

Awareness and Current Therapeutics of Asthma

Dose-Response:
An International Journal
July-September 2019:1-11
© The Author(s) 2019
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/1559325819870900
journals.sagepub.com/home/dos



Rida Zainab¹ , Muhammad Akram¹, Muhammad Daniyal²,
and Muhammad Riaz³

Abstract

Introduction: Asthma is a serious allergic disorder of the respiratory system. It affects about 300 million people worldwide. This has a great burden on medical treatment. Several medicines are available, but they have many serious side effects. Therefore, there is a need to search for a new therapeutic agent with no or minimal side effects while most economical for patients. In folk medicine, antiasthmatics herbal medicine has been used and showed potential therapeutic antiasthmatic efficacy due to the presence of potential bioactive compounds.

Methods: Different databases were searched (ie, Embase, PubMed, CBM, AMED, and CINAHL). We have reviewed the published data of the last 20 years. We used MeSH terms “asthma” herbal treatment of asthma, allopathic treatment of asthma, and treatment strategies for asthma. The traditional medicine was compared with modern medicine and the same pharmacotherapies alone or with placebo. The methodology was evaluated by using the GRADE summary of Finding tables and Cochrane Risk of Bias Tool.

Results: There have been some clear-cut indications toward the recognition of further molecular and cellular mechanisms of asthma. Most of them recommend a further target for treatment. The novel procedures, biologics, and pharmaceuticals are evaluated. Both allopathic and herbal treatments of asthma are effective. Due to none or lesser side effects, herbal medicines are safer than conventional medicine.

Conclusion: The preliminary documentation of the plants discussed in the review show the presence of several secondary metabolites that are responsible for the management of asthma and its relevant complications. Further research studies are needed to identify the bioactive compounds from these plants that have potential efficacy to cure asthma, and clinically based studies are needed to search for a complete cure for this disease.

Keywords

asthma, allopathic medicine, alternative medicine, efficacy, literature review

Introduction

Bronchial asthma is a paroxysmal attack of breathlessness, chest tightness, and wheezing resulting from paroxysmal narrowing of the bronchial airways. Asthma is characterized by inflammation, obstruction, and hyper-responsiveness of the airway. Patients cough more during sleep and when awake in the morning. Asthma affects 10% of the population. Epidemiology will help us to study prevalence, morbidity, and mortality rate of asthma. About 235 million people worldwide have been affected. Many people die from this deadly disease due to its high prevalence rate in many countries. Number of patients has been increasing day by day. Millions of people have died from

¹ Department of Eastern Medicine, Government College University Faisalabad, Faisalabad, Pakistan

² TCM and Ethnomedicine Innovation & Development International Laboratory, School of Pharmacy, Hunan University of Chinese Medicine, Changsha, China

³ Department of Allied Health Sciences, University of Sargodha, Sargodha, Pakistan

Received 08 October 2018; received revised 11 March 2019; accepted 18 June 2019

Corresponding Author:

Rida Zainab, Department of Eastern Medicine, Government College University Faisalabad, Faisalabad, Pakistan.

Email: ridazainab357@gmail.com



Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (<http://www.creativecommons.org/licenses/by-nc/4.0/>) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (<https://us.sagepub.com/en-us/nam/open-access-at-sage>).

asthma. The highest incidence is in New Zealand, Australia, and the United Kingdom, and the lowest incidence rate is in China and Malaysia. About 7% of adults and 15% of children have asthma.¹

Types of Asthma

Allergic Asthma

Allergic asthma is a disorder that it occurs due to airborne substances. It mostly affects children due to environmental factors because children play in a dirty environment and inhale in a dusty environment.²

Nonallergic Asthma

Nonallergic asthma occurs in adults older than 35 years and in individuals with no previous allergic histories. It mainly sheds an epithelial layer in the lungs, causing thickening of the overlying basement membranes, hypertrophy of bronchial smooth muscle, hyperplasia of lungs muscle due to allergy, and vascularization of neurons.³

Allergic Bronchopulmonary Mycosis

It is caused by an exaggerated immune response to the fungus *Aspergillus*.⁴

Aspirin-Induced Asthma

It is caused by overuse of nonsteroidal anti-inflammatory drugs such as aspirin.⁵

Exercise-Induced Asthma

Strenuous exercise exerts pressure on lungs, and dust deposits on the lungs and causes narrowing of the airways. Bronchial muscles change due to environmental humidity and temperature.⁶

Cough-Variant Asthma

It is a type of cough that is not productive, and mucous does not come out from the lungs but deposits in lungs which makes it thicker and causes difficulty in breathing.

Occupational Asthma

It is a disorder that occurs while at work when medical professional dealing with patients inhale allergens; it induces allergic reactions.⁷

Nocturnal Asthma

It occurs during sleep; when the person lies down, the nasal secretions start to accumulate in the lungs and cause breathing to be harder.⁸

Classification of nocturnal asthma.

Intermittent Asthma: Symptoms of intermittent asthma occurs 2 days per week or less. It is rare to wake up at night.

Persistent Mild: It has symptoms more than twice a week but not every day. In this, the patient occasionally wakes up at night.

Persistent Moderate: It has symptoms every day. Kids and adults wake up at least once a week.

Pathology of Allergic Asthma

Asthma is an allergic disease. B cells are important immunological cells in the body which recognize specific antigen cells and produce immunoglobulin E (IgE) in response. It also helps in the production of dependent mast cells, basophils, leukotrienes, and cytokines. B cells in airways act as foreign detectors to detect allergens for endocytosis which comes from airborne substances and present it to the T cells. Respiratory epithelium is activated by the environmental and inflammatory mediators and release lymphopoietin from stromal cells of thymic tissues in airways and inflammatory mediators and attracts leukocytes and recruits more leukocytes to skew dendritic cells toward allergic reaction. These dendritic cells cause differentiation of T cells into T helper cells as well as type II cells. These T cells induce production of IgE antibody from B cells by stimulation of interleukin (IL) mediators. Immunoglobulin binds to receptors on B cells and releases cytokines and basophils from mast cells in the presence of allergens that block the receptors and cause bronchoconstriction and enhance inflammatory response. Production of IL and T cells raise eosinophil levels in the body. Inflammatory mediators release from eosinophils, macrophages, neutrophils, and T cells resulting in damage or destruction of airways and cause bronchoconstriction and stimulate airways epithelium to release more inflammatory mediators. The role is played by cytokines, basophils, eosinophils, T cells, antigen presenting cells (APCs), chemokines, macrophages, neutrophils, stem cells, necrotic factors, epithelial cells, IL-4, IL-5, IL-13, prostaglandin, colony-stimulating factors and ligands, and so on.⁹ We have to determine how environmental factors activate Blimp-1 and how Blimp-1 causes T cells to drive allergic asthma.

Defective receptors. B-receptors are found in the lungs and have an agonist effect as a bronchodilator.

Autoimmune receptors. Autoimmune nerve influences airway tone by activating specific receptors on airways smooth muscle. Cholinergic receptor stimulation occurs as a result of acetylcholine release from postganglionic cells.

A considerable number of patients with asthma have a history of additional allergic disorders and elevated level of immunoglobulin. In the earliest part of the 20th century, the allergic theory was considered as the major cause of asthma.¹⁰ Nervous system theory explains that cases with asthma have defective β -receptors, which cause an imbalance between sympathetic and parasympathetic nerves. The imbalance

overstimulates the parasympathetic nerves, leading to bronchial constriction.¹¹ Gene theory explains that patients with asthma get asthma genes from parents. The patient with asthma invariably has asthmatic parents or grandparents. There seems to be a genetic predisposition to asthma.¹² The viral theory explains that respiratory infections especially viral infections often precipitate bronchial asthma. The initial event seems to be the epithelial damage and airway wall inflammation. Viral infection in asthmatic genetic diathesis can be devastating, since viral infections can attack and damage β -receptors and may cause wheezing for a long period. If β -receptors are damaged permanently, then asthma may last for months and years.¹³ Mast cell theory explains that millions of mast cells line up on the skin, nose, bronchial tree, and intestines. Mast cells contain leukotrienes and histamines. When any antigen from outside enters the respiratory tract and encounters the IgE antibodies, the mast cells liberate chemicals in the respiratory tract and cause tissue inflammation and swelling. In the nose, mast cells cause sneezing, asthma in the lungs, and itching in skin.^{14,15} Inflammation plays an important role in the pathogenesis of asthma.

