



A comprehensive review of the selected Flora of Iran on improving symptoms of Chronic Obstructive Pulmonary Disease (COPD)

Ali Lotfi Orimi¹, Alireza Shahriary², Reza Mohtashami², Parsa Ghorbanpourkhamse¹, Ebrahim Salimi-Sabour^{3*}, Sakineh Dadashpour⁴

¹Student Research Committee, Baqiyatallah University of Medical Sciences, Tehran, Iran.

²Chemical Injuries Research Center, Systems Biology and Poisonings Institute, Baqiyatallah University of Medical Sciences, Tehran, Iran.

³Department of Pharmacognosy and Traditional Pharmacy, Faculty of Pharmacy, Baqiyatallah University of Medical Sciences, Tehran, Iran.

⁴Department of Medicinal Chemistry and Radiopharmacy, Faculty of Pharmacy, Baqiyatallah University of Medical Sciences, Tehran, Iran.

***Corresponding author:** Ebrahim Salimi-Sabour, Assistant Professor of Pharmacognosy, Department of Pharmacognosy and Traditional Pharmacy, Baqiyatallah University of Medical Sciences, Tehran, Iran, Email: e.salimisabour@gmail.com

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ABSTRACT

A partially irreversible expiratory airflow restriction, uncontrolled chronic inflammation, and emphysematous lung damage are the hallmarks of chronic obstructive pulmonary disease (COPD), a leading cause of mortality and morbidity in the globe. The standard treatments for COPD are still palliative, and there are no regenerative methods for disease management currently, despite the fact that it is a constantly expanding worldwide healthcare concern. Mustard gas is an alkylating chemical warfare agent that has respiratory side effects causing airway obstructive disease and bronchiectasis. Chronic pulmonary involvement following exposure to mustard gas, is known as “mustard lung” is considered a form of COPD. Herbal medicines can be used to treat COPD and in the present study, we aim to provide an overview of key pre-clinical and clinical studies addressing herbal therapy of COPD and mustard lung, using the flora of Iran, published in the past decades.

Keywords: *Chronic Obstructive Pulmonary Disease, COPD, Mustard Gas, Mustard Lung, Herbal Medicine, Phytotherapy*

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a persistent and ongoing lung condition. The World Health Organization (WHO) has listed it as the fourth most common cause of death. The symptoms of COPD include persistent cough, excessive sputum production, chest tightness, and functional shortness of breath. According to studies, COPD will move up from seventh to fifth place in terms of disability adjusted life

years (DALYs) by 2030. An exaggerated inflammatory response to inhaled particles and gases in the lungs is one of the harmful processes that make up the pathophysiology of COPD. Additionally, extracellular matrix breakdown (protease/antiprotease imbalance), oxidative stress (oxidant/antioxidant imbalance), improper cell repair, inappropriate cellular maintenance programs, inability to resolve inflammation, and apoptosis are involved in pathogenesis of COPD.

Genetic and epigenetic variables affect how the body reacts inflammatorily on exposure to active and passive tobacco smoking, as well as to urban and rural air pollution. Mucus hypersecretion, airway remodeling, and alveolar damage are the results of the ensuing chronic inflammatory reactions. In order to diagnose COPD, pulmonary function tests has long been regarded as the gold standard. Some studies have demonstrated the effectiveness of herbal remedies, including Chinese medicine and medicinal plants or their derivatives from other nations, in treating COPD by lowering the intensity and frequency of exacerbations, enhancing quality of life, and lung function. Newer research has also shown that herbal medication has an anti-inflammatory and antioxidant impact on COPD. In the current study, we examined the pre-clinical and clinical trials on the effectiveness of herbal treatments for COPD. Mustard gas or Sulfur Mustard (SM) is an alkylating and vesicant chemical warfare agent which has been used by Iraqi troops in the war between Iraq and Iran. SM has short and long-term side effects . Studies show that the most prevalent long-term disorders caused by SM have a respiratory nature, with symptoms including coughing, sputum, hemoptysis, and chest pain. Airway obstructive disease, bronchiectasis, and pulmonary fibrosis are common in SM-exposed patients. Mustard lung (ML) is considered a form of COPD. Cellular and molecular structural changes in the airway wall under the concept of airway remodeling, are one of the major pathological consequences in ML patients and their clinical picture is similar to what is seen in COPD patients.

METHODS

A first step towards reviewing the available data

on phytomedical studies, was to understand that this was a science mostly developed under the influence of cultural and geographical factors. Different plants have historically been growing in different regions of the world. Therefore, it would be more efficient to focus our attention towards the studies conducted in the place we ourselves lived, i.e. the Iranian flora. We also considered countries sharing geobotanical characteristics with the Iranian flora, including India, Pakistan, Iraq, and Afghanistan. As the first stage, electronic databases including (1) PubMed; (2) SCOPUS; and (3) Web of Science; were searched, from their respective inception to March 2022. We used search functions to combine the country of origin and affiliation of authors with search terms such as “chronic bronchitis”, “chronic obstructive pulmonary disease”, “COPD”, “lung injury”, and “sulfur mustard”. At this stage, a very broad and less specific approach was taken, and every study conducted in the aforementioned countries with the above keywords in their title or abstract was considered. More than 9200 articles were reviewed. Based on the titles and abstracts we came to a list of plants. These plants or their specific ingredients were the focus of a clinical or animal study regarding COPD or COPD-like conditions. Although expected to yield the fewest results, we implemented a third stage in our study in which we performed a global search on all the specific plants or ingredients of the 2nd stage, regardless of the country of origin. This way, the possibility of a certain plant being studied outside our designated zone was also considered. In the end we also excluded all the titles studying complex traditional formulas containing extracts from multiple plants or ingredients.



