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A Review on Respiratory Disorders and Herbal Remedies as a Source Potential with Anti-Respiratory Agents

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Abstract

Traditional systems of medicine have been in vogue for treating various ailments in many countries such as China, Japan and India since immemorial time. The importance of herbal medicine in the treatment of Respiratory disorders is indisputable and Asthma is the most common disorder of respiratory tract. Four of the five classes of drugs currently used to treat asthma namely; β2-agonists, anticholinergic, methyl xanthines and cromones have origins in herbal treatments going back at least 5000 years. In the present article an attempt has been made to review anti-respiratory medicinal plants with their active chemical constituent and possible mechanism of action.

Keywords: Asthma, Cystic fibrosis, COPD, Bronchiectasis, Chronic Bronchitis, Pulmonary Fibrosis, Herbal remedies.

Contents

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1. Introduction

Respiratory disease is a medical term that encompasses pathological conditions affecting the organs and tissues that make gas exchange possible in higher organisms, and includes conditions of the upper respiratory tract, trachea, bronchi, bronchioles, alveoli, pleura and pleural cavity, and the nerves and muscles of breathing. Respiratory diseases range from mild and self-limiting, such as the common cold, to life-threatening entities like bacterial pneumonia, pulmonary embolism, and lung cancer. Respiratory disease is a common and significant cause of illness and death around the world. In the US, approximately 1 billion "common colds" occur each year [1]. A study found that in 2010, there were approximately 6.8 million emergency department visits for respiratory disorders in the U.S. for patients under the age of 18[2] .In the UK, approximately 1 in 7 individuals are affected by some form of chronic lung disease, most commonly chronic obstructive pulmonary disease, which includes asthma, chronic bronchitis and emphysema.[3] Respiratory diseases (including lung cancer) are responsible for over 10% of hospitalizations and over 16% of deaths in Canada.[4].According to WHO 235 million people currently suffer from asthma and almost 3 million peoples died of COPD in 2005.(Figure 1)(Table 1).

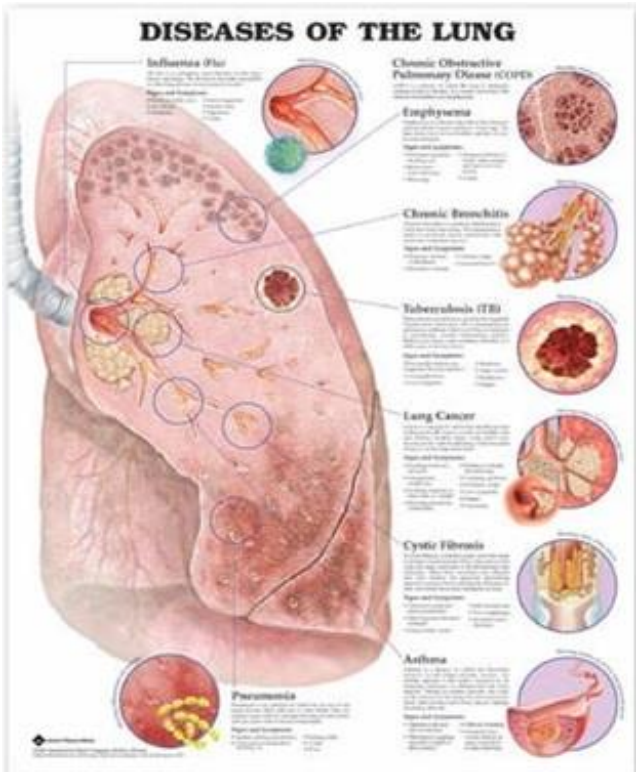

Fig.1 Diseases of the Lung

Table 1:Classification of Drugs used in respiratory disease [41]

Bronchodialator		
Sympathomimetic	**Methyl xanthine**	**Anticholinergic**
Adrenalin Ephedramine Isoprenaline Salbutamol Tolbutamide	Theophyllin Aminophyllin Hydroxy ethyl theophylline Choline Theophylline ethanolate of peperazine	Atropine Methonitrate Ipratropium bromide Tiotropium bromide
Leucotrine antagonist		
Montelukast, Zafirlucast		
Mast Cell Stabilizers		
Sod. Cromo glycate, Nedocromil.		
Cortico Steroids		
Systemic Hydrocortisone Predinisolon	Inhalational Di-Propionate Beclomethasone	