In an immediate response, usually, allergens are involved. Response occurs within 15 minutes to 1 hour of allergen exposure. Activation of mast cells causes the release of chemical mediators that are involved in inflammatory reactions and manifestations of asthma. Late-phase response occurs after 4 to 6 hours of allergen exposure. In this phase, neutrophils and eosinophils are involved that release chemical mediators resulting in the inflammatory response and symptoms formation.

Various allopathic medicines are available that are used to treat asthma, but they have side effects.¹⁶ Salbutamol and theophylline are effective in the treatment of the early phase inflammation in patients with asthma. Anti-inflammatory drugs and cromolyn sodium are effective in the late phase of inflammation. Early-onset asthma occurs in patients with atopy and in children. Patients with atopy form IgE antibodies against fungal spores, animal dander, feathers, house dust, pollen, and ingested allergen obtained from wheat, yeast, milk, eggs, and fish. Allergic diseases including eczema and allergic rhinitis are usually present. In this type of asthma, certain mediators are released that produces mucus hypersecretion, mucosal swelling, and muscle spasm. Late-onset asthma usually occurs in adults. The autonomic nervous system controls the bronchial secretion and bronchial smooth muscles. Bronchoconstriction occurs due to adrenergic and cholinergic stimulation, while relaxation occurs because of β -adrenergic stimulation. Aspirin, emotion, pollution, and cold stimulate α -adrenergic and cholinergic system causing bronchial constriction and enhancing the mucus secretion. The term atopy is employed to describe people who rapidly develop IgE antibodies against the foreign antigen. The allergen enters the bronchi with the inspired air. The antigen-antibody reaction in the bronchi causes the release of biochemical mediators that are involved in the bronchial constriction. T-lymphocytes, macrophages, neutrophils, and eosinophils are also involved in the inflammatory reactions. Airways hyperactivity to the nonspecific stimuli has been

observed in the tracheobronchial tree of people with asthma. The abnormalities may occur in the nerves in such a way that stimulation of parasympathetic system and deficiency of sympathetic system occurred causing hyperactivity to result in constriction of bronchi. Bronchial reactivity can be checked by asking the people to inhale histamine methacholine (bronchial provocation test). It causes a transient episode of narrowing of the airway to susceptible people. The precipitating factors are sudden climatic change, use of medicines such as β -blockers and nonsteroidal anti-inflammatory drugs, atmospheric pollution, tobacco smoke, dust, emotional stress, respiratory viral infection, and exercise. In this inflammatory disorder, several well-known hereditary components and cells such as mast cells, lymphocytes, and eosinophils are involved. Airway inflammation leads to airway edema and hyperactivity resulting in reversible bronchoconstriction. If left untreated, the inflammatory changes may eventually become chronic and irreversible, a process termed airway remodeling. From both laboratory and epidemiological studies, a protective role for infection against the subsequent development of asthma has been established.¹⁷

In comparison to the allopathic treatment of asthma, herbs provide additional effects, and these are used as important regimens in certain areas. Some of the medicines are evidence based and have been prescribed in clinical practice.^{18,19} Various researchers are doing experimental studies on herbal medicine and recommending these drugs for clinical practice. In this review, an effort has been made to document the mechanism of action of some medicinal plants (Table 1). Various comparative studies are being conducted all over the world.

This review focuses on novel and promising conventional treatment of asthma. In this review, preliminary documentation of these plants showed the presence of several secondary metabolites that are responsible for the management of asthma and its relevant complication. In this review, we explained the pharmacological properties of plants and demonstrated its importance for the treatment of the asthmatic problems.

Severe Asthma and Its Mechanism

Nowadays, most of the cases with asthma were considered similar but differ only on the basis of disease severity. Therefore, the treatment of patients with asthma requires difference in dose, route of intake or frequency of taking the β_2 -adrenoceptor agonist, and corticosteroids that are essential to manage asthma disease.³⁵ However, asthma subphenotypes identification has challenged this view in modern medicinal system. Since past 2 decades, research has identified the fundamental source of asthma is the allergic pathways and a prominent role of T-cells designated as Th2-like producing cytokines and chemokines involved in IgE regulation, maturation, recruitment, priming, and white cells activation including basophils, mast cells, and neutrophils. Allergic pathways contributing the dysfunction of airways in mild-to-moderate asthma are mainly corticosteroid sensitive. Nonetheless, the profile of

Table 1. Mechanism of Action of Antiasthmatic Plants.

Plant Name	Common Name	Family	Mechanism of Action	References
<i>Achyranthes Aspera</i>	Chaff-flower, devil's horsewhip, prickly chaff flower	Amaranthaceae	Decreases eosinophil count, decreases ESR	20
<i>Adhatoda vasica</i>	Adusa	Acanthaceae	Bronchodilator, antianaphylactic	20
<i>Albizia lebbek</i>	Lebbek tree, flea tree	Leguminosae	Mast cell stabilizer	21
<i>Banksia serrata</i>	Old Man Banksia, Saw Banksia	Proteaceae	Inhibition of LT formation and blocks synthesis of 5-HETE & LTB ₄	22
<i>Calotropis gigantea</i>	Swallow wort, Madar	Apocynaceae	Anti-inflammatory, Bronchodilator	23
<i>Cedrus deodara</i>	Deodar Cedar, Himalayan Cedar	Pinaceae	Mast cell stabilizer	24
<i>Clerodendrum serratum</i>	Beetle Killer, Babhneti	Verbenaceae	Bronchodilator	25
<i>Curcuma longa</i>	Turmeric	Zingiberaceae	Inhibition of histamine release from rat peritoneal mast cells	26
<i>Inula racemosa</i>	Pushkarmool	Asteraceae	Antihistaminic, antiserotogenic	27
<i>Picrorhiza kurroa</i>	Kutki	Plantaginaceae	Inhibits release of histamine and SRS-A	28
<i>Solanum xanthocarpum</i>	Kantakari	Solanaceae	Bronchodilator	29
<i>Sarcostemma brevistigma</i>	Moon Plant, Soma Plant	Asclepidaceae	Inhibits passive cutaneous anaphylaxis in rats	30
<i>Tephrosia purpurea</i>	Wild indigo	Fabaceae	Bronchodilator, antianaphylactic	31
<i>Tinospora cordifolia</i>	Guduchi, giloy, heart leaved moonseed	Menispermaceae	Mast cell stabilizing activity	32
<i>Tamarindus indica</i>	Tamrhindi, Tamarind	Leguminosae	Bronchodilator, membrane stabilizer	33
<i>Vitex negundo</i>	Chaste tree	Verbenaceae	Bronchodilator, membrane stabilizer	34

Abbreviation: ESR, erythrocyte sedimentation rate; 5-HETE, 5-hydroxyeicosatetraenoic acid; LTB₄, leukotriene B₄; SRS-A, slow-reacting substance of anaphylaxis.

