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ASTHMA MANAGEMENT: A REVIEW

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ABSTRACT

Asthma is a chronic inflammatory disease of the airways that causes a high burden on the global health care system. Despite advances in therapy, asthma remains a disease that, in many patients, is not optimally controlled. Efforts has been made to make a document that discusses the medications for asthma management, the long-term management of asthma; the management of asthma exacerbations ; the management of asthma in special populations; findings of research literatures, and Herbal therapy for asthma management. Various herbs are used as antiasthmatic with efficient therapeutic response. An attempt has been made to review antiasthmatic drugs and medicinal plants, in the present article.

KEY WORDS : Antiasthmatic, global health care, asthma.

1.0 INTRODUCTION[1,2]

Asthma is a chronic inflammatory disease of the airways, characterized by recurrent attacks of airflow obstruction, bronchial hyperresponsiveness, and an underlying inflammation which vary in severity and frequency from person to person. The interaction of these features determines the clinical manifestations and severity of asthma[1]. During an asthma attack, the lining of the bronchial tubes swells, causing the airways to narrow and reducing air flow into and out of the lungs. The term "asthma" comes from the Greek meaning, "to breathe hard". Based on functional consequences of airway inflammation, an operational description of asthma (GINA report 2012) is: asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyper responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing, particularly at night or in the early morning.

These episodes are usually associated with widespread, but variable, airflow obstruction within the lung that is often reversible either spontaneously or with treatment.

1.1 Prevalence

According to WHO estimates (GINA report 2012)[2], 300 million people suffer from asthma. Asthma is the most common chronic disease among children and is a public health problem for all countries, as it is for high income countries. Over 80% of asthma deaths occur in low and lower middle income countries. WHO has estimated that disability adjusted life years (DALYs), lost annually due to asthma are 15 million, representing burden of 1% of the total global disease. Annual worldwide deaths from asthma have been estimated at 250,000 and mortality does not appear to correlate well with prevalence[3]. Two large multinational studies have assessed the prevalence of asthma around the world: the European Community Respiratory Health Survey (ECRHS) in adults and the International Study of Asthma and Allergies in Childhood (ISAAC) in children. It is estimated that there may be an additional 100 million people with asthma by 2025[3].

2.0 Pathophysiology of Asthma[1, 13]

Interaction between airway inflammation and the clinical symptoms and pathophysiology of asthma (figure-1).

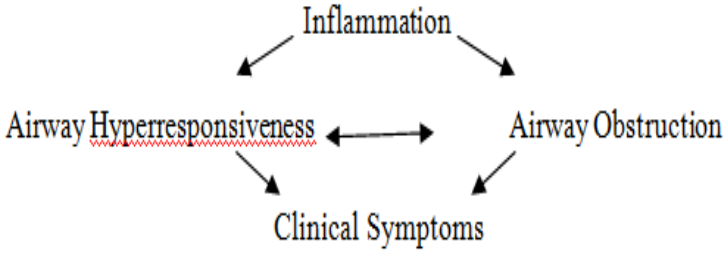

Figure1: Interaction between airway inflammation and the clinical symptoms and pathophysiology of asthma.

The mechanisms involved in persistence of inflammation in asthma are still not completely understood. Many different inflammatory cells are involved in asthma like mast cells macrophages, dendritic cells, eosinophils, neutrophils, T-lymphocytes, B-lymphocytes, basophils, platelets and structural cells of airways including epithelial cells. Not a single cell accounts for the complex pathophysiology of asthma, but some cells predominate.

Also many inflammatory mediators have been implicated in asthma like lipid mediators, cytokines, chemokines, oxidative stress, endothelines, nitric oxide generated in airway cells by NO syntheses. Recurrent Airflow limitation in asthma is caused by variety of changes in the airway[1]. These include.

Bronchoconstriction

In asthma, airway narrowing and interference of airflow are the dominant physiological events, leading to clinical symptoms. In acute exacerbations of asthma, bronchial smooth muscle contraction occurs in response to exposure to a variety of stimuli including allergens or irritants leading to narrow airways. Allergen-induced acute bronchoconstriction results from an IgE-dependent release of mediators from mast cells that includes histamine, tryptase, leukotrienes, and prostaglandins that directly contract airway smooth muscle.

Airway edema

Airway edema, inflammation, mucus hypersecretion and the formation of inspissated mucus plugs, as well as structural changes including hypertrophy and hyperplasia of the airway smooth muscle are the other factors limiting airflow.

Airway hyperresponsiveness

Airway hyperresponsiveness is an exaggerated bronchoconstrictor response to a wide variety of stimuli. The mechanisms influencing airway hyperresponsiveness include inflammation, dysfunctional neuroregulation, and structural changes; inflammation appears to be a major factor in determining the degree of airway hyperresponsiveness. Reducing inflammation can reduce airway hyperresponsiveness and improve asthma control.

Airway remodelling

Airflow limitation may be only partially reversible in some asthma patients. Permanent structural changes can occur in the airway (figure 2); which are associated with a progressive loss of lung function. Airway remodelling involves activation of many structural cells, with consequent permanent changes in the airway that increase airflow obstruction and airway rendering patients less responsive to therapy.

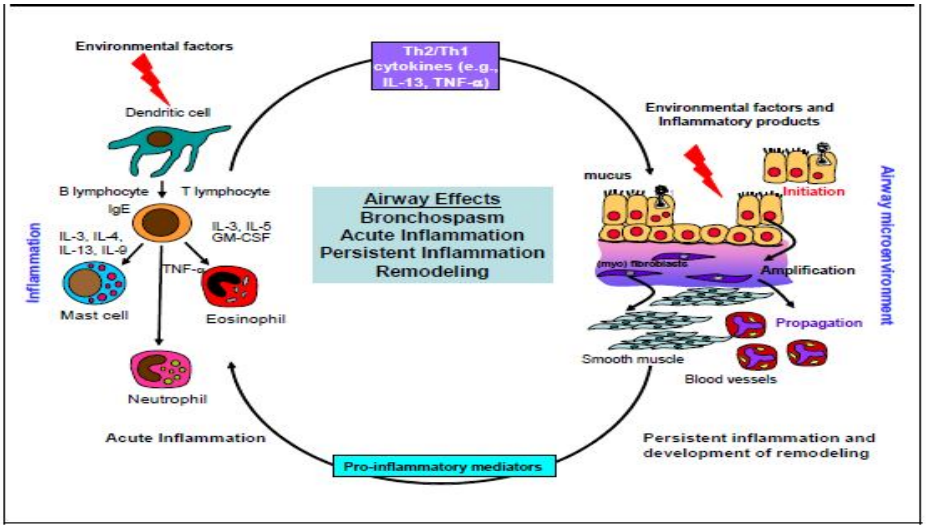

Figure 2: Factors limiting airflow in acute and persistent asthma[1] (reference EPR 3)

3.0 Severity of Asthma[1,8]

Severity of asthma is classified as intermittent mild persistent, moderate persistent and severe persistent (fidure 3) and the asthma severity is characterised by its components, at impairment or at risk.

Components of Severity		Intermittent			Persistent								
					Mild			Moderate			Severe		
		Ages 0–4 years	Ages 5–11 years	Ages ≥12 years	Ages 0–4 years	Ages 5–11 years	Ages ≥12 years	Ages 0–4 years	Ages 5–11 years	Ages ≥12 years	Ages 0–4 years	Ages 5–11 years	Ages ≥12 years
Impairment	Symptoms	≤2 days/week			>2 days/week but not daily			Daily			Throughout the day		
	Nighttime awakenings	0	≤2x/month		1–2x/month	3–4x/month		3–4x/month	>1x/week but not nightly		>1x/week	Often 7x/week	
	SABA* use for symptom control (not to prevent EIB*)	≤2 days/week			>2 days/week but not daily	>2 days/week but not daily and not more than once on any day		Daily			Several times per day		
	Interference with normal activity	None			Minor limitation			Some limitation			Extremely limited		
	Lung function		Normal FEV_1 between exacerbations	Normal FEV_1 between exacerbations									
	➔ FEV_1* (% predicted)	Not applicable	>80%	>80%	Not applicable	>80%	>80%	Not applicable	60–80%	60–80%	Not applicable	<60%	<60%
	➔ FEV_1/FVC*		>85%	Normal†		>80%	Normal†		75–80%	Reduced 5%†		<75%	Reduced >5%†
Risk	Asthma exacerbations requiring oral systemic corticosteroids‡	0–1/year			≥2 exacerb. in 6 months, or wheezing ≥4x per year lasting >1 day AND risk factors for persistent asthma	≥2/year		Generally, more frequent and intense events indicate greater severity.			Generally, more frequent and intense events indicate greater severity.		
		Consider severity and interval since last asthma exacerbation. Frequency and severity may fluctuate over time for patients in any severity category. Relative annual risk of exacerbations may be related to FEV_1.*											

Figure 3: Level of severity of asthma.[1] (reference EPR 3: Guidelines for the Diagnosis and Management of Asthma)

4.0 Causes/Risk Factors[1, 2]

The risk factors for developing asthma are a combination of genetic predisposition with environmental exposure to inhaled substances and particles that may provoke allergic

reactions or irritate the airways. Asthma symptoms may be due to liberation of endogenous and intrinsic mediators like histamine, leukotrienes, bradykinin, prostaglandins, nitric oxide, platelet activating factors, chemokines and endothelin from mast cells during the allergic reactions and inflammation of the air passages in the lungs. It is also known that asthma can be triggered by various infections, dust, cold or warm air, exercise, emotion, perfumes, chemicals, various foods, tobacco smoke, genetics and histamine. Other triggers can include cold air, extreme emotional arousal such as anger, fear, and physical exercise. Even certain medications can trigger asthma: aspirin and other non-steroid anti-inflammatory drugs, and beta-blockers. It is reported that urbanization has been associated with an increase in asthma[3], But the exact relationship is unclear.

Genetics

The role of genetics involved in the eventual development of asthma is complex. The complexity of genes involvement in clinical asthma is noted by linkages to certain phenotypic characteristics, but not necessarily the pathophysiologic disease process.

Obesity

Asthma is more frequently observed in obese subjects.

(BMI>30kg/m^2) and is more difficult to control. Obese people with asthma have lower lung function and more co-morbidity compared with normal weight people with asthma.

Sex

In early life, the prevalence of asthma is nearly twice as great in boys as in girls. At puberty, however, the sex ratio shifts, and asthma appears predominantly in women. The exact relationship is not clear.