2. Description

Our work in respiratory diseases focuses on:

1. Asthma
2. Cystic Fibrosis
3. Chronic Obstructive Pulmonary Disease (COPD)
4. Bronchiectasis
5. Chronic Bronchitis
6. Pulmonary Fibrosis

1.1 Asthma: Asthma is a serious condition in which the small airways of the affected person's lungs suddenly constrict when they are exposed to certain triggers, such as dust mites, pollen, exercise, or even dry air. During an asthma 'attack', the person's airway lining rapidly becomes inflamed and swollen, the muscles around the airways tighten, and excess mucus is produced as the body reacts to the trigger. This reaction causes reduced airflow into and out of the lungs, and the person has to gasp for breath. Asthma is a major public health problem affecting 52 million

people around the world, including 2million Australians and 15 million Americans. The disease is usually life-long and each year claims around 400 lives in Australia and 4,500 lives in the US. Recent studies have shown that the incidence of asthma in Australian children is increasing. The disease has a major impact on the quality of life of asthmatics and their families, with many sufferers requiring daily medication and modifications in their lifestyle. In addition to the human price, asthma is a major component of the cost of the healthcare system. For example, the cost to the US healthcare system is in excess of US$15 billion per year.(Figure 2).

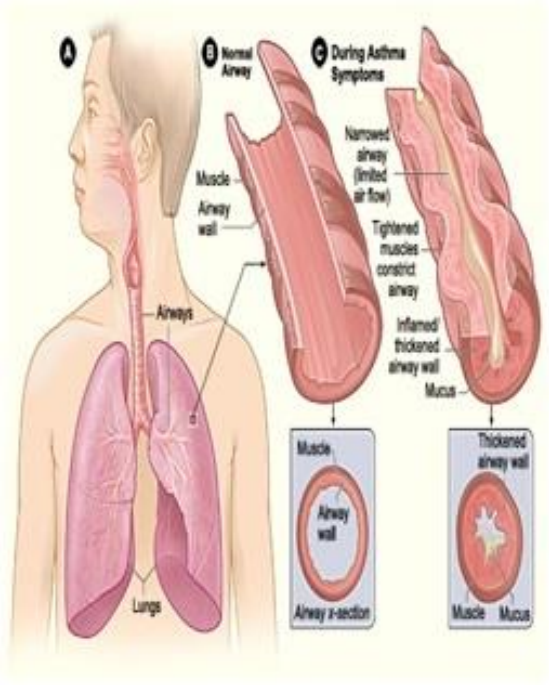

Figure.2

Table.2 Classification of drugs used for cough and bronchial asthma[41]

Pharangeal Demulcent	
Provide relief in dry cough arising from throat	Lozenges, Cough drops, Linctus's, Containing syrups Glycerines, Liquorice.
Expectorants (Mucokinetics)	
Increase bronchial secretion and reduce its viscosity and loose cough.	Directly Acting: Sod pot citrate and acetate, Balsam of Tolu, Vasaka, Terpine hydrate, Glycerol guaiacolate.
	Reflex acting: Ammonium chloride, Potassium iodide.
	Mucolytic: Bromo hexine, Acetyl cysteine, Carbo Cysteine.
Anti-Tussive	
Used in the treatment of dry unproductive cough	Opiod: Codine, Phocodine, Morphine, Ethyl morphine.
	Non-Opiod: Noscapine, Dextromethorphan, Chlophedianol.
	Anti-histamine: Chlorpheniramine, Diphenhydramine, Promethazine.