inflammatory process changes frequently with larger contribution of neutrophils, airway remodeling, and substantial tissue devastation in patients with more severe asthma (Figure 1).^{37,38} In patients with severe asthma, the airways show features of chronic wound as an indication of enduring epithelial injury and repair.³⁹ Necessary stimuli are created in response to any injurious wound to recruit the primary mesenchyme for participation in repair process by releasing certain growth factors such as vascular endothelial growth factors, heparin-binding like growth factor, epidermal growth factor (EGF), amphiregulin, insulin-like growth factors, fibroblast growth factors, keratinocyte growth factor, transforming growth factor (TGF)- β , and TGF α , which in combination promote vasculogenesis and remodeling.⁴⁰ Reduced antioxidant defenses and overexpression of EGF receptors are the characteristics of injury and stress displayed by airway epithelium.^{41,42} Derangement of epithelial function and mesenchymal response augmentation emphasize the likely responsibility of epithelial-mesenchymal trophic unit which is linked with the lung development and disease remodeling and chronicity (Figure 1).^{43,44} This process includes augmented matrix deposition in the subendothelial lamina reticularis of basement membrane, deposition of types 1, 3, 5, and 6 repair collagens, and disruption of elastin filaments and proteoglycans all the way through airway wall resulting in stiffer and thickened airways.^{45,46} In severe asthma, the smooth muscle spiral bundles are increased both in size and in number and spread upward affecting the larger airways, alveolar ducts, and respiratory bronchioles.⁴⁷ The ability of

recruitment, retainment, and activation of selective cells responsible for inflammation such as neutrophils, mast cells, and monocytes changes within this microenvironment. Consequently, regardless of high dose intake of oral corticosteroids, the mast cells may increase in number or persist, particularly those close to or within the smooth muscle bundles of the airway with most of the cells containing increased tumor necrosis factor α (TNF α).⁴⁸ The TNF α is raised in airway biopsies at messenger RNA level and in bronchoalveolar lavage fluid.⁴⁹ Mast cells are also vital source of cytokines such as IL-13 with driving potential for both the inflammatory and the remodeling processes.

Results

Allopathic Treatment

The 2 major features of bronchial asthma include bronchoconstriction and inflammation; thus, the allopathic drugs are used to prevent or reverse the bronchoconstriction and decrease the inflammation via a different mechanism (Figure 2). Smooth muscles of the bronchial tree mainly contain β_2 receptors, stimulation of which causes bronchodilation. All those sympathomimetic that cause stimulation of β_2 adrenoceptors are useful in the treatment of bronchial asthma, especially those acting mainly on β_2 receptors. Sympathomimetic are epinephrine, ephedrine, isoproterenol, albuterol, levalbuterol, bitolterol, metaproterenol, terbutaline, ritodrine, procaterol, isoetarine, formoterol, pirbuterol, and salmeterol.⁵⁰ Adrenaline is available as injection and inhaler. The 0.3 to 0.5 mL of 1:1000

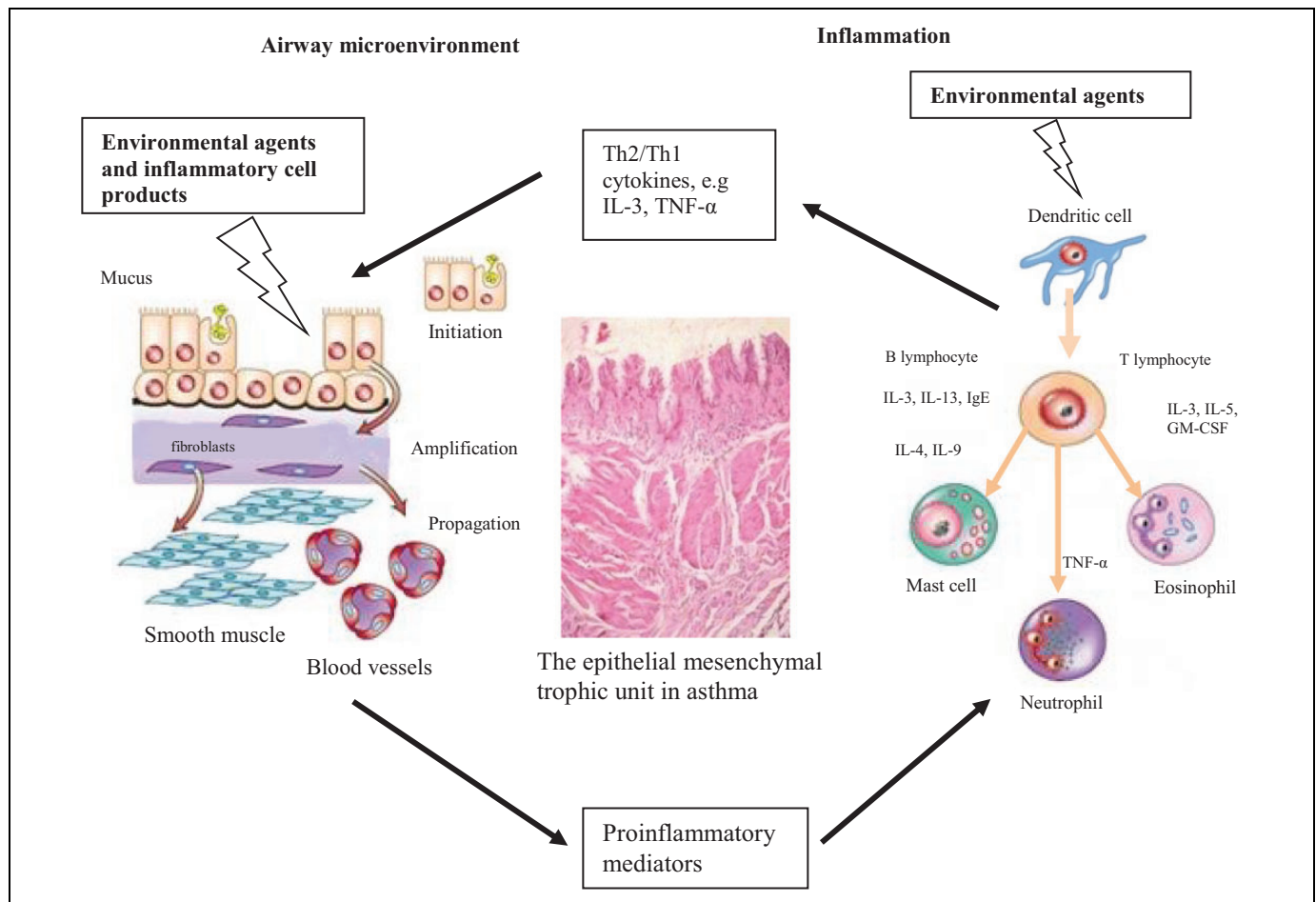


Figure 1. Responses during inflammation and remodeling process in asthma activating the epithelial–mesenchymal trophic unit. Communication set point between bronchial epithelium and underlying mesenchymal cells alters by the epithelial damage, resulting in the activation of myofibroblasts with raised mesenchymal volume and induction of structural changes throughout the airway wall. (Adapted from Holgate and Polosa).³⁶

solutions can be used subcutaneously for asthma, which can be repeated after 15 to 20 minutes. It is mostly metabolized in the body, and metabolites are excreted in the urine. Adrenaline is metabolized in the body by 2 enzymes, monoamine oxidase and catechol-o-methyl transferase. It produces bronchodilation by stimulating β_2 adrenoreceptors on the smooth muscles of the bronchial tree. It is avoided in elderly individuals, ischemic heart disease, cardiac arrhythmias, and hypertension.⁵¹ Albuterol can be used orally, by injection, or by inhalation. When given orally, its absorption is good from gastrointestinal tract (GIT). Bronchodilation occurs in about 1 hour and remains for 6 to 8 hours. When used by inhalation it acts in about 15 minutes and remains effective for 3 to 4 hours. By subcutaneous injection, its effects occur in 5 minutes and last for 3 to 4 hours.⁵² Tiotropium is a long-acting antimuscarinic drug. It is especially effective in cases of the chronic obstructive pulmonary disease. It also decreases the acute exacerbation in patients with chronic obstructive pulmonary disease.⁵³ Methyl xanthine drugs are theophylline, aminophylline, theobromine, caffeine, oxtriphylline, dyphylline, pentoxifylline, and acefylline.