Environmental Factors

Two major environmental factors are most important in the development, persistence, and possibly severity of asthma: airborne allergens and viral respiratory infections. Both have a major influence on asthma development and its persistence. Allergen exposure, allergic sensitization, and respiratory infections function interactively in the eventual development of asthma.

Allergens

Allergens are classified as Indoor allergens like Domestic mites, furred animals (dogs, cats, mice), cockroach, fungi, molds, yeasts. Children under age 5 and women are more vulnerable

population and Outdoor allergens like Pollens, fungi, molds, and yeasts. Sensitization and exposure to house-dust mite and *Alternaria* are important factors in the development of asthma in children. Animal dander, particularly dog and cat, were associated with the development of asthma. Recent data suggest dog and cat exposure in early life may actually protect against the development of asthma. The determinant of these outcomes has not been well-known. House-dust mite and cockroach exposure study have revealed that prevalence of sensitization and subsequent development of asthma are linked. Allergen exposure can promote the persistence of airway inflammation and likelihood of an exacerbation.

Respiratory infections

Numeral respiratory viruses have been associated with the inception or development of the asthma during childhood. Respiratory syncytial virus (RSV) and parainfluenza virus in particular, cause bronchitis in early life. This wheezing or asthma is observed in later childhood in around 40 percent children. Symptomatic rhinovirus infections in early life also are emerging as risk factors for recurrent wheezing.

The exposure to infections early in life influences the development of a child's immune system along a "nonallergic" pathway, leading to a reduced risk of asthma and other allergic diseases. The influence of viral respiratory infections on the development of asthma may depend on an interaction with atopy. The atopic state can influence the lower airway response to viral infections and viral infections may then influence the development of allergic sensitization. The airway interactions may occur when individuals are exposed simultaneously to both allergens and viruses.

Occupational sensitizers

More than 300 substances have been associated with occupational asthma. These substances include highly reactive small molecules like isocyanates, irritants, and known immunogens like metal salts, and animal biological products that stimulate the production of IgE. High risk occupations include farming and agricultural work, cleaning work, painting (including spray painting), and plastic manufacturing.

Tobacco smoke

Tobacco smoking is associated with accelerated decline of lung function, increases asthma severity, may render patients less responsive to treatment with glucocorticoids, and reduces the likelihood of asthma being controlled.

Outdoor/indoor air pollution

Asthma exacerbations have been shown to occur in relationship to increased levels of air pollution, which in turn related to general increase in the level of pollutants or to specific allergens to which individuals are sensitized. Similar association have been observed in relation to indoor pollutants e.g. smoke and fumes from gas and biomass fuels used for heating and cooling, molds, and cockroach infestations.

Diet

The role breast feeding in relation to the development of asthma has been studied in detail and the data reveal that infants fed with intact cow's milk or soy protein have a higher incidence of wheezing illness in early childhood, compared with those fed breast milk.

5.0 Asthma Management[1]

5.1 The four components of asthma management suggested in EPR 3

1. Measures of assessment and monitoring, to diagnose and assess, characteristics and severity of asthma and to monitor whether asthma control is achieved and maintained.
2. Education for patients corporation in asthma care.
3. Control of environmental factors and comorbid conditions that affect asthma.
4. Pharmacologic therapy.

5.2 Asthma Therapy[2]

Medications for asthma are categorized into two general classes: quick-relief medications (relievers) and long-term control medications (controllers). Relivers are the quick-acting bronchodilators used only on demand to relieve acute intercurrent asthma symptoms and exacerbations, at the minimum required dose and frequency. Relievers are best represented by the inhaled short-acting b2-agonists. Controllers are used to achieve and maintain control of persistent asthma includes anti-inflammatory medications, such as glucocorticosteroids, mast cell stabilisers like nedocromil, cromoglycate and leukotriene modifiers. These agents are generally taken regularly to control asthma and prevent exacerbations. Inhaled glucocorticosteroids are the most effective agents in this category. The controller group also includes combination therapy containing bronchodilators that are taken regularly in addition to inhaled glucocorticosteroids to help attain and maintain asthma control.

5.3 Medications for asthma management with their key benefits and therapeutic issues.

(Table 1)

Table 1: Medications for asthma management with their key benefits and therapeutic issues[1, 11, 102, 103]

Category	Mechanism	Key benefits	Adverse effects	Therapeutic issues
A. Long-term control medications				
1. Corticosteroids- **a) Glucocorticosteroids (for inhalation)** Triamcinolone acetonide, Budesonide, flunisolide, Beclomethasone dipropionate, and Fluticasone propionate, New ICS products Ciclesonide and Mometasone furoate	Glucocorticosteroids downregulates the production of many inflammatory cytokines, chemokines, enzymes, and cell-adhesion molecules as well as inhibiting the activity of inflammatory mediators.	Evidence from bronchial biopsies and bronchoalveolar lavage has confirmed that correct use of corticosteroids can reduce cellular infiltrates and inflammatory proteins. Proper use of ICS results in better lung function with fewer disease exacerbations and hospitalizations that are associated with a better quality of life. Inhaled corticosteroids (ICS) are considered	Incidence of systemic side effects. Currently available ICS products have limitations for long-term use that include both local and systemic side effects. Local effects include oral candidiasis and hoarseness, whereas systemic effects include cortisol suppression, steroid-induced osteoporosis, slower growth in children, and adverse ocular and dermal effects.	• Spacer/holding chamber devices with non breathactivated MDIs and mouth washing after inhalation decrease local side effects. • Preparations are not absolutely interchangeable on mcg or per puff basis. • New delivery devices may provide greater delivery to airways; this change may affect dose. • The risk of uncontrolled asthma should be weighed against the limited risks of ICS therapy. The potential but small risk of adverse events is well balanced by their efficacy. • "Adjustable dose" approach to treatment may enable reduction in cumulative dose of ICS treatment over
Category	**Mechanism**	**Key benefits**	**Adverse effects**	**Therapeutic issues**
		the first-line therapy in treating asthma and are approved for chronic use in children as young as 12 months of age.		time without sacrificing maintenance of asthma control.
b) Systemic glucocorticosteroids Prednisolone, Methyl prednisolone	Block late reaction to allergen and reduce airway hyperresponsiveness.	Cough, dysphonia, oral thrush (candidiasis). In high doses, systemic effects may occur,	Long-term use: adrenal axis suppression, growth suppression, dermal thinning,	Use at lowest effective dose. For long-term use, alternate-day a.m. dosing produces the least toxicity. If daily doses are required, one study shows improve

	Inhibit cytokine production, adhesion protein activation, and inflammatory cell migration and activation. Reverse beta2-receptor downregulation. Inhibit microvascular leakage.	although studies are not conclusive, and clinical significance of these effects has not been established (e.g., adrenal suppression, osteoporosis). In low-to-medium doses, suppression of growth velocity has been observed in children,	hypertension, diabetes, Cushing's syndrome, cataracts, muscle weakness, and—in rare instances impaired immune function. -Consideration should be given to coexisting condition that could be worsened by systemic corticosteroids, such as	efficacy with no increase in adrenal suppression when administered at 3 p.m. rather than in the morning.
Category	**Mechanism**	**Key benefits**	**Adverse effects**	**Therapeutic issues**
		but this effect may be transient, and the clinical significance has not been established.	herpes virus infections, tuberculosis, peptic ulcer, hypertension, diabetes mellitus etc.	
2. Mast cell stabilisers Cromolyn sodium and nedocromil sodium	The precise mode of action of has not been completely elucidated. Because the drugs do not pass the cell membrane and enter the cell, they are virtually not metabolized, do not exert a systemic action. Mast cell stabilizers act on mast cells and prevent them from releasing substances that cause allergic reactions. They block a calcium channel that is important for	Prevent airways from swelling when they come in contact with an asthma trigger. These nonsteroids can also be used to prevent asthma caused by exercise.	Cough and irritation. 15–20 percent of patients complain of an unpleasant taste from nedocromil.	Therapeutic response to cromolyn and nedocromil often occurs within 2 weeks, but a 4- to 6-week trial may be needed to determine maximum benefit. Dose of cromolyn by MDI (1 mg/puff) may be inadequate to affect airway hyperresponsiveness. Nebulizer delivery (20 mg/ampule) may be preferred for some patients. Safety is the primary advantage of these agents. May take upto 6 weeks to achieve therapeutic effects. Frequent daily dosing is required.

Category	Mechanism	Key benefits	Adverse effects	Therapeutic issues
	degranulation (which occurs after exposure to specific antigens) of sensitized mast cells, and inhibits the release of histamine and slow-reacting substances of anaphylaxis. Inhibits acute response to exercise, cold dry air, and SO2.			
3. Immunomodulator Monoclonal anti IgE antibody Omalizumab	Binds to circulating IgE, preventing it from binding to high-affinity IgE receptor, (also known as FcεRIs), on basophils and mast cells. Decreases mast cell mediator release from allergen exposure,	Approved for treating moderate to severe per-sistent asthma related to allergies in patients whose symptoms are not controlled with ICS	Anaphylaxis, an allergic reaction that may include trouble breathing, chest tightness, dizziness, fainting, itching and hives, and swelling of the mouth and throat.	Monitor patients following injection. Be prepared and equipped to identify and treat anaphylaxis that may occur. The dose is administered either every 2 or 4 weeks and is dependent on the patient's body weight and IgE level before therapy. A maximum of 150 mg can be administered in one injection.
Category	**Mechanism**	**Key benefits**	**Adverse effects**	**Therapeutic issues**
	decreases the number of FcεRIs in basophils and submucosal cells.			Needs to be stored under refrigeration at 2–8 °C. Whether patients will develop significant antibody titers to drug, with long-term administration is unknown.
4. Leukotriene modifiers: **a) Leukotriene biosynthesis inhibitor/ 5-Lipoxygenase**	Inhibits the production of leukotrienes from arachidonic acid, both LTB4 and the cysteinyl leukotrienes**.**	Approved for allergies or allergic rhinitis, EIB	Elevation of liver enzymes has been reported. Limited case reports of reversible hepatitis and	Zileuton is microsomal P450 enzyme inhibitor that can inhibit the metabolism of warfarin and theophylline. Doses of these drugs should be monitored accordingly.

