

# Asthma and chronic obstructive pulmonary disorder - phytomedicine

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## Abstract

Asthma and chronic obstructive pulmonary disorder (COPD) are well known chronic inflammatory respiratory disease affecting millions of people worldwide. Asthma originates in childhood, is associated with allergies and related to eosinophils, whereas, COPD occurs in adults who smoke, due to involvement of neutrophils. The current allopathic system of medicine aims to alleviate symptoms rather than cure, basically these treatments include anti-inflammatory therapy, corticosteroids, and bronchodilators. Over use of some therapies can lead to adverse effects among patients, such as pneumonia and cardiac comorbidities. Nowadays, the interest of people diverts toward the area of phytomedicine. Phytomedicine is a plant-based traditional medical practice which provides an alternative source or as an add-on therapy to the existing one. Some herbs, such as *Khella* and *Lobelia* are widely used as vasodilators and bronchodilators having no side effects. This review focuses on recent human clinical trials using plant-based medicines for treatment of asthma and COPD.

**Key words:** Asthma, bronchodilators, chronic obstructive pulmonary disorder, phytomedicine, pathophysiology, traditional Chinese medicines

## INTRODUCTION

Asthma and chronic obstructive pulmonary disorder (COPD) are characterized as different diseases with unique features and mechanisms. Asthma is an allergic disease that can develop during childhood, can also be diagnosed in adults. It is characterized by airway hyperresponsiveness that leads to reversible airway obstruction. COPD is a chronic respiratory disease that is linked to smoking tobacco, usually, presents in 40 years of age, and is characterized by progressive and irreversible airway obstruction.<sup>[1,2]</sup> It is characterized by symptoms such as respiratory problems, including wheezing, shortness of breath, chest tightness, and coughing.<sup>[3]</sup> Asthma and COPD are common inflammatory obstructive lung diseases which affect many millions of people worldwide.<sup>[4,5]</sup> While in basic and clinical research has led to important advances, both conditions are increasing day-by-day. Although mortality rates for asthma are relatively low, representing only 1%.<sup>[6]</sup> Current treatment for allergic asthma includes steroidal anti-inflammatory compounds,

leukotriene antagonists, bronchodilators, and recent anti-IgE antibody. These drugs are still with certain shortcomings such as side effects, effectiveness, and cost.<sup>[7]</sup> Thus, there is a need to consider other therapeutic options including phytomedicine.

Phytomedicine is defined as a plant-based traditional medical practice that uses plant materials in modalities considered both preventive and therapeutic.<sup>[8]</sup> The word "Phyto" derives from the Greek means plant; hence, it means plant-based medicine. Phytomedicine is rooted in scientific research.<sup>[9]</sup> Current treatments such as that of steroids, bronchodilators, and anti-IgE antibodies have shortcomings side effects and cost-effective. Therefore, complementary methods such as Chinese, Japanese, and Indian herbal medication have been very much improved. However, our study focuses only on Indian and Chinese herbal treatments available for treating asthma and COPD.<sup>[10]</sup>

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**Received:** 15-10-2016

**Revised:** 20-03-2017

**Accepted:** 22-07-2017

## SIMILARITIES AND DIFFERENCES BETWEEN COPD AND ASTHMA

Cause of asthma is unknown but many factors play a part.

### Genetic Factors

Asthma and COPD tends to run in the family.

### Environmental Factors

Pollen, dust, mold, and tobacco smoke.

### Occupational Exposure

Chemicals and gases.

Summarization of similarities and differences between COPD and asthma is shown in Table 1.

## EPIDEMIOLOGY

### COPD

COPD is the fourth leading cause of death in the United State of America (USA). In 2001, the World Health Organization reports that COPD was the fifth cause of death in high-income

countries and the sixth leading cause of death in middle-income countries.

COPD usually presents in middle age, is slowly progressive and is associated with the history of cigarette smoking in 75-90% of patients.<sup>[14]</sup> Patients usually present with a chronic productive cough is not a frequent finding. Clinical symptoms are slowly progressive, and airflow limitation is only partially reversible after tobacco cessation and bronchodilator use. T lymphocytes, with macrophages and neutrophils, are the predominant inflammatory cell types.

Recent studies concluded that women as compared with men shows a higher incidence of asthma-COPD overlap and also that all-cause mortality is greater in younger participants and women with overlap of asthma-COPD than participants suffering from asthma and COPD alone.

