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ASTHMA: A CRITICAL REVIEW ON CURRENT THERAPY

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ABSTRACT

Asthma is a widespread long term inflammatory disease of the airways of the lungs. Asthma is notion to be caused by a grouping of genetic and environmental factors. Asthma is chronic respiratory disease and it affects all groups of peoples, mainly this is caused by environmental factors comprise exposure to allergens and air pollution. Despite of all the advances in modern and orthodox medicine, traditional medicine still plays a significant role in the lives of many people suffering with respiratory diseases like asthma, bronchitis etc. Potential medications such as β-blockers, Bronchodilators, anti-inflammatory agents, β-adrenergic agonists, Anticholinergics, methylxanthines, and steroidal compounds are used in the treatment of asthma frequently based on the outline of symptoms, but currently available antiasthmatic drugs have more adverse effects. More number of medicinal plants like *Picrorrhiza kurroa*, *Solanum xanthocarpum, Boswellia serrata, Tylophora indica, Curcuma longa, Ocimum sanctum, Acorus calamus* etc. provide therapeutic compounds, for the treatment of respiratory diseases with fewer side effects.

KEYWORDS: Asthma, *Picrorrhiza kurroa, Solanum xanthocarpum, Boswellia serrata, Acorus calamus* etc.

INTRODUCTION

Asthma is a widespread long term inflammatory disease of the airways of the lungs. Asthma is notion to be caused by a grouping of genetic and environmental factors.[1] Environmental factors comprise exposure to allergens and air pollution. Further potential triggers comprise medications such as beta blockers and aspirin.[2] Diagnosis is frequently based on the outline of symptoms, response to therapy over time, and spirometry. Asthma is categorized according to the occurrence of symptoms, forced expiratory volume in one second (FEV1), and peak expiratory flow rate.[3] It is characterized by erratic and frequent symptoms, reversible airflow obstruction, and bronchospasm. Symptoms comprise episodes of coughing, wheezing, chest tightness, and shortness of breath. These episodes may arise a few times a day or a few times per week. There is no cure for asthma. Symptoms can be barred by avoiding triggers, such as irritants and allergens and by the exploit of inhaled corticosteroids.[4] Long-acting beta agonists or antileukotriene agents may be used in adding to inhaled corticosteroids if asthma symptoms remain unrestrained. Treatment of swiftly aggravation symptoms is typically with an inhaled short-acting beta-2 agonist such as salbutamol and corticosteroids.[5]

Epidemiology

235–330 million people global are affected by asthma and roughly 250,000–345,000 people die per year from the disease. It is more widespread in developed than developing countries. While asthma is twice as frequent in boys as girls. In contrast adult women have a superior rate of asthma than men and it is more widespread in the young than the old. In children, asthma was the most ordinary cause for admission to the hospital subsequent an emergency department visit.[6,7]

Causes

Asthma is caused by a mixture of compound and moderately unstated environmental and genetic interactions. Asthma is caused by a combination of complex and incompletely understood environmental and genetic interactions. These factors influence both its severity and its responsiveness to treatment. It is believed that the recent increased rates of asthma are due to changing epigenetics (heritable factors other than those related to the DNA sequence) and a changing living

environment. Onset before age 12 is more likely due to genetic influence, while onset after 12 is more likely due to environmental influence.

Environmental

Numerous environmental factors have been linked with asthma's progress and exacerbation including air pollution, allergens, and other environmental chemicals. Smoking during pregnancy and after delivery is connected with a greater risk of asthma-like symptoms. Exposure to interior volatile organic compounds may be a cause for asthma. There is an involvement between acetaminophen use and asthma. Asthma is allied with exposure to indoor allergens. General indoor allergens comprise cockroaches, dust mites, fragments of fur or feathers, and mold. Definite viral respiratory infections (respiratory syncytial virus and rhinovirus) may augment the risk of rising asthma when acquired as young children.[8-10] Many environmental factors have been associated with asthma's development and exacerbation including allergens, air pollution, and other environmental chemicals. Smoking during pregnancy and after delivery is associated with a greater risk of asthma-like symptoms. Low air quality from factors such as traffic pollution or high ozone levels, has been associated with both asthma development and increased asthma severity. Over half of cases in children in the United States occur in areas with air quality below EPA standards. Exposure to indoor volatile organic compounds may be a trigger for asthma; formaldehyde exposure, for example, has a positive association. Also, phthalates in certain types of PVC are associated with asthma in children and adults.

There is an association between acetaminophen (Paracetamol) use and asthma. The majority of the evidence does not, however, support a causal role. A 2014 review found that the association disappeared when respiratory infections were taken into account. Use by a mother during pregnancy is also associated with an increased risk as is psychological stress during pregnancy.

Asthma is associated with exposure to indoor allergens. Common indoor allergens include dust mites, cockroaches, animal dander (fragments of fur or feathers), and mold. Efforts to decrease dust mites have been found to be ineffective on symptoms in sensitized subjects. Certain viral respiratory infections, such as respiratory syncytial virus and rhinovirus, may increase the risk of developing asthma when acquired as young children. Certain other infections, however, may decrease the risk

Genetic

Family history is a risk factor for asthma, with many different genes being implicated. If one identical twin is affected, the probability of the other having the disease is approximately 25% By the end of 2005, 25 genes had been associated with asthma in six or more separate populations, including GSTM1, IL10, CTLA-4, SPINK5, LTC4S, IL4R and ADAM33, among others. Many of these genes are related to the immune system or modulating inflammation. Even among this list of genes supported by highly replicated studies, results have not been consistent among all populations tested. In 2006 over 100 genes were associated with asthma in one genetic association study alone; more continue to be found.