inhibitor -Zileutine			hyperbilirubinemia.	Monitor hepatic enzymes (ALT).
b) Leukotriene receptor antagonist Monteleukast, Zafirlukast (Pranlukast)	Selective competitive inhibitor of CysLT1 receptor.	Approved for allergies or allergic rhinitis, EIB	No specific adverse effects have been identified. Rare cases of Churgstrauss have occurred, but the association is unclear.	May attenuate EIB in some patients, but less effective than ICS therapy. Montelukast granules- A flat dose-response curve without further benefit, if dose is increased above those recommended. Zafirlukast- Administration with meals decreases bioavailability; take at least 1 hour before or 2 hours after meals.
Category	**Mechanism**	**Key benefits**	**Adverse effects**	**Therapeutic issues**
				Zafirlukast is a microsomal P450 enzyme inhibitor that can inhibit the metabolism of warfarin. INRs should be monitored during coadministration. Patients should be warned to discontinue use if they experience signs and symptoms of liver dysfunction (right upper quadrant pain, pruritis, lethargy, jaundice), and patients' ALTs should be monitored.
5. Bronchodilators Long acting b agonists (LABAs): **a) Inhaled:** Salmeterol, formoterol, Carmoterol Indacaterol	Bronchodilation. Smooth muscle relaxation following adenylate cyclase activation and increase in cyclic AMP, producing functional antagonism of bronchoconstriction. Compared to SABA, salmeterol (but not	To reduce the dose frequency to the minimum necessary to maintain asthma control	A diminished bronchoprotective effect may occur within 1 week of chronic therapy. Clinical significance has not been established. Potential risk of uncommon, severe, life threatening	Not to be used to treat acute symptoms or exacerbations. Should not be used as monotherapy for long-term control of asthma or as anti-inflammatory therapy. May provide more effective symptom control when added to standard doses of ICS compared to increasing the ICS dosage

Category	Mechanism	Key benefits	Adverse effects	Therapeutic issues
	formoterol) has slower onset of action (15–30 minutes). Both salmeterol and formoterol have longer duration (>12 hours) compared to SABA. Tachycardia, skeletal muscle tremor, hypokalemia, prolongation of QTc interval in overdose.		or fatal exacerbation; see text for additional discussion regarding safety of LABAs.	Clinical significance of potentially developing tolerance is uncertain, because studies show symptom control and bronchodilation are maintained. Decreased duration of protection against EIB may occur with regular use.
Tiotropium bromide	Tiotropium is a muscarinic receptor antagonist, often referred to as an antimuscarinic or anticholinergic agent. Although it does not display selectivity for specific muscarinic.	Management of chronic obstructive pulmonary disease (COPD).	severe sudden worsening of breathing problems	May cause paradoxical bronchospasm. Used with caution in patients with severe hypersensitivity to milk proteins. Bronchodilation following inhalation of tiotropium is predominantly a site-specific effect
Category	**Mechanism**	**Key benefits**	**Adverse effects**	**Therapeutic issues**
	receptors, on topical application it acts mainly on M3 muscarinic receptors located in the airways to produce smooth muscle relaxation, thus producing a bronchodilatory effect			
b) Oral:	Salbutamol is a ß2	Prevention and relief of	Tremor, Tachycardia,	Inhaled route is preferred because

Salbutamol	adrenergic agonist and thus it stimulates ß2adrenergic receptors. Binding of Salbutamol to ß2 receptors in the lungs results in relaxation of bronchial smooth muscles.	bronchospasm in patients 4 years of age and older with reversible obstructive airway disease, and for the prevention of exercise induced bronchospasm in patients 4 years of age and older.	nausea in children	LABAs are longer acting and have fewer side effects than oral sustained release agents. Oral agents have not been adequately studied as adjunctive therapy with ICS.

Category	Mechanism	Key benefits	Adverse effects	Therapeutic issues
Methylxanthines-oral-Theophylline, Dyphylline	Bronchodilation. Smooth muscle relaxation from phosphodiesterase inhibition and possibly adenosine antagonism. May affect eosinophilic infiltration into bronchial mucosa as well as decreases T-lymphocyte numbers in epithelium. Increases diaphragm contractility and mucociliary clearance.	Treatment of nocturnal bronchospasm and airways hyperresponsiveness. Addition of theophylline to effective doses of beta-agonists and corticosteroids leads to further improvement in symptom control	Dose-related acute toxicities include tachycardia, nausea and vomiting, tachyarrhythmias (SVT), central nervous system stimulation, headache, seizures, hematemesis, hyperglycemia, and hypokalemia.	Maintain steady-state serum concentrations between 5 and 15 mcg/mL. Routine serum concentration monitoring is essential due to significant toxicities, narrow therapeutic range, and individual differences in metabolic clearance. Absorption and metabolism may be affected by numerous factors which can produce significant changes in steady-state serum theophylline concentrations. Patients should be told to discontinue if they experience toxicity. Not generally recommended for exacerbations. There is minimal evidence for added benefit to optimal doses of SABA. Serum concentration monitoring is mandatory.

B Quick-relief medications				
Category	**Mechanism**	**Key benefits**	**Adverse effects**	**Therapeutic issues**
1. Anticholinergics Ipratropium bromide	Bronchodilation. Competitive inhibition of muscarinic cholinergic receptors. Reduces intrinsic vagal tone of the airways. May block reflex bronchoconstriction secondary to irritants or to reflux esophagitis. May decrease mucous gland secretion.	Indicated for maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema.	Drying of mouth and respiratory secretions, increased wheezing in some individuals, blurred vision if sprayed in eyes. If used in the ED, produces less cardiac stimulation than SABAs.	• Reverses only cholinergically mediated bronchospasm; does not modify reaction to antigen. Does not block EIB. • Multiple doses of ipratropium in the ED provide additive effects to SABA. • May be alternative for patients who do not tolerate SABA. • Treatment of choice for bronchospasm due to beta-blocker medication. • Has not proven to be efficacious as long-term control therapy for asthma.
2. Short acting b agonist (SABAs) Salbutamol(Albuterol),levalbuterol, pirbuterol, metaproterenol, Terbutaline, Bitolterol Fenoterol	Bronchodilation. Binds to beta2-adrenergic receptor, producing smooth muscle relaxation following adenylate cyclase activation and increase in cyclic AMP	Approved for symptomatic relief and prevention of bronchospasm due to bronchial asthma, chronic bronchitis, and other chronic	Tachycardia, skeletal muscle tremor, hypokalemia, increased lactic acid, headache, hyperglycemia. Inhaled route, in	• For acute bronchospasm these are the drugs of choice. Inhaled route has faster onset, fewer adverse effects, and is more effective than systemic routes. The less beta2-selective agents (isoproterenol, metaproterenol, isoetharine, and epinephrine) are not
Category	**Mechanism**	**Key benefits**	**Adverse effects**	**Therapeutic issues**
	producing functional antagonism of bronchoconstriction.	bronchopulmonary disorders such as COPD.	general, causes few systemic adverse effects. Patients with pre-existing cardiovascular disease, especially the elderly, may have adverse cardiovascular reactions with inhaled therapy.	recommended due to their potential for excessive cardiac stimulation, especially in high doses.Oral systemic beta2-agonists are not recommended. • Regular use >2 days/week for symptom control (not prevention of EIB), increasing use, or lack of expected effect indicates inadequate asthma control. • For patients frequently using SABA, anti-inflammatory medication should be

				initiated or intensified. › Levalbuterol at one-half the mcg dose produces clinically comparable bronchodilation and systemic side effects as racemic albuterol.
3. Systemic Glucocorticosteroids: Prednisolone, Methyl prednisolone,	Refer long term controllers	Used as short-term treatment for severe asthma episodes or as long-term therapy for	Short-term use: reversible abnormalities in glucosemetabolism,	› Short-term therapy should continue until patient's symptoms resolve. This usually requires 3–10 days but may require longer. Action may begin
Category	**Mechanism**	**Key benefits**	**Adverse effects**	**Therapeutic issues**
Hydrocortisone		some people with severe asthma.	increased appetite, fluid retention, weight gain, facial flushing, etc. Consideration should be given to coexisting conditions that could be worsened by systemic corticosteroids, such as herpes virus infections, tuberculosis etc.	within an hour. › There is no evidence that tapering the dose following improvement is useful in preventing a relapse in asthma exacerbations. › Other systemic corticosteroids such as hydrocortisone and dexamethasone given in equipotent daily doses are likely to be as effective as prednisolone.

5.4 Long term Asthma management[1,2]

Long-term, regular follow-up care to maintain asthma control focuses on two domains (Figure 4).

Achieving and maintaining asthma control requires providing appropriate medication, helping patients learn self-management skills, and long term monitoring to assess control and adjust therapy accordingly.

Reduce Impairment	Reduce Risk
Prevent chronic symptoms. Require infrequent use of short-acting beta2-agonist (SABA). Maintain (near) normal lung function and normal activity levels.	Control the likelihood of future asthma attacks Prevent exacerbations. Minimize need for emergency care, hospitalization. Prevent loss of lung function (or, for children, prevent reduced lung growth). Minimize adverse effects of therapy.

Stepwise approach for managing asthma long term[1]

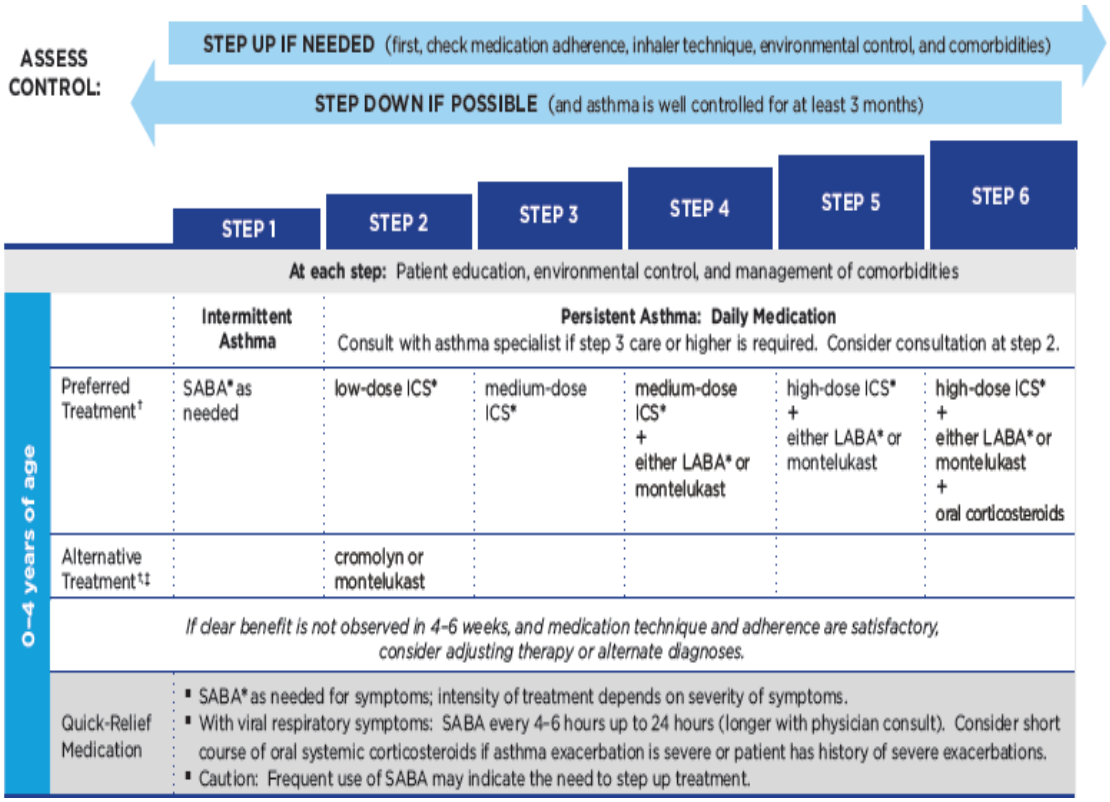

Figure: 4 Components for maintenance of asthma control.