### Asthma

In 2005, an estimated 22.2 million Americans had asthma: 6.5 million children and 15.7 million adults. The public health impact of asthma is significant. In 2003, asthma accounted for 1.4 deaths/100,000 persons in the USA.<sup>[15]</sup> According to the National Center for Health Statistics, in 2003, children between the age of 5 and 17 years with a history of at least one asthma attack in the previous year accounted for 12.6 million missed school days, and adults with a history of at least one asthma attack in the previous year account for 10.1 million missed workdays.

**Table 1: Summarization of similarities and differences between COPD and asthma<sup>[11-13]</sup>**

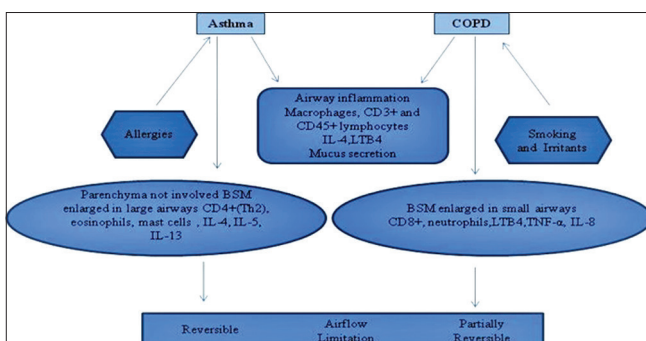
Symptoms	Asthma	COPD
	Chronic coughing, wheezing, shortness of breath, chest tightness, and spasms in bronchioles. Symptoms go away between episodes	Decreased airflow, increased inflammation, spasms in the bronchioles, and morning cough with phlegm. Symptoms never disappear, but progressively worsen
Nature of cough	Dry	"Productive" (yields mucus)
Diagnosis	Physical exam, medical history, including history of allergies typically in children	Spirometry measures lung function and capacity, CT scans typically in adults over 40 current or former smokers
Classical presentation	Younger patient, recurrent episodes of wheezing and coughing, accompanying tight chest, and breathlessness. Symptoms quickly respond to bronchodilators	Older patient, smoker or former smoker, progressive shortness of breath and cough with mucus, accompanied by decreased physical activity. Responds to bronchodilator, but the lung function does not return
Triggers	Allergens, cold air, and exercise	Environmental pollutants, respiratory tract infections – pneumonia, influenza
Risk factors	Allergies, eczema, and rhinitis	Asthma, smoking
Medical treatment	Bronchodilators airway opening medication inhaled corticosteroids to reduce inflammation oral steroids for moderate to severe cases	Bronchodilators airway opening medication pulmonary rehabilitation oxygen support for advanced stages hospitalization
Lifestyle changes	Cease smoking, avoid allergens, and air pollution	Cease smoking, avoid air pollution

COPD: Chronic obstructive pulmonary disorder

## PATHOPHYSIOLOGY

Asthma and COPD are diseases that cause chronic inflammation of the airways but have distinct characteristics. In asthma, mast cells, eosinophil, and cluster of differentiation 4 (CD4), T-lymphocytes represent the predominant cell types in the inflammatory process. In contrast, COPD demonstrates a greater number of neutrophils, macrophages, and CD8 T lymphocytes.<sup>[16-18]</sup> Pathophysiology for asthma and COPD shown in Figure 1.

Asthmatic patients have airway obstruction which is characterized by bronchoconstriction through the activation of the smooth muscle and membrane thickening. These alterations are positively correlated with the frequency of asthma attacks and bronchial hyper responsiveness.<sup>[19,20]</sup> COPD patients exhibit a reduced airway caliber, which is associated with cell damage is induced by external toxic agents, especially cigarette smoke, through reactive oxygen species.<sup>[21,22]</sup> The presence of goblet cells (mucous metaplasia) in the small airways and mucous hypersecretions results from the process of airway narrowing.<sup>[23,24]</sup> Despite the prevalence of inflammation in COPD, which occurs because of the presence of neutrophils and macrophages, several studies have demonstrated the presence of eosinophilic inflammation both in stable patients and in patients with acute exacerbations of the disease.<sup>[25]</sup> In exacerbations of COPD and asthma the pattern of inflammation is similar. During exacerbations of asthma triggered by viruses, there can be increases in the number of neutrophils in addition to the proliferation of eosinophils. Moreover, in COPD exacerbations, there may be an increase in eosinophil numbers.<sup>[26]</sup> This helps explain the prescribing of corticosteroids to COPD patients to manage an acute exacerbation or frequent exacerbations.<sup>[27]</sup> In asthma, airway obstruction results from constriction of bronchial smooth muscle, airway hyperreactivity to allergens, and inflammation accompanied by increased eosinophils and activated T-cells. In COPD, airway smooth muscle is not usually constricted and obstruction is associated mainly with mucus hypersecretion and mucosal infiltration by inflammatory cells, leading to cellular damage, and the loss of alveolar structure and structural changes associated with COPD interfere with oxygenation and pulmonary circulation.