Diagnosis: The effective diagnosis, monitoring and management of asthma remain key challenges for doctors and asthmatics. The primary method currently used to diagnose asthma has remained unchanged for many years, with a diagnosis arrived at through a detailed history and physical examination of the patient. Exercise challenge tests and methacholine inhalation tests are procedures used most frequently in clinical laboratories to evaluate airway responsiveness. While these tests can indicate the presence of asthma, they are not sensitive or specific enough for asthma, nor do they give a precise or objective measure of the seriousness of the patient's condition. As a consequence, under-diagnosis and misdiagnosis of asthma continue to be serious medical issues that impact extensively onpeople's health and quality of life. There are a number of therapeutic options to treat the symptoms of asthma, including inhalers that expand the airways, and preventative measures such as anti-inflammatory medications. The absence of an accurate test not only hinders the diagnosis of asthma, but also makes it difficult for

doctors to monitor the severity of their patients' asthma to ensure they receive the most appropriate dose of medication. Many asthma sufferers have poor control of their disease, placing an over reliance on bronchodilators to control their asthma symptoms. At the other extreme, many people with asthma have few outward symptoms and can become less diligent with their asthma management. Much of the deterioration in the quality of life of asthma sufferers could be prevented through correct early diagnosis of the disease, appropriate treatment, and effective ongoing monitoring. Pharmaxis is committed to meeting this medical need.(Table 2)

1.2 **Cystic Fibrosis:** Cystic fibrosis (CF) is an inherited, life-limiting disease that affects the body's exocrine glands, which produce mucus, saliva, sweat and tears. In CF, a genetic mutation disrupts the delicate balance of sodium, chloride and water within cells, causing the exocrine glands to secrete fluids that are poorly hydrated and therefore thicker and stickier than fluids in people without CF. This leads to chronic problems in various systems of the body, particularly the lungs and pancreas, and the digestive and reproductive systems. In the lungs of a Patient, the thick mucus and the thinning of the airway surface liquid make it nearly impossible for the cilia to clear bacteria from the airway. This severely impairs the natural airway-clearing processes and increases the potential for bacteria to be trapped, leading to respiratory infections that may require hospitalisation. Impairments in these vital lung defence mechanisms typically begin in early childhood and often result in chronic secondary infections, leading to progressive lung dysfunction and deterioration. Although the life expectancy of CF sufferers has increased over the past few decades due to better management of the disease, the median life expectancy today for patients with cystic fibrosis is only 31 years of age. There are 33,000diagnosed CF patients in the US and 75,000 in the eight major pharmaceutical markets. In Australia, 2,500 people suffer from the disease, a quarter of whom are children under five years of age.

Diagnosis: Currently, there is no cure for CF. The goal for doctors treating CF sufferers is to hydrate, breakdown and move the excessive, sticky mucus secretions to improve lung function and reduce the number and severity of secondary lung infections. CF sufferers and their careers are generally able to manage the condition at home using a combination of exercise, daily physiotherapy, postural drainage, and chest percussion (to assist the sufferer to expel mucus from their lungs). Depending on the severity of the condition, caring for a person with CF can take several hours of at-home treatment every day. Medications to treat CF are limited, and not beneficial in all patients. Nebulised medications, delivered by aerosol or a face mask, are used to make the mucus less thick and sticky and open up the airways. Antibiotics, either nebulised or by oral or intravenous administration may also be required to treat secondary infections.

1.3 Chronic Obstructive Pulmonary Disease (COPD):

Chronic Obstructive Pulmonary Disease, or COPD, is a generalized term for a group of diseases that involve progressive narrowing of the airways that service the lungs. This airway narrowing cannot generally be reversed resulting in laboured breathing and poor oxygen transfer from the lungs. People with COPD have excessive mucus build up in their airways and a chronic troublesome cough. The most common diseases classified as COPD are emphysema, chronic bronchitis and bronchiectasis. In chronic bronchitis, the airways become inflamed, and the bronchial walls thicken. These changes and the loss of supporting alveoli limit airflow by allowing the airway walls to deform and narrow.

