1.0 INTRODUCTION:
1.1 ASTHMA:
1.1.1 DEFINITIONS:
According to WORLD HEALTH ORGANIZATION, Asthma is a chronic, episodic disease of the airways that is best viewed as a syndrome [1]. In 1997, the National Heart, Lung, and Blood Institute (NHLBI) included the following features as integral to the definition of asthma: recurrent episodes of respiratory symptoms; variable airflow obstruction that is often reversible, either spontaneously or with treatment; presence of airway hyper-reactivity; and importantly chronic airway inflammation in which many cells and cellular elements play a role. Particularly, mast cells, eosinophil, T lymphocytes, macrophages, neutrophils, and epithelial cells. All of these features need not be present in any given asthmatic patient [2].

![Figure 1.1: The Interplay and Interaction Between Airway Inflammation and the Clinical Symptoms and Pathophysiology of Asthma.](image)

The Expert Panel Report (EPR) 3 guidelines, issued in 2007, state that the immune-histopathologic features of asthma include inflammatory cell infiltration involving neutrophils (especially in sudden-onset, fatal asthma exacerbations; occupational asthma; and patients who smoke), eosinophils, and lymphocytes, with activation of mast cells and epithelial cell injury. Heterogeneity in the pattern of asthma inflammation has been recognized, consistent with the interpretation that phenotypic differences exist that influence treatment response. The inflammation of asthma leads to an associated increase in the existing bronchial hyperresponsiveness to a variety of
stimuli. Although the absolute minimum criteria to establish a diagnosis of asthma are not widely agreed on, the presence of airway hyper-reactivity can be regarded as a sine qua non for patients with current symptoms and active asthma.

1.1.3 CLASSIFICATION OF ASTHMA\textsuperscript{[2,3]}:

Mcfadden et.al gave the classification of asthma as,

Asthma is of two types,

- Extrinsic or atopic asthma, and
- Intrinsic or non-atopic asthma.

Extrinsic asthma:

In extrinsic asthma an increased responsiveness of the airways is caused by exposure to environmental trigger factors. These initiating factors cause an allergic reaction in susceptible individuals.

Intrinsic asthma:

Intrinsic asthma generally occurs in the adulthood in which allergic factors may not be demonstrated, for example, stimuli like emotional state, exposure to cold air or inert dusts are responsible for the episode of intrinsic asthma.

1.1.4 SIGNS AND SYMPTOMS\textsuperscript{[4]}:

Asthma exists in two states: the steady-state of chronic asthma, and the acute state of an acute asthma exacerbation. The symptoms are different depending on what state the patient is in.

Chronic Asthma:

Symptoms of chronic asthma include,

- Shortness of breath or dyspnea,
- Wheezing,
- Cough,
- Sputum production.

Chest “tightness” is a common complaint among patients with asthma; symptoms may occur continuously or may be episodic.

Acute Asthma:

Symptoms of acute asthma are similar to those of chronic asthma and are characterized by shortness of breath, wheezing, cough, and chest tightness.

- Tachypnea,
- Tachycardia,
- Retractions,
- Cyanosis, and
- Hypoxemia may also be present.

1.1.4 PATHOGENESIS \[^{4,10,11}\]:
What initiates the inflammatory process in the first place and makes some persons susceptible to its effects is an area of active investigation. There is not yet a definitive answer to this question, but new observations suggest that the origins of asthma primarily occur early in life. The expression of asthma is a complex, interactive process that depends on the interplay between two major factors—host factors (particularly genetics) and environmental exposures that occur at a crucial time in the development of the immune system.

![Figure 1.2: Host Factor and Environmental Exposure.](image)