**Figure 1:** Pathophysiology for asthma and chronic obstructive pulmonary disorder

## TEST AND DIAGNOSIS

Lung (pulmonary) function tests to determine how much air moves in and out as you breathe. These tests may include:

- Lung function test: In asthma, the finding of airflow obstruction that is characterized by a decrease of VEF1/FVC with a disorder reversal after the administration of a bronchodilator is the mainstay in the diagnostic confirmation of the disease. However, many patients may present with a reversal after the use of a bronchodilator without exhibits normalization in pulmonary function tests, thus indicating signs of bronchial remodeling. Moreover, clinically stable patients may present with normal spirometry but a positive bronchial provocation test. The use of the FEV1/FVC ratio remains the most widely accepted parameter for diagnostic confirmation.

In COPD, a post-bronchodilator FEV1 < 85% that is associated with a FEV1/FVC ratio < 70% confirms the obstructive disorder, which is characterized by a lack of complete reversibility of airflow. However, a significant response to the bronchodilator does not exclude a COPD diagnosis.<sup>[28]</sup>

- Spirometry: This test estimates the narrowing of your bronchial tubes by checking how much air you can exhale after a deep breath and how fast you can breathe out.
- Peak flow: A peak flow meter is a simple device that measures how hard you can breathe out. Lower than usual peak flow readings are a sign your lungs may not be working as well and that your asthma may be getting worse. Your doctor will give you instructions on how to track and deal with low peak flow readings.<sup>[29]</sup>

Lung function tests often are done before and after taking a medication called a bronchodilator, such as albuterol, to open your airways. If your lung function improves with the use of a bronchodilator, it is likely you have asthma.

### Additional Tests

Other tests to diagnose asthma and COPD include:

- Methacholine challenge: Methacholine is a known asthma trigger that, when inhaled, will cause mild constriction of your airways. If you react to the methacholine, you likely have asthma. This test may be used even if your initial lung function test is normal.
- Nitric oxide test: This test, though not widely available, measures the amount of the gas, nitric oxide that you have in your breath. When your airways are inflamed - a sign of asthma - you may have higher than normal nitric oxide levels.
- Imaging tests: A chest X-ray and high-resolution computerized tomography scans of your lungs and nose cavities (sinuses) can identify any structural abnormalities or diseases (such as infection) that can cause or aggravate breathing problems.

- Allergy testing: This can be performed by a skin test or blood test. Allergy tests can identify allergies to pets, dust, mold, and pollen. If important allergy triggers are identified, this can lead to a recommendation for allergen immunotherapy.
- Sputum eosinophils: This test looks for certain white blood cells (eosinophils) in the mixture of saliva and mucus (sputum) you discharge during coughing. Eosinophils are present when symptoms develop and become visible when stained with a rose-colored dye (Eosin).
- Provocative testing for exercise and cold-induced asthma. In these tests, your doctor measures your airway obstruction before and after you perform vigorous physical activity or take several breaths of cold air.<sup>[30]</sup>

## CURRENT TREATMENT

Current treatment for asthma and COPD include the pharmacological and non- pharmacological managements in pharmacological management drugssteroidal anti-inflammatory compounds, leukotriene antagonists, bronchodilators, and recent anti-IgE antibody. These drugs are still with certainshortcoming such as side effects, effectiveness, and cost mentioned in the Table 2.

## Non-Pharmacological Management of Asthma and COPD<sup>[33]</sup>

Non-pharmacological management of asthma and COPD includes some life modification, surgical options and other therapies as listed below.

- Smoking cessation
- Immunization
- Pulmonary rehabitalisation
- Non-invasive ventilation: Acute and chronic
- Long-term oxygen therapy
- Ambulatory oxygen therapy
- Short burst oxygen therapy
- Extracorporeal membrane oxygenation
- Lung volume reduction surgery (LVRS)
- Lung transplant
- End-of-life (EOL) care.

