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Review

Comprehensive Review of Asthma: Pathophysiology, Genetic Influences, and Emerging Treatment Strategies

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Abstract

The review article provides an in-depth exploration of asthma, a chronic inflammatory disease influenced by a complex interplay of genetic and environmental factors. It traces the historical development of asthma's definition and diagnosis, from early medical descriptions to modern epidemiological studies that reveal its rising prevalence. The article discusses the pathophysiology of asthma, focusing on immune responses involving T helper type 2 (Th2) cells and cytokines, along with molecular mechanisms like IgE production and airway remodeling. Genetic factors, such as mutations in the ADAM33 and filaggrin genes, are examined for their role in asthma susceptibility and disease progression. Different asthma types—such as adult-onset, exercise-induced, and cough-induced—are reviewed, highlighting their unique triggers and diagnostic challenges. Treatment strategies, including conventional medications (inhaled corticosteroids, β2-agonists) and alternative therapies (phytochemicals), are evaluated, along with the limitations of current treatments and the need for improved therapeutic options. The article underscores the importance of personalized approaches to asthma management based on individual genetic and environmental profiles.

Keywords: Asthma, inflammation, treatment, medicinal plant

INTRODUCTION

Since the word "asthma" comes from the Greek for "short of breath," any patient who experienced dyspnea was diagnosed with asthma. Henry Hyde Salter's dissertation "On Asthma and its Treatment," which was published in the second half of the 19th century, helped to refine the word. Salter described asthma in this academic work as "Paroxysmal dyspnea of a peculiar character with intervals of healthy respiration between attacks," which perfectly encapsulates his idea of a condition in which the smooth muscle in the airways contracts, narrowing the airways.(1) About 30 years before Paul Ehrlich established aniline stains for eosinophils (eosin) and mast cells (toluidine blue), his book includes surprisingly accurate pictures of the airways in asthma and bronchitis as well as the cellular appearance of asthmatic sputum. Additionally, he explained that black coffee, a beverage that contains a lot of theobromine, a byproduct of theophylline, and theophylline itself, can be used to relieve asthmatic spasms. Because Dr. Salter has asthma himself, he has a unique perspective on the condition. By the late nineteenth century, doctors therefore came to believe that asthma was a unique illness with a particular set of causes, clinical implications, and therapeutic needs.(2,3)

Asthma

Asthma, conventionally defined as chronic inflammatory disease caused by a large number of gene environment interplays, manifests with variable airway obstruction and bronchial hyperresponsiveness, ultimately causing cough, wheeze, shortness of breath, and chest tightness.(4,5) Frequent triggers of asthma episodes include viral infections, exposure to allergens and/or pollutants, cigarette smoking, sudden temperature variations, stress, and exercise among others. Patients with persistent asthma disease shall be subjected to more aggressive care, aimed at lowering an otherwise high risk of developing important—often life-threatening complications, such as enhanced vulnerability to respiratory infections, pneumothorax, emphysema, loss of lung function, respiratory failure, up to death. (6)

Epidemiology

During the second half of the Twentieth century, notably since the 1960s, a sharp increase in asthma prevalence was observed in a number of developed countries. This observation was a result of repeated cross-sectional surveys of prevalence of asthma, mainly in children but also in adults. As a result of this observation, in the 1990s, a series of epidemiological studies were established across the world to estimate global asthma prevalence and incidence, and identify risk factors associated with these outcomes. These include large multinational studies in children [such as the International Study of Asthma and Allergies in Childhood (ISAAC; http://isaac.auckland.ac.nz/) (7–8)] and in adults [such as the European Community Respiratory Health Survey (ECRHS; http://www.ecrhs.org/) (9)]. These studies confirmed that asthma is one of the most common chronic diseases across the globe in all age groups and there is substantial variation in asthma prevalence worldwide.