FIGURE 1: Researches conducted in the designated areas were included in this review.

Herbal medicine

Traditional medicine's foundation, pharmacognosy, and usage of medicinal plants are studied in herbal medicine. In 21st-century herbalism, which typically lacks criteria for purity or dose, there is little scientific data supporting the safety and effectiveness of plants. Minerals, shells, and some animal parts are frequently used in herbal medicine, along with fungi and bee products. Using unprocessed plant or animal extracts as suspect medications or health enhancers is known as "paraherbalism", an alternative and pseudoscientific approach. There is no evidence to support the idea that maintaining different compounds from a single source with less processing is safer or more effective than using manufactured goods, which is the foundation of paraherbalism. According to estimates from the WHO, certain Asian and African nations' populations currently utilize herbal medicine as a component of basic healthcare. Artemisinin, digitalis, quinine, and taxanes are just a few of the pharmaceutical medications that have their roots in herbal formulations. People with chronic illnesses including cancer, diabetes, asthma, and end-stage renal disease use herbal therapies more frequently than those without such conditions. The prevalence of the use of herbal treatments has also been linked to a number of variables, including gender, age, ethnicity, education, and socioeconomic status.

Inflammation, Oxidative Stress and Herbal Medicine

An uncontrolled inflammatory response, is the primary cause of a wide range of disorders, including allergies, cardiovascular dysfunctions, metabolic syndrome, cancer, and autoimmune diseases, placing a significant financial burden on individuals and, as a result, on society. On the other hand, inflammation is a defense response of our body to harmful stimuli, such as allergens and/or tissue injuries. There are several treatments available to regulate and decrease inflammatory crises; steroids, nonsteroidal anti-inflammatory agents, and immunosuppressants are some of the examples, all of which have been known to cause side effects. In order to improve

pharmacological response and minimize unfavorable results, natural anti-inflammatory (primarily herbal) agents may be included in drug therapy. The primary sources of information on herbal medications are complementary, alternative, and traditional therapies, however modern medicine must first validate these recommendations using scientific techniques.

Redox process, which can occur as a part of the inflammatory response, is responsible for the production of reactive species in biological systems. Toxic reactive oxygen and nitrogen species, including hydrogen peroxide, organic peroxides, hydroxyl radicals, superoxide anions, and nitric oxide, are produced as a result of a disruption in pro-oxidant/antioxidant equilibrium. Reactive species are known to cause cellular damage, oxidation of macromolecules, and inactivation of metabolic enzymes. Similarly, oxidative stress has been linked to more than 100 pathologies, including cancer, aging, atherosclerosis, diabetes, cardiovascular disease, pancreatic and liver disease, joint disorders, cardiac fibrosis, acute respiratory distress syndrome, neurological diseases (such as amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease, and Alzheimer's disease), and more. Integrated antioxidant systems, which contain both enzymatic and non-enzymatic antioxidants, counteract the toxicity of reactive species. Free radicals (pro-oxidants) are eliminated or quenched as part of antioxidant treatments or defenses to safeguard biological locations. Medical plants can not only reduce oxidative damage but also play a crucial part in maintaining health and preventing chronic degenerative disorders.

COPD and Mustard Lung

COPD, especially in view of cigarette smoke (CS) effect, can be considered a very complex disease. CS as the main initiator of the disease process, contributes to formation of Reactive Oxygen Species (ROS) which leads to increased oxidative stress (further discussed above). This process causes lung damages and induces cellular senescence, initiating an abnormal and exaggerated immune response that leads to chronic inflammation. Cell death involving

necroptosis and autophagy is also a major part of the COPD equation. (Fig. 2)

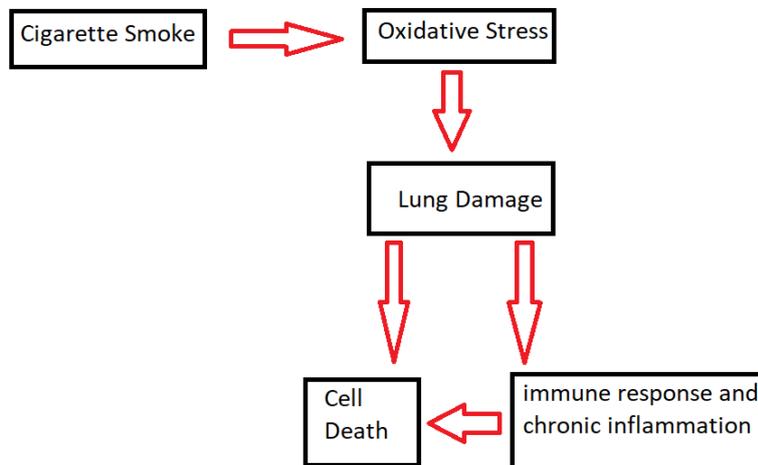


FIGURE 2: A simplified look into the pathogenesis of COPD

Mustard gas, a compound used in chemical warfare, on top of its widespread systemic effects, can cause a similar chronic condition in

lungs, with tissue fibrosis being a major component. This process is summarized in Fig. 3.