## PHYTOMEDICINE IN THE TREATMENT OF ASTHMA AND COPD

In recent years, natural products have received great attention for disease prevention because of the health benefits and noticeable lack of toxicity and side effects.<sup>[34]</sup> Many dietary plant, fruits, vegetables, medicinal plants, and herbs contain

**Table 2:** Pharmacological management of asthma and COPD<sup>[31,32]</sup>

Class	Drugs	Mechanism of action	Side effects
Corticosteroids			
Inhaled	Beclomethasone, budesonide	Inhibition of cytokines,	Sore throat, voice
Systematic	fluticasone propionate, flunisolide, and ciclesonide	lymphocytic, and eosinophilic	changes, and allergic reaction muscle weakness, and weight gain
	Hydrocortisone, prednisolone		
Bronchodilators			
Long acting $\beta_2$ agonist	Salbutamol, salmeterol,	Inhibit the release of	Blurry vision, rapid heart
Short acting $\beta_2$ agonist	indacaterol	bronchoconstrictor mediators	rate, and an allergic reaction with rash or swelling
	Albuterol, levabuterol	from inflammatory cells and neurotransmitters	
Anticholinergics	Ipratropium bromide, tiotropium bromide	Competitively inhibit the cholinergic receptors in bronchial smooth muscle, block Ach	Closed-angle glaucoma, eye pain blurry vision
Methylxanthines	Theophylline, aminophylline	Inhibits the cyclic nucleotide 5' phosphodiesterase (PDE)	Nausea or vomiting, tremors, and trouble sleeping
Anti-leukotrienes	Montelukast, zafirlucast	Inhibit the cystenyl leukotrienes mediators	Dyspepsis, insomnia liver dysfunction, diarrhea
Mast cell stabilizers	Sodium cromoglycate and ketitofen	Inhibits degranulation of mast cells by trigger stimuli	Sedation irritation headache
Phosphodiesterase 4 inhibitors	Refluminast	Inhibition of breakdown of intracellular cyclic AMP	Reduce appetite, abdominal pain, sleep disturbance, nausea
Anti-IgE antibody	Omalizumab	Inhibit the binding of IgE to mast cells	Hoarseness of voice, sore throat

various phytochemical constituents, such as alkaloids, nitrogen compounds, and vitamins.<sup>[35]</sup> Phytomedicine is known as the branch of plant-based traditional medical practice that uses various plant materials considered both preventive and therapeutic. Herbs usually naturally contain many important chemicals and thus medicines derived from such sources can have multiple health benefits when administered to patients. Because of the presence of many active compounds in phytomedicines, they are an ideal candidate for treating conditions with a variety of symptoms such as inflammatory diseases which basically affect multiple systems.

Historically, particularly in Chinese and other Asian cultures, plant-based medicines have been used to treat and prevent lung disease, and to this day remain a major therapeutic option; thus, the idea of using plant-derived medicines for treatment of asthma and COPD is not a latest concept. However, despite the antimucus secreting properties and smooth muscle relaxant effect, atropine was found to be ineffective in improving the symptoms of asthma in clinical trials.<sup>[36]</sup> Atropine remains a treatment of cardiac bradyarrhythmias, and has been used successfully in the treatment of conditions such as amblyopia, also known as lazy eye.<sup>[8]</sup>

Various phytomedicines for treating asthma are available. These are Oregano, Ginkgo Biloba, Ginger, Garlic, Slippery Elm, Liquorice, Turmeric, Lemongrass, Stinging Nettle, and Bishop's Weed.

### Oregano

Contains carvacrol, flavonoids, and terpenes that work as lung-cleansing elements.

### Ginkgo Biloba

Contains antihistamine properties that help treat asthma.

### Ginger

Helps reduce airway inflammation and inhibit airway contraction. Garlic is a popular medicinal herb helps in clearing congestion in the lungs. In addition, its antibiotic and antiviral properties help boost immunity and fight infections that can trigger asthma.

### Slippery Elm

Is another effective herb having anti-inflammatory properties that helps thin the mucus that clogs the airways.

### Liquorice

Has a systemic anti-inflammatory effect on the lungs, which helps reduce inflammation of the bronchial tubes, calm the

airways, and restore normal breathing. In addition, it has immune-stimulant properties.