Emphysema is an abnormal, permanent enlargement of the alveoli that ultimately results in destruction of the alveoli walls. COPD was responsible for 3 million deaths in 2005 and the WHO predicts that by 2030, it will be the third largest cause of mortality worldwide. More than 12 million people in the U.S. are diagnosed with COPD, although, because the disease develops slowly, many people have may have the disease and not be diagnosed. The symptoms of COPD often worsen over time and when the disease becomes severe will prevent the conducting of even basic activities such as walking, cooking, or washing. As symptoms worsen, there is an increased risk of an acute exacerbations (or worsening of symptoms) of the condition, that usually results in hospitalisation of the patient. More than 30 million people are affected with COPD in the seven major pharmaceutical markets. In 2005 there were more than 10 million physician office visits and two million hospitalizations per year. The disease was estimated to cost the U.S. healthcare system U.S. $30 billion in 2000. While the worldwide prevalence of COPD is growing, much of this is due to developing countries where smoking rates remain high. Western markets are estimated to have a growth rate of +1.5% year on year as screening rates for COPD detection improve, despite long-term smoking rates starting to decrease.

Diagnosis: While many medications are available to treat COPD, no drug has demonstrated effectiveness in halting the progression of the disease. Rather, the goal of drug therapy at this time is to maintain control of symptoms and prevent COPD exacerbation. For example, tiotropium is used to control the symptoms of COPD. Tiotropium is a prescription medicine used once every day to relax the airways and keep them open. Tiotropium also reduces the

likelihood of flare-ups and worsening of COPD symptoms (exacerbations). In 2008, the worldwide sales of tiotropium were US$3 billion. Management of COPD generally involves bronchodilators such as tiotropium and inhaled steroids. However, only an estimated 20%-25% of patients respond positively to steroids and it is currently not practical to determine in advance which patients will respond to steroids. Therefore, as with asthma, there is room to improve both the diagnosis and management of COPD.(Figure 3).

Figure.3

While the asthma market is relatively well served by existing treatments controlling the disease, thus allowing patients to enjoy a good quality of life, there is a significant need for better therapies to treat COPD, which remains a progressive disease.

1.4 Bronchiectasis:

Bronchiectasis is a progressive lung disease, affecting 600,000 people worldwide. It is often mistaken for asthma or pneumonia and misdiagnosis is common. In this disease the airway walls are chronically inflamed, with poor clearing of the increased mucus production. Chronic inflammation of the walls of the airway is common to all types of bronchiectasis. This is often a result of a vicious cycle of bacterial infection, in which damage to the lungs further predisposes the lung to more infections. The body repairs the damaged lung tissue by forming tough, fibrous material, which leads to changes that impair normal lung structure and function.

Effects include:

Reduced lung capacity; Poor gas-exchange; Changes of the organisation of blood vessels; and Overall increased blood flow through the lungs.

These changes can ultimately lead to heart failure. Recurrent lung infections commonly reduce patients' quality of life; progressive respiratory insufficiency is the most common cause of death. Most cases of bronchiectasis develop during childhood, and can be a result of infections such as pneumonia or the inhalation of noxious substances.

Diagnosis:

Treatment today is aimed at controlling infections, secretions, airway obstructions and complications. There are no therapeutic products available to effectively clear excess mucus secretions and improve the quality of life of sufferers. Current management of bronchiectasis often involves:

a. Bronchodilators, to dilate the airways to help mucus clearance;
b. Steroids. However, only a minority of mild-moderate bronchiectatic patients respond positively to steroids;
c. Antibiotics to clear infections; and
d. Regular, daily postural drainage to remove bronchial secretions.

1.5 Chronic Bronchitis :

Patients with chronic bronchitis experience persistent airway inflammation and airflow obstruction, with symptoms including a chronic mucus-producing cough and shortness of breath. Due to the difficulties they have in clearing

mucus from their lungs, sufferers are prone to periodic bacterial infections where their cough worsens, mucus production increases and breathing becomes more difficult. These episodes damage and scar the bronchial lining and contribute to continued chronic inflammation and immune-mediated cell damage as the body struggles to fight the infections. This cycle of infection and internal scarring may cause a progressive decline in lung function, reducing quality of life and ultimately causing death.