Some genetic variants may only cause asthma when they are combined with specific environmental exposures. An example is a specific single nucleotide polymorphism in the CD14 region and exposure to endotoxin (a bacterial product). Endotoxin exposure can come from several environmental sources including tobacco smoke, dogs, and farms. Risk for asthma, then, is determined by both a person's genetics and the level of endotoxin exposure[11].

Hygiene hypothesis

The hygiene hypothesis attempts to explain the increased rates of asthma worldwide as a direct and unintended result of reduced exposure, during childhood, to non-pathogenic bacteria and viruses. It has been proposed that the reduced exposure to bacteria and viruses is due, in part, to increased cleanliness and decreased family size in modern societies. Exposure to bacterial endotoxin in early childhood may prevent the development of asthma, but exposure at an older age may provoke bronchoconstriction. Evidence supporting the hygiene hypothesis includes lower rates of asthma on farms and in households with pets.

Use of antibiotics in early life has been linked to the development of asthma.[12] Also, delivery via caesarean section is associated with an increased risk (estimated at 20–80%) of asthma—this increased risk is attributed to the lack of healthy bacterial colonization that the newborn would have acquired from passage through the birth canal. There is a link between asthma and the degree of affluence.

Medical conditions

A chord of allergic rhinitis, atopic eczema and asthma is called atopy. Asthma has been related with eosinophilic granulomatosis with polyangiitis. Individuals with definite types of urticaria may also occurrence symptoms of asthma.[13]

Medications

Beta blocker medications such as propranolol can cause asthma in those who are vulnerable. Further medications that can cause problems in asthmatics are aspirin, angiotensin-converting enzyme inhibitors and NSAIDs.[14]

Pathophysiology

Asthma is the consequence of chronic inflammation of the conducting zone of the, which consequently results in augmented contractibility of the nearby smooth muscles.

This among other factors leads to bouts of tapering of the airway and the common symptoms of wheezing. The tapering is normally reversible with or without treatment. Infrequently the airways themselves vary. Characteristic changes in the airways comprise an augment in eosinophils and thickening of the lamina reticularis. Continually the airways' smooth muscle may amplify in size along with an augment in the figures of mucous glands. Additional cell types concerned include macrophages, T lymphocytes and neutrophils. There may also be participation of other components of the immune system counting chemokines, cytokines, histamine, and leukotrienes among others. [15,16]

Symptoms of Asthma include

- **Cough**: Cough can be productive or dry, and is espe cially seen in early morning and at night.
- **Breathlessness**: Difficulty in breathing due to muco us plugging
  and airway spasm is worse by any physical activity l ike climbing stairs.
- **Chest tightness**: Tightness of chest or pain in chest i s present along with other symptoms of asthma.
- **Wheezing**: wheezing is an abnormal whistling sound more commonly seen in children due to difficult respiration

Symptoms of Asthma in severe cases include

- Bluish discoloration of lips and face with nasal flarin g.
- Rapid pulse Sweating.
- Decreased level of consciousness.

Diagnosis

There is presently no exact test for the diagnosis, which is characteristically based on the outline of symptoms and reaction to therapy over time. A diagnosis of asthma should be suspected if there is a history of repeated coughing; wheezing, or complexity breathing and these symptoms occur or deteriorate due to exercise, allergens, viral infections, or air pollution. Spirometry is used to authenticate the diagnosis.[17]

Spirometry

Spirometry is optional to aid in diagnosis and management. If the FEV1 calculated by this system improves more than 12% subsequent administration of a bronchodilator such as salbutamol, this is helpful of the diagnosis.[18]

Others

The methacholine challenge involves the inhalation of escalating concentrations of a substance that causes airway narrowing in those predisposed. If negative it means that a person does not have asthma; if positive, conversely, it is not specific for the disease.[19]

Differential diagnosis

Numerous other conditions can cause symptoms similar to those of asthma. In children, other upper airway diseases such as sinusitis and allergic rhinitis should be measured as well as other causes of airway obstruction counting foreign body aspiration, tracheal stenosis or laryngo tracheomalacia, vascular rings, enlarged lymph nodes or neck masses. In adults, congestive heart failure, COPD, airway masses, as well as drug-induced coughing due to ACE inhibitors should be measured. In both populations vocal cord dysfunction may present equally.[20]

Classification

Asthma is clinically classified according to the frequency of symptoms, forced expiratory volume in one second (FEV_1), and peak expiratory flow rate. Asthma may also be classified as atopic (extrinsic) or non-atopic (intrinsic), based on whether symptoms are precipitated by allergens (atopic) or not (non-atopic). While asthma is classified based on severity, at the moment there is no clear method for classifying different subgroups of asthma beyond this system. Finding ways to identify subgroups that respond well to different types of treatments is a current critical goal of asthma research.