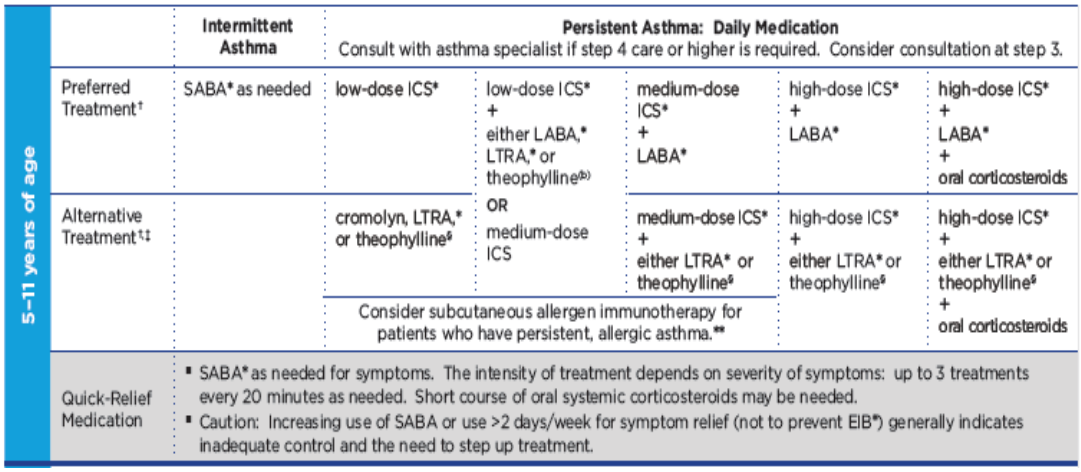

Figure 5 Stepwise approach for managing asthma long term[1] (reference EPR3)

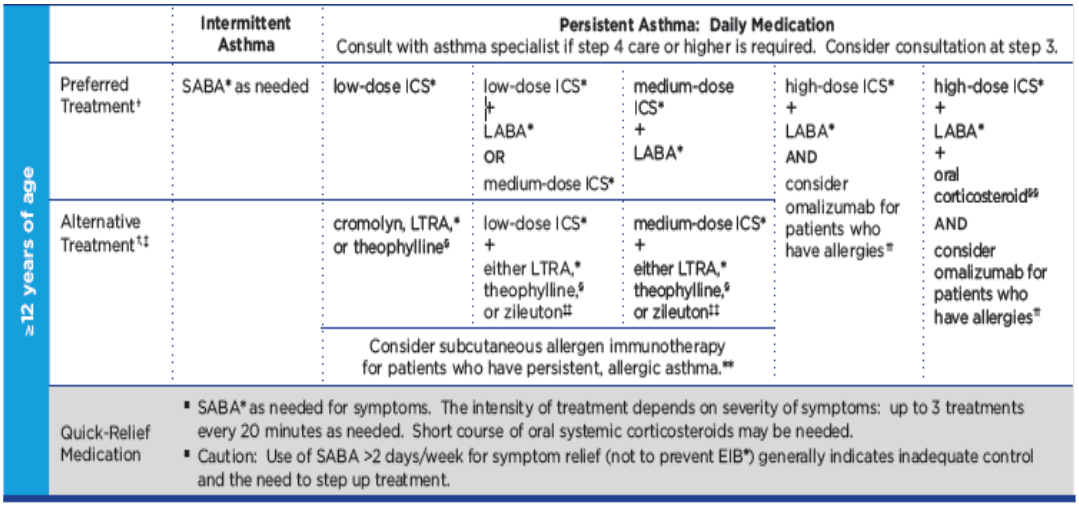

Figure 6: Inhalation devices for children (reference EPR 3)

§ Theophylline is a less desirable alternative as associated with serum concentration level monitoring.

†† Immunotherapy or omalizumab therapy is associated with anaphylaxis.

‡‡ Zileuton is less desirable because of the need to monitor liver function.

§§ Before oral corticosteroids are introduced, an assessment of high-dose ICS + LABA + either LTRA, theophylline, or zileuton, may possibly be considered.

5.4 Management of Asthma Excerbations[1, 2]

Acute or subacute episodes of progressively worsening shortness of breath, cough, wheezing, and chest tightness or a few combination of these symptoms leads to asthma exacerbations. Exacerbations are characterized by decrease in expiratory airflow that can be quantified by measurement of lung function (spirometry or PEF).

1 Management of asthma exacerbations requiring urgent medical care (e.g., in the urgent care setting or emergency department (ED) includes:

2. Oxygen supplement to relieve hypoxemia.
3. SABA to relieve airflow obstruction, with addition of inhaled ipratropium bromide in severe exacerbations.
4. Systemic corticosteroids to decrease airway inflammation in moderate or severe exacerbations or for patients who fail to respond promptly and completely to a SABA. Consideration of adjunct treatments, such as intravenous magnesium sulfate or heliox, in severe exacerbations unresponsive to the initial treatments listed above.
5. Monitoring response to therapy with serial measurements of lung function.
6. Preventing relapse of the exacerbation or recurrence of another exacerbation by providing: referral to followup asthma care within 1–4 weeks; an ED asthma discharge plan with instructions for medications prescribed at discharge and for increasing medications or seeking medical care if asthma worsens; review of inhaler techniques whenever possible; and consideration of initiating inhaled corticosteroids (ICSs).

For the treatment of exacerbations, the current update (EPR 3)

1. Adds levalbuterol as a SABA treatment for asthma exacerbations.
2. For home management of exacerbations, no longer recommends doubling the dose of ICSs.
3. For prehospital management (e.g., emergency transport), encourages standing orders for albuterol and—for prolonged transport—repeated treatments and protocols to allow consideration of ipratropium and oral corticosteroids.
4. For ED management, reduces dose and frequency of administration of oral corticosteroids in severe exacerbations, adds consideration of magnesium sulfate or heliox for severe exacerbations, and adds consideration of initiating an ICS upon discharge.
5. For hospital management, no longer recommends ipratropium bromide.

The Cochrane database review on Corticosteroids for acute severe asthma in hospitalised patients found that, lower doses of corticosteroids work as well, as higher doses, to start with, when a person is hospitalised with an asthma attack.

5.5 Asthma management in special considerations

Asthma patients require special consideration in some situations, to manage their asthma and to keep it under control. These special situations include.

5.5.1 Excercise induced bronchospasm[1, 11]

Exercise-induced bronchoconstriction (EIB) describes acute airway narrowing that occurs as a result of exercise. Exercise indicates asthma symptoms for some patients. EIB is a bronchospastic event that is caused by a loss of heat, water, or both from the lung during exercise because of hyperventilation of air that is cooler and dryer than that of the respiratory tree. These patients should be monitored regularly to ensure that they have no symptoms of asthma or to ensure that there is reduction in Peak Expiratory Flow (PEF) in the absence of exercise, because EIB is often a marker of inadequate asthma management and responds well to regular anti-inflammatory therapy.

Management strategies

- **Long-term control therapy**

Appropriate long-term control of asthma with anti-inflammatory medication reduces airway responsiveness, and this is associated with a reduction in the rate and severity of EIB.

- **Pretreatment before exercise with inhaled beta2-agonists**

1. **SABA** administration, 15 min before exercise may be helpful for 2–3 hours.
2. A controller agent is generally added whenever SABA therapy is used frequently.
3. For patients who have symptoms despite using an inhaled SABA before exercise, or who require frequent SABA administration inhaled long acting b2-agonist as single therapy is strictly prohibited.
4. Monitor treatment with Inhaled corticosteroid (ICS).
5. **LABAs** can be effective up to 12 hours

   LTRAs can attenuate EIB in up to 50 percent of patients

   Cromolyn or nedocromil taken shortly before exercise is an alternative treatment to prevent EIB, but it is not as effective as SABAs

   A warmup period before exercise may reduce the degree of EIB

   A mask or scarf over the mouth may attenuate cold-induced EIB

5.5.2 Pregnancy[1, 12]

Maternal asthma increases the risk of perinatal mortality, preeclampsia, preterm birth, and low-birth-weight. Monitoring asthma management Long-Term during pregnancy may be required to maintain lung function and, hence, blood oxygenation that ensures oxygen supply to the fetus and prevents asthma exacerbations.

Management strategies

1. Monitoring of asthma status during prenatal visits is encouraged. Albuterol is the preferred SABA because it has an excellent safety profile.
2. ICSs are the preferred treatment for long-term control medication. Budesonide is the preferred ICS than other available ICSs.
3. For the treatment of comorbid conditions, intranasal corticosteroids are recommended for treatment of allergic rhinitis because of their low risk of systemic effect.
4. Alternative daily medications are leukotriene receptor antagonists, cromolyn, or theophylline.

5.5.3 Surgery[1]

Patients who have asthma are at risk for specific complications during surgery.

Management strategies

1. Patients who have asthma should have an assessment before surgery for review of symptoms, medication use (particularly for Long Term use of oral systemic corticosteroids), and measurement of pulmonary function.
2. Attempts should be made to improve lung function preoperatively (FEV1 or peak expiratory flow rate [PEFR]).