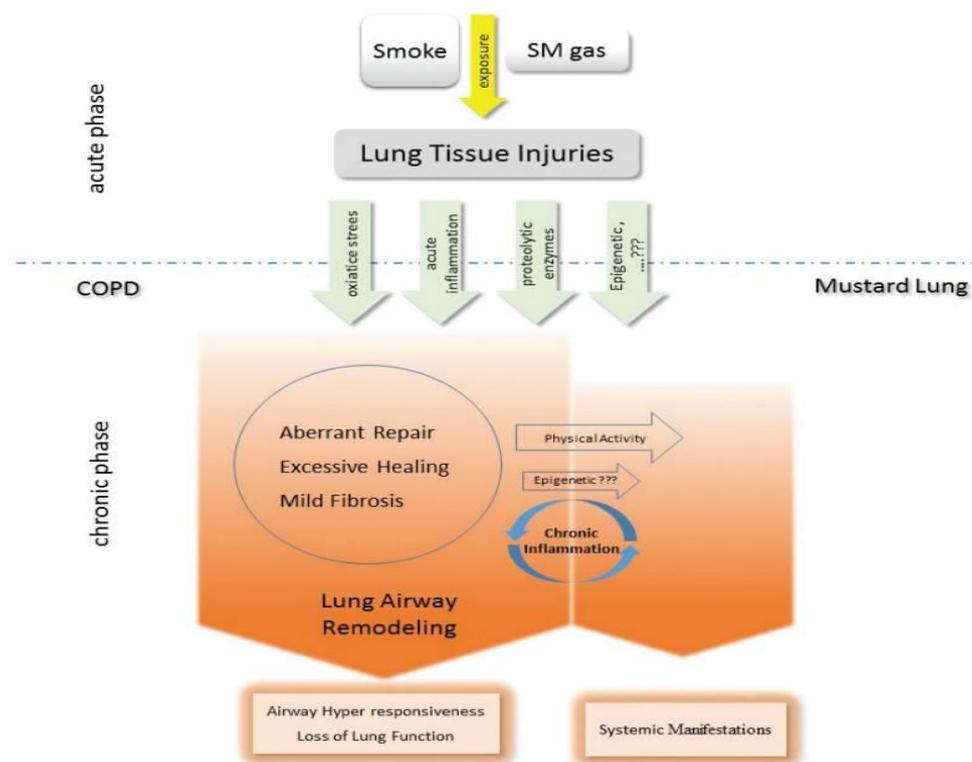


FIGURE 3: A summary of mustard gas effects on the respiratory system.

Animal Model of COPD

The fundamental mechanisms of chronic obstructive pulmonary disease (COPD) are elucidated using animal models of inflammatory processes and COPD. Several animal species, including rats, dogs, guinea pigs, monkeys, and sheep, have been utilized as COPD models; however, the most suitable model relies heavily on the study's objectives. The evaluated publications state that rats, mice, and guinea pigs are typically used as animal models for COPD. This model was created in the majority of research by inhaling cigarette smoke (CS), intra-tracheal lipopolysaccharide (LPS), and intranasal elastase. The inducers utilized in various experiments varied in terms of their dosage and time period. In most research, lung pathology information and lung inflammation (both inflammatory cells and inflammatory mediators) were the primary assessed parameters, while tracheal responsiveness (TR) was only examined in a small number of investigations.

COPD and Herbal medicine

Animal Studies

Prior to testing a drug on a final target population, i.e., people, preclinical investigations are carried

out through in-vitro, in-vivo, ex-vivo, and in-silico models to gather fundamental data regarding its safety and biological effectiveness. GLP/GSP guidelines (good laboratory practice and good scientific procedures) are mostly followed during preclinical investigations or testing to ensure the accuracy and repeatability of results. The Food and Drug Administration of the United States and the European Medicines Agency need fundamental preclinical data to be submitted with an investigational new drug (IND) application, including data on toxic effects, safety profiles, pharmacokinetics, and pharmacodynamics. Preclinical trial data must be precise, dependable, and based on the most applicable and similar model accessible to the target population. This often entails a series of thorough tests and investigations, employing in-vitro, in-vivo, ex-vivo, and in-silico models in accordance with the requirements of specific indication and regulatory criteria. We, therefore, first report our review of the available preclinical studies. Table 1 lists our selected animal research on the use of plants growing as a part of the flora of Iran, and used as possible treatments for COPD.

TABLE 1: Animal studies on herbal therapy of COPD

Herb	Model	Author	Title	Effects	Ref
Aloe vera	Mice	Koul et al.	Aloe vera affects changes induced in pulmonary tissue of mice caused by cigarette smoke inhalation	The findings imply that alterations induced by cigarette smoke (CS) in the pulmonary tissue may be modulated by Aloe vera, which may have significance for the treatment of pulmonary disorders linked to CS.	39
Aloe vera	Rats	Atik et al.	Aloe vera protect the rat's lung after cigarettes smoke inducement: a histological study	The findings showed that taking 1 cc of aloe gel orally each day before being exposed to cigarette smoke helped prevent lung damage.	40
Aloe vera	Rats	Atik et al.	The Effect of Aloe vera L. in Rat Lungs After Cigarette Smoke Induction	This study demonstrated that Aloe vera gel boosts Bcl2 expression and macrophage number and activity in the lungs of CS-exposed rats.	41
Chlorella vulgaris	Rats		Protective Effect of Chlorella Vulgaris on	Days 15 and 30 after exposure to cigarette smoke, rats showed	42

