings. It increased NOS3 protein levels and cGMP levels that prevented muscle contraction in the guinea pig. This preclinical experiment suggested mangiferin to be a potent component for treatment in human lung diseases [178]. It was found to be effective as an immunotherapeutic agent against allergic asthma. The reported results confirmed that mangiferin inhibited PGD2 expression, mediated the level of LTC4, attenuated Th2 cytokines, and displayed a significant role in reducing asthma in a mouse model [179]. The recent studies on mangiferin found the antiallergic properties using a mouse model with allergic rhinitis (AR). The use of mangiferin had a prominent effect in anti-inflammation on nasal tissues. This study further demonstrated the potential of mangiferin in treatment for AR by activating the Nrf2/H-O1 signaling pathway and inhibiting NF-κB [180]. Mangiferin also prevented the formation of the proinflammatory leukotriene LTB4 and decreased the expression of prostaglandin-endoperoxide synthase 2 [173, 181].

7.4. Glycyrrhizin

Glycyrrhizin is a triterpene glycoside made up of one molecule of 18-glycyrrhetinic acid and two glucuronic acid molecules of the composition 18-beta-glycyrrhetinic acid-3-O-beta-D-glucuronopyranosyl-(1→2)-beta-D-glucuronide [182, 183]. It is a key active ingredient reported from the root of *Glycyrrhiza glabra* [70]. To examine the effects of glycyrrhizin, a significant anti-inflammatory component found in *G. glabra* was introduced on mice with OVA-induced asthma; it resulted in the alleviation of asthma diseases by lowering the airway hyperreactivity to methacholine, OVA-induced airway constriction, and lung inflammation including significant eosinophil infiltration [70]. Glycyrrhizin was reported for its antiviral properties against a wide range of RNA and DNA viruses. By observing both *in vitro* and *in vivo* experiments, glycyrrhizin had been shown to affect SARS-CoV-2 replication, adsorption, and penetration [184]. Glycyrrhizin dosing could be employed as COVID-19 adjuvant or prophylactic therapy [185]. The data showed that applying glycyrrhizin to the nasal and oral cavities could be the first line of defense against SARS-CoV-2 infection in upper respiratory tract cells. Recent clinical studies of anosmia, hyposmia, and dysgeusia in COVID-19 patients reported the nasal and lingual epithelium serves as a gateway for SARS-CoV-2 entrance [186, 187]. This hypothesis is supported by the fact that glycyrrhizin possesses excellent physical features such as amphiphilicity and the capacity to change the characteristics of lipid bilayer membranes.

7.5. Curcumin

Curcumin is a polyphenolic compound that is biologically active and found in the roots of *Curcuma longa.* It is the active component having wide pharmacological benefits. This compound was reported to suppress inflammation and showed pulmonoprotective effects. It inhibited the NF-κB and mitogen-activated protein kinase (MAPK) signaling pathways. Treatment with curcumin attenuated the secretion of TNF-α, IFN-α, and IL-6 and deals efficiently with the complications [188]. The efficacy of curcumin was reported by various pieces of evidence in lung diseases and was found to be effective and reliable to be used in various respiratory complications like asthma, COPD, lung cancer, and other lung injuries. It was reported to reduce the degree of inflammatory cells and alleviates dysregulation [189]. Curcumin was reported to hold the ability to bind with receptors, blocked the entry of the virus into the cells, and interfered with its replication. Lung inflammation due to COVID-19 can be mediated by its uses. Some reports from *in silico* analysis supported the issue. This potential serves to recommend its implication in therapeutics in COVID-19-induced respiratory complications [190].

7.6. Zingerone

Zingerone is the major component found in the ginger root to about 9.25%. This compound was reported to be closely related to the vanillin from vanilla and eugenol from clove [191]. This compound was reported as a nontoxic compound bearing various pharmacological importance. This compound was extensively studied for its effect on lung injuries. It significantly lessened the pulmonary edema, attenuated the amount of TNF-α and IL-β in BALF, and inhibited proinflammatory cytokine release in acute

lung injury in mice [151]. The hepatoprotective effect of zingerone had been studied in the LPS-induced hepatic injury in mice in terms of liver histology, liver function marker, and several other inflammatory markers such as TNF-α, TLR4, and iNOS parameters. The zingerone-treated group showed significant improvement in liver histology, decreased endotoxin level, improved liver function markers, and downregulation of mRNA expression of TNF-α, TLR4, and iNOS indicating better anti-inflammatory activities.

7.7. Vitexin

Vitexin (apigenin-8-C-β-D-glucopyranoside) is a flavone glycoside of apigenin found in food and medicinal plants such as the hawthorn leaf [192], bamboo [193], buckwheat [194], Passiflora [195], and Echinodorus [196]. Vitexin was reported as a significant polyphenol present in foods such as mung beans [197], which are frequently utilized in traditional Chinese medicine [192]. In the gastrointestinal tract, vitexin is poorly absorbed. It is rapidly eliminated from the bloodstream, primarily eliminated in the urine and bile [198]. This compound is reported to have very poor absolute oral bioavailability and is quickly and broadly disseminated throughout the body. The buildup of reactive oxygen species (ROS) exacerbated inflammatory reactions by boosting the release of proinflammatory cytokines and inflammatory cell infiltration [199]. When compared to vehicle-treated mice, vitexin administration reduced LPS-induced ROS levels by 44%. Vitexin therapy reduced neutrophils and the production of proinflammatory cytokines. This compound reduced pulmonary edema and protein concentration in the alveoli. The activity of Nrf2 and HO-1 was significantly increased after treatment with vitexin. Vitexin also boosted the activity of its target gene, heme oxygenase (HO)-1, via activating nuclear factor erythroid-2-related factor 2 (Nrf2) [103].

8. Conclusion and Future Perspective

In this review, the drawbacks and limitations of currently adopted treatment procedures and available drugs have been highlighted. This study also reported the several plant species that are being used in the treatment of respiratory complications in the traditional medicinal system based on traditional knowledge and indigenous knowledge. The reported bioactive compounds and their mechanism of action have been critically analyzed for possible therapeutic compounds. Some of the plant products are promising against respiratory diseases and can be the best source of alternative medicine. Although, some clinical shreds of evidence have been reported for some of the compounds, there needs to be an extensive study on the toxicological aspect and interaction with other therapeutics. The detail studies on the formulations, forms of doses, evaluation of pharmacokinetic parameter, and safety are necessary. The future study should focus on the identification and isolation of more effective compounds, their mechanism of action, and formulations. This study can facilitate the newly discovered compounds to

enter a clinical trial. Therefore, it is concluded that further research on the traditionally used plants and plant-derived products could lead to the discovery of a new kind of therapeutic drug of high potential and interest.

Conflicts of Interest

The authors declare no potential conflict of interest.

Authors' Contributions

D.T. conceived the idea and prepared the first draft of the manuscript. D.B. and K.P. searched the literature and added it to the manuscript. D.T. supervised the project and revised the manuscript. All authors read and approved the final version of the manuscript before submission.

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