5.6 Inhaler devices used for drug delivery

The mainstay of treatment is by inhalation of medication to the site of the infection. This can be achieved by a number of different types of device. A number of different inhalation devices are available. The pressurised metered-dose inhaler (pMDI) is commonly used device, which may be used along with a spacer device. Chlorofluorocarbons (CFC)-free inhaler devices using hydrofluoroalkanes (HFAs) have been developed and contains drug dissolved or suspended in the propellant under pressure. When activated, a valve system releases a metered volume of drug. Other devices include breath-actuated pMDIs (BA-pMDI), such as Autohaler and Easi-Breathe. They incorporate a mechanism activated during inhalation that triggers the metered-dose inhaler. Dry powder inhalers (DPI), such as Turbohaler, Diskhaler, Accuhaler and Rotahaler, are activated by inspiration by the patient. The powdered drug is dispersed into particles by the inspiration. With nebulisers oxygen, compressed air, or ultrasonic power is used to break up solutions or suspensions of medication into droplets for inhalation.

For young children or infants or those who are unable to cooperate to routine delivery of drug, can use spacer and valve holding chamber and have someone else actuate the device without loss of the actuated dose, to breathe normally and preventing the need for coordinating actuation. “Spacer” refers to simple open tubes that are placed on the mouthpiece of an MDI to extend it away from the mouth of the patient. Valved holding chambers, (VHCs) are manufactured devices that have one-way valves that do not allow the patient to exhale into the device. Both spacers and VHCs are intended to retain large particles emitted from the MDI.

Children Age (yr)	Preferred device	Alternative device
< 4	pMDI plus dedicated spacer with face mask	Nebulizer with face mask
4-6	pMDI plus dedicated spacer with mouthpiece	Nebulizer with mouthpiece
>6	DPI, or breath actuated pMDI or pMDI with spacer and mouthpiece	Nebulizer with mouthpiece

5.7 Combination therapy for management of asthma.

ICS/LABA combination therapy

Inhaled steroids plus leukotriene-receptor antagonists

Leukotriene-receptor antagonist plus antihistamines

5.7.1 ICS/LABA combination therapy

The ICSs are considered the most effective anti-inflammatory treatment for control of persistent asthma, and inhaled β2-adrenergic agonists are the most effective bronchodilators. A Cochrane database systemic review of 30 randomised, controlled studies demonstrated that the addition of a LABA to ICS therapy was more effective than higher dose ICS monotherapy in preventing treatment discontinuation because of deteriorating asthma control in patients with primarily moderate disease. (Refer Table 7).

Table 2: Pharmacokinetic properties of antiasthamatic drugs and their marketed preparations [103, 104, 105].

Category/ Drug	Absorption window	Half life (hr)	Bioavailability (%)	Dosage form available in market	Common marketed preparation / dosage form	Available in dose	Labelled uses	Mfg by
Triamcinolone acetonide	GIT	88 min	22-25%	Inhalation aerosol, injection, Suspension for injection	Inhalation aerosol			Abbott laboratory (Phased out by fda in 2010)
					Acort /Suspension for injection	10 mg*1ml/ 40mg*1ml	Prophylaxis and treatment of allergic rhinitis Allergic and inflammatory responses	Abbott laboratory
Flunisolide	Lung	1.8	4-4.5	Inhalation aerosol, injection, nasal spray	Inhalation aerosol			Forest laboratory (Phased out by fda in 2010)
Beclomethasone dipropionate	Nasal mucosa	0.5	1-4	MDI	Beclate / MDI	200 md (50/puff, 100, 200, 250/puff)	prophylaxis asthma	Cipla

Category/ Drug	Absorption window	Half life (hr)	Bioavailability (%)	Dosage form available in market	Common marketed preparation / dosage form	Available in dose	Labelled uses	Manufactured by
Fluticasone propionate	Nasal mucosa	15.1	<2	Nasal spray	FLONASE / nasal spray	120 md (50 mcg/actuation)		GlaxoSmithKline
Ciclesonide	Nasal mucosa	--	<1	MDI	CICLOHALE / MDI	120 md (80mcg/puff, 160mcg/puff)	maintenance treatment in persistent asthma	Cipla
Mometasone furoate	Lungs	5.8hr	--	Nasal spray	AQUAMET / Nasal spray	120md (0.5 % w/v/ puff)	maintenance treatment of asthma	Sun
2. Mast cell stabilisers								
Cromolyn sodium	Lungs	1.3	< 7	Inhalation aerosol Nasal spray, inhaler	Inhalation aerosol		Prophylaxis of asthma	King Pharma (Phased out by fda in 2010)
					IFIRAL / Nasal spray	20 mg x 10ml	AIRYFEN	JB chemicals
Kitotifen	Stomach	12	60	Tablet, syrup	Airyfen /Tablet	1 mg x 10's	Prophylaxis of asthma	Panacea

Category/ Drug	Absorption window	Half life (hr)	Bioavailability (%)	Dosage form available in market	Common marketed preparation / dosage form	Available in dose	Labelled uses	Manufactured by
Nedocromil sodium	Lungs	3.3	89	Inhalation aerosol	Inhalation aerosol	210 mg/puff	Moderate to severe persistent allergic asthma	King Pharma (Phased out by fda in 2010)

					Tilade / Mint Aerosol	60 *1s (2 mg/puff)	Preventive management of asthma.	Sanofi (singapur)
3. Immunomodulator Monoclonal anti IgE antibody Omalizumab	SC	26 days	62 (SC)	Sc injection	xolair /Lyophilized, sterile powder	Lyophilized, sterile powder 5ml vial, 150 mg	Moderate to severe persistent allergic asthma	Novartis
4. Leukotriene modifiers								
a) Leukotriene biosynthesis inhibitor Zileutine	GIT	2.5	---	Tablet	Zyflo /ER tablet	600 MG **(** 120's)	Prophylaxis and chronic treatment of asthma	Abbott laboratories

Category/ Drug	**Absorption window**	**Half life (hr)**	**Bioavailability (%)**	**Dosage form available in market**	**Common marketed preparation / dosage form**	**Available in dose**	**Labelled uses**	**Manufactured by**
b) Leukotriene receptor antagonist Monteleukast	stomach	3-6	60	Tablet, chewable Tablet	Montair /Tablet	4mg, 5mg, 10 mg	Chronic asthma; Allergic rhinitis Prophylaxis of exercise-induced asthma	cipla
					SINGULAIR/ Tablet	10 mg	Chronic asthma; Allergic rhinitis	MSD pharma pvt.ltd
					SINGULAIR / tablet	4 mg, 5 mg	Chronic asthma; Allergic rhinitis	MSD pharmaceuticals
Zafirlukast	stomach	8-12	--		ZUVAIR /Tablet	10 mg (10's)	Chronic asthma	Dr. Reddys laboratories
5. Bronchodilators								

a) Long acting β agonists (LABAs):								
Fluticasone propionate	Nasal mucosa	5.6	21	MDI	FLOHALE INHALER/ MDI	120md (25 mcg / puff, 50 mcg/puff, 125 mcg/puff)	Prophylaxis of asthma, Chronic severe asthma	Cipla
Category/ Drug	**Absorption window**	**Half life (hr)**	**Bioavailability (%)**	**Dosage form available in market**	**Common marketed preparation / dosage form**	**Available in dose**	**Labelled uses**	**Manufactured by**
Salmeterol xinafoate	--	5. 5	--	DPI	Serevent Diskhaler Disk, Servent Diskus/ DPI	50 mg/blister	Prevention of bronchospasm; prevention of exercise-induced bronchospasm; maintenance treatment of asthma	Glaxo smithkline Inc
Formoterol	GIT	10	---	MDI	DERIFORM/ MDI	120 md (12mcg/puff)	Acute ronchospasm; Reversible airways obstruction, Prevention of exercise-induced bronchospasm	Zydus Cadila (German Remedies)
Carmoterol		--	<5	NA	--	--	--	--
Indacaterol	Lungs	>30 hr	43-45 (inhalation)	NA	--	--	--	--
Category/ Drug	**Absorption window**	**Half life (hr)**	**Bioavailability (%)**	**Dosage form available in market**	**Common marketed preparation / dosage form**	**Available in dose**	**Labelled uses**	**Manufactured by**
Budesonide	GIT	2-4	10-20/IV	Respules	budate	0.5 mg x 2ml	Asthma, COPD	lupin

b) Methylxanthines-								
Theophylline	GIT	7-12	100/ IV	Tablet	PHYLOBID	200, 300 mg	Bronchospasm	Wockhardt
Dyphylline (diprophylline)	GIT	1.8-2.1	--	NA	--	--	Bronchodilator	--
Doxophylline	GIT	7 hr	--	Tablet	doxovent /Tablet	400 mg /800 mg SR	Reversible airways obstruction	Glenmark
B Quick-relief medications								
1. Anticholinergics Ipratropium bromide		-	-	MDI	IPRAVENT	20 mcg	Chronic obstructive pulmonary disease	Cipla
2. Short acting b agonist (SABAs)								
Salbutamol xinafoate	β2-adre-nergic receptor	4-6	50	inhalant	SERVENT	50 mcg*1S	Asthma, COPD	GSK
Levosalbutamol	β2-adre-nergic receptor	3-3.4	-	Inhaler	Levolin inhaler	200md (50 mcg/puff)	Asthma, COPD	Cipla

Category/ Drug	**Absorption window**	**Half life (hr)**	**Bioavai lability (%)**	**Dosage form available in market**	**Common marketed preparation / dosage form**	**Available in dose**	**Labelled uses**	**Manufactured by**
Pirbuterol	β2-adre-nergic receptor	2	-	Inhalation aerosol	Inhalation aerosol	--	--	Graceway Pharma (Phased out by fda in 2010)
Metaproterenol	β2-adre-nergic receptor	6	Inhalati on-3, Oral - 40	Inhalation aerosol	Inhalation aerosol	--	--	Boehringer Ingelheim Pharma (Phased out by fda in 2010)
Bitolterol	-	-	-	--	--	--	Discontinued	--
Fenoterol	-	-	-	NA	--	--	Discontinued	--
Bambuterol hydrochloride	GIT	13	20	Tablet	ASTHAFREE/ Tablet	10 mg*10s	long-term management of	Zuventus

							persistent asthma	
3. Systemic Glucocorticosteroids								
Hydrocortisone	GIT	6-8	--	Powder for injection	ACUCORT /Powder for injection	100 mg*1s, 200 mg*1s	Acute asthma Asthma excerbations	Macleods