It is now acknowledged that the prevalence of both childhood and adult asthma may have peaked in some areas, predominantly in high-income countries, whereas an increase may be continuing in low and mid-income countries (10). It is important to note that a reduction in the prevalence of current asthma is determined by improved asthma control and/or reduced asthma incidence at a population level. Thus, a reduction in prevalence of current asthma may well-reflect improved asthma control through increased medication use from more widespread prescribing habits and better compliance. Documenting reductions in asthma incidence is complicated as parallel cohort studies with specific age windows are needed to establish patterns with the comparison group ideally from the same geographical region. These challenges might in part explain why studies from Australia and UK have not consistently shown reductions in asthma prevalence and why temporal trends in European and Asian countries between the 1970s and mid-2000s have been conflicting. (11)

Types of asthma

Adult-onset asthma

The term used for asthma that emerges after the age of 20 is adult-onset asthma. This condition tends to impact women more than men and is notably less prevalent compared to childhood-onset asthma. Allergies can also act as triggers for adult-onset asthma. It's estimated that as much as 50% of adult-onset asthma cases are associated with allergic reactions.(12,13)

Exercise-induced asthma

Exercise-induced asthma refers to symptoms such as coughing, wheezing, or breathlessness experienced during or after physical exertion. The level of fitness plays a significant role in this condition. An individual who is not physically fit and engages in intense exercise, like running for ten minutes at a fast pace, is likely to experience breathlessness, which can mimic symptoms of asthma

Cough-induced asthma

Diagnosing cough-induced asthma presents a significant challenge for doctors. They must systematically rule out other potential causes, such as chronic bronchitis, post-nasal drip from hay fever, or sinus disease. In cases of cough-induced asthma, coughing may occur independently, without accompanying asthma symptoms. Moreover, the coughing episodes can manifest at any time, day or night, potentially disrupting sleep if they occur during nighttime.

Occupational asthma

Occupational asthma arises from triggers present in the patient's workplace environment. These triggers encompass a range of factors including chemicals, vapors, gases, smoke, dust, fumes, or other particles. Additionally, asthma episodes can be instigated by viral infections like the flu, molds, animal products, pollen, fluctuations in humidity and temperature, and even stress.

Causes of asthma (14)

Fig 1: Causes of asthma

Pathophisiology

Asthma is linked with T helper cell type-2 (Th2) immune responses, akin to those observed in other atopic disorders. Triggers for asthma include a spectrum of allergic factors such as dust mites, cockroach residue, pet dander, molds, and pollens. Moreover, non-allergic factors like infections, exposure to tobacco smoke, cold air, and physical exertion can also provoke asthma symptoms**.** Triggers set off a chain of immune-mediated responses culminating in chronic inflammation of the airways Elevated levels of Th2 cells within the airways release specific cytokines, notably interleukin (IL)-4, IL-5, IL-9, and IL-13. These cytokines promote eosinophilic inflammation and stimulate mast cells to produce immunoglobulin E (IgE). IgE production, in turn, prompts the release of inflammatory mediators like histamine and cysteinyl leukotrienes. These mediators induce bronchospasm (smooth muscle contraction in the airways), edema (swelling), and increased mucous secretion (mucous hypersecretion), thereby eliciting the hallmark symptoms of asthma. *(15,16)*

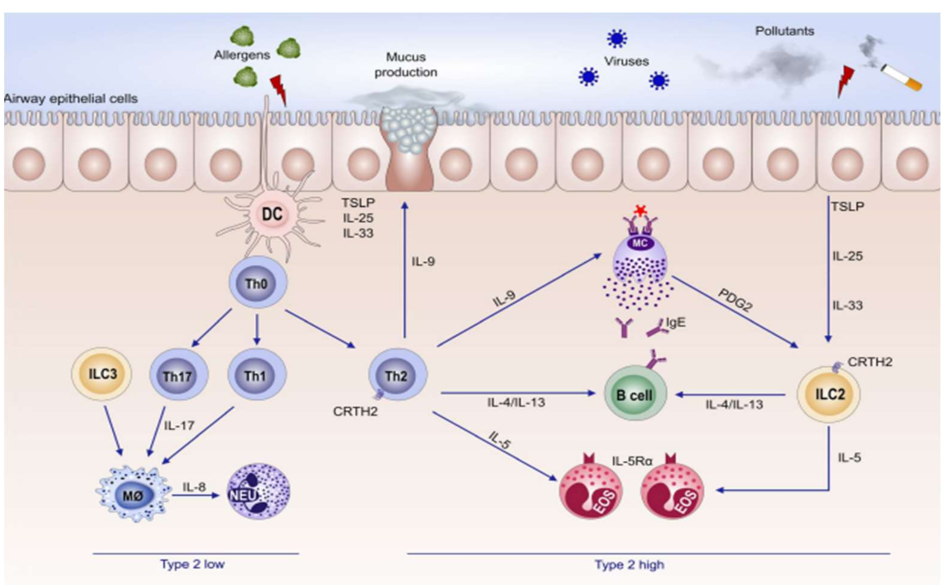


Fig 2: Pathophysiology of asthma

Molecular mechanism of bronchial asthma

In recent years, much work has been done to help deepen our understanding of the molecular mechanisms of bronchial asthma. Chief among them is the molecular differences that split the mechanism of asthma into two distinct Asthma.