Aminophylline is prescribed to patients who develop paradoxical abdominal and diaphragmatic fatigue. Aminophylline infusion is effective in improving diaphragmatic contractility.⁵⁴ Mast cell stabilizers are cromolyn sodium, nedocromil Na, and ketotifen. These important anti-inflammatory drugs prevent activation of many inflammatory cells, particularly mast cells, eosinophils, and epithelial cells. These agents have no direct bronchodilator activity. Therefore, they are not effective in relieving acute symptoms of asthma. They are effective in mild persistent asthma, particularly when exercise is a precipitating factor. Cromolyn sodium is derived from an Egyptian plant called khellin. It inhibits the release of chemicals from mast cells and therefore prevents all phases of asthmatic attack. It is used 3 to 4 times a day. The drug in powder form can be inhaled and has been developed as 1% Intel solution which is used in the nebulized device and now is available in Intel pocket inhalers.⁵⁵ Corticosteroids are triamcinolone, prednisone, mometasone, methylprednisolone, hydrocortisone, fluticasone, flunisolide, dexamethasone, budesonide, and beclomethasone. Corticosteroids are the most effective and constantly successful

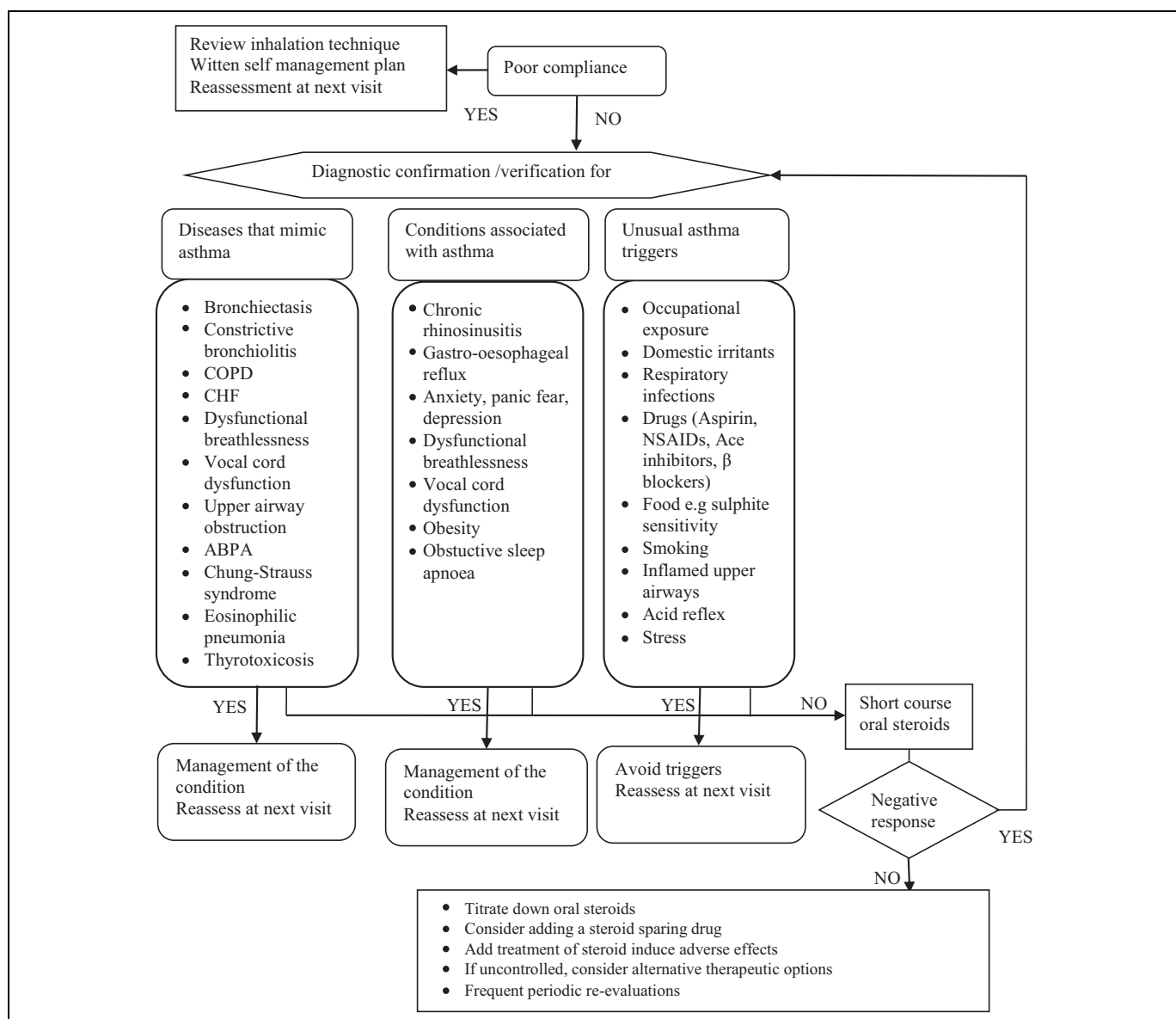


Figure 2. Possible algorithmic strategies and recommendations for managing patients with difficult to control asthma, despite maximum combination treatment. CS indicates cystic fibrosis; COPD, chronic obstructive pulmonary disease; CHF, chronic heart failure, ABPA, allergic bronchopulmonary aspergillosis; NSAIDs, nonsteroidal anti-inflammatory drugs.³⁶

anti-inflammatory drugs. Corticosteroids reduce inflammation resulting in control of asthma manifestations and prevention of asthma exacerbation.⁵⁶ Side effects observed by long use of corticosteroids are an adrenal failure, delay in wound healing, weight gain, osteoporosis, cataract, and growth retardation in children.⁵⁷ Cortisone inhalers give local relief in asthma with minimum side effects. Cortisones are effective in asthma and persistent, abnormal breathing. Cortisone inhalers cause hoarseness and oral thrush which can be minimized by mouthwash and use of myostatin locally.⁵⁸ The 5-lipoxygenase inhibitor is zileuton, and leukotriene D₄ (LTD₄)-receptor antagonists are zafirlukast and montelukast. Leukotrienes receptor antagonists are the novel group of medicines for the treatment of asthma. Leukotrienes induce asthma manifestations and airway

obstruction by contracting smooth muscle cells, attracting inflammatory cells, and enhancing mucus secretion and vascular permeability.⁵⁹

Herbal Treatment

Adhatoda vasica Linn

Adhatoda vasica Linn belongs to family Acanthaceae. Parts used are roots, leaves, flowers, and barks. Chemical constituents include vasicinol, vaccine, adhatodic acid, salts, alkaloids, essential oil, volatile odorous principle, salts, and pyroquinazoline alkaloids.⁶⁰ It is used in tuberculosis, asthma, and sore throat.⁶¹ It is an expectorant, bronchodilator, and

antibacterial.⁶² Gupta et al reported the antiasthmatic activity of different formulations of *Adhatoda vasica*.⁶³

Asystasia gangetica

Asystasia gangetica belongs to family Acanthaceae. Parts used are roots and leaves. It is used in asthma, wound healing, and cardiovascular disorders.⁶⁴ It is antiasthmatic and antihypertensive.⁶⁵ Akah et al reported the antiasthmatic property of *A gangetica* leaf extract. This plant is used in the management of asthma in various countries. A study was conducted to investigate its efficacy as an antiasthmatic drug. Methanol, ethyl acetate, and hexane extract of *A gangetica* were used for the study. The extract was able to inhibit the contraction induced by spasmogens. Histamine-precontracted tracheal strips were relaxed by the use of extract. The most active extract was ethyl acetate. This study indicated that *A gangetica* is effective in asthma.⁶⁶