Category/ Drug	**Absorption window**	**Half life (hr)**	**Bioavailability (%)**	**Dosage form available in market for asthma**	**Common marketed preparation / dosage form**	**Available in dose**	**Labelled uses**	**Manufactured by**
Prednisolone	GIT	2-3	70	Tablet,	OMNACORTIL /Dispersable tablet	(2.5mg, 5mg, 10, 20 mg, 30 mg)*10S	Anti-inflammatory	Macleods
Methyl prednisolone	GIT	18-28		Injection, tablet	MEDROL/ Tablet	4 mg, 8 mg /10 mg	Anti-inflammatory or immunosuppresive	pfizer
4.Tiotropium	Lungs	5-6	19.5 (Inhalation)	Handihaler	SPIRIVA HandiHaler /Capsules	18 mcg/cap	long-term treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema.	Pfizer
5. Orciprenaline sulphate / metaproterenol	GIT	6	40	Tablet	ALUPENT /Tablet	10 mg*10s	Bronchial asthma, chronic bronchitis	Zydus (G rem)

Table 3: Marketed ICS/LABA combination preparations[49]

Sr no	Category/ Drug	Common marketed preparation / dosage form	Available in dose	Labelled uses	Manufactured by
1	Beclometasone dipropionate , salbutamol sulphate	AEROVENT/ MDI	120 md (50 mcg /100 mcg)	Prophylaxis of asthma	Cipla (Omnicare)
2	Salbutamol choline theophyllinate	AIROMOL/ liquid	100 ml (2/100)	Bronchial asthma; Chronic bronchitis; Emphysema	Zydus (liva)
3	Salbutamol sulphate , budesonide	Budesal 1 mg /respules	(2.5mg/1 mg)/2.5 ml	Prophylaxis of asthma	Cipla
4	Formoterol fumarate dihydrate Mometasone furoate,	Evocort /Rotacap	400 mcg /6mcg 30 s (200 mg)	Maintenance treatment of asthma	cipla
5	Formoterol fumarate, budesonide.	QUIKHALE-FB / MDI	160 md (6 mcg/200 mcg)/puff	Asthma, COPD	Intas
		FORACORT/ rotacap	30'S (100 mcg/ 6 mcg)/puff	Asthma, COPD	Cipla
6	Formoterol fumarate, Ciclesonide	SIMPLYONE/ rotacap	100mcg/6 mcg	Obstructive airway diseases	Cipla
7	Formoterol fumarate dihydrate Fluticasone propionate,	MAXIFLO/ MDI	120 md(250 mcg/6 mcg)	Prophylaxis of asthma , COPD	Cipla
8	Formoterol fumarate, Tiotropium bromide	DUOVA INHALER/ MDI	120 md (9mcg/puff/ 12mcg/puff).	Acute bronchospasm; Reversible airways obstruction, Prevention of EIB	Cipla
9	Fluticasone propionate , salmeterol	SEROFLO-50 INHALER /MDI	(50 mcg/25 mcg)/puff	COPD	Cipla

10	Salmeterol, fluticasone propionate.	AIRTEC-SF/ MDI	150 md (25/250, 25 /125, 25 /50)	Asthma, COPD	Glenmark
		ADVAIR DISKUS	50/100, 50 /250, 50 /500	Chronic bronchitis, Maintenance treatment of asthma, COPD	Glaxo Smithkline Inc
		ADVAIR	25/ 50, 25 /125, 25 /250	Chronic bronchitis, Maintenance treatment of asthma, COPD	Glaxo Smithkline Inc
10	Salmeterol, fluticasone propionate.	AIRTEC-SF/ MDI	150 md (25/250, 25 /125, 25/50)	Asthma, COPD	Glenmark (Respiratory)
		ADVAIR DISKUS	50/100, 50/250, 50/500	Chronic bronchitis, asthma, COPD	Glaxo Smithkline Inc
Sr no	**Category/ Drug**	**Common marketed preparation / dosage form**	**Available in dose**	**Labelled uses**	**Manufactured by**
		ADVAIR	25/ 50, 25/125, 25/250	Chronic bronchitis, Maintenance treatment of asthma, COPD	Glaxo Smithkline Inc
11	Ipratropium bromide, levosalbutamol	IPRAZEST	500 mcg /1,25mg	Seasonal allergic rhinitis Rhinorrhoea associated with rhinitis COPD	Macleods
		DUOLIN/MDI	200md (50/20 mcg)/ puff	COPD	Cipla
12	Guaiphenesin, terbutaline, bromhexine	ASTHAKIND TAB /Tablet	10s	Acute and severe bronchospasm	Mankind
13	Salmeterol beclometasone				
B	**Inhaled steroids plus leukotriene-receptor antagonists**				
	Zileuton + Beclometasone				
	Montelukast + (ICS / ICS in combination)				
	Zafirlukast + (ICS / ICS in combi)				
C	**Leukotriene-receptor antagonist plus antihistamines**				
	Montelukast, citrizine				

	Zafirlukast, citrizine			

6.0 FINDINGS OF LITERATURE REVIEW-ASTHMA

Table 4: Findings of literature review

Sr no	Category/ Drug	Dosage form	Method/polymer used	Author	Published by & yr
A	**Long-term control medications**				
1.	**Corticosteroids-Glucocorticosteroids (for inhalation)**				
	Triamcinolone acetonide	Submicron emulsion[16]	High pressure homogenization	Cuilian Peng et al	Asian Journal of Pharmaceutical Sciences 2010
		Bilayer buccal adhesive film[17]	Solvent casting method HPMC, shitosan, eudragit, ethyl cellulose	R. Bahri-Najafi et al	Research in pharmaceutical sciences, 2012
		Solid lipid nanoparticles (SLN)[18]	High shear homogenization and ultrasound method for SLN and direct compression	M. Kazemipour S. OrmoAz et al	Research in pharmaceutical sciences 2012
	Budesonide	Suspension, MDI[19]	Pressure filling method, HFA 134a (Zephex 134a)	Murthy Tegka et al	Asian Journal of Pharmaceutical Sciences 2011
		Suspension[20]	Hydrofluoroalkanes, HFA 134a, HFA 227	Nichakorn Sukasamea et al	Science Asia, 2011
		Liposomes[21]	Film hydration method, hydroxypropyl-B cyclodextrin	J. J. Parmar et al	Indian journal of pharmaceutical sciences 2010

Sr no	Category/ Drug	Dosage form	Method/polymer used	Author	Published by & yr
		Noval spray dried microparticles viz., pulmosols microspheres and porous particles[22]	Spray drying	Sonali Naikwade et al	Scientica Pharmaceutica Sci Pharm. 2009
		CFC free pMDI[23]	--	D. Gandertonn et al	Elsevier- Respiratory Medicine 2003
		DPI	Capsule for DPI	Marina Andrade-	Jornal Brasileiro de Pneumologia,

				Lima et al	2012
		Porous PLGA microparticles[25]	water-in-oil-in-water double emulsion method	Yu Jin Oh et al	Journal of controlled release 2011
		Transdermal drug delivery system[26]	Solvent casting on mercury substrate, Eudragit RL-100, Eudragit RS-100, PEG-400, Ethyl cellulose (14 cps), PVP (MW 40,000)	Updesh B. Lade et al	Scientific research, Pharmacology & Pharmacy, 2011,
	Flunisolide	Nil			
	Beclomethasone dipropionate	DPI and HFA based MDI[27]	DPI, MDI	Gopala Krishna Murthy Talasila et	Brazilian Journal of Pharmaceutical Sciences, 2013
Sr no	**Category/ Drug**	**Dosage form**	**Method/polymer used**	**Author**	**Published by & yr**
	Fluticasone propionate	DPI[28]	Nanoprecipitationmethod, Poloxamer	Raisuddin Ali et al	Journal of Microencapsulation, 2013:
		CFC free propellent driven MDI[29]	Pressure filling method	TEG Murthey et al	Journal of scientific and industrial research, 2010
	Ciclesonide	DPI[30]	Manual capsule filling machine	Kapileshwar Swain et al	Research Journal of Pharmaceutical, Biological and Chemical sciences, 2012
	Mometasone furoate	Nil			
2.	**Mast cell stabilisers**				
	Cromolyn sodium	DPI[31]	Abstract	Elbary AA et al	Arch Pharm Res. 2007
		Ethosomes for TDDDS[32]	Dispersion	R. Rakesh et al	J Pharm Bioallied Sci. 2012
		Liposomes[33]	Abstract	M S Nagarsenker et al	International Journal of Pharmaceutics 2003
	Nedocromil sodium	DPI[34]	Abstract	Martyn J. Clarke et al	Journal of Pharmaceutical Sciences 2001

Sr no	Category/ Drug	Dosage form	Method/polymer used	Author	Published by & yr
3.	**Immunomodulator**	Nil			
	Monoclonal anti IgE antibody Omalizumab				
4.	**Leukotriene modifiers**				
A	**Leukotriene biosynthesis inhibitor** Zileutine	Sustained-release multiparticulate formulations[35]	Extrusion/spheronization techniques	Yihong Qiu et al	International Journal of Pharmaceutics 1996
		Sustained-release hydrophilic matrix tablet[36]	Wet granulation	Yihong Qiu et al	Journal of Controlled Release 1997
		Liposomes[37]	Extrusion/spheronization techniques.	Pramod Gupta et al	International Journal of Pharmaceutics 1996
B	**Leukotriene receptor antagonist** Monteleukast	Mouth dissolving tablets[38]	Direct compression, croscarmellose sodium, crospovidone	Ajaykumar Patil et al	Research Journal of Pharmaceutical,Biological and Chemical Sciences 2011
		Chewable tablets[39]	Wet granulation ,MCC, HPC	Priyanka et al	Journal of Chemical and Pharmaceutical Sciences 2013

Sr no	Category/ Drug	Dosage form	Method/polymer used	Author	Published by & yr
		Solid lipid nanoparticles[40]	Hot homogenization, ultrasonication Compritol 888ATO	K Priyanka et al	J Young Pharm., 2012
		Chewable tablets using modified karaya gum[41]	WET granulation , Hydroxy Propyl Cellulose	K Shruthi et al	Pelagia Research Library Der Pharmacia Sinica, 2013
		Buccoadhesive Tablet[42]	Direct compression, HPMC , Sodium Carboxy Methyl Cellulose	Rahul saxena et al	Asian Journal of Pharmaceutical and Clinical Research 2011
		Tablet -Pulsatile	Compression coating technique,	Krishnaveni.G et	Int J Adv Pharm Genuine Res 2013

		Drug Delivery System[43]	xanthan gum	al	
		Fast Dissolving Tablets[44]	Direct compression, Crospovidone and Sodium starch glycolate	Kiran GB Kumar et al	Asian journal of biomedical and pharmaceutical sciences 2012
	Zafirlukast	Nil			
	Pranlukast	Nil			