Type 2 asthma, is bronchial asthma in which type 2 helper T (Th2) cytokines, such as interleukin-4 (IL-4), IL-5, and IL-13 increase; Th2 cytokines play an important role in its pathophysiology, hence the term type 2 Th2 cytokines are produced not only by Th2 cells but also by basophils, mast cells, and type 2 innate lymphoid cells (ILC2s).(17,18)Antigen presenting cells (APCs) such as dendritic cells (DCs) and macrophages phagocyte the antigen and move to the regional lymph node, in which they deliver an antigen peptide to naive T cells via MHC class II switch (antigen presentation). Antigen stimulation differentiates naive T cells into Th2 cells. Th2 cells activate B cells to produce immunoglobulin E (IgE). The IgE produced binds the high-affinity IgE receptor (FcεRI) on the cell surface of the mast cell (sensitization). (19,20)

When the invading antigen binds to antigen-specific IgE on mast cells, the mast cells release mediators (degranulation). This early-phase reaction occurs within minutes after antigen exposure. The released mediators consist of histamine, prostaglandin, leukotriene and several cytokines such as IL-8, IL- 13, tumor necrosis factor (TNF)-a and chemokine (CeC motif) ligand (CCL) 2 . These mediators induce mucus production, broncho-constriction, and the recruitment of leukocytes such as neutrophil, lymphocyte, and eosinophil. In mice, eosinophils are divided into two subtypes based on the expression of surface markers: resident eosinophils (rEos) residing in the lungs and inflammatory eosinophils (iEos) induced in the lungs during inflammation In the late-phase reaction, which occurs hours after antigen exposure, the iEos release several cytokines, which induce bronchoconstriction and epithelial cell damage, leading to airway hyperresponsiveness (AHR) and tissue remodeling However, these subtypes and specific mechanisms of eosinophils are yet to be fully confirmed in humans(21)

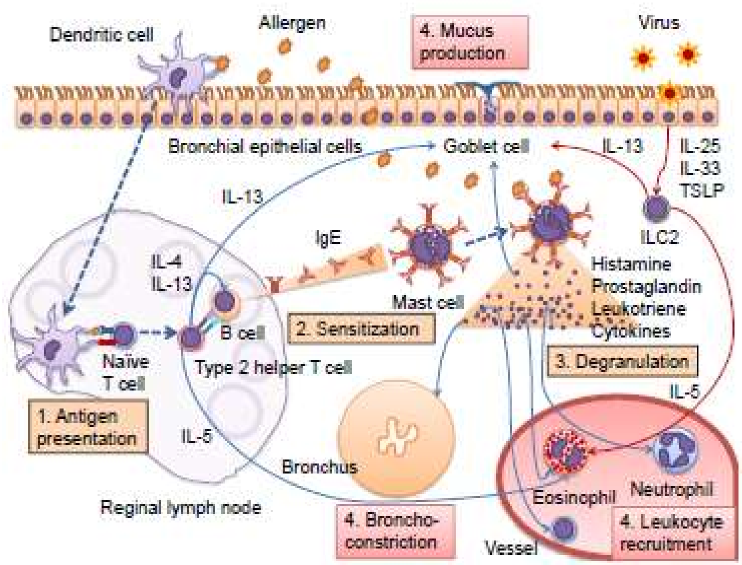


Fig 3: Mechanism of asthma

Molecular genetics of asthma

Over a hundred different genes have been associated with asthma and the list is still growing. Asthma susceptibility genes fall mainly into three categories relating to 1) functioning of the immune system, 2) mucosal biology and function, and 3) lung function and disease expression. However, just because a gene has been associated with asthma in a single study does not necessarily establish a connection between that gene and the disease.