Although asthma is a chronic obstructive condition, it is not considered as a part of chronic obstructive pulmonary disease as this term refers specifically to combinations of disease that are irreversible such as bronchiectasis, chronic bronchitis, and emphysema. Unlike these diseases, the airway obstruction in asthma is usually reversible; however, if left untreated, the chronic inflammation from asthma can lead the lungs to become irreversibly obstructed due to airway remodeling. In contrast to emphysema, asthma affects the bronchi, not the alveoli. An acute asthma exacerbation is commonly referred to as an *asthma attack*. The classic symptoms are shortness of breath, wheezing, and chest tightness. The wheezing is most often when breathing out. While these are the primary symptoms of asthma, some people present primarily with coughing, and in severe cases, air motion may be significantly impaired such that no wheezing is heard. In children, chest pain is often present.

Signs which occur during an asthma attack include the use of accessory muscles of respiration (sternocleidomastoid and scalene muscles of the neck), there may be a paradoxical pulse (a pulse that is weaker during inhalation and stronger during exhalation), and over-inflation of the chest. A blue color of the skin and nails may occur from lack of oxygen.

In a mild exacerbation the peak expiratory flow rate (PEFR) is ≥200 L/min or ≥50% of the predicted best. Moderate is defined as between 80 and 200 L/min or 25% and 50% of the predicted best while severe is defined as ≤ 80 L/min or ≤25% of the predicted best.

Acute severe asthma, previously known as status asthmaticus, is an acute exacerbation of asthma that does not respond to standard treatments of bronchodilators and corticosteroids. Half of cases are due to infections

with others caused by allergen, air pollution, or insufficient or inappropriate medication use.
Brittle asthma is a kind of asthma distinguishable by recurrent, severe attacks. Type:1. Brittle asthma is a disease with wide peak flow variability, despite intense medication. Type 2 brittle asthma is background well-controlled asthma with sudden severe exacerbations.

Exercise-induced
Exercise can trigger bronchoconstriction both in people with or without asthma. It occurs in most people with asthma and up to 20% of people without asthma. Exercise-induced bronchoconstriction is common in professional athletes. The highest rates are among cyclists (up to 45%), swimmers, and cross-country skiers. While it may occur with any weather conditions it is more common when it is dry and cold. Inhaled beta2-agonists do not appear to improve athletic performance among those without asthma however oral doses may improve endurance and strength.

Occupational
Asthma as a result of (or worsened by) workplace exposures, is a commonly reported occupational disease. Many cases however are not reported or recognized as such. It is estimated that 5–25% of asthma cases in adults are work–related. A few hundred different agents have been implicated with the most common being: isocyanates, grain and wood dust, colophony, soldering flux, latex, animals, and aldehydes. The employment associated with the highest risk of problems include: those who spray paint, bakers and those who process food, nurses, chemical workers, those who work with animals, welders, hairdressers and timber workers.

Aspirin-induced asthma
Aspirin-exacerbated respiratory disease, also known as aspirin-induced asthma, affects up to 9% of asthmatics. Reactions may also occur to other NSAIDs. People affected often also have trouble with nasal polyps. In people who are affected low doses paracetamol or COX-2 inhibitors are generally safe.

Alcohol-induced asthma
Alcohol may worsen asthmatic symptoms in up to a third of people. This may be even more common in some ethnic groups such as the Japanese and those with aspirin-induced asthma. Other studies have found improvement in asthmatic symptoms from alcohol.

Nonallergic asthma
Nonallergic asthma, also known as intrinsic or nonatopic asthma makes up between 10 and 33% of cases. There is negative skin test to common inhalant allergens and normal serum concentrations of IgE. Often it starts later in life and women are more commonly affected than men. Usual treatments may not work as well.

Clinical Management
While there is no cure for asthma, symptoms can typically be improved. A specific, customized plan for proactively monitoring and managing symptoms should be created. This plan should include the reduction of exposure to allergens, testing to assess the severity of symptoms, and the usage of medications. The treatment plan should be written down and advise adjustments to treatment according to changes in symptoms.

The most effective treatment for asthma is identifying triggers, such as cigarette smoke, pets, or aspirin, and eliminating exposure to them. If trigger avoidance is insufficient, the use of medication is recommended. Pharmaceutical drugs are selected based on, among other things, the severity of illness and the frequency of symptoms. Specific medications for asthma are broadly classified into fast-acting and long-acting categories.

Bronchodilators are recommended for short-term relief of symptoms. In those with occasional attacks, no other medication is needed. If mild persistent disease is present (more than two attacks a week), low-dose inhaled corticosteroids or alternatively, an oral leukotriene antagonist or a mast cell stabilizer is recommended. For those who have daily attacks, a higher dose of inhaled corticosteroids is used. In a moderate or severe exacerbation, oral corticosteroids are added to these treatments.

Lifestyle modification: Avoidance of triggers is a key component of improving control and preventing attacks. The most common triggers include allergens, smoke (tobacco and other), air pollution, non selective beta-blockers, and sulfite-containing foods. Cigarette smoking and second-hand smoke (passive smoke) may reduce the effectiveness of medications such as corticosteroids. Laws that limit smoking decrease the number of people hospitalized for asthma. Dust mite control measures, including air filtration, chemicals to kill mites, vacuuming, mattress covers and others methods had no effect on asthma symptoms. Overall, exercise is beneficial in people with stable asthma. Yoga could provide small improvements in quality of life and symptoms in people with asthma.