			DNA Damage, Oxidative Stress, and Lung Morphological Changes, in Cigarette Smoke-Exposed Rats	increased DNA damage and high MDA levels, although <i>Chlorella vulgaris</i> (ChV) treatment for both days greatly mitigated these effects. Hematoxylin and eosin staining revealed that rats exposed to cigarette smoke frequently had enlarged airspaces and a high number of inflammatory cells, both of which were diminished when the rats were given ChV.	
Glycyrrhiza glabra	Mice	Kim et al.	Herbal Combinational Medication of Glycyrrhiza glabra, Agastache rugosa Containing Glycyrrhizic Acid, Tiliarin Inhibits Neutrophilic Lung Inflammation by Affecting CXCL2, Interleukin-17/STAT3 Signal Pathways in a Murine Model of COPD	By controlling the production of inflammatory cytokines and CXCL-2 through limiting the IL-17/STAT3 pathway, the herbal combinational mixture studied successfully suppressed neutrophilic airway inflammation.	43
Glycyrrhiza glabra	Mice	Kao et al.	Glycyrrhizic acid and 18 β -glycyrrhetic acid inhibit inflammation via PI3K/Akt/GSK3 β signaling and glucocorticoid receptor activation	CS-exposed <i>Glycyrrhiza glabra</i> treated mice, revealed an apparent decrease in pulmonary inflammation as well as a strong inhibitory effect on mucus producing goblet cells of the big airways.	44
Glycyrrhiza glabra	Rats	Yang et al.	Magnesium isoglycyrrhizinate inhibits airway inflammation in rats with chronic obstructive pulmonary disease	The study suggests that <i>Glycyrrhiza glabra</i> may be a new option for treating COPD, and its mode of action may be connected to the inhibition of NLRP3 inflammasome.	45
Glycyrrhiza glabra	Mice	Guan et al.	Protective effects of liquiritin apioside on cigarette smoke-induced lung epithelial cell injury	The results indicate that protective roles of liquiritin apioside (LA), a natural product found in <i>Glycyrrhiza glabra</i> , on the CS-induced lung epithelial cell injury are mediated by inhibiting TGF- β and TNF- α expression and increasing anti-oxidative levels of GSH, suggesting that LA might be effective as a protective agent against epithelial injury in COPD.	46

Glycyrrhiza glabra / Solanum xanthocarpum	Rats	Manek et al.	Liquorice exaggerates protective action of Solanum xanthocarpum against cigarette smoke induced pulmonary inflammation	LE+SXE effectively attenuated CS-induced pulmonary inflammation through inhibition of inflammatory cell infiltration, reduction of oxidative stress markers and reduction of pro-inflammatory mediator expression in lungs, providing a the potential rationale for developing an anti-inflammatory combination.	47
Glycyrrhiza glabra	Mice	Ren et al.	Licochalcone A protects against cigarette smoke-mediated acute lung injury in mice by suppressing ERK1/2/NF- κ B pathways	LA (Licochalcone A) has protective effects on CS-exposed acute lung injury in mice by preventing pulmonary inflammation, oxidative stress and protease accumulation. An exploration of the mechanisms suggests that LA exerts protective effects via suppressing ERK1/2/NF- κ B pathways.	48
Glycyrrhiza glabra	Mice	Yu et al.	Isoliquiritigenin Inhibits Cigarette Smoke-Induced COPD by Attenuating Inflammation and Oxidative Stress via the Regulation of the Nrf2 and NF- κ B Signaling Pathways	ILG (Isoliquiritigenin, a phenolic constituent of Glycyrrhiza glabra) protected against CS-induced COPD by inhibiting inflammatory and oxidative stress in mice, via regulation of the Nrf2 and NF- κ B signaling pathways.	49
Ocimum sanctum	Mice	Srivastava et al.	Ocimum inhibits airway inflammation in cigarette smoke induced COPD	The total cell count, which was raised in COPD mice, was dose-dependently decreased by Ocimum ethanolic extract. Additionally, animals given Ocimum showed dose-dependent attenuation of the inflammatory markers eosinophil peroxidase, myeloperoxidase, and neutrophil elastase. In mice with COPD and animals given ocimum, the histology of the lung sections showd decreased bronchioles and architectural abnormalities in the alveolar spaces.	50
Thymus vulgaris	Rats	Engelbertz et al.	Thyme extract, but not thymol, inhibits endothelin-induced	Although thymol is not implicated for this effect, thyme extract may be helpful in	51

			contractions of isolated rat trachea	conditions like asthma and COPD, which are linked to endothelin hyper-reactivity of the bronchus system.	
Zataria multiflora	Guinea pigs	Boskabady et al.	Effect of the Zataria multiflora on systemic inflammation of experimental animals model of COPD	Results demonstrated that hydroethanolic extract from Z. multiflora had a preventative impact on all parameters tested in animals with a COPD model that was equivalent to or even greater (in the highest concentration) than the effect of dexamethasone at the concentration employed.	52
Zataria multiflora	Mice	Games et al.	Structurally Related Monoterpenes p-Cymene, Carvacrol and Thymol Isolated from Essential Oil from Leaves of Lippia sidoides Cham. (Verbenaceae) Protect Mice against Elastase-Induced Emphysema	P-cymene, carvacrol (a Zataria multiflora constituent), and thymol, three monoterpenes, decreased inflammation and pulmonary emphysema in mice. There were no discernible differences between the three monoterpene treatments, indicating that the hydroxyl group in the molecules of thymol and carvacrol does not significantly contribute to their anti-inflammatory properties.	53
Zataria multiflora	Guinea pigs	Mahtaj et al.	The effect of carvacrol on systemic inflammation in guinea pigs model of COPD induced by cigarette smoke exposure	Results showed a preventive effect of carvacrol on all measured parameter in COPD guinea pigs which was comparable to the effect of dexamethasone at used concentrations.	54
Zataria multiflora	mice	Carvalho et al.	Effects of the solid lipid nanoparticle of carvacrol on rodents with lung injury from smoke inhalation	Results showed:that the SLN containing carvacrol minimized oxidative stress and histological damages generated from smoke inhalation in rodents.	55
Zataria multiflora	Guinea pigs	Boskabady et al.	Lung inflammation changes and oxidative stress induced by cigarette smoke exposure in guinea pigs affected by Zataria multiflora and its constituent, carvacrol	The results showed a preventive effect of Z. multiflora extract and its constituent carvacrol on lung inflammation and oxidative stress in an animal model of COPD.	56
Zataria multiflora	Guinea pigs	Gholami et al.	The Effect OF Zataria Multiflora and Its Constituent Carvacrol on Systemic	The results indicated a preventive effect of Z. multiflora extract and its constituent, carvacrol, on	57