A major problem in many genetic studies of asthma is the lack of replication of results from previous studies. Notably, only a subset of identified genes has been found to be associated with asthma in more than one study; and many regard replication as one of the most important features of a gene's candidacy. However, some genes may be important only in a subset of asthmatics, for example, in childhood-onset asthma, atopic asthma, house dust mite sensitive asthma, or occupational asthma, and therefore replication across these different populations cannot always be expected. Moreover, some genes are expressed only in certain environmental contexts, for instance, in children growing up with a cat or in those exposed to passive smoking in the first years of life(22,23)

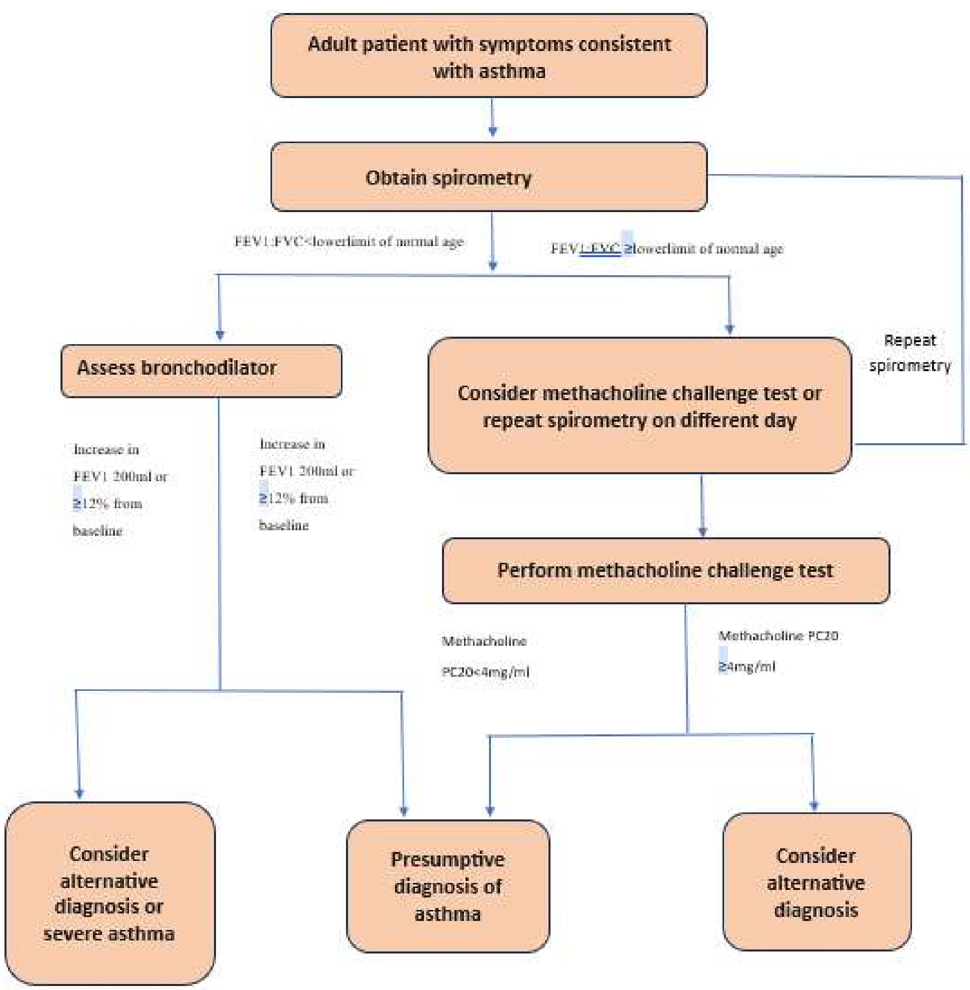
ADAM33

A disintegrin and metalloproteinase 33 (ADAM33) was the first positionally cloned asthma susceptibility gene, meaning that its exact position in the genome was identified before knowing about the function of the gene.(24) ADAM33 is located on chromosome 20p13 and is expressed in bronchial smooth muscle cells and lung fibroblasts. When initially discovered in 2002, it was shown to be strongly linked both to asthma and bronchial hyperresponsiveness. (25) More recently its role has been extended to also involve more subtle aspects of asthma pathogenesis, such as airway remodelling, progression of disease and also chronic obstructive pulmonary disease