Medical Treatment
Medications used to treat asthma are alienated into two broad classes: quick-relief medications used to treat acute symptoms; and long-term control medications used to avert extra exacerbation.

Fast–acting
- Short-acting beta$_2$-adrenoceptor agonists (SABA), such as salbutamol are the first line treatment for asthma symptoms. They are optional before exercise in those with exercise induced symptoms.
- Anticholinergic medications, such as ipratropium bromide, afford extra benefit when used in mixture with SABA in those with moderate or severe

symptoms. Anticholinergic bronchodilators can also be used if a person cannot endure a SABA.

- Older, less selective adrenergic agonists, such as inhaled epinephrine, have parallel efficacy to SABAs. They are however not suggested due to concerns regarding extreme cardiac stimulation.[21-23]

Long–term control

- Corticosteroids are usually measured the most effectual treatment obtainable for long-term control. Inhaled forms such asbeclomethasone are frequently used apart from the case of severe persistent disease, in which oral corticosteroids may be wanted. It is typically optional that inhaled formulations be used once or twice daily, depending on the severity of symptoms.
- Long-acting beta-adrenoceptor agonists (LABA) such as salmeterol and formoterol can advance asthma control, at least in adults, when given in mixture with inhaled corticosteroids. In children this benefit is unsure. When used without steroids they increase the risk of severe side effects and even with corticosteroids they may somewhat increase the risk.
- Leukotriene receptor antagonists (montelukast and zafirlukast) may be used in totaling to inhaled corticosteroids, classically also in combination with a LABA. A similar class of drugs, 5-LOX inhibitors (zileuton), may be used as a substitute in the chronic treatment of mild to moderate asthma among older children and adults.
- Mast cell stabilizers (cromolyn sodium) are one more non-preferred option to corticosteroids. [24-28] Medications are characteristically provided as metered-dose inhalers (MDIs) in mixture with an asthma spacer or as a dry powder inhaler. The spacer is a plastic cylinder that mixes the medication with air, assembly it easier to receive a full dose of the drug. A nebulizer may also be used. Nebulizers and spacers are uniformly efficient in those with mild to moderate symptoms. However, inadequate evidence is available to conclude whether a disparity exists in those with severe disease. Long-term use of inhaled corticosteroids at conservative doses carries a minor risk of adverse effects. Risks comprise the development of cataracts and a mild deterioration in stature.

For emergency management other options comprise:

- Oxygen to ease hypoxia if saturations fall below 92%
- Oral corticosteroids are optional with five days of prednisone being the same 2 days of dexamethasone.
- Magnesium sulfate intravenous treatment increases bronchodilation when used in addition to other treatment in moderate severe acute asthma attacks.
- Heliox, a mixture of helium and oxygen, may also be measured in severe unresponsive cases.
- Intravenous salbutamol is not supported by obtainable evidence and is thus used only in extreme cases.
- Methylxanthines (such as theophylline) were once widely used, but do not add considerably to the effects of inhaled beta-agonists.
- The dissociative anesthetic ketamine is hypothetically useful if intubation and mechanical ventilation is needed in people who are impending respiratory arrest; however, there is no confirmation from clinical trials to support this.

Pharmacotherapy of bronchial asthma

In the past most clinicians managed asthma mainly according to the patient's symptom. Asthma was regarded primarily as a problem of bronchospasm and measures to prevent or reverse bronchospasm comprised the mainstay of therapy. However, during early 1980s when asthma emerged as an inflammatory rather than primarily a bronchospastic disorder, the basic approach switched from control of symptoms to control of underlying airway inflammation[29]. According to guidelines of The National Asthma Education and Prevention Program's (NAEPP) guidelines for the diagnosis and management of asthma, the treatment should have following goals:

1. Maintain normal activity levels, including exercise.
2. Maintain normal or near normal pulmonary function.
3. Prevent chronic and troublesome symptoms.
4. Prevent recurrent exacerbations.
5. Avoid adverse effects from medications.

The pharmacological management of asthma depends upon frequency and severity of patient's symptoms. Infrequent attacks can be managed by treating each attack when it occurs, but with more frequent attacks preventive therapy needs to be used. The following categories of drugs are used in asthma:

1. Bronchodilators

1. β-adrenergic agonists: e.g. Metaproterenol, terbutaline, albuterol, formoterol, bitolterol, salmeterol, pirbuterol.
2. Anticholinergics: e.g. Ipratropium bromide, Tiotropium bromide.
3. Methylxanthines: e.g. Theophylline, aminophylline, acepiphylline, diprophylline, proxophylline.

2. Anti-inflammatory agents

1. Corticosteroids: e.g. Prednisolone, dexamethasone, beclomethasone dipropionate, dexamethasone, budesonide, fluticasone.
2. Anti-leukotrienes: e.g. Probilukast, Iralukast, Zieluton, Montelukast, zafirlukast, pranlukast.
3. Mast Cell Stabilizers: e.g. Cromolyn Sodium, Nedocromil sodium.