1.1.5 PATHOPHYSIOLOGY \[^{8,7,12,13,14,15}\]:
The Pathophysiology of asthma is characterized by a variable degree of airflow obstruction secondary to bronchial smooth muscle constriction, airway wall inflammation and edema, epithelial desquamation, mucous hypersecretion, bronchial hyperresponsiveness, and, in some but not all, airways remodeling. Airway wall inflammation is characterized by an influx of eosinophils, neutrophils, lymphocytes, and degranulated mast cells. Airway inflammation is considered to be the primary
pathologic event in asthma. Initially, it was described in postmortem observations of patients with asthma who died from an attack of asthma or from other causes; however, both bronchial biopsy and bronchoalveolar lavage (BAL) studies have consistently demonstrated most if not all the above components of inflammation in all patients with asthma, regardless of the variant of asthma, the disease severity, or the principal triggering event (allergy, virus, or occupational trigger). More recently, remodeling of the airways thought to be secondary to persistent inflammation has been described in a number of patients with asthma. Airway remodeling refers to structural changes that consist of collagen deposition in the subbasement membrane, airway smooth muscle hypertrophy and hyperplasia, increased numbers of mucus glands and enhanced vasculature of the airway walls. These changes may lead to irreversible narrowing of the airway lumen. It has been hypothesized that airway remodeling is the cause of the increased loss in lung function over time reported in adults with asthma compared with normal adults without asthma [5, 6]. However,
certain aspects of airway remodeling have been noted in airway tissues from children and adults with asthma and those with normal lung function. The precise pathologic mechanism for the development and persistence of airway inflammation in asthma has yet to be elucidated. However, a large body of research has described the cells and mediators that are involved in the inflammatory process; these are briefly described here. It appears that there are two predominant forms of asthma: extrinsic or allergic (atopic) asthma, and intrinsic or nonallergic asthma. Atopy is associated with 40% to 50% of patients with asthma, but not all allergic patients develop asthma. However, much of our understanding of the pathophysiology of asthma comes from studies of patients with this phenotype. Intrinsic asthma commonly follows respiratory viral infection; it is not associated with specific immunoglobulin E (IgE) antibodies, is associated with aspirin sensitivity, and may be more severe than extrinsic asthma. Although intrinsic asthma is clinically different from extrinsic asthma and is not associated with high serum IgE concentrations, it is not necessarily immunopathologically distinct, as patients with intrinsic asthma also have shown a Th2 cytokine profile in biopsy studies. However, it should be remembered that well over 20 cytokines alone have been described that could be involved in regulating the inflammation of asthma, and that the cytokine system is a highly duplicative process with more than one cytokine performing specific functions. Thus, it is no wonder that therapies that reduce the presence of one cytokine have not been successful in treating asthma.

1.1.6 DIAGNOSIS [16, 17]:

There are given some test to diagnose the asthma and they are as follows;

- Pulmonary Function Tests - For the determination of lung function.
- Chest x-ray - This test is take because to find the difficulty in breathing and cough.
- Nitric oxide Test - This test regulates the binding and release of oxygen to hemoglobin.
- Peak flow measurements - To measure the lung problems.
- An arterial blood gas test can measures the levels of oxygen and carbon dioxide in the blood.
- Anti-IgE therapy is given by injection to patients with severe asthma.
Reversibility test by using this test the peak flow rate is measured.

A spirometry test can measure how well your lungs are functioning.

Breathing Techniques - for reducing the asthma attack breathe out through pursed lips when whistling.

Allergy skin or blood tests.

Eosinophil count (white blood cell)

Detailed allergy and asthma history

Physical examination

Pulmonary Function Testing (peak flow, spirometry, complete lung volumes, methacholine challenge)

**METHACHOLINE TEST FOR DIAGNOSING ASTHMA** [18]:

When the pulmonary function testing reveals an obstructive pattern with significant reversibility of the obstruction with a bronchodilator it reveals dealing with asthma. A methacholine challenge test is the best way to objectively confirm the presence of airway hyper-reactivity, the hallmark of asthma. Asthmatic individuals are highly sensitive to tiny amounts of inhaled methacholine whereas non-asthmatic individuals are generally unaffected. Therefore, if asthmatic patients inhale methacholine, they experience a significant decrease in pulmonary functions. This also can be accompanied by mild asthmatic symptoms. A methacholine challenge test is the standard to confirm the diagnosis of asthma [18].

The diagnosis of asthma is the basic measurement of peak flow rates and the diagnostic criteria are

A) \( \geq 20\% \) difference on at least three days in a week for at least two weeks;

B) \( \geq 20\% \) improvement of peak flow following treatment, for example:

- 10 minutes of inhaled \( \beta \)-agonist (e.g., salbutamol);
- Six weeks of inhaled corticosteroid (e.g., beclometasone);
- 14 days of 30 mg prednisolone.

C) \( \geq 20\% \) decrease in peak flow following exposure to a trigger [19].

**1.1.7 TREATMENT:**

Perhaps the most important step in controlling asthma is establishing a partnership between doctor and patient (whether child or adult) to create a specific, customized plan for proactively monitoring and managing symptoms. It is essential to be certain
that someone who has asthma understands (and takes an active part in deciding) what needs to be accomplished, including reducing exposure to allergens, taking medical tests to assess the severity of symptoms, and possibly using medications. The treatment plan should be written down, consulted at every visit, and adjusted according to changes in symptoms.\textsuperscript{[20, 21]}

The most effective treatment for asthma is identifying triggers, such as pets or aspirin, and limiting or eliminating exposure to them. If trigger avoidance is insufficient, medical treatment is available. Desensitization has been suggested as a possible cure\textsuperscript{[20]}. Additionally, some trial subjects were able to remove their symptoms by retraining their breathing\textsuperscript{[22, 23]}.

**Drugs used to treat asthma:**
Asthma is an abnormal condition which can be preventable to a large extent by avoiding environmental pollutants that triggers the allergy\textsuperscript{[54]}. For many years, effective therapy for management of asthma consists primarily of the following classes:

1.1.8 **CLASSIFICATION OF ANTI-ASTHMATIC DRUGS:**

I. **Bronchodilators\textsuperscript{[25]}:**
   - Methyl Xanthines: Theophylline, Aminophylline, Choline theophyllinate, Hydroxy ethyl theophylline, Theophullineethanolate of piperazine.
   - Anticholinergics: Atropine, Methonitrate, Ipratropiumbromide, Tiotropiumbromide, Oxitropium, Retatropate, Darifenacin.