Filaggrin

Filaggrin is a protein that helps maintain an effective skin barrier. Loss-of-function mutations in the filaggrin gene situated on chromosome 1q21 were first associated with the skin disease ichthyosis vulgaris and more recently with atopic dermatitis. Mutations are present in a little under 10% of individuals from Western populations and in up to 50% of individuals with atopic dermatitis.(26,27) It is considered the strongest genetic determinant of atopic dermatitis, increasing the risk about four-fold Moreover, filaggrin mutations have been associated with development of allergic sensitisation, hay fever, and asthma, but only in subjects with atopic dermatitis Interestingly, studies have found that dysfunction of the skin barrier not only enhances sensitisation to allergens but also leads to systemic allergic responses, such as increased IgE levels and airway hyperresponsiveness, indicating that absorption of allergens through the skin of patients with atopic dermatitis is a prerequisite for the development of other allergic conditions, such as asthma and hay fever. (28,29,30)

Diagnosis



The first diagnostic test should be forced expiratory spirometry, categorized as obstructed (ratio of forced expiratory volume in first second of expiration [FEV1] to forced vital capacity [FVC] less than lower limit of normal) or not obstructed. If airway obstruction is present, a bronchodilator response following 2 to 4 puffs of short-acting β2-agonist should be determined. Fixed or partially reversible airway obstructionsuggests alternative diagnoses, although severe asthma may be present. PC20 indicates the methacholine concentration required to achieve a 20% decrease in FEV1.(31,32)

Differential diagnosis of asthma

Upper respiratory tract

- Vocal cord dysfunction
- Congestive rhinopathy
- Obstructive sleep apnea syndrome

Lower respiratory tract

- Chronic obstructive pulmonary disease
- Occupational bronchitis
- Cystic fibrosis
- Bronchiectasis
- Pneumonia

Gastrointestinal tract

Gastroesophageal reflux disease

Cardiovascular system

- Congestive heart failure
- Pulmonary hypertension
- Chronic thromboembolic pulmonary disease

Central nervous system

- Habitual cough.

Current treatments

Asthma is a chronic inflammatory airway disease arising from a complex interaction between the immune system and resident cells of the lung to induce the cardinal features of bronchial hyper-responsiveness, increased mucus production, narrowing of the airways and airway re modelling. A detailed review of the pathophysiology of asthma has been covered extensively elsewhere and is outside the scope of our article [33,34,35). The most important clinical consequences of this inflammatory process are the exacerbations of disease causing airway narrowing and debilitating bouts of shortness of breath, wheezing, chest tightness and cough. Most asthma treatments aim to control these symptoms and reduce the frequency of exacerbations and current recommendations advocate the use of anti-inflammatory treatments, in particular inhaled corticosteroids (ICS) and bronchodilators such as short and long acting β2-adrenergic agonists (LABA; 5). However, there is concern around the inappropriate use of asthma medications, in particular the overuse of inhaled corticosteroids in children, which can effect bone growth, and the inappropriate use of long acting bronchodilator therapy in isolation which has been associated with increased morbidity [36]. As well as the risk of these possible adverse effects not all patients respond to these treatments and non-adherence to treatment is common due to issues such as complex treatment regimens, poor inhalation technique and delayed results [37] thus there is an unmet medical need for complementary therapies for asthma.

Commonly used drugs in the management of Asthma

- *β*2-Agonists
- Short-acting
  - Albuterol
  - Levalbuterol
- Long-acting
  - Formoterol
  - Salmeterol
- Theophylline
- Anticholinergics
  - Ipratropium
  - Tiatropium
- Anti-inflammatory agents
- Inhaled corticosteroids

- Beclomethasone
- Budesonide
- Ciclesonide
- Flunisolide
- Fluticasone
- Mometasone
- Triamcinolone

➢ Cromolyn

➢ Leukotriene receptor modifiers
- Montelukast
- Zafirlukast
- /Zileuton

➢ IgE binding antibodies
- Omalizumab

Phytochemicals used for management of asthma

Table 1: Phytochemicals used for management of asthma

S.No	Bio Active Compounds	Activity And Potential Mechanisms Of Effect
I)	**POLYPHENOLS**	
	Flavans	Donation of hydrogen atom to radicals
	Flavanones	Chelation of redox-active metals
	Isoflavanones	Inhibition of lipid peroxidation
	Flavones	Regulation of the enzyme activities
	Isoflavones	Inhibition of mast cell/basophil activation
	Anthocyanidins	Switching allergic immune response to Th1 profile
	Chalcones	Regulation of various transcription factors and mediators
	Flavonolignans	involving angiogenesis: HIF-1, VEGF, MMPs, EGFR and inhibit NF-κB, PI3K/Akt, and ERK1/2 signaling pathways
	CURCUMIN	Prevention of lipid peroxidation
	RESERVATROL	Inducing and stabilizing antioxidant enzymes