Bronchodilators

Bronchodilator drugs have an anti-bronchoconstrictor effect that may be demonstrated directly in vitro by drug-induced relaxation of precontracted airways.[30] Bronchodilators promptly reverse airway obstruction in

asthmatics. This action believed to be mediated by a direct effect on airway smooth muscle. However, additional pharmacologic effects on the other airway cells (such as capillary endothelium to reduce microvascular leakage and mast cells to reduce release of bronchoconstrictor mediators) may contribute to the overall reduction in airway narrowing. Only three types of bronchodilators are in current clinical use: β-adrenergic agonists, methylxanthines, and anticholinergics.

***β*-adrenergic agonists**

Epinephrine has been used to treat asthma since the beginning of the 20th century. β Adrenergic agonists are most widely used and effective bronchodilators for the treatment of asthma. Bronchodilation is mediated by β_2 receptors; β_2 selective drugs (Salmeterol and Formoterol) have been developed that have long duration of effect. β Adrenergic agonists lead to relaxation of bronchial smooth muscle that promote bronchodilation. Activation of adenylate cyclase increases the concentration of intracellular cyclic adenosine 3′, 5′-monophosphaste (cAMP), leading to activation of specific cAMP-dependent protein kinases that cause relaxation. Relaxation may also be due to inhibition of myosin phosphorylation. β-adrenergic agonists reverse bronchoconsriction irrespective of the contractile agent. β-adrenergic agonists prevent release of mediators from a number of inflammatory cells in vitro.[31] In addition, β adrenergic agonists increase mucus secretion from submucosal glands and ion transport across airway epithelium. These effects enhance mucociliary clearance caused by asthma.[32]

The inhaled route of administration is preferable to the oral route because adverse effects caused by systemic action of the drug are less and also because this route may be more effective. The inhaled drug reaches surface cells (e.g., mast cells or epithelial cells), which are less accessible to the orally administered drug.

Metaproterenol, terbutaline, albuternol, formopterol, bitolterol, salmeterol, and pirbuterol are the classic examples of selective β_2-adrenergic agonists.

β agonists improve respiratory symptoms and exercise tolerance despite the small improvement in spirometric measurements. The long acting β-agonists decrease infection exacerbations as an additional potential benefit. Salmeterol has been shown to reduce adherence of bacteria such as *H. influenza* to airway epithelial cells.

β_2 selective agents cause tachycardia and palpitation by reflex cardiac stimulation secondary to peripheral vasodilation. Muscle tremor is caused by stimulation of β_2 adrenergic receptors in skeletal muscle and is the primary adverse effect of albuterol and bitolterol. Transient hypokalemia may be induced by high dose of these agents.

Anticholinergics

Datura plants contain the muscarinic antagonist and were smoked for relief of asthma centuries ago. Now a days, atropine and ipratropium bromide are the most commonly available anticholinergics.

Antimuscarinic agents specifically antagonize muscarinic receptors. They inhibit reflex cholinergic bronchoconstriction and do not significantly block the direct effects of inflammatory mediators such as histamine and leukotrienes on bronchial smooth muscle and vessels. When given by inhalation, anticholinergics produce bronchodilation by competitively inhibiting cholinergic receptors in bronchial smooth muscle. This activity blocks acetylcholine with the net effect being a reduction in cyclic guanosine monophosphate (cGMP) that normally acts to constrict bronchial smooth muscle. Anticholinergic drugs usually are less effective as bronchodilators in asthmatic subjects than β adrenergic agonists. Nevertheless, they may have an additive effect with β adrenergic agonists.

Atropine reduces mucociliary clearance in normal subjects and in patients with asthma and chronic bronchitis, but the quaternary derivative, ipratropium bromide, even when given in high doses, has no such detectable effect either on normal subjects or in patients with airway disease.

Ipratropium bromide has been shown to decrease the effectiveness of voluntary cough on clearing mucus from the airways, which may affect its role in the treatment of patients who have excessive mucus production. Ipratropium has a slower onset of action and a more prolonged bronchodilator effect compared with standard β_2-agonists and has been considered to be less suitable for use on an as needed basis for immediate relief of bronchospasm.

The lack of systemic absorption of ipratropium greatly diminishes the anticholinergic side effects such as blurred vision, urinary retention, nausea, and tachycardia associated with atropine. A significant unwanted effect of inhaled ipratropium bromide is dryness of mouth and throat, bitter taste, cough and nausea. Nebulized ipratropium bromide may precipitate glaucoma in elderly patients because of its direct mydriatic effect on the eye. During sleep, ipratropium also has been shown to improve arterial oxygen saturation and sleep quality.

Tiotropium bromide is a long acting quaternary anticholinergic agent. Tiotropium in human lungs shows approximately 10 fold more potency than ipratropium and protects against cholinergic bronchoconstriction for greater than 24 h.

Methylxanthines

Methylxanthines such as theophylline are related to caffeine and have been used to treat asthma since 1930.

The methylxanthines may produce bronchodilation through numerous mechanisms, including,

- inhibition of phosphodiesterase, thereby increasing cAMP levels
- inhibition of calcium ion influx into smooth muscle
- prostaglandin antagonism
- stimulation of endogenous catecholamines
- adenosine receptor antagonism
- Inhibition of release of mediators from mast cells and leukocytes.