Clitoria ternatea L

Clitoria ternatea L. belongs to family Fabaceae. Parts used are roots. Its chemical constituents are glycosides, saponins, and flavonoids.⁶⁷ It is used to treat constipation, intestinal worm, and diabetes mellitus.⁶⁸ It is antiasthmatic, hypoglycemic, antioxidant, antihyperlipidemic, memory enhancer, immunostimulant, and antibacterial.⁶⁹ The antiasthmatic activity of *C ternatea* L. roots has been reported. A study was conducted to investigate the efficacy of *C ternatea* L. in the treatment of asthma. Ethanolic extract of this plant was used for the study. Rats and mice were selected for the study. Mast cells degranulation was induced by egg albumin in rats. Eosinophilia and leukocytosis were induced by milk. The dose of the extract was 100 to 150 mg/kg administered intraperitoneally. Leukocytosis, eosinophilia, and mast cell degranulation were reduced significantly. This study indicated that this plant has antiasthmatic activity due to the presence of flavonoids or saponins.⁷⁰

Curculigo orchoides Gaertn

Curculigo orchoides Gaertn belongs to family Hypoxidaceae. Part used is root. Derivatives of this plant are used in asthma and Alzheimer disease.⁷¹ It is antiasthmatic, antiosteoporotic, and immunostimulant.⁷² The antiasthmatic activity of *C orchoides* has been reported. Ethanol extract of this plant was used for the study. Antiasthmatic activity has been investigated in vivo and in vitro. Animal models were used for the study. Mechanism of action of the extract was investigated in isolated goat tracheal chain preparation and isolated guinea pig ileum preparation. This in vitro study indicated that extract has muscle relaxant activity. Furthermore, its antihistamine-induced contraction has been reported. Maximum muscle relaxant effect was observed at a dose of 100 µg/mL in isolated goat tracheal chain preparation. The extract exhibited maximum muscle relaxant activity at a dose of 25 µg/mL in ileum preparation isolated from the guinea pig. Bronchospasm was induced by histamine in guinea pigs. After treatment with the

extract of this plant, there was an increase in leukocytes and reduction in eosinophils that indicates its efficacy in asthma.⁷³ Venkatesh et al. investigated mast cell stabilizing on isolated mice peritoneal mast cells and stated that plant has mast cell stabilizing activity and antihistamine activity.⁷⁴

Elephantopus scaber

Elephantopus scaber L. belongs to family Asteraceae. Parts used are roots and whole plant. Chemical constituents include steroids, saponin, flavonoids, and phenolic compounds. It is used to treat cough, malaria, and cancer.⁷⁵ It is anti-inflammatory.⁷⁶ The antiasthmatic activity of ethanolic extract of *E scaber* L. leaves has been reported. Ethanol extract of this plant was used for the study. Leaves of this plant were used for study purpose. Different dose levels of the extract were used. Bronchospasm was induced by histamine and acetylcholine. Isolated guinea pig tracheal chain was chosen for study. There was a significant reduction in bronchospasm in the test group when compared to control. This effect was dose dependent. This efficacy of plant is due to flavonoids.⁷⁷

Ficus religiosa L

Ficus religiosa L. belongs to the family Moraceae. Parts used are bark and seeds. It is used in gonorrhea, scabies, and herpes infection.⁷⁸ It is anticonvulsant, anti-inflammatory, and antiparkinsonism.⁷⁹ Kapoor et al reported the antiasthmatic activity of *F religiosa* leaves (150 and 300 mg/kg) in guinea pigs. Bronchospasm was produced by administration of acetylcholine and histamine. This study was done in comparison to aminophylline. Aqueous extract of the plant was introduced to guinea pig. Aminophylline was administered at a dose of 25 mg/kg. Furthermore, aqueous extract of the plant was investigated in comparison to ketotifen. Dose of extract was 10, 20, and 30 g/mL. There was a delay in the onset of histamine-induced preconvulsive dyspnea when compared to vehicle control. When an aqueous extract of the plant was administered at the dose of 150 and 300 mg/kg intraperitoneally, there was a significant effect on latency to develop histamine and acetylcholine-induced preconvulsive dyspnea. In vitro studies, the number of intact cells increased in the mast cell stabilizing model at the dose of 10, 20, and 30 µg/mL.⁸⁰

Hyssopus officinalis

Hyssopus officinalis belongs to family Lamiaceae. Parts used are flowers and leaves. Active ingredients include flavonoids, glycosides, tannin, resin, essential oil, fats, sugar, mucilage, isopinocampheol, limonene, and β-pinene.⁸¹ It is an antioxidant,⁸² stimulant, and smooth muscle relaxant.⁸³ Wang et al reported the efficacy of *H officinalis* in asthma and explored the mechanism of action in asthma. Rats were selected for the study. Water extract of *H officinalis* was administered. Extract affected differentiation of Th1, Th2, and Th17 on transcription level and played an important role as an antiasthmatic agent.

Hypericum perforatum Linn

Hypericum perforatum Linn belongs to family Hypericaceae. Parts used are leaves, buds, and flowers. Chemical constituents include essential oil, glycoside hyperin, hyperforin, and other fluorescent chemicals.⁸⁴ It decreases LDL cholesterol and reduces oxidative stress.⁸⁵ It is an antidepressant, antiasthmatic, and neuroprotective.⁶⁹ Khan et al reported the calcium channel blocking activity of *H perforatum*.⁸⁶

Nigella sativa

Nigella sativa belongs to family Ranunculaceae. Parts used are seeds. Melanthin, nigellin, nigellone, carvone, D-limonene, and thymoquinone are active principles of *N sativa*.⁸⁷ *Nigella sativa* is used in arthritis, other inflammatory diseases, oral disorders, and arthritis.⁸⁸ It is a galactagogue, antibacterial, and anti-inflammatory.⁸⁹ Gilani et al reported the bronchodilator, spasmolytic, and calcium antagonistic activities of *N sativa* (Kalonji).⁹⁰ Boskabady et al conducted a study to investigate the antiasthmatic potential of *N sativa* in the treatment of asthma. Bronchodilator potential of the boiled extract of *N sativa* (50 and 100 mg/kg) was compared to theophylline (6 mg/kg) in 15 patients with asthma. Effect of *N sativa* extract was relatively less than theophylline.⁹¹

Picrorhiza kurroa

Picrorhiza kurroa belongs to family Plantaginaceae. Part used is rhizome. Its active compounds are iridoid glucoside, phenolic, flavonoids, and cucurbitacins.⁹² It is used in jaundice, asthma, and arthritis.⁹² It is hepatoprotective, antiasthmatic, anti-inflammatory, and anticancer in nature.⁹³ The antiasthmatic effect of *P kurroa* has been reported. It is prescribed to treat liver and lung diseases. An active compound androsin has been isolated from this plant. Androsin was found effective against bronchial obstruction induced by allergen and platelet-activating factor.⁹⁴

Spinacia oleracea Linn

Spinacia oleracea Linn belongs to family Amaranthaceae. Parts used are leaves. Chemical constituents include iodine, lecithin, chlorophyll, carolin, oxalic acid, saponin, and flavonoids.⁵⁶ It is used in cardiovascular disorders, obesity, and cancer.⁹⁵ It is an antioxidant.⁹⁶ Heo et al reported the antiasthmatic activity of *S oleracea* Linn (SoL). Aqueous extract of SoL was used for study in mice. Asthma was induced by albumin. The extract was administered orally to those mice that were sensitized to ovalbumin. Hematoxylin and eosin staining was used to examine lungs for IL-4/13 cytokine expression. The extract exhibited antiasthmatic activity that is evident from the reduction in the CD4+ cell number and IL-4/13 in the lung. This study indicated that extract has an antiasthmatic activity that is evident in a mouse ovalbumin-challenge model.⁹⁷

Discussion

The present approach to treat asthma is mostly based on the use of corticosteroids and inhaled bronchodilators.⁹⁸ For a majority of individuals, these therapies are efficient at humanizing function of lung and life quality and decreasing manifestations and disease exacerbations.⁹⁹ Apprehension exists concerning the adverse reactions of these therapies in some individuals, particularly when prescribed in high dose.¹⁰⁰ Additionally, there is increasing identification of subgroups of individuals who emerge refractory to existing treatment and who are thought “complex to manage.” At present, new and costly biologic treatments are being emerged to tackle this unmet requirement. Traditional medicines to tackle the concern of adverse reactions and decrease the effectiveness comprises of the application of phytomedicine.¹⁰¹ However, development in this vicinity is vulnerable by the deficiency of convincing proof. Therefore, there is a necessity for an appropriately carried out controlled study on safe medicine derived from plants. The articles included in this article are mostly comprised of in vitro trials, which indicate that most scientists or researchers consider traditional medicines as effective treatment for different ailments rather than holistic or homeopathic medicines.