### Turmeric

Is a powerful herb to prevent asthma attacks and other allergies. It contains the active ingredient curcumin, a powerful antioxidant and anti-inflammatory compound that helps fight asthma symptoms.

### Lemongrass

It is widely used in traditional medicines for treating asthma, coughs, and other respiratory disorders. It also has antibacterial and antifungal properties that help reduce inflammation and fight infections. In addition, it has Vitamin C that boosts your immune system.

### Stinging Nettle

Is an excellent treatment for allergy-related asthma. This herb contains natural antihistamines and anti-inflammatory properties that help open up constricted bronchial and nasal passages to relieve asthma symptoms. In addition, it is rich in butyric acid, which helps maintain a healthy immune system and metabolism.

### Bishop's Weed

Commonly known as carom seeds or ajwain, is also useful for treating asthma. It exerts a strong antispasmodic effect on the inflamed bronchioles, which in turn relieves asthma symptoms.<sup>[8]</sup>

The various remedies for COPD are Omega 3 having beneficial anti-inflammatory effects, Essential amino acids, which are basically building block of protein improves cognitive function, quality of life, and muscle strength, especially in underweight people, antioxidant vitamins such as Vitamin A, C, and E, Essential oils such as Myrtle, Eucalyptus oil, and Orange oil that can reduce airway inflammation, *zataria multiflora*.

List of some other phytomedicines with their plant origin<sup>[37]</sup>:

- *Angelica sinensis* (Bark/root/leaf extract)
- *Hedera helix* (Leaf extract)
- *Jinshuilijun* (Decoction)
- *Stephaniatetrandra* (Root)
- *Allium sativum L.* (Bulb).

## PLANT-BASED THERAPIES FOR ASTHMA

### Anti-asthma Herbal Medicine Intervention (ASHMI)

Plant-based medicine a number of plant-based medicines have shown promising results in studies of asthma, such as

ASHMI. ASHMI is a combination of three extracts; Ling Zhi from Ganoderma lucidum, Ku Shen from Sophora flavescens and Gan Cao from Glycyrrhiza, which has shown potential for the treatment of asthma in both *in vitro* and *in vivo*. A native tree of Indonesia and India which is used in traditional remedies not only for the treatment of asthma but for pain, fever, and headaches.<sup>[37]</sup> ASHMI had a beneficial effect on both TH1 and TH2 cytokine levels and absolutely no adverse effects on adrenal function in the study participants.

### ***A. mollucana***

More recently, the antinociceptive effects of *A. mollucana* and its mechanical antihypersensitivity activities have been investigated. *A. mollucana* has also been found to possess antiviral and antimicrobial properties showing how the existence of multiple active compounds in plant extracts can have several benefits to patients. Due to this historical link between *A. mollucana* and antinociceptive and anti-inflammatory therapies, *A. mollucana* extracts have been used to produce analgesic and anti-inflammatory phytomedicines. There is a possibility for the active compounds of *A. mollucana* to be adapted to produce a phytomedicine for asthma and its related symptoms.<sup>[38]</sup> The results were very positive.

### ***Nigella sativa***

A plant native to Southeast Asia is known for its relaxing effect on smooth muscle tissue. In addition, Boskabady and colleagues have demonstrated that extracts and oils from *N. sativa* have inhibitory effects on histamine (H<sub>1</sub>) receptors, stimulatory effects on  $\beta$ -adrenergic receptors and antitussive effects.<sup>[35]</sup>

To translate these promising *in vitro* findings Boskabady and colleagues set out to investigate the effect of boiled *N. sativa* extract on lung function in asthmatic patients.<sup>[36]</sup> In this study, they compared the bronchodilatory effects of *N. sativa* with those of theophylline in 16 asthmatics. They found that *N. sativa* did induce bronchodilation within 35 min of administration, but the magnitude was significantly less than observed with theophylline and that both agents were significantly less effective than beta-2 agonist salbutamol. Nonetheless, they concluded that *N. sativa* has relatively potent bronchodilatory effects but when given orally it is less effective than conventional bronchodilators. It is possible that the bronchodilatory effects of compounds such as *N. sativa* could be enhanced if formulated as inhaled therapy with delivery of the active compounds directly to the airway.<sup>[8]</sup> Tianjiu therapy in Sanfu days Zhu *et al.* studied the effect of Tianjiu therapy in Sanfu days for treatment of asthmatic children. Tianjiu therapy in Sanfu days is a classic prevention treatment for asthma.<sup>[37]</sup> Sanfu Days means the three hottest days in a year, which are calculated by ancient calendar. The results suggested that Tianjiu therapy could decrease the asthma attack.