Theophylline inhibits release of mediators from mast cells, increases mucocilliary clearance, and prevents the development of micro vascular leakiness, as would an "anti-inflammatory" drug[33] Theophylline also inhibits some functions of T lymphocytes, which may be relevant to control of chronic inflammation of the airway.
For nocturnal asthma, a single dose of slow release theophylline at bedtime often is effective. This has been demonstrated to reduce overnight declines in FEV_1 and morning respiratory symptoms. Taken alone it increases exercise tolerance without improving spirometry tests.

Other theophylline salts, such as choline theophyllinate, offer no advantages over theophylline. The ethylenediamine component of aminophylline has been implicated in allergic reactions. Some derivates such as acepiphylline, diprophylline, and proxophylline, are less effective than theophylline.[34] The most common adverse effects are headache, nausea and vomiting, abdominal discomfort, and restlessness.

Anti-inflammatory drugs
Although the type of inflammatory responses may differ among diseases, inflammation is a common denominator of several lung diseases. Anti-inflammatory drugs suppress the inflammatory response by inhibiting infiltration and activation of inflammatory cells as well as their synthesis or release of mediators or effects of inflammatory mediators themselves.

Corticosteroids
Since asthma is viewed as a chronic inflammatory disease and inhaled corticosteroids are known to have low toxicity, they may be considered as first line therapy. Prednisolone and dexamethasone were effective when they were given systematically to treat asthma but they had no anti-asthmatic activity when they were given by inhalation. Other corticosteroids e.g. beclomethasone dipropionate (BDP), betamethasone and budesonide, were effective in treating asthma when given by inhalation. The antiasthmatic potency of an inhaled steroid is approximately proportional to its potency as an anti-inflammatory agent.

Corticosteroids inhibit the release of arachidonic acid metabolites and platelet activating factor (PAF) from lungs and macrophages by enhancing the production of proteins called lipocortin. Thereby they inhibit the formation of prostaglandins and leukotrienes. These effects occur because of ability of steroid—receptor complex to be transported to the nucleus, where it initiates DNA transcription of specific mRNAs. Corticosteroids potentially inhibit the accumulation of neutrophils, inhibit secretion of human pulmonary macrophages of leukotrienes and prostaglandins, inhibit formation of interleukins (ILs) such as IL-1, IL-2, IL-3 and IL-5, inhibit degranulation and adherence of eosinophils, reduce number of circulating T lymphocytes and formation of an IgE binding suppressive factor.

Steroids prevent and reverse the increase in vascular permeability due to inflammatory mediators and may therefore lead to resolution of airway edema. Corticosteroids remain the most effective therapy available for asthma but the legitimate fear of their adverse effects makes using them difficult. Steroids potentiate the effects of β adrenergic agonists on bronchial smooth muscle. Methylprednisolone is given intravenously to patients with severe acute asthma. Inhaled steroids have no proven value in the management of acute asthma. Patients with chronic bronchitis occasionally respond to steroids, possibly because some have an element of undiagnosed asthma.

Corticosteroids inhibit release of ACTH and secretion of cortisol by a negative feedback effect on the pituitary gland. Adverse effects of corticosteroids include fluid retention, increased cell mass, increased appetite, weight gain, osteoporosis, capillary fragility, hypertension, peptic ulceration, diabetes, cataract, and psychosis.[35]

Anti-leukotrienes
Leukotrienes possess potent pro-inflammatory actions resulting in increased vascular permeability, mucus secretion and bronchial hyperresponsiveness. They are derived from the 5-lipoxygenase pathways in mast cells, eosinophils and macrophages. Anti-leukotrienes improve lung function and diminish symptoms, exacerbation rate and the need for rescue bronchodilator. These are drugs of choice in case of aspirin induced asthma, in which patients have high LTE_4 levels in urine and nasal secretions and even higher after taking aspirin.[36]

Leukotriene modifiers are drugs that modify the response of these mediators of inflammation by one of the four ways:

1. Cysteinyl LT receptor inhibitors
C-LTs promote eosinophil influx, bronchospasm and mucus hypersecretion, all are considered hallmarks of asthma. C-LT receptor inhibitors antagonize or inhibit leukotrienes predominantly LTD_4. These agents inhibit phospholipases, prostaglandins, leukotrienes, and IL-1 synthesis. Probilukast and Iralukast belong to this class.

2. 5-lipoxygenase inhibitors
They prevent the formation of leukotrienes by blocking a 5-lipoxygenase pathway in their synthesis. Zileuton, ZD-2138, ABt-761 belongs to this class.[37]

3. 5-lipoxygenase activating protein (FLAP) inhibitors

MK-0591 and MK-886 attenuated the early and late asthmatic response following antigen challenge but not the attendant increase in airway responsiveness to spasmogens.

4. Leukotrienes receptor antagonists

Montelukast, Zafirlukast, Pranlukast are selective and high affinity LT_1 antagonists (Adcock and Matthews 1998).

Zileuton has shown efficacy in exercise-induced asthma, aspirin induced bronchospasm and following chronic administration, an improvement in pulmonary function (FEV1) and a reduction in oral and inhaled corticosteroid use.[38] Furthermore, in a small study, zileuton attenuated both airway and blood eosinophilia in nocturnal asthmatics.

Zafirlukast has been demonstrated to attenuate the acute airway obstructive response to allergen and exercise challenge and to improve chronic asthma control both objectively (FEV1, nocturnal awakenings, β-agonist use) and subjectively.