Many of the deaths associated with chronic bronchitis are included in the COPD figure that now accounts for over 100,000 deaths a year in the U.S. The disease is predominately caused by inhaling some form of lung irritant repeatedly for many years, usually cigarette smoke. Chronic bronchitis is slow to develop and is often not diagnosed until the sufferer is in their 40s or 50s.

Diagnosis:

Management of chronic bronchitis includes various general supportive measures such as giving up smoking, limiting exposure to dust and chemicals, avoiding sudden temperature changes, undertaking chest physiotherapy and deep-breathing exercises, and increasing fluid intake to keep the bronchial secretions thin. While there are a number of medications that dilate the airway and reduce airway inflammation, for chronic bronchitis sufferers, there are few therapeutic products available to effectively clear excess mucus secretions.

This presents a major medical challenge, as ineffective mucus clearance is a major cause of infection and progression of the disease. Treatments for chronic bronchitis include anti-cholinergic agents, steroids, antibiotics and oxygen. Anticholinergic agents, also known as anti-muscarinic, are bronchodilators used for the relief of acute symptoms in both asthma and COPD, but tend to be more effective in COPD. Inhaled corticosteroids are less likely to cause systemic side effects than oral corticosteroids, and have been shown to be effective in asthmatics. However, the role of these agents in the management of COPD remains unclear. According to a recent scientific report (Chest, 2004, 126, 1815) there are no indications that early treatment with inhaled corticosteroids modifies a rapid decline in lung function or respiratory symptoms and quality of life.

1.6 Pulmonary Fibrosis:

Pulmonary fibrosis is a serious disease that causes progressive scarring of the lung tissue. The scar formation is preceded by, and associated with, inflammation. Some common and some rare diseases can cause pulmonary fibrosis, but in the majority of cases the cause is never found. Pulmonary fibrosis can be a mild or severe disease; it can be so mild as to cause few symptoms, or it can be fatal. If the disease progresses, the lung tissues eventually thicken and become stiff. The work of breathing then becomes difficult, causing breathlessness. It can run a gradual course, remain unchanged or run a rapid course. It can also be fatal. Pulmonary fibrosis most often begins with repeated injury to the tissue within and between the tiny air sacs (alveoli) in your lungs. The damage eventually leads to scarring or fibrosis, which stiffens the lungs and makes breathing difficult. The most common symptoms are shortness of breath and a dry cough.

Diagnosis:

Current treatments for pulmonary fibrosis include medications and therapy to improve lung function and quality of life. A number of new therapies for pulmonary fibrosis are in clinical trials. In the meantime, a lung transplant may be an option for some people with pulmonary fibrosis [5].

Herbal Remedies used for cough and Bronchial Asthma

Plants have been used in traditional medicine for several thousand years. The knowledge of medicinal plants has been accumulated in the course of many centuries based on different medicinal systems such as Ayurveda, Unani and Siddha. In India, it is reported that traditional healers use 2500 plant species and 100 species of plants serve as regular sources of medicine (Pei, 2001). During last few decades there has been an increasing in the study of medicinal plants and their traditional use in different parts of the world (Lev, 2006).

Herbal remedies are considered the oldest forms of health care known to mankind on this earth. Prior to the development of modern medicine, the traditional systems of medicine that have evolved over the centuries within various communities, are still maintained as a great traditional knowledge base in herbal medicines (Mukherjee and Wahil, 2006). Traditionally, this treasure of knowledge has been passed on orally from generation to generation without any written document (Perumal Samy and Ignacimuthu, 2000) and is still retained by various indigenous groups around the world. Among the plants surveyed, Ocimum basilicum, Adhatoda vasica are used frequently for the preparation of medicines for the treatment of respiratory disorders. The result showed that Cassia tora, Solanum xanthocarpum are weeds, which is used as a vegetable[6] (Table 3).