Table 2: Some adverse effects of current orthodox treatments for asthma

Orthodox Drug	Common Adverse Effects Encountered
Isoprenaline	Tachycardia
Salbutamol	Muscle tremors (dose related), palpitation, restlessness, nervousness, throat irritation and ankle edema
Theophylline	Convulsions, shock, arrhythmias, increased muscle tone, tachapnoea, (dose dependent) flushing, hypotension, restlessness, tremors, vomiting, palpitation, diuresis, dyspepsia, insomnia etc.
Anticholinergics	Dry mouth, difficulty in swallowing and talking, scarlet rash, photophobia, blurring of near (Atropine and its congeners) vision, palpitation, ataxia, delirium, hallucinations, hypotension, weak and rapid pulse, cardiovascular collapse with respiratory depression, convulsions and coma (in severe poisoning).
Ketotifen	Sedation, dizziness, dry mouth, nausea and weight gain.
Corticosteroids	Cushing's habitus, fragile skin, purple striae, hyperglycemia, muscular weakness, susceptibility to infection, delayed healing of wounds and surgical incisions, peptic ulceration, osteoporosis, glaucoma, growth retardation, psychiatric disturbances, suppression of hypothalamo-pituitary-adrenal (HPA) axis etc.

Table 3: Medicinal plants used in the management of asthma

Botanical Name (Family)	Common Name	Extract/compound	Model	Reference
Aerva lanta (Amaranthaceae)	Mountain knotgrass	Ethanol	A	[18]
Abrus precatorius (Papilionaceae)	Love pea	Ethanol	b.c	[27][28]
Aegle marmelos (Rutaceae)	Golden apple	Alcoholic extract of the leaves	H	[32]
Alstonia scholaris (Apocynaceae)	Black board tree. Indian devil tree	Ethanol extracts of leaves	G	(33)
Casuarina equisetifolia (Casuarinaceae)	Australian pine	Methanol extract of extracts of wood and bark	a.b.g	(35)
Clerodendrum serratum (Verbenaceae)	Glory bower. bag flower	Ethanol extract of roots	a.d	(36)
Clerodendrum serratum (Verbenaceae)	Glory bower. bag flower	Ethanol extract of roots	a.d	(36)
Crinum glaucum (AmaryHidaceae)	Poison bulb	Aqucous extract	b.c	(26)
Curculigo orchioides Gaertn (Amaryllidaceae)	Golden eye grass	Alcoholic extract of rhizome	a,b.d.e.f.	[27]
Camellia sinensis (Theaceae)	Tea plant. tea shrub	Tea-leaf saponins	b.f	[28]
Eclipta alba (Asteraceae)	False daisy	Ethanol extract	b.f	1391
Euphorbia hirta (Euphorbiaceac)	Asthma plant	Ethanol extract of aerial part of the plant	B	(20)
Garcinia kola (Guttiferae)	Bitter kola	Phenols, alkaloids, xanthones and flavonoids		[29]
Hemidesmus indicus (Asclepiadaceae)	Nannari	Ethanol extract	A	[36]
Mimosa pudica(leguminosac)	Sensitive plant	Ethanol extract	F	(NO)
Momordica dioica (Curcubitaceae)	Balsam pear	Aqueous and methanol of fruit	A	(17)

CONCLUSION

The contents up, this review offers an in-depth examination of asthma, looking at its intricate pathophysiology, inherited tendencies, and environmental triggers. It emphasizes how the deeper mechanisms of asthma, specifically those related to immune system responses and certain gene alterations, influence the onset and individual heterogeneity of the disease. The study emphasizes the value of a customized strategy to asthma management by examining both established and new treatment approaches. Considering therapeutic advances, the review emphasizes the need for new, more potent treatments because of the shortcomings of existing drugs and issues with patient adherence. In order to obtain the strongest possible control of asthma, it typically advocates a balanced mix of conventional and alternative therapy.

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