Montelukast has been shown to block the early and late response to allergen challenge following single dosing, to improve FEV1 in both children (6–14 years) and adults and to protect against the development of exercise induced bronchoconstriction in both children and adults. Tolerance to the bronchoprotective effects of montelukast in attenuating exercise-induced bronchospasm does not develop following at least 12 weeks of therapy.

Pranlukast increases FEV1 within 1 h of dosing, improves patient summary symptom and nighttime asthma scores and reduces the use of rescue bronchodilators. In patients with moderate persistent asthma, it prevents exacerbations of asthma during reduction of high dose inhaled corticosteroids therapy.[39]

Mediator release inhibitors

Cromolyn Sodium (Sodium cromoglycate) is a derivative of khellin, an Egyptian herbal remedy. Cromolyn inhibited the release of mediators by allergen in passively sensitized animal and human lung preparations. Cromolyn was classified as mast cell stabilizer. Cromolyn has variable inhibitory actions on other inflammatory cells including macrophages and eosinophils that may participate in allergic inflammation. In vivo cromolyn can block both the early response that may be mediated by mast cells to allergens and the late response and bronchial hyper responsiveness. Cromolyn Sodium is used for prophylactic treatment and consequently needs to be taken regularly. It is the first choice anti-inflammatory drug for children because it has few adverse effects.[40] Cromolyn sodium is classified as an antiallergic drug because it appears to have a specific effect on allergy based inflammation. Several other drugs also may be included in this category.

Nedocromil sodium is a new drug used for prophylaxis. It has a similar pharmacologic profile of activity to cromolyn, is more potent in various tests, and may have a longer duration of action. Ketotifen also is described as a drug to be used for prophylaxis against asthma.

Newer targets in asthma therapy

The current pharmacotherapeutic approaches to asthma have several limitations. First, there is no known asthma cure and little evidence that prevention is possible in susceptible persons. Hence, patients continue to be at risk of symptoms and exacerbations. Mortality remains a severe problem. Finally, the medications have adverse effects. There is even some evidence, albeit conflicting, that cataract formation, osteoporosis and growth impairment, as associated with systemic glucocorticoids, may arise from topical steroids, depending on dosages used. New inhalation devices and new generation beta-agonists are available. At the same time, new understanding of the molecular pathology of asthma has identified several novel therapeutic targets. Agents being tested in early phase clinical trials include antagonists of IgE, cytokines, adhesion molecules and transcription factors.

TXA_2 inhibitors

TXA_2 is a potent bronchoconstrictor, mucus producer and blood vessel permeability inducer and causes airway hyper responsiveness. Serabenast, domitroban and ozagrel are the examples of these TXA_2synthetase inhibitors. Ozagrel reduced cough sensitivity to capsaicin and bronchoconstriction due to acetaldehyde. TXA_2 antagonists *BAYu3405* produced a modest decrease in airways responsiveness to methacholine following 2 weeks treatment in asthmatics.

Tachykinin receptor antagonists

The first nonpeptide tachykinin receptor antagonist was CP-96345, which is a potent NK_1 receptor antagonist. SR 48968, GR 159897 and SR 144190 are selective nonpeptide NK_2 receptor antagonists. SR 142801 and SB 223412 are selective NK-3 receptor antagonists.

Tryptase inhibitors

Tryptase inhibitors inhibit both early and late reactions. *APC-366* inhibited antigen induced late phase response and bronchial hyperresponsiveness to carbachol in sheep. Lactoferrin disrupts the quaternary structure of tryptase, also attenuates antigen induced late response and bronchial hyperresponsiveness in allergic sheep.

Cytokine inhibitors

One of the novel approaches for the treatment of asthma is to target cytokines and develop cytokine modulators as drugs. Two humanized anti-IL-5 monoclonal antibodies, *Sch-55700* and *SB-240563* reduced blood

eosinophil count for several weeks and prevented eosinophils recruitment into the airways after allergen challenge in asthmatic patients. IL-5 signaling inhibitor *GCC-AP0341* inhibited IL-5 mediated survival of eosinophils. IL-4 receptor antibodies inhibited allergen induced airway hyperresponsiveness, goblet cell metaplasia and pulmonary eosinophilia in a murine model.

Chemokine inhibitors

A variety of chemokines, one of which is the chemoattractant eotaxin, are secreted by inflamed lung tissue thereby attracting eosinophils. Eotaxin receptor blockers are being investigated, as eosinophils are believed to be major contributors to the pulmonary damage seen in asthma. Monoclonal antibody (7B11) for human CCR_3 has shown to completely block the binding and signaling of the known CCR_3 ligands, thus blocking the chemotactic response of human eosinophils to all chemokines.