			Inflammation in Guinea Pigs Model of COPD Induced by Cigarette Smoke Exposure	tracheal responsiveness and pathological changes of the lung	
Zataria multiflora	Guinea pigs	Boskabady et al.	Effect of the Zataria multiflora on systemic inflammation of experimental animals model of COPD	Results showed a preventive effect of hydroethanolic extract from Z. multiflora on all measured parameters in animal models of COPD.	58
Nigella sativa	Guinea pigs	Hossein et al.	The protective effect of Nigella sativa on lung injury of sulfur mustard-exposed Guinea pigs.	The outcome demonstrated that Nigella sativa had a preventative impact on the tracheal responsiveness of guinea pigs exposed to SM.	59
Nigella sativa	Rats	Khazdair et al.	The protective effects of thymoquinone on lung damage caused by cigarette smoke	According to the results, Nigella sativa reduces inflammation brought on by CS and may prevent apoptosis if given in the right amounts. However, long-term exposure to Nigella sativa or DMSO may result in cumulative harmful consequences.	60
Nigella sativa	Guinea pigs	Boskabady et al.	The effect of Nigella sativa alone, and in combination with dexamethasone, on tracheal muscle responsiveness and lung inflammation in sulfur mustard exposed guinea pigs	These results showed a preventive effect of <i>Nigella sativa</i> on TR and lung inflammation of SM exposed guinea pigs.	61
Nigella sativa	in cell culture conditions	Kacem et al.	Effects of Nigella (<i>Nigella sativa</i> L.) Seed Extract on Human Neutrophil Elastase Activity	Essential oil extract from Nigella sativa has an inhibitory effect on human neutrophil elastase (HNE) mostly due to the presence of 5-isopropyl-2-methyl phenol (Carvacrol), which could be considered as a natural antielastase agent and possible candidate for phytotherapy in the treatment of injuries appearing in pathologic cases such as COPD and emphysema.	62
Nigella sativa	Guinea pigs	Keyhanmanesh et al.	Nigella sativa Pretreatment in Guinea Pigs Exposed to Cigarette Smoke Modulates In Vitro	Results indicated a preventive effect of N. Sativa on tracheal responsiveness to methacholine and to a less extent to ovalbumin in guinea pigs with COPD.	63

			Tracheal Responsiveness		
Nigella sativa	in cell culture conditions	Barnawi et al.	Pro-phagocytic Effects of Thymoquinone on Cigarette Smoke-exposed Macrophages Occur by Modulation of the Sphingosine-1-phosphate Signalling System	Thymoquinone (a Nigella sativa constituent) enhanced efferocytic/phagocytic function, antagonized the effects of CS and LPS on phagocytosis and S1PR5, and protected bronchial epithelial cells against CS-induced apoptosis, and therefore, is worth further investigation as a potential therapeutic strategy for smoking-related lung diseases.	64
Nigella sativa	in cell culture conditions	Dera et al.	Thymoquinone (Tq) protects necroptosis induced by autophagy/mitophagy-dependent oxidative stress in human bronchial epithelial cells exposed to cigarette smoke extract (CSE)	CSE caused necroptosis in human bronchial epithelial cells that was mediated by oxidative stress-dependent autophagy/mitophagy. Pretreatment with Tq significantly abrogated CSE cellular damage.	65

Clinical studies

Table 2 shows the selected clinical studies involving plants of the flora of Iran and COPD/mustard lung.

TABLE 2: Clinical studies on herbal therapy of COPD

Herb	Author	Title	Effects	Ref
Chlorella vulgaris	Panahi et al.	Impact of Adjunctive Therapy with Chlorella vulgaris Extract on Antioxidant Status, Pulmonary Function, and Clinical Symptoms of Patients with Obstructive Pulmonary Diseases	Both groups experienced a substantial decrease in the frequency of coughing, shortness of breath, wheezing, and sputum production. When compared to the control group, the Chlorella vulgaris group showed a statistically significant improvement in sputum brought up and wheezing. Although it was shown that Chlorella vulgaris improved serum antioxidant status, treatment with it had no bronchodilatory effects.	66
Thymus vulgaris	Yonsi et al.	Effect of Thymus vulgaris Inhaling on Arterial Oxygen Saturation and Heart Rate in Patients with Acute Exacerbation of Chronic Obstructive Pulmonary Disease	The results revealed that T. vulgaris inhaling is effective on the levels of arterial oxygen saturation and heart rate in patients with acute exacerbation of COPD.	67