## **PLANT-BASED THERAPIES FOR COPD**

Evidence from three double-blind placebo-controlled studies enrolling a total of 49 individuals suggests that the supplement L-carnitine can improve exercise tolerance in COPD, presumably by improving muscular efficiency in the lungs and other muscles.

Eucalyptus is a standard ingredient in cough drops and in oils sometimes added to humidifiers. A combination essential oil therapy containing cineole from eucalyptus, d-limonene from citrus fruit, and alpha-pinene from pine has been studied for a variety of respiratory conditions. Because these oils are all in a chemical family called monoterpenes, the treatment is called essential oil monoterpenes. A 3-month, double-blind trial of 246 individuals with chronic bronchitis found that oral treatment with essential oil monoterpenes helped prevent acute flare-ups of chronic bronchitis. A previous double-blind study, too small to provide reliable results, hints that oral use of 26 essential oil monoterpenes can enhance the effects of antibiotics for acute flare-ups once they do occur. It is thought that essential oil monoterpenes work by improving the lungs' ability to clear secretions.

A mixture of extracts from echinacea, wild indigo, and white cedar has shown promise for treating a variety of respiratory infections. A well-designed double-blind, placebo-controlled trial of 53 people tested its benefits in acute exacerbations of chronic bronchitis.<sup>[39]</sup> All participants in this trial received standard antibiotic therapy. The results showed that people receiving the herbal medication experienced more rapid improvements in lung function than those given placebo.

In one poorly designed and reported study, use of an Ayurvedic herbal combination appeared to offer some 36 benefit. It has been suggested that the sports supplement creatine might improve muscle strength in people with COPD, but results from small double-blind studies have been inconsistent. Slight evidence from a small open trial suggests that coenzyme Q improves lung function in individuals with COPD.<sup>[40,41]</sup> The herbs ivy leaf and plantain have been suggested for chronic bronchitis, but there is no meaningful evidence that they actually help.<sup>[42]</sup> One study failed to find pomegranate juice helpful for COPD.

Qigong is an ancient form of Traditional Chinese Medicine consisting of deep breathing accompanied by slow, rhythmic movements. It is intended to promote the healthy flow of "qi" (or vital "energy") within the body. In a randomized trial involving 206 patients with COPD, Qigong appeared to improve respiratory function and activity tolerance.<sup>[43]</sup> In another trial, 80 people with COPD were randomized to receive Qigong or conventional rehabilitation for 6 months. At the end of the trial, there were no significant differences between the two groups.<sup>[44]</sup>

Cineole (Eucalyptus, Myrtaceae) has positive effects on the beat frequency of the cilia and bronchodilation, it may show positive influence on the exacerbations of COPD and lung function tests. Patients who received 200 mg of cineole tablets three times a day had a reduction of exacerbations such as dyspnea and improvements of lung function and health status.<sup>[44]</sup>

- Astragalus (Milk Vetch Root, Huang Qi, Leguminosae) and *Codonopsis pilosula* are used for their immune modulatory and anti-inflammatory effects. The effects of Astragalus polysaccharides (APS) and *C. pilosula* polysaccharides on alveolar macrophage (AM) phagocytosis and inflammation in COPD.<sup>[8]</sup>
- *Pseudolysimachion rotundum* var. *subintegrum* (Speedwell, Plantaginaceae) is used as a traditional herbal medicine for treating bronchitis inflammation, autophagy has been recently reported to contribute to COPD.

## CONCLUSION

Although COPD and asthma are two different forms of chronic pulmonary disease, there is considerable overlap in presentation and management. Both conditions are caused by an interaction between intrinsic, genetic factors, and environmental exposures. Treatment of these diseases is similar in that they can both be managed with pharmacological and non-pharmacological strategies focused on treating bronchoconstriction and airway inflammation. The current treatment shows the adverse effect related to their high dose will surely hamper their prestige in the upcoming years. To conclude, we can say that phytomedicine field also needs to be explored because there is a lack of proper evidence, but it has huge potential as lesser side effects are associated than conventional treatment. Thus, in coming era the phytomedicines will outshine.

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**Source of Support:** Nil. **Conflict of Interest:** None declared.