Conclusion

The medicinal plants and their extracts possess significant antiasthmatic activities. This article provides up-to-date information regarding patients with asthma and potential medicinal plants having antiasthmatic activity. The medicinal plants have confirmed effectiveness as antiasthmatic agent on a scientific base. The method of action of many medicinal plants has been recognized. This review emphasizes randomized clinical studies using traditional medicines for the management of asthma. Additional research is necessary to determine the bioactivity of additional compounds in simple extracts and to explore their bioactivity as antiasthmatic agents. Thence, novel and effective drugs can be developed by way of detailed investigation of the properties of various constituents.

Authors' Note

Authors have agreed for publication. Muhammad Daniyal is now affiliated with Faculty of Eastern Medicine, Hamdard University Karachi-Pakistan.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Rida Zainab  <https://orcid.org/0000-0002-3335-5436>

Muhammad Riaz  <https://orcid.org/0000-0002-5524-7735>

References

- Yang L, Guo YS, Jiang JQ, et al. The effect of stimuli on basophil-mediated atopic responses during asthmatic lying-in women and in newborns. *Hybridoma*. 2012;31(4):255-261.
- Matsuoka T, Hirata M, Tanaka H, et al. Prostaglandin D2 as a mediator of allergic asthma. *J Sci*. 2000;287(5460):2013-2017.
- Leynaert B, Sunyer J, Garcia-Esteban R, et al. Gender differences in prevalence, diagnosis and incidence of allergic and non-allergic asthma: a population-based cohort. *Thorax*. 2012;67(7):625-631.
- Denning DW, Pleuvry A, Cole DC. Global burden of allergic bronchopulmonary aspergillosis with asthma and its complication chronic pulmonary aspergillosis in adults. *Med Mycol*. 2013;51(4):361-370.
- Szczeklik A, Nizankowska E, Duplaga M. Natural history of aspirin-induced asthma. AIAANE investigators. *Eur Resp J*. 2000;16(3):432-436.
- Anderson SD, Daviskas E. The mechanism of exercise-induced asthma. *J Allergy Clin Immunol*. 2000;106(3):453-459.
- Mapp CE, Boschetto P, Maestrelli P, Fabbri ML. Occupational asthma. *Am J Respir Crit Care Med*. 2005;172(3):280-305.
- Diette GB, Markson L, Skinner EA, Nguyen TT, Algatt-Bergstrom P, Wu AW. Nocturnal asthma in children affects school attendance, school performance, and parents' work attendance. *J Amer Med Assoc*. 2000;154(9):923-928.
- Barrios RJ, Kheradmand F, Batts L, Corry DB. Asthma: pathology and pathophysiology. *Arch Pathol Lab Med*. 2006;130(4):447-451.
- Kheradmand F, Rishi K, Corry DB. Environmental contributions to the allergic asthma epidemic. *Environ Health Perspect*. 2002;110(suppl 4):553.
- Walter MJ, Holtzman MJ. A centennial history of research on asthma pathogenesis. *Amer J Resp Cell Mol Biol*. 2005;32(6):483-489.
- Vercelli D. Discovering susceptibility genes for asthma and allergy. *Nat Rev Immunol*. 2008;8(3):169.
- Kumar A, Grayson MH. The role of viruses in the development and exacerbation of atopic disease. *Ann Allergy, Asthma Immunol*. 2009;103(3):181-187.
- Gangi S, Johansson O. A theoretical model based upon mast cells and histamine to explain the recently proclaimed sensitivity to electric and/or magnetic fields in humans. *Med Hypothes*. 2000;54(4):663-671.
- Lynch BA, Fenta Y, Jacobson RM, et al. Impact of delay in asthma diagnosis on chest X-ray and antibiotic utilization by clinicians. *J Asthma*. 2012;49(1):23-28.
- Sonibare M, Gbile Z. Ethnobotanical survey of anti-asthmatic plants in South Western Nigeria. *Afr J Tradit Complement Altern Med*. 2008;5(4):340-345.
- Albert P, Agusti A, Edwards L, et al. Bronchodilator responsiveness as a phenotypic characteristic of established chronic obstructive pulmonary disease. *Thorax*. 2012;67(8):701-708.
- Agrawal B, Mehta A. Antiasthmatic activity of *Moringa oleifera* Lam: a clinical study. *Ind J Pharmacol*. 2008;40(1):28-31.
- Singh BB, Khorsan R, Vinjamury SP, Der-Martirosian C, Kizhakkeveetil A, Anderson TM. Herbal treatments of asthma: a systematic review. *J Asthma*. 2007;44(9):685-698.
- Paliwa J, Dwivedi A, Singh S, et al. Pharmacokinetics and in-situ absorption studies of a new anti-allergic compound 73/602 in rats. *Inter J Pharmaceut*. 2000;197:213-220.
- Tripathi R, Das P. Studies on anti-asthmatic and anti-anaphylactic activity of *Albizia lebbbeck*. *Ind J Pharmacol*. 1977;9(3):189-194.
- Gupta I, Gupta V, Parihar A, et al. Effects of *Boswellia serrata* gum resin in patients with bronchial asthma: results of a double-blind, placebo-controlled, 6-week clinical study. *Eur J Med Res*. 1998;3(11):511-514.
- Sangraula H, Kumar V. Anti-inflammatory studies on latex of *Calotropis procera*. *Ind J Pharmacol*. 1999;31:1-78.
- Shind UA, Phadke AS, Nair AM, Mungantiwar AA, Dikshit VJ, Saraf MN. Preliminary studies on the immunomodulatory activity of *Cedrus deodara* wood oil. *Fitoterapia*. 1999;70(4):333-339.
- Gupta S. Prospects and perspectives of natural plant products in medicine. *Indian J Pharmacol*. 1994;26(1):1-12.
- Ammon HP, Anazodo MI, Safayhi H, Dhawan BN, Srimal RC. Curcumin: a potent inhibitor of leukotriene B4 formation in rat peritoneal polymorphonuclear neutrophils (PMNL). *Planta Medica*. 1992;58(2):226.
- Srivastava S, Gupta P, Prasad R, et al. Evaluation of antiallergic activity (type I hypersensitivity) of *Inula racemosa* in rats. *Indian J Physiol Pharmacol*. 1999;43(3):235-241.
- Doshi VB, Shetye VM, Mahashur AA, Kamat SR. *Picrorrhiza kurroa* in bronchial asthma. *J Postgrad Med*. 1983;29(2):89.
- Govindan S, Viswanathan S, Vijayasekaran V, Alagappan R. A pilot study on the clinical efficacy of *Solanum xanthocarpum* and *Solanum trilobatum* in bronchial asthma. *J Ethnopharmacol*. 1999;66(2):205-210.
- Saraf M, Patwardhan B. Pharmacological studies on *Sarcostemma brevistigma*. Part II Bronchodil Activity Drugs. 1988;26:54-57.
- Gokhale A, Damre A, Kulkarni K, et al. Preliminary evaluation of anti-inflammatory and anti-arthritis activity of *S. lappa*, *A. speciosa* and *A. aspera*. *Phytomed*. 2002;9(5):433-437.
- Sunanda SN, Desai N, Ainapure S. Antiallergic properties of *Tinospora cordifolia* in animal models. *Ind J Pharmacol*. 1986;18(4):250-252.
- Nayampalli S, Sheth U. Evaluation of anti-allergic activity of *Tylophora indica* using rat lung perfusion. *Ind J Pharmacol*. 1979;11(3):229-232.
- Nair A, Saraf M. Inhibition of antigen and compound 48/80 induced contractions of guinea pig trachea by the ethanolic extract of the leaves of *Vitex negundo* Linn. *Ind J Pharmacol*. 1995;27(4):230-232.
- Heaney LG, Robinson DS. Severe asthma treatment: need for characterising patients. *Lancet*. 2005;365(9463):974-976.
- Holgate ST, Polosa R. The mechanisms, diagnosis, and management of severe asthma in adults. *Lancet*. 2006;368(9537):780-793.
- Jatakanon A, Uasuf C, Maziak W, Lim S, Chung KF, Barnes PJ. Neutrophilic inflammation in severe persistent asthma. *Am J Respir Crit Care Med*. 1999;160(5 pt 1):1532-1539.