Nepeta bracteata	Abdolahinia et al.	Effect of Nepeta bracteata benth. on chronic obstructive pulmonary disease: a triple-blinded, randomized clinical trial	The research had 64 people finish it. In comparison to the placebo and control groups, the Nepeta bracteata group's CAT score significantly improved in the study's findings. The adequate reaction of COPD patients to this medication, particularly in terms of quality of life, seems to point toward it being a viable option for supplemental therapy in chronic respiratory disorders.	68
Tinospora cordifolia	Hannan et al.	Effect of Tinospora cordifolia in chronic bronchitis patients	Tinospora cordifolia lessens recurrent infections, enhances symptoms, raises quality of life, and also enhances lung functions in chronic bronchitis patients, As a result, it can be administered to such patients as an addition to the normal care.	69
Zataria multiflora	Ghorani et al.	The effect of two-month treatment with Zataria multiflora on inflammatory cytokines, pulmonary function testes and respiratory symptoms in patients with chronic obstructive pulmonary disease (COPD)	COPD patients (41 cases) were divided into three groups: one placebo group (P) and two groups receiving Z. multiflora extract (one group 3 and another 6 mg/kg/day) After two months of therapy, TNF and IL-8 serum levels were considerably lower and PFT values - including forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV1) - significantly higher than those of the control group. Treatment with both dosages of Zataria multiflora, markedly reduced the respiratory symptoms— including coughing, tightness in the chest, and the modified Medical Research Council (mMRC) dyspnea scale— compared to baseline, after both 1 and 2 months of therapy.	70
Zataria multiflora	Khazdair et al.	Carvacrol ameliorates haematological parameters, oxidant/antioxidant biomarkers and pulmonary function tests in patients with sulphur mustard-induced lung disorders: A randomized double-blind clinical trial	In SM-exposed patients, two months of carvacrol (a Z. multiflora constituent) treatment decreased inflammatory cells and oxidant biomarkers while increasing antioxidant biomarkers and improving PFT tests.	71
Zataria multiflora	Khazdair et al.	The effect of carvacrol on inflammatory mediators and respiratory symptoms in veterans exposed to sulfur mustard, a	In SM exposed patients, carvacrol treatment for two months decreased inflammatory cytokines and chemokines, raised anti-inflammatory cytokines, and improved respiratory symptoms and FEV1 values.	72

		randomized, placebo-controlled trial		
Zataria multiflora	Khazdair et al.	A double-blind, randomized, placebo-controlled clinical trial on the effect of carvacrol on serum cytokine levels and pulmonary function tests in sulfur mustard induced lung injury	Two months of carvacrol therapy improved PFT testing and lowered inflammatory cytokines while increasing anti-inflammatory cytokines in SM-induced lung damage.	73
Zataria multiflora	Ghorani et al.	A Randomized, Doubled-Blind Clinical Trial on the Effect of Zataria multiflora on Clinical Symptoms, Oxidative Stress, and C-Reactive Protein in COPD Patients	In COPD patients, a two-month treatment with Z. multiflora reduced oxidative stress, C-reactive protein, pulmonary function tests, and clinical symptoms. The outcomes point to the potential therapeutic usefulness of this herbal remedy as a COPD medication.	74
Zataria multiflora	Khazdair et al.	Effect of Zataria multiflora on serum cytokine levels and pulmonary function tests in sulfur mustard-induced lung disorders: A randomized double-blind clinical trial	Z. multiflora therapy for two months decreased inflammation, increased anti-inflammatory cytokines, and boosted PFT indicators in SM-exposed patients.	75
Zataria multiflora	Khazdair et al.	The effect of Zataria multiflora on pulmonary function tests, hematological and oxidant/antioxidant parameters in sulfur mustard exposed veterans, a randomized doubled-blind clinical trial	In SM-exposed patients, Z. multiflora lowers inflammatory cells, increases antioxidant biomarkers, and improves PFT tests over the course of a two-month therapy period.	76
Zingiber officinale	Pratama et al.	The effect of ginger (Zingiber officinale) extract on the neutrophil level and CAT (COPD Assessment Test) scores in workers with COPD due to dust exposure	The unpaired difference test on the post-pre values showed that the treatment group had significantly higher CAT decrease than the control group overall. The test also revealed that the treatment group had a significantly greater neutrophil drop than the control group. It is concluded that ginger extract administration can lower neutrophil counts and CAT scores in COPD workers.	77
Zingiber officinale	Brockwell et al.	Adjunctive treatment with oral AKL1, a botanical nutraceutical, in chronic obstructive pulmonary disease	Subjects were divided into AKL1 (a patented botanical formulation containing Zingiber officinale) group and control group and parameters were compared between baseline and week 8. St George's Respiratory Questionnaire score improved substantially in the AKL1 treatment group, while other patient-reported	78

			variables, lung function, and the 6-minute walk distance test did not significantly differ between two groups.	
Nigella sativa	Al-Azzawi et al.	Therapeutic effects of black seed oil supplementation on chronic obstructive pulmonary disease patients: A randomized controlled double blind clinical trial	The BSO group (treated with black seed oil, which is extracted from <i>Nigella sativa</i>) showed a significant drop in inflammatory markers and a significant rise in antioxidant levels. The BSO group also benefited from a significant improvement in PFTs. Results suggest that patients with COPD may benefit from taking supplements of black seed oil to reduce inflammation and oxidative stress, and improve oxidant-antioxidant balance and pulmonary function.	79

DISCUSSION

Aloe vera

Aloe vera is a shrubby or arborescent, perennial, xerophytic, succulent, pea-green plant that is a member of the Liliaceae family. Africa, Asia, Europe, and America's dry climates are where it primarily grows. It can be found in Tamil Nadu, Gujarat, Maharashtra, Rajasthan, and Andhra Pradesh in India. *Aloe vera* and its constituents have qualities that make it possible to preserve the integrity and moisture of skin. Due to the presence of mucopolysaccharides, amino acids, zinc, and water, it also helps to prevent skin ulcers. In terms of the quality and speed of wound healing, *Aloe vera* is far more efficient and also less expensive than the other available treatments. Three animal studies were performed studying the effects of *Aloe vera*, one on mice and the other two on rats; All three of which suggest that *Aloe vera* has the potential to modulate cigarette induced changes in the animal pulmonary tissue which could have implications in the management of cigarette smoke associated pulmonary diseases including COPD. **Bookmark not defined.** However, further investigations are required to explore its complete mechanism of action.