Sr no	Category/ Drug	Dosage form	Method/polymer used	Author	Published by & yr
5. A	**Bronchodilators : Long acting b agonists (LABAs)**				
	Salmeterol Xinafoate	Microparticles[45]	Spray freeze drying (SFD) technique; hydroxy propyl beta cyclodextrin (HPβCD)	Mohammad Reza Rahmati et al	Advanced Powder Technology 2013
		Fast Dissolving Tablets[46]	Direct compression, Crospovidone	Shikhar Baboo et al	Pharma research library, 2013
		Dry Powder Formulation[47]	Spray drying of suspensions obtained by Antisolvent method/ Poloxamer 188.	Shah Vishal Vilas et al	International journal of pharmaceutical and chemical sciences, 2013
		Dry powder formulations.[48]	Microcrystallization, poly(ethylene glycol)	Darragh Murnane et al	Journal of Pharmaceutical Sciences 2009
		DPI [49]	Liquid anti-solvent precipitation method, HPMC	Nutan shah et al	Asian Journal of Pharmaceutical and Clinical Research 2011

Sr no	Category/ Drug	Dosage form	Method/polymer used	Author	Published by & yr
	Formoterol	HFA pMDI[50]	Introduction of active/excipients into pressure vessel, polyethylene glycol (0.05-2.5% w/w), PVP	D purohit et al	Indian J Pharm Sci. 2009
		EVA copolymer	N methyl 2 pyrrolidone	Kakubari i et al	Biol Pharm Bull. 2006

		matrix patches.[51]			
	Carmoterol	Nil			
	Indacaterol	Nil			
	Budesonide	Refer 1			
	Tiotropium bromide	Inhalation formulation[52]	O/W emulsion, Poly lactide co glycolide (PLGA)	Nam Muk oh et al	Journal of pharmaceutical investigation 2013
B	**Methylxanthines**				
	Theophylline	Time and pH dependent colon specific pulsatile delivery[53]	Abstract Capsule, Eudragit L-100 and S-100	V.S. Mastiholimath et al	International Journal of Pharmaceutics 2007
		Microspheres[54]	Abstract, Emulsion solvent evaporation, Ethyl cellulose	L Pachuau et al	Tropical journal of pharmaceutical research, 2008
		Transdermal Patches[55]	Abstract, HPMC	S. Narasimha Murthy et al	Drug development and industrial pharmacy, 2001
Sr no	**Category/ Drug**	**Dosage form**	**Method/polymer used**	**Author**	**Published by & yr**
		SR Tablet[56]	Wet granulation, HPMC, ethyl cellulose	Tetsuo Hayashi et al	International journal of pharmaceutics, 2005
		Microspheres[57]	Emulsion solvent evaporation, Eudragit S 100	Wasfy M. Obeidat et al	Journal of Microencapsulation, 2006
		SR Tablets [58]	Direct compression, HPMC, Xanthan gum	Sunita s shinde et al	Research journal of pharmacy and technology 2013
	Doxofylline	SR matrix tablet[59]	Wet granulation, HPMC k4M	Pandya Hima V. et al	International research journal of pharmacy, 2011
	Bamifylline	Nil			
	Etophylline	Nil			
	Enprophylline	Nil			
	Dyphylline	Nil			
B. Quick –relief medications					
1.	**Anticholinergics**	Hollow, spherical	Spray-drying	Taylor M K et al	Pharmceutical Development

	Ipratropium bromide	particles[60]			Technology. 2006
Sr no	**Category/ Drug**	**Dosage form**	**Method/polymer used**	**Author**	**Published by & yr**
2.	**Short acting ß agonist (SABAs)**				
	Salbutamol	DPI[61]	Liquid antisolvent precipitation method.	Bhavna et al	European Journal of Pharmaceutics and Biopharmaceutics, 2009
		Modified push–pull osmotic system[62]	Abstract, Oral osmotic pump, Hydrophilic polymers	D. Prabakaran et al	International journal of pharmaceutics, 2004
		Mucoadhesive Microspheres[63]	Abstract, Emulsion solvent method, Chitosan	S. K. Jain et al	Drug Delivery, 2004
		Transdermal delivery of salbutamol sulphate[64]	Abstract, Casting method, Eudragit	Nashwa A. El-Gendy et al	Pharmaceutical development and technology, 2009
		Mucoadhesive buccal patches[65]	Solvent casting method, Eudragit, HPMC Carbopol	Prasanth Viswanadhan Vasantha et al	Saudi pharmaceutical journal, 2011
		Microspheres[66]	Spray drying, chitosan	Dinal Patel et al	International Journal Pharmaceutical Sciences and Research, 2013.
	Levalbuterol	ODT[67]	Abstract, Direct compression	Hu Shujuan et al	Shanghai Medical & Pharmaceutical Journal 2007
		Mucoadhesive microspheres[68]	Spray drying method, Chitosan	D. Dinal Patel et al	J Pharm Bioallied Sciences; 2012
Sr no	**Category/ Drug**	**Dosage form**	**Method/polymer used**	**Author**	**Published by & yr**
	Pirbuterol	Nil			
	Metaproterenol	Nil			

	Terbutaline	Microspheres[69]	Solvent evaporation, PLGA (25/75) and L-PLA	Selek H et al	J Microencapsul. 2003
		Fast melting tablet[70]	Direct compression Croscarmellose Na, Crospovidone	Mathew Tet al	Research Journal of Chemical Sciences 2011
		Buccal patches[71]	Solvent casting method, HPMC E 50 carbopol 934	Peeyush singhal et al	International Journal of Research in Pharmaceutical Sciences 2010
		SR tablet [72]	Wet granulation, HPMC K15 and HPMC K4M	Rajeswari Kola et al	Indian Journal of Research in Pharmacy and Biotechnology; 2013
		Mucoadhesive SR tablets [73]	Wet granulatio	Ranabir Chandaa et al	Asian Journal of Pharmaceutical Sciences 2010
		Mucoadhesive buccal talets[74]	Direct compression, Sodium alginate	Gururaj s kulkarni et al	International research journal of pharmacy; 2013
		Buccoadhesive tablet[75]	Direct compression Carbopol 934P, Methocel K4M, Methocel K15M	Nakhat P D et al	Indian Journal of Pharmaceutical Sciences 2007
		Mouth dissolving tablets[76]	Direct Compression, Microcrystalline Cellulose	S. Dineshmohan et al	Der Pharmacia Lettre, 2014

Sr no	Category/ Drug	Dosage form	Method/polymer used	Author	Published by & yr
		Bilayer tablet [77]	Wet granulation, HPMC 5cps	Dr.N. G. Raghavendra rao, et al	Int J Pharm Bio Sci, 2012
		Mucoadhesive tablet [78]	wet granulation, Zizyphus mauritiana and Aegle marmelos HPMC K4M	Ranabir Chanda et al	Iranian journal of pharmaceutical sciences, 2009
		Delayerd release capsule[79]	Direct compression, polyethylene oxide (PEO) WSR N-10, N-80, N-750	Mahajan AN et al	Ars Pharmaceutica, 2010
		Mouth dissolving Drug delivery systems [80]	Wet granulation, gelatin	Debashrita Sahoo, et al.	Indian Journal of Pharmaceutical Science & Research, 2014
		Microsponge,	Oil solvent diffusion method,	Biswajit Basu et al	Pharmaceut Anal Acta, 2013, 4(2):87

		compression coated tablets [81]	HPMC K100M, Eudragit RS100		
		Transdermal Patches [82]	Sodium alginate, Chitosan, HPMC, HPMC-E5, HEC	Shobhraj Malvi et al	International Journal of Pharmaceutical Sciences, 2012
		DPI[83]	Emulsification and ionotropic gelation method, Chitosan	Deepak J Singh et al	International Journal of advances Pharmaceutical Sciences, 2010
Sr no	**Category/ Drug**	**Dosage form**	**Method/polymer used**	**Author**	**Published by & yr**
		Liposomes [84]	Lipid film mhydration technique	Mayank R Joshi et al	Indian journal of experimental biology, 1999
		Rapid release mouth disintegrating tablets [85]	Direct compression, T-314, indion 414, tulsion 339, crospovidone	S. Bhagat	International Journal of Research in Pharmacy and Chemistry; 2014
		Dry powder inhaler/Rotahaler[86]	Powder	JO Onyechi et al	Journal of Pharmaceutical and Allied Sciences, 2010
		Mucoadhesive Buccal Tablets [87]	Direct compression method. Carbapol 934P, chitosan, HPMC K4M and HPMC K15M	V. M. Vaidya et al	International Journal of Pharm Tech Research, 2009
		Pulsatile Drug Delivery System [88]	Direct Compression, EudragitS-100, EudragitL-100	Vaishali patil et al	American Journal of Advanced Drug Delivery 2013
		Fast dissolving sublingual films [89]	Maltodextrin, Na alginate, Carpabol 430, xanthan gum, HPMC E5, PVP K-25, and Na CMC	Soha Sayed et al	Molecular Pharmaceutics, 2013
		Fast Dissolving Tablet[90]	Direct compression, MCC	Sanjay Kumar Bhupathi et al	Research Journal of Pharmaceutical, Biological and Chemical Sciences, 2012
Sr no	**Category/ Drug**	**Dosage form**	**Method/polymer used**	**Author**	**Published by & yr**
		Fast Dissolving Tablet[91]	Direct compression, Explotab, Ac-Di-Sol and Polyplasdone XL	Rangasamy M et al	Asian J Pharm, 2009

		Sustained Release Matrix Tablets[92]	Wet granulation, HPMC K200M, Ethylcellulose	Mohd Abdul Hadi et al	Research Journal of Pharmaceutical Dosage Form and Technology, 2013
		Mucoadhesive buccal talets[93]	Direct compression, guar gum	Gururaj s kulkarni et al	Journalof pharmacy research 2013
		Sustained release microspheres[94]	Emulsion solvent evaporation process, Eudragit RSPM	Khattab I et al	Drug discoveries & therapeutics; 2009
	Bitolterol	Nil			
	Fenoterol	Nil			
3	**Systemic Glucocorticosteroids**				
	Hydrocortisone	Fast dissolving tablets[95]	Direct compression, crosspovidone, microcrystalline cellulose	Tank Nimit A et al	Res. Journal of Pharma, Biological and Chemical Sciences, 2011
	Prednisolone	Sustained-release matrix[96]	Polyvinyl chloride	P F Darcy et al	Journal of Pharmaceutical Sciences 2006
		Tablet -Colon targeted DDS [97]	Direct compression, Eudragit L100, Eudragit S 100	Chetan Singh Chauhan et al	Journal of Chemical and Pharmaceutical Research 2010
	Methyl prednisolone	Parenteral depot suspension[98]	Rapid stirring and colloid milling method, PEG 3350	Alam a et al	Indian J Pharm Sci. 2009

7.0 HERBAL THERAPY FOR ASTHMA

The traditional medicinal systems and the availability of a large variety of medicinal plants in universe have greatly facilitated the researchers to develop keen interest in their screening, research and development. Ayurveda offers comprehensive approach to management of asthma by proper concern of the respiratory tract. This includes maintaining the nourishing functions of the lungs in providing oxygen to the body. Ayurvedic formulations used in the management of asthma combine herbs for breathing support with antioxidant herbs to support digestive, cardiac and nerve functions, expectorant herbs as well as soothing herbs. Pulmonary tonic, expectorant, antispasmodic, demulcents, antimicrobials, and Nervine support herbs are the components normally included in the ayurvedic system for management of asthma. Refer table 5 for anti-asthmatic plants.