Adhesion molecule antagonists

Interactions of eosinophils with intra cellular adhesion molecule-1 (ICAM-1) are thought to be necessary for eosinophils recruitment into airways. Antibodies to ICAM-1 blocked both eosinophils recruitment into the airways in the monkey model of asthma and importantly the increase in airway reactivity associated with allergen challenge

Phosphodiesterase inhibitors

Considerable interest has been generated in the potential utility of isoenzyme-selective inhibitors of cyclic nucleotide Phosphodiesterase (PDE) in the treatment of asthma and other inflammatory disorders. The scientific foundation for this interest is based upon two fundamental principles. First, inhibition of PDE activity increases the cellular content of two key second messengers, cAMP and cGMP, thereby activating specific protein phosphorylation cascades that elicit a variety of functional responses. Increases in cAMP content suppress a broad array of functions in inflammatory and immune cells. Both cAMP and cGMP mediate bronchodilation. PDE3 inhibitor enoxamine was shown to decrease lung resistance and increase compliance in patients with decompensated chronic pulmonary disease. Benzafentrine administered to normal volunteers by inhalation produced bronchodilation. Zaprinast is PDE5 inhibitor; it reduced exercise-induced bronchoconstriction but not histamine-induced bronchoconstriction. Most of the work now is focused on selectively targeting PDE4, primarily because inhibitors of this isoenzyme family have a notably appealing therapeutic profile; broad-spectrum anti-inflammatory activity coupled with additional bronchodilatory and neuromodulatory action. Rolipram, *LAS-31025, RP-73401* and denbufylline are selective PDE_4 inhibitors. *SB 207499, V11294A, CP-220* and roflumilast are PDE_4 inhibitors with less gastrointestinal side effects.

Endothelin modulators

There are two approaches for ET-1 directed therapeutics- (1) Inhibitors of endothelin-converting enzyme (ECE), which mediates the synthesis of ET-1 from its precursor; (2) Receptor antagonists of the effects of ET-1 at the end organ level. These agents reverse and/or prevent the increase in pulmonary artery pressure and vascular remodeling elicited by acute or chronic hypoxia. Examples are BQ-123, SB-217242 and bosentan.

Exacerbation

Some individuals will have stable asthma for weeks or months and then suddenly develop an episode of acute asthma. Different individuals react to various factors in different ways. Most individuals can develop severe exacerbation from a number of triggering agents.

Home factors that can lead to exacerbation of asthma include dust, animal dander (especially cat and dog hair), cockroach allergens and mold. Perfumes are a common cause of acute attacks in women and children. Both viral and bacterial infections of the upper respiratory tract can worsen the disease. Psychological stress may worsen symptoms-it is thought that stress alters the immune system and thus increases the airway inflammatory response to allergens and irritants.

Herbal Theray

Many Ayurvedic plants have been described to be useful in the treatment of various bronchial disorders including bronchial asthma.[41] The use of medicinal plants and natural products increased dramatically in the last two decades in all over the world. More than 400 medicinal plant species have been used ethanopharmacologically and traditionally to treat the symptoms of asthmatic and allergic disorders worldwide.

Picrorrhiza kurroa: *Picrorrhiza kurroa* (P kurroa) is a small herb with tuberous roots that is used in Ayurvedic medicine for the treatment of various conditions including lung diseases such as asthma and bronchitis. In a randomised, crossover, double blind trial[42] used P kurroa to treat 72 patients aged 14–60 years suffering from bronchial asthma over a 14 week period.The main outcome parameters were lung function tests including FEV1 and daily diary symptom scores. There was no significant change in any of the parameters measured.[43]

S xanthocarpum*: S xanthocarpum* and S trilobatum as a powder of the whole dried plant or decoction are widely used to treat respiratory disorders by practitioners of the Sidda system of medicine in Southern India. Sixty adult patients with bronchial asthma were randomised in a four-arm study. Lung function tests were performed before and two hours after drug administration. FEV1 was significantly increased above baseline levels in all groups. S xanthocarpum and S trilobatum increased FEV1 by 65% and 67%, respectively,at two hours but this effect was less than with conventional drugs.[44]

Boswellia serrata: The gum resin of B serrata is known in the Indian Ayurvedic system of medicine as Salai guggal and contains boswellic acids which have been shown to inhibit leukotriene biosynthesis.[45] In a six week, double blind, randomised clinical trial of 80 adult patients with bronchial asthma Gupta and coworkers compared the effect of B serrata gum resin with placebo (lactose).[46] The authors reported a significant increase in FEV1 in the B serrata group compared with placebo.

Tylophora indica: *Tylophora Indica* (T indica) is a plant indigenous to India and reputed to be able to provide relief to patients with bronchial asthma. Five randomised clinical trials have been published on the use of T indica in the treatment of asthmatic symptoms.[47-50]

CONCLUSION

In traditional systems of medicine, many plants have been documented to be useful for the treatment of various respiratory disorders including asthma. In the last two decades the use of medicinal plants and natural products has been increased dramatically all over the world. Current synthetic drugs used in pharmacotherapy of asthma are unable to act at all the stages and targets of asthma. However some herbal alternatives employed in asthma are proven to provide symptomatic relief and assist in the inhibition of disease progression also. The herbs have shown interesting results in various target specific biological activities such as bronchodilation, mast cell stabilization, anti-anaphylactic, anti-inflammatory, anti-spasmodic, anti-allergic, immunomodulatory and inhibition of mediators such as leukotrienes, lipoxygenase, cyclooxygenase, platelet activating, phosphodiesterase and cytokine, in the treatment of asthma. This paper is an attempt to classify these pharmacological and clinical findings based on their possible mechanism of action reported. It also signifies the need for development of polyherbal formulations containing various herbs acting at particular sites of the pathophysiological cascade of asthma for prophylaxis as well as for the treatment of asthma.

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