FIGURE 4: *Aloe vera*

Chlorella vulgaris

The microalgae *Chlorella vulgaris* (ChV), of the family Oocytaceae, order Chlorococcales, and genus *Chlorella*, are green in color because of their chloroplasts content. Its size ranges from 1 to 10 microns, and its form is spherical. These microalgae are widely used for the production of cosmetics, medical treatments, and even the detoxification of heavy metals in wastewater, because they contain significant amounts of intracellular proteins, carbohydrates, lipids, vitamin C, β -carotenes, and B vitamins (B1, B2, and B12), in addition to chlorophyll. We have reviewed one human study on the effects of ChV on COPD. Ninety-seven patients with COPD or asthma who were under conventional treatment regimens were randomly assigned to ChV extract or no adjunctive therapy. Serum levels of antioxidants along with spirometric parameters and clinical symptoms were evaluated pre- and

post-trial. The results did not support any clinical efficacy for ChV in patients with obstructive pulmonary disorders **Error! Bookmark not defined.** which makes *Chlorella vulgaris* a less prominent candidate for designing a pharmaceutical product for COPD patients.



FIGURE 5: *Chlorella vulgaris*

Glycyrrhiza glabra

The Fabaceae family (also known as Leguminosae), which includes *Glycyrrhiza glabra*, is one of the most well-known groups of medicinal plants, having both food and medicinal functions. The Greek words glykos (sweet) and rhiza (root) are the origin of the genus *Glycyrrhiza*. Although it is originally from the Mediterranean region, this species is now found in China, India, and Russia. Currently, the extracts are employed in the food and pharmaceutical industries, as well as in the production of functional meals and nutritional supplements. Although no human trials have been done to evaluate its effects on COPD or mustard lung, we have found *Glycyrrhiza glabra* to reduce inflammatory responses in lungs in seven different animal studies, although it has been used in combination with another plant in one those seven. *Glycyrrhiza glabra* treatment predominantly suppresses neutrophil infiltration as demonstrated in the results. The efficacy of this plant on human subjects is yet to be determined and clinical research in this field is expected.



FIGURE 6: *Glycyrrhiza glabra*

Ocimum sanctum

Ocimum sanctum L. (Labiatae) is a tiny, fragrant annual herb that can grow to be up to 18 inches tall and develop into a low bush. It is also known as holy basil or tulsi. *Ocimum sanctum* (OS) is a significant herb among the plants with therapeutic properties, with a variety of pharmacological qualities. *Ocimum sanctum* L. has a significant biological potential, and has a long history as a traditionally used medicinal herb. Effects of OS extract on airway inflammation caused by COPD in mice were reported in an animal study. Results show that OS ethanolic extract dose-dependently decreases total cells in mice. OS caused attenuation of the inflammatory markers, including eosinophil peroxidase, myeloperoxidase, and neutrophil elastase. Lung histology of COPD afflicted mice treated by OS revealed less architectural abnormalities in the alveolar spaces and bronchioles. For this plant more in-depth preclinical studies seem necessary before making it a viable option for human trials.



FIGURE 7: *Ocimum sanctum*

Thymus vulgaris

Thymus vulgaris (TV), sometimes known as "thyme," is one of the well-known species of the genus "Thymus" (family Lamiaceae), and is particularly widespread in the Mediterranean region, North Africa, Asia, and Europe. The Thymus family is well known for its biological and natural activities, including its use as a food additive, in traditional medicine, and in pharmaceutical preparations. Another animal study showed that thyme extract can inhibit endothelin-induced contraction, although another major compound of thyme extract (thymol) did not seem to have any interaction with the endothelin system. Researchers concluded that thyme but not thymol extract may help in airway obstructive diseases such as asthma and COPD. A blind randomized clinical trial on patients with COPD exacerbation showed that *Thymus vulgaris* inhaling is effective on the levels of arterial oxygen saturation and heart rate.



FIGURE 8: *Thymus vulgaris*

Zataria multiflora

Z. multiflora of the Lamiaceae family, has tiny, slender, elliptical leaves, is known locally as "Avishan Shirazi" (in Persian), and exclusively grows in central and southern Iran, Pakistan, and Afghanistan. Traditional medicine has for long utilized the analgesic, antiseptic, carminative, antihelminthic, and antidiarrheal qualities of *Z. multiflora* aqueous extract. Studies have also revealed that traditional Iranian healers have used *Z. multiflora* extract as an antibacterial agent in oral hygiene to treat coughs brought on by colds, bronchitis, and problems of the oral cavity.

In COPD patients, *Zataria multiflora* has been shown to have equal or greater effects on all parameter of inflammation, when compared to dexamethasone administration in pigs. Four other studies have shown positive effects of *Z. multiflora* on the lung tissues of CS-exposed animals. *Z. multiflora* extract was also effective on all COPD parameters in an animal study in pigs. Two month treatment with *Zataria multiflora* has been shown to reduce inflammation, respiratory symptoms and improve PFT. Based on the studies that we reviewed and presented in this article, more insight into the extracts of *Z. multiflora* seems reveal more of its potential in to turn into a market-ready drug, specifically for COPD patients.