S.no	Plant name	Family	Plant part used	Chemical constituents	Mechanism of action
1.	Acalypha indica	Euphorbiaceae	Leaves, roots, stalk and flowers	-	Bronchodialator
2.	Achyranthes aspera Allium cepa	Amaranthaceae	Fruit	Saponin C Saponin D	Mast cell stabilizer
3.	Adhatoda vasica	Liliaceae	Bulb	Quercetin	1. Mast cell stabilizer 2. Lipoxygenase inhibitor 3. PAF inhibitor 4. COX inhibitor
4.	Albizzia lebbeck	Leguminosae	Bark	Alkaloids, tannins, flavonoids,	1. Bronchodilator 2. Mast cell stabilizer
5.	Achillea mellifolium	Asteraceae (compositae)	Flower	Alkaloids	Inhibits action of histamine, acetylcholine and 5-HT
6.	Asystasia gangetica	Acanthaceae	Leaves	Triterpenoids, saponins, Steroidal aglycone	1. Bronchodilator 2. Anti-inflammatory
7.	Acorus calamus	Araceae	Rhizome	Asarone	Inhibits action of histamine, acetylcholine and 5-HT
8.	Ammi visnaga	Umbelliferae	Seeds	Khellin	Bronchodilator
9.	Boswellia serrata	Burseraceae	Root	Boswellin, Boswellic acid	Inhibits leukotriene biosynthesis
10.	Balanites roxburghii	Simarubaceae	Stem bark	Alkaloids	1. Bronchodilator 2. Mast cell stabilizer
11.	Cedrus deodara	Pinaceae	Wood	Himacholol	Mast cell stabilizer
12.	Curculigo orchioides	amarylliaceae	Rhizomes	Triterpenoids sapogenins and saponin glycosides	1. Antihistaminic 2. Anti-inflammatory
13.	Clerodendron phlomidis	Verbenaceae	Leaves	Flavonoids, terpenoids, steroids	1. Antihistaminic 2. Mast cell stabilizer
14.	Curcuma longa	Zingiberaceae	Rhizome	Curcuminoids	Inhibits histamine release
15.	Albizzia lebbeck	Leguminosae	Bark	Alkaloids, tannins, flavonoids,	1. Bronchodilator 2. Mast cell stabilizer
16.	Achillea mellifolium	Asteraceae (compositae)	Flower	Alkaloids	Inhibits action of histamine, acetylcholine and 5-HT
17.	Asystasia gangetica	Acanthaceae	Leaves	Triterpenoids, saponins, Steroidal aglycone	1. Bronchodilator 2. Anti-inflammatory
18.	Acorus calamus	Araceae	Rhizome	Asarone	Inhibits action of histamine, acetylcholine and 5-HT
19.	Ammi visnaga	Umbelliferae	Seeds	Khellin	Bronchodilator

20.	Boswellia serrata	Burseraceae	Root	Boswellin, Boswellic acid	Inhibits leukotriene biosynthesis
21.	Balanites roxburghii	Simarubaceae	Stem bark	Alkaloids	1. Bronchodilator 2. Mast cell stabilizer
22.	Cedrus deodara	Pinaceae	Wood	Himacholol	Mast cell stabilizer
23.	Curculigo orchioides	amarylliaceae	Rhizomes	Triterpenoids sapogenins and saponin glycosides	1. Antihistaminic 2. Anti-inflammatory
24.	Clerodendron phlomidis	Verbenaceae	Leaves	Flavonoids, terpenoids, steroids	1. Antihistaminic 2. Mast cell stabilizer
25.	Curcuma longa	Zingiberaceae	Rhizome	Curcuminoids	Inhibits histamine release
26.	Cassia sophera	Caesalpiniaceae	Leaves	Flavonoids, glycosides	1. Bronchodilator 2. Antihistaminic 3. Antiallergic 4.anti-inflammatory
27.	Centipeda minima	Compositae	Whole plant	Pseudoguainolide, sesquiterpene, lactone, flavonoids	Anti-allergic
28.	Ephedra gerardiana	Ephedraceae	Stem	Ephedrine	Bronchodilator
29.	Eucalyptus globules	Myrtaceae	Leaves	Volatile oil	Anti-inflammatory
30.	Aegle marmelos	Rutaceae	Leaves	Alkaloid-aegeline	Antihistaminic
31.	Hedychium spicatum	Zingiberaceae	Rhizome	Sitosterol, Volatile oil	Anti-inflammatory
32.	Glycyrrhiza glabra	Leguminosae	Root	Glycyrrhizinic acid	1.Antihistaminic 2.Antiallergic
33.	Inula racemosa	Asteraceae	Roots	Inulin, sesquiterpene lactone-alantolactone	Antihistaminic
34.	Moringa oleifera	Morangaceae	Seed	Tannins, steroids, triterpenoids, flavonoids, alkaloids, saponins	Antihistaminic
35.	Myrica sapida	Myricaceae	Bark	Glycosides	Mast cell stabilizer
36	Nigella sativa	Ranunculaceae	Seed	Volatile oil, fatty acid	Bronchodilator
37	Ocimum sanctum	Labiateae	Leaves	Ursolic acid	Mast cell stabilizer
38.	Picorrhiza kurroa	Scrophulareaceae	Roots	Picorrhizin	Antihistaminic
39.	Lipidum sativum	Cruciferae	Seeds	Alkaloids, Flavonoids	Bronchodilator
40.	Passiflora incarnata	Passifloraceae	Leaves	Benzoflavone	Bronchodilator
41.	Solanum xanhocarpum	Solanaceae	Flowers	Phyto-sterol, alkaloids, flavonooooids, Steroids	1. Antihistaminic 2. Mast cell stabilizer