38. Hamilton L, Torres Lozano C, Puddicombe S, et al. The role of the epidermal growth factor receptor in sustaining neutrophil inflammation in severe asthma. *Clin Exp Allergy*. 2003;33(2): 233-240.
39. Holgate ST, Davies DE, Lackie PM, Wilson SJ, Puddicombe SM, Lordan JL. Epithelial-mesenchymal interactions in the pathogenesis of asthma. *J Allergy Clin Immunol*. 2000;105(2pt 1):193-204.
40. Holgate ST, Holloway J, Wilson S, et al. Understanding the pathophysiology of severe asthma to generate new therapeutic opportunities. *J Allergy Clin Immunol*. 2006;117(3):496-506.
41. Puddicombe S, Polosa R, Richter A, et al. Involvement of the epidermal growth factor receptor in epithelial repair in asthma. *FASEB J*. 2000;14(10):1362-1374.
42. Comhair SA, Xu W, Ghosh S, et al. Superoxide dismutase inactivation in pathophysiology of asthmatic airway remodeling and reactivity. *Am J Pathol*. 2005;166(3):663-674.
43. Knight DA, Holgate STJR. The airway epithelium: structural and functional properties in health and disease. *J Respiriol*. 2003;8(4): 432-446.
44. Holgate ST, Holloway J, Wilson S, Bucchieri F, Puddicombe S, Davies DE. Epithelial-mesenchymal communication in the pathogenesis of chronic asthma. *Proc Am Thorac Soc*. 2004; 1(2):93-98.
45. Marchac V, Emond S, Mamou-Mani T, et al. Thoracic CT in pediatric patients with difficult-to-treat asthma. *Amer J Roentgenol*. 2002;179(5):1245-1252.
46. Bumbacea D, Campbell D, Nguyen L, et al. Parameters associated with persistent airflow obstruction in chronic severe asthma. *Eur Respir J*. 2004;24(1):122-128.
47. Sutherland ER, Martin RJ, Bowler RP, Zhang Y, Rex MD, Kraft M. Physiologic correlates of distal lung inflammation in asthma. *J Allergy Clin Immunol*. 2004;113(6):1046-1050.
48. Balzar S, Chu HW, Strand M, Wenzel S. Relationship of small airway chymase-positive mast cells and lung function in severe asthma. *Am J Respir Crit Care Med*. 2005;171(5):431-439.
49. Howarth PH, Babu KS, Arshad HS, et al. Tumour necrosis factor (TNF α) as a novel therapeutic target in symptomatic corticosteroid dependent asthma. *Thorax*. 2005;60(12):1012-1018.
50. Rodrigo GJ, Nannini LJ. Comparison between nebulized adrenaline and β_2 agonists for the treatment of acute asthma. A meta-analysis of randomized trials. *Amer J Emer Med*. 2006;24(4): 217-222.
51. Donohue JF, Hanania NA, Ciubotaru RL, et al. Comparison of levalbuterol and racemic albuterol in hospitalized patients with acute asthma or COPD: a 2-week, multicenter, randomized, open-label study. *Clin Ther*. 2008;30:989-1002.
52. Befekadu E, Onofrei C, Colice GL. Tiotropium in asthma: a systematic review. *J Asthma Allergy*. 2014;7:11.
53. Asl BH, Vaez H, Imankhah T, et al. Impact of caffeine on weight changes due to ketotifen administration. *Adv Pharm Bull*. 2014; 4(1):83-89.
54. Finn D, Walsh J. Twenty-First century mast cell stabilizers. *Brit J Pharmacol*. 2013;170(1):23-37.
55. Hashimoto S, Bel E. Current treatment of severe asthma. *Clin Exp Allergy*. 2012;42(5):693-705.
56. MacGregor RR, Sheagren JN, Lipsett MB, Wolff SM. Alternate-day prednisone therapy: evaluation of delayed hypersensitivity responses, control of disease and steroid side effects. *New Engl J Med*. 1969;280(26):1427-1431.
57. Sobande PO, Kerckmar CM. Inhaled corticosteroids in asthma management. *Resp Care*. 2008;53(5):625-634.
58. Harmanci K. Montelukast: its role in the treatment of childhood asthma. *Ther Clin Risk Manag*. 2007;3(5):885-892.
59. Murphy DM, O'Byrne PM. Recent advances in the pathophysiology of asthma. *Chest*. 2010;137(6):1417-1426.
60. Singh A, Kumar S, Bajpai V, Kumar B. Simultaneous determination of pyroquinazoline alkaloids and flavonoids in *Adhatoda beddomei* and *Adhatoda vasica* and their marketed herbal formulations using ultra-high-performance liquid chromatography coupled with triple quadrupole linear ion trap mass spectrometry. *Biomed Chromatogr*. 2017;31(3):e3827.
61. Mehreen A, Waheed M, Liaqat I, Arshad N. Phytochemical, antimicrobial, and toxicological evaluation of traditional herbs used to treat sore throat. *BioMed Res Inter*. 2016;2016: 8503426.
62. Latha M, Priyanka M, Rajasekar P, Manikandan R, Prabhu NM. Biocompatibility and antibacterial activity of the *Adathoda vasica* Linn extract mediated silver nanoparticles. *Microb Pathogen*. 2016;93:88-94.
63. Gupta A, Prajapati P. A clinical review of different formulations of Vasa (*Adhatoda vasica*) on *Tamaka Shwasa* (asthma). *Ayu*. 2010;31(4):520-524.
64. Aslam MS, Ahmad MS, Mamat AS, Ahmad MZ, Salam F. Antioxidant and wound healing activity of polyherbal fractions of *Clinacanthus nutans* and *Elephantopus scaber*. *Evid Based Complement Altern Med*. 2016;2016:4685246.
65. Mugabo P, Raji IA. Effects of aqueous leaf extract of *Asystasia gangetica* on the blood pressure and heart rate in male spontaneously hypertensive Wistar rats. *BMC Complement Altern Med*. 2013;13:283.
66. Akah P, Ezike A, Nwafor S, Okoli CO, Enwerem NM. Evaluation of the anti-asthmatic property of *Asystasia gangetica* leaf extracts. *J Ethnopharmacol*. 2003;89(1):25-36.
67. Kazuma K, Noda N, Suzuki M. Flavonoid composition related to petal color in different lines of *Clitoria ternatea*. *Phytochem*. 2003;64(6):1133-1139.
68. Chayaratanasin P, Barbieri MA, Suanpairintr N, Barbieri MA, Suanpairintr N, Adisakwattana S. Inhibitory effect of *Clitoria ternatea* flower petal extract on fructose-induced protein glycation and oxidation-dependent damages to albumin in vitro. *BMC Complement Altern Med*. 2015;15:27.
69. Nguyen KNT, Nguyen GKT, Nguyen PQT, Ang KH, Dedon PC, Tam JP. Immunostimulating and Gram-negative-specific antibacterial cyclotides from the butterfly pea (*Clitoria ternatea*). *FEBS J*. 2016;283(11):2067-2090.
70. Taur DJ, Patil RY. Evaluation of antiasthmatic activity of *Clitoria ternatea* L. roots. *J Ethnopharmacol*. 2011;136(2):374-376.
71. Wu XY, Li JZ, Guo JZ, Hou BY. Ameliorative effects of curculigoside from *Curculigo orchoides* Gaertn on learning and memory in aged rats. *Mol*. 2012;17(9):10108-10118.