Zingiber officinale

Zingiber officinale (more broadly known as ginger) belongs to the Zingiberaceae plant family, which has 1300 species, 80–90 of which are Zingiber. This family is indigenous to East and Southern Asia. The Latin word "Zingiber", meaning "fashioned like a horn", alludes to the roots of this plant, which resemble a deer's antlers, and is taken from the Greek "Zingiberis", which in turn is derived from the Sanskrit name of the spice, "Singabera" which refers to the geographical origins of *Z. officinale*. Since ancient times, ginger has been used both as a medicinal herb and an essential cooking spice all over the world. It is a plant that originated in Southeast Asia and was used in folk medicine there. It is also grown for medicinal purposes in Brazil, Australia, Africa, China, India, Bangladesh, Taiwan, Mexico, Japan, Jamaica, the Middle East, and some regions of the United States. We have shown the effects of this plant on animal and human subjects in several studies. A study using COPD assessment test in workers with COPD caused by exposure to dust (rather than CS) has shown promising results in COPD treatment using *Zingiber officinale* extract by controlling the neutrophil levels and also decreasing CAT scores in patients. Although the two etiologies create a similar clinical picture, it is not clear if the extract can produce the same

outcome in the more common CS-induced COPD. Another study using subjective patient-reported parameters however, administered a formulation containing not only *Zingiber officinale*, but also *Picrorhiza kurroa*, and *Ginkgo biloba*. While we excluded some of the studies reporting on complex formulations containing multiple plants, we chose to include this study in our review because the number of constituents was limited and they had been clearly stated to be *Picrorhiza kurroa*, and *Ginkgo biloba*. The studied formulation significantly improved St George's Respiratory Questionnaire score, but not other investigated parameters including lung function, and 6-minute walk distance. While further studies seem necessary regarding the nature of *Z. officinale*'s effects on COPD, results of the two human studies reported above imply that the this plant might be a good choice for improving symptoms and patient's quality of life rather than disease course and outcome.



FIGURE 9: *Zingiber Officinale* rhizome

Nigella sativa

The seeds of *Nigella sativa* L., often known as black cumin seed or black seed, are an annual herb in the Ranunculaceae family that contain 34–39% oil. The food sector and conventional medicine both make extensive use of its oil. Essential fatty acids, tocopherols (91-246 ppm), phytosterols (1993–2182 ppm), polyphenols (245–309 ppm), essential oils, and other bioactive substances are all abundant in the black seed oil. Thymoquinone is one of the most

significant active ingredients of black seed oil with a number of health-improving effects. Whether used alone or in conjunction with other vegetable oils, black seed oil is gaining a lot of interest regarding its positive health effects. Its qualities are greatly influenced by the environment, cultivation areas, maturation duration, and storage conditions. More consideration should be given to black seed oil as a possible all-purpose good. *Nigella sativa* has been shown to reduce inflammation and apoptosis in CS-exposed rats and increase tracheal responsiveness in a COPD model in guinea pigs. *Nigella sativa* has also been experimented on cultivated human tissue. It has a potential for treating lung injuries due to its inhibitory function on elastase activity and its effects on macrophages. Thymoquinone, a *Nigella sativa* derivative, has been shown to protect against necroptosis induced by oxidative stress in human bronchial epithelial cells after exposure to CS extract. One Clinical study has shown the efficacy of black seed oil supplements in reducing inflammation and oxidative stress as well as enhancing oxidant – antioxidant imbalance. More studies, specifically on clinical grounds, are necessary to confirm *Nigella sativa* as a candidate for managing COPD.



FIGURE 10: *Nigella sativa*

Nepeta bracteata

One of the most commonly mentioned medicinal plants for respiratory problems like chronic cough (Soale-mozmen), catarrh (Nazleh), asthma

(Rabu), and dyspnea (Osral-Nafas) in traditional manuscripts, is *Nepeta bracteata* Benth. (Lamiaceae). The observed therapeutic properties of *Nepeta* species are most likely due to the presence of terpenoids, particularly the abundant iridoids and diterpenes in this genus, as well as flavanones, flavonoids, and derivatives of phenolic acids. Recent studies have found evidence of its benefits for asthma, bronchitis, the common cold, and chronic cough. *Nepeta bracteata*'s effect on COPD was assessed by a triple blinded clinical study using COPD assessment test (CAT score). Promising results in terms of quality of life improvement were reported **Error! Bookmark not defined.**

Tinospora cordifolia

Tinospora cordifolia belongs to family Menispermaceae and is a genetically diverse, large, deciduous climbing shrub with greenish yellow flowers. Several medicinal applications including diabetes management, anti-spasmodic activity, anti-inflammatory properties, anti-oxidant activity, and immunomodulatory effects have been reported for this plant. *Tinospora cordifolia* administration has been studied in chronic bronchitis patients and reported to prevent infections as well as enhancing lung functions and thus can be considered for COPD patients.



FIGURE 11: *Tinospora cordifolia*

Mustard lung and Herbal Medicines

Two animal studies observed the effect of *Nigella sativa* on the lungs of sulfur mustard-exposed pigs. Both studies showed a promising effect on tracheal responses and lung inflammation

A two-month course of therapy with carvacrol (a *Z. multiflora* constituent) in SM-exposed patients has been shown to increase anti-inflammatory factors, decrease inflammatory cells. *Z. multiflora* seem to be the most prominent candidate to use for SM-exposed patients, which is in line with the rather strong evidence for its effects on COPD patients.

CONCLUSION

COPD remains one of the leading causes of death and morbidity across the world. Additionally, mustard lung has been shown to have similar pathophysiology to COPD. In this article, we reviewed the literature discussing the role of herbal and traditional medicine in management of obstructive pulmonary diseases. As it was shown mostly in animal models; these medicinal plants can have a promising role in COPD treatment, while some plants have proven to be clinically effective on human subjects. Conducting more clinical studies might be necessary to further promote the use of herbal medicine in obstructive diseases of the lung.

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Ethics approval and consent to participate

The study protocol was reviewed and approved by the ethics committee of the Baqiyatallah University of Medical Sciences (IR.BMSU.REC.1401.088). All tests were carried out following the Baqiyatallah University of Medical Sciences Ethical Committee.

CONFLICT OF INTERESTS

The authors declare not to have any conflict of interests

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