Table 5: Anti-asthmatic plants and their active principles[99, 101, 110]

Sr. No.	Plant /family	Parts used	Active principle	Pharmacological action/ indications	Marketed preparation
1	**Achyranthes aspera** (Amaranthaceae)	Roots	Flavonoids, alkaloids, saponins and triterpenoids	Asthma and COPD	ASTHA-15 capsules
2	**Aerva lanta Linn** (Amaranthaceae)	Roots /Leaves	Alkaloids	Bronchodilator, anti anaphylactic	NA
3	**Ageratum conyzoides** (Asteraceae)	Leaves	Tannins and flavonoids	Bronchodilator	NA
4	**Amburana cearensis** (Fabaceae)	Trunk bark or seed	Flavonoids isokaempferide	Bronchodilator	NA
5	**Argemone Mexicana** (Papaveraceae)	Seeds and seed oil	Alkaloids	Bronchial asthma	NA
6	**Asystasia gangetica** (Acanthaceae)	Leaves	Alkaloids, flavonoids, reducing sugars, and triterpenoids	Anti inflammatory, management of asthma	NA
Sr. No.	**Plant /family**	**Parts used**	**Active principle**	**Pharmacological action/ indications**	**Marketed preparation**
7	**Atropa belladonna** (Solanaceae)	Leaves	Alkaloids, atropine hyoscyamine, scopolamine	Asthma	NA
8	**Azadirachata indica** (Meliaceae)	Leaves	Tannins, alkaloids, phenols, flavonoids, glycosides	Bronchitis, bronchial asthma	NA
9	**Bacopa monnieri**	Leaves	Alkaloids brahmine,	Mast cell	BACUP

	L (Scrophulariaceae)		herpestatine	inhibitor, bronchitis	capsule (keshav HC)
10	**Boswellia serrata** (Burseraceae)	Roots	Boswellin, boswellic acids	Leukotriene biosynthesis inhibitor	NA
11	**Cassia sophera** (Caesalpiniaceae)	Leaves	Flavonoids.	Cough associated with COPD	KOFLET syrup
12	**Casuarina equisetifolia Linn** (Casuarinaceae)	Leaves, wood and bark	Alkaloids, phytosterols	Antihistamine	NA
13	**Clerodendrum Serratum Linn** (Verbenaceae)	Roots and leafs	Flavonoids	Bronchial asthma	KOFOL syrup (charak)
14	**Cnidium monnieri** (Umbelliferae)	Seeds and fruits	Osthole	Anti allergic, Asthma management	NA
15	**Crinum glaucum** (Amaryllidaceae)	Seeds	Alkaloids	Mast cell stabilizer	NA
16	**Curculigo orchioides Gaertn** (Amaryllidaceae)	Rhizomes	Flavanoids, tannins, glycosides, alkaloids saponnis	Mast cell stabilizer, bronchial asthma	NA
17	**Curcuma longa** (Zingiberaceae)	Roots	Curcumin, Curcuminoids	Mast Cell Stabilizers bronchial asthma, whooping cough	ASTHA-15 capsule (dalmia)
Sr. No.	**Plant /family**	**Parts used**	**Active principle**	**Pharmacological action/ indications**	**Marketed preparation**
18	**Cynodon dactylon** (Poaceae)	Doob	Alkaloids, flavanoids	Bronchitis, asthma	NA
19	**Eclipta alba Linn** (Asteraceae)	Leaves	Alkaloids, flavanoids	Bronchitis, asthma	NA
20	**Emblica officinalis** (Euphorbiaceae)	Leaves, fruits	Tannins, alkaloids, and phenolic compounds	Asthma, cough	NA
21	**Euphorbia hirta** (Euphorbiaceae)	aerial part	Sterols, alkaloids, tannins	Mast cell stabilizer	NA
22	**Ficus bengalensis Linn** (Moraceae)	Fruits	Alkaloids and flavonoids	Bronchodilator Asthma	NA
23	**Fumaria parviflora** (Fumariaceae)	Leaves	Kaempferol and quercetin glycosides.	Bronchitis	NA
24	**Gmelina arborea** Verbenaceae	Leaves	Alkaloids	Bronchitis	NA
25	**Hemidesmus indicus R.** (Asclepiadaceae)	Roots	Tannins, flavonoids, hyperoside, rutin and coumarino	Chronic bronchitis	NA
26	**Inula Racemosa** (Asteraceae)	Bark, roots	Alkaloids, Myrcenol, Nerol	Mast cell stabilizer	TUSIDAC PLUS

				bronchitis, asthma	syrup(zydus)
27	**Lepidium sativum Linn** (Cruciferae)	Roots	Alkaloids lepidine, glucotropaeolin anthracene glycosides	Hiccough asthma	NA
28	**Leptadenia reticulate** (Asclepiadaceae)	Leaves	Alkaloid and steroids	Asthma, Rhinitis	NA
29	**Liquorice** (Papilionaceae)	Leaves	Alkaloids	Bronchial asthma	Biocivas syr. (maximaa proyurveda)
Sr. No.	**Plant /family**	**Parts used**	**Active principle**	**Pharmacological action/ indications**	**Marketed preparation**
30	**Mentha spicata L** (Lamiaceae)	Leaves, roots	Phenols	Bronchitis	NA
31	**Mimosa pudica** (Fabaceae)	Whole plant	Alkaloid mimosine, glycoside, flavonoid and tannis.	Bronchitis	NA
32	**Momordica dioica** (Cucurbitaceae)	Fruits and leaves	Alkaloids, steroids, triterpenoids and saponins	Asthma	NA
33	**Mucuna pruriens** (Fabaceae)	Seeds, Roots	alkaloids	mast cell stabiliser, Bronchial Asthma	NA
34	**Myrica esculenta Buch. (**Myricaceae)	Bark	Phenol, tannin, flavonoid, saponin, and alkaloid	Bronchial asthma	NA
35	**Nyctanthes arbortristis** (Oleaceae)	Leaves	Alkaloid nyctanthin	Bronchodilator	NA
36	**Olea europea** (Oleaceae)	Whole plant	Glycosides, alkaloid s	Bronchial asthma	NA
36	**Ocimum sanctum L** Lamiaceae	leaves	Tannins, alkaloids, carbohydrates, phenols, flavonoids, glycosides	Bronchitis, Bronchial asthma	NA
37	**Phymatodes scolopendria** (Polypodiaceae)	Bronchod ilato	Alkaloids	Bronchodilator	NA
38	**Piper betel Linn** (Piperaceae)	Leaves	Essential oil, alkaloids	Bronchodilator	NA
39	**Pinus roxburghii** (Pinaceae)	Resin	Turpentine oil	Bronchitis	NA
40	**Plants from Zinziberaceae**	Rhizome	NA	Expectorant, asthma	NA
Sr. No.	**Plant /family**	**Parts used**	**Active principle**	**Pharmacological action/ indications**	**Marketed preparation**

41	**Premna obtusifolia** (Verbenaceae)	Roots	Flavanoids, diterpenes and alkaloids	Bronchitis	NA
42	**Semecarpus anacardium** (Anacardiaceae)	Fruit	Alkaloids, flavonoids and phenols	Bronchitis	NA
43	**Striga oroban-chioides Benth** (Scrophulariaceae)	Whole plant	Alkaloids	Mast cell stabilizing	NA
44	**Sphaeranthus indicus Kurz (**Asteraceae)	Whole plant	Glycoside, flavonoid, alkaloids, sterols	Bronchodilator	NA
45	**Swertia chirata** (Gentianaceae)	Whole plant	Xanthones, flavonoids,alkaloids	Bronchial asthma	NA
46	**Terminalia belerica** (Combretaceae)	Fruit	termilignan, thannilignan	Bronchodilator	HALEEZY Tablet/ syrup (Charak)
47	**Terminalia chebula** (Combretaceae)	Fruit	Chebulagic, chebulinic acid and corilagin	Antiallergic, Bronchodilator	KOFLET LOZ (Himalaya)
48	**Tephrosia purpurea** (Leguminosae)	Whole plant	Flavones, flavanones and phenylated flavonoids	Immunomodulato rs Bronchodilator	NA
49	**Trachyspermum ammi L** (Apiaceae)	Fruit	Essential oil, essential oil, with thymol, thymol	Bronchodilator	NA
50	*Vitex negundo*	Leaves	Alkaloids, flavonoids, tannins and a phenolic acid	Mast cell stabilizer, bronchodilator	NA

8.0 Review Of Guidelines/Reports

Table 6: Asthma guidelines/ Reports

Sr no	Title of doc	Authority	Current doc and yr of publication	Document history
1	Guidelines for diagnosis and management of asthma[1]	National Asthma Education and Prevention Program (NAEPP) National Heart, Lung, and Blood Institute	Expert panel report (EPR) 3, 2007	EPR 1-1991 EPR 2- 1997, EPR update 2002
2	Global strategy for asthma management and prevention[2]	Global initiative for asthma (GINA)	Global strategy for asthma management and prevention-2012	1995, 2002, 2006
3	Canadian asthma consensus report, 1999[9]	1999 Canadian Medical Association	Canadian asthma consensus	1999

			report, 1999	
4	British Guideline on the Management of Asthma[10]	British Thoracic Society	Revised may 2011	2003, 2008, 2009
5	An Official American Thoracic Society/European Respiratory Society Statement: Asthma Control and Exacerbations[7]	American Thoracic Society	American journal of respiratory and critical care medicine 2009	2009

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