72. Lakshmi V, Pandey K, Puri A, Saxena RP, Saxena KC. Immunostimulant principles from *Curculigo orchoides*. *J Ethnopharmacol*. 2003;89(2-3):181-184.
73. Pandit P, Singh A, Bafna A, Kadam PV, Patil MJ. Evaluation of antiasthmatic activity of *Curculigo orchoides* Gaertn rhizomes. *Ind J Pharmaceut Sci*. 2008;70(4):440-444.
74. Venkatesh P, Mukherjee PK, Nema NK, et al. Mast cell stabilization and antihistaminic potentials of *Curculigo orchoides* rhizomes. *Thorax*. 2009;126(3):434-436.
75. Geetha B, Latha P, Remani P. Evaluation of *Elephantopus scaber* on the inhibition of chemical carcinogenesis and tumor development in mice. *Pharm Biol*. 2010;48(3):342-348.
76. Abhimannue AP, Mohan MC, B PK. Inhibition of tumor necrosis factor- α and interleukin-1 β production in lipopolysaccharide-stimulated monocytes by methanolic extract of *Elephantopus scaber* Linn and identification of bioactive components. *Appl Biochem Biotechnol*. 2016;179(3):427-443.
77. Sagar R, Sahoo H. Evaluation of antiasthmatic activity of ethanolic extract of *Elephantopus scaber* L. leaves. *Ind J Pharmacol*. 2012;44(3):398-401.
78. Ghosh M, Civra A, Rittà M, et al. *Ficus religiosa* L. bark extracts inhibit infection by herpes simplex virus type 2 in vitro. *Arch Virol*. 2016;161(12):3509-3514.
79. Bhangale JO, Acharya SR. Anti-Parkinson activity of petroleum ether extract of *Ficus religiosa* (L.) leaves. *Adv Pharmacol Sci*. 2016;2016:9436106.
80. Kapoor M, Jasani N, Acharya N, Acharya S, Kumar V. Phytopharmacological evaluation and anti-asthmatic activity of *Ficus religiosa* leaves. *Asian Pac J Trop Med*. 2011;4(8):642-644.
81. Fathiazad F, Mazandarani M, Hamedeyazdan S. Phytochemical analysis and antioxidant activity of *Hyssopus officinalis* L. from Iran. *Adv Pharm Bull*. 2011;1(2):63-67.
82. Jahantigh O, Najafi F, Badi HN, Khavari-Nejad RA, Sanjarian F. Changes in antioxidant enzymes activities and proline, total phenol and anthocyanine contents in *Hyssopus officinalis* L. plants under salt stress. *Acta Biol Hungar*. 2016;67(2):195-204.
83. Lu M, Battinelli L, Daniele C, Melchioni C, Salvatore G, Mazzanti G. Muscle relaxing activity of *Hyssopus officinalis* essential oil on isolated intestinal preparations. *Planta Med*. 2002;68(3):213-216.
84. Gaid M, Haas P, Beuerle T, Scholl S, Beerhues L. Hyperforin production in *Hypericum perforatum* root cultures. *J Biotechnol*. 2016;222:47-55.
85. Moghaddam MHG, Roghani M, Maleki M. Effect of *Hypericum perforatum* aqueous extracts on serum lipids, aminotransferases, and lipid peroxidation in hyperlipidemic rats. *Res Cardiovasc Med*. 2016;5(2):5-8.
86. Khan AU, Gilani AH, Najeeb-u- RJP. Pharmacological studies on *Hypericum perforatum* fractions and constituents. *Pharm Biol*. 2011;49(1):46-56.
87. AlAttas SA, Fat'heya MZ, Turkistany SA. *Nigella sativa* and its active constituent thymoquinone in oral health. *Saud Med J*. 2016;37(4):235-244.
88. Ahmad A, Husain A, Mujeeb M, et al. A review on therapeutic potential of *Nigella sativa*: a miracle herb. *Asian Pac J Trop Biomed*. 2013;3(5):337-352.
89. Gholamnezhad Z, Havakhah S, Boskabady MH. Preclinical and clinical effects of *Nigella sativa* and its constituent, thymoquinone: a review. *J Ethnopharmacol*. 2016;190:372-386.
90. Gilani A, Aziz N, Khurram I, Chaudhary KS, Iqbal A. Bronchodilator, spasmolytic and calcium antagonist activities of *Nigella sativa* seeds (Kalonji): a traditional herbal product with multiple medicinal uses. *J Pak Med Assoc*. 2001;51(3):115-120.
91. Boskabady M, Mohsenpoor N, Takaloo L. Antiasthmatic effect of *Nigella sativa* in airways of asthmatic patients. *Phytomed*. 2010;17(10):707-713.
92. Kumar R, Gupta YK, Singh S, Arunraja S. *Picrorhiza kurroa* inhibits experimental arthritis through inhibition of pro-inflammatory cytokines, angiogenesis and MMPs. *Phytother Res*. 2016;30(1):112-119.
93. Rajeshkumar N, Kuttan R. Protective effect of Picroliv, the active constituent of *Picrorhiza kurroa*, against chemical carcinogenesis in mice. *Teratogen Carcinogen Mutagen*. 2001;21(4):303-313.
94. Dorsch W, Stuppner H, Wagner H, Gropp M, Demoulin S, Ring J. Antiasthmatic effects of *Picrorhiza kurroa*: androsin prevents allergen- and PAF-induced bronchial obstruction in guinea pigs. *Inter Arch Allergy Immunol*. 1991;95(2-3):128-133.
95. Bergquist SÅ, Gertsson UE, Knuthsen P, Olsson ME. Flavonoids in baby spinach (*Spinacia oleracea* L.): changes during plant growth and storage. *J Agri Food Chem*. 2005;53(24):9459-9464.
96. Ko SH, Park JH, Kim SY, Lee SW, Chun SS, Park E. Antioxidant effects of spinach (*Spinacia oleracea* L.) supplementation in hyperlipidemic rats. *Prevent Nutr Food Sci*. 2014;19(1):19.
97. Heo JC, Park CH, Lee HJ, Kim SO, Kim TH, Lee SH. Amelioration of asthmatic inflammation by an aqueous extract of *Spinacia oleracea* Linn. *Inter J Mol Med*. 2010;25(3):409-414.
98. Price DB, Buhl R, Chan A, et al. Fractional exhaled nitric oxide as a predictor of response to inhaled corticosteroids in patients with non-specific respiratory symptoms and insignificant bronchodilator reversibility: a randomised controlled trial. *Lancet Respir Med*. 2018;6(1):29-39.
99. Panettieri RA, Pera T, Liggett SB, Benovic JL, Penn RB. Pepducins as a potential treatment strategy for asthma and COPD. *Curr Opin Pharmacol*. 2018;40:120-125.
100. Li Q, Zhan S, Liu Q, et al. Preparation of a sustained-release nebulized aerosol of r-terbutaline hydrochloride liposome and evaluation of its anti-asthmatic effects via pulmonary delivery in guinea pigs. *AAPS Pharm Sci Tech*. 2018;19(1):232-241.
101. Azevedo BC, Morel LJF, Carmona F, et al. Aqueous extracts from *Uncaria tomentosa* (Willd. ex schult.) DC. reduce bronchial hyperresponsiveness and inflammation in a murine model of asthma. *J Ethnopharmacol*. 2018;218:76-89.