42.	Cassia sophera	Caesalpiniaceae	Leaves	Flavonoids, glycosides	1. Bronchodilator 2. Antihistaminic 3. Antiallergic 4.anti-inflammatory
43.	Centipeda minima	Compositae	Whole plant	Pseudoguainolide, sesquiterpene, lactone, flavonoids	Anti- allergic
44.	Ephedra gerardiana	Ephedraceae	Stem	Ephedrine	Bronchodilator
45.	Eucalyptus globules	Myrtaceae	Leaves	Volatile oil	Anti-inflammatory
46.	Aegle marmelos	Rutaceae	Leaves	Alkaloid-aegeline	Antihistaminic
47.	Hedychium spicatum	Zingiberaceae	Rhizome	Sitosterol, Volatile oil	Anti-inflammatory
48.	Glycyrrhiza glabra	Leguminosae	Root	Glycyrrhizinic acid	1.Antihistaminic 2.Antiallergic
49.	Terminalia belerica	Combrataceae	fruits	Beta sitosterol, Gallic acid, ellagic acid, glycoside	Mast cell stabilizer
50.	Tinospora cordifolia	Mensipermaceae	Stem	Alkaloids	1. Antihistaminic 2. Mast cell stabilizer
51.	Tamarindus indica	Caesalpiniaceae	leaves	Flavone, Glycosides	1. Brochodialator 2. Antihistaminic 3. Anti-inflammatory
52.	Terminalia belerica	Combrataceae	fruits	Beta sitosterol, Gallic acid, ellagic acid, glycoside	Mast cell stabilizer
53.	Tinospora cordifolia	Mensipermaceae	Stem	Alkaloids	1. Antihistaminic 2. Mast cell stabilizer
54.	Tamarindus indica	Caesalpiniaceae	leaves	Flavone, Glycosides	1. Brochodialator 2. Antihistaminic 3. Anti-inflammatory
55.	Terminalia belerica	Combrataceae	fruits	Beta sitosterol, Gallic acid, ellagic acid, glycoside	Mast cell stabilizer

Table.3 Herbal remedies as a source potential of anti-respiratory agent[7-40]

3. Conclusion

Respiratory disorders like asthma, cystic fibrosis, COPD, Bronchiectasis Chronic Bronchitis, Pulmonary Fibrosis caused by dust mites, pollen, exercise, or even dry air, which produce mucus, saliva, pain on breathing or unusual breathing. It is basically diagnosed by some synthetic and herbal remedies like cough drops and Glycyrrhiza glabra etc. the review revelled that to many of herbal remedies used by traditionally as an anti- respiratory agent are reported to have scientific evidence. All the natural products discussed in this review exhibit anti-respiratory activities.

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