II. **Mast Cell Stabilizers\textsuperscript{[25]}:** (Cromones) Sodium cromoglycolate, Nedocromil, Ketotifen.

III. **Histamine H\textsubscript{1} receptor antagonist\textsuperscript{[26]}:**
   - Ethanolamines: Diphenhydramine, Dimenhydrinate.
   - Ethylenediamines : Pyrilamine
   - Alkylamine: Chlorpheniramine
   - Piperazine: Chlorcyclizine
   - Phenothiazines: Promethazine

IV. **Anti-inflammatory agents\textsuperscript{[25]}:**
Corticosteroids:

- Systemic: Hydrocortisone, Prednisolone.
- Inhalational: Beclometasonedipropionate.

V. Newer Approaches $^{[25, 27]}$:

- Phosphodiesterase inhibitors
  a) Non-selective PDE inhibitors: Methyl xanthenes, caffeine.
  b) Selective PDE inhibitors: Vinpocetine, Anagrelide, Luteolin, Rolipram

- Leukotrine receptor antagonist:
  a) Cysteinylleukotrine inhibitors: Montelukast, Zafirlukast
  b) 5-lipoxygenase inhibitors: Zileuton

- Single mediator antagonist and combination
  a) PAF inhibitors
  b) Thromboxane $A_2$ inhibitors
  c) Tachykinin receptor antagonist
  d) Triphase inhibitor
  e) Chemokine inhibitors.

1.2 HIPTAGE BENGALENSIS (L) KURZZ.

![Figure 1.6: Leaves and Flowers of Hiptage Benghalensis (L) Kurzz.](image)

**Family name** $^{[28]}$: Malpighiaceae.

**Vernacular name** $^{[7, 18]}$:

- Hindi name : Madhavilata, Madhmalti.
- Sanskrit name : Madhavi, Atimukta.
- Marathi name : Madhavi, Haladvel.
- Gujarati name : Madhavi, Rakatpiti.
- Tamil name : Madavi.
- Kanar name: Vasantaduti.

Taxonomic notes [29, 30]: The genus, Hiptage, contains about 25 species of erect or climbing Shrubs, native to tropical Asia.

Nomenclature [30]: The genus name, Hiptage, is derived from the Greek, hiptamai, which means "to fly" and refers to the fruit, a 3 winged samara.

History [7, 18, 31]:
Benghalensis has several vernacular names, including Madhavi, Vasantduti, Chandravalli, Madhalata, Madhumalati, Madhavi and Madhavilata, "Madhav" being a reference to Lord Krishna. Madhavilata, native from India to the Philippines, is a vine like plant that is often cultivated in the tropics for its attractive and fragrant flowers. The genus name, Hiptage, is derived from the Greek hiptamai, which means "to fly" and refers its unique three-winged fruit known as "samara". "Benghalensis" is derived from the historic region of Bengal, where it is a native species. Taxonomic synonyms for H.benghalensis include:

- Banisteriabenghalensis L.
- BanisteriatetrapteraSonnerat.
- Banisteriaunicapsularis Lam.
- Hiptagebenghalensis (L.) Kunz forma longifoliaNied.
- Hiptagebenghalensis (L.) Kurzforma cochinchenensis Pierre.
- Hiptagebenghalensis (L.) Kurz forma latifoliaNied.
- Hiptagebenghalensis (L.) Kurz forma macroptera (Merr.) Nied.

1.2.1DESCRIPTION [28]:
H.benghalensis is a stout, high-climbing liana or large shrub, with white or yellowish hairs on the stem. Its leaves are lanceolate to ovate-lanceolate and approximately 20 cm (8 in) long, and 9 cm (4 in) broad; petioles are up to 1 cm long. It has scandent branches up to 5 m (16 ft) high.
H.benghalensis flowers intermittently during the year, and produces fragrant flowers borne in compact ten-to-thirty-flowered axillary racemes. The flowers are pink to white, with yellow marks. Fruits are samaras with three spreading, papery oblong to elliptic wings, 2-5 cm long, and propagate via wind or by cuttings.

Traditional therapeutic Uses [28, 33, 36, 37]:
H. benghalensis is widely cultivated in the tropics for its attractive and fragrant flowers; it can be trimmed to form a small tree or shrub or can be trained as a vine. It is also occasionally cultivated for medicinal purposes in the alternative medicine practice of ayurveda: the leaves and bark are hot, acrid, bitter, insecticidal, vulnerary and useful in the treatment of biliousness, cough, burning sensation, thirst and inflammation. It also has the ability to treat skin diseases and leprosy.