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Review Article

Therapeutic Applications of Antiasthmatics, Consequences and Remedies

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Abstract

Multiple factors are involved in allergic diseases including asthma. The factors could be associated to the individual genetic background exposure to allergens, air pollutants, obesity, eosinophilia, and respiratory infections. The therapeutic medications to treat asthma include corticosteroids, cromolyn sodium and nedocromil, methylxanthines, leukotriene modifiers, and long-acting β2-adrenoreceptor agonists. The medications for quick relief of bronchoconstriction and acute asthmatic symptoms include short-acting β2- adrenoreceptor agonists, and anticholinergics. The β2-Adrenoceptor agonists evolved from the catecholamines from adrenal medulla and the corticosteroids from adrenal cortex have proved to be potential bronchodilators and most effective modulators of the bronchial inflammatory processes. In addition, several phytochemicals have been explored in past for their antiasthmatic properties. Some of them belong to saponins isolated from *Clerodendron serratum, Gardenia turgida, Albizzia lebbeck* and *Solanum xanthocarpum*. The phytochemicals obtained from these plants have been shown to render protection from allergic reactions including asthma. Though the existing therapies against asthma are relatively safer and more effective, still new drugs are needed to cure severe asthmatic patients as the current drugs fail to control the disease. Keeping in view the side effects induced by synthetic antiasthmatics and their inability to manage severe asthma, there is a need to develop safe, potential and cost effective antiasthmatic drugs to impart quick relief to the patients. Plant based principles in this context are believed to offer a potential solution to this challenging issue. This mini review presents an updated account of antiasthmatics in current therapeutic utility, their consequences and prospective remedies of the disease.

Keywords: *Asthma; Antiasthamtics; Factors; Side effects; Phytochemicals*

Background

Asthma is a common airway chronic inflammatory disorder in which many cells and cellular elements play a role. It is characterized by pulmonary dysfunction that is correlated with age, disease duration and severity [1]. According to an estimate, about 300 million people are suffering from Asthma globally with high rate of disability; out of it about 30 million people constitute from India [2-6] and the prevalence is ever on increase due to increasing pollution.

A cross-sectional observation analysis on the number of cases and the trends in asthma attacks in UK studied by Simpson and Sheikh [7] revealed increasing trends of asthma prevalence over the time. However, in general and especially in younger children a declining trend of disease has been observed [7]. The latest estimates show that the prevalence of asthma in the U.S. was 7.8 percent in 2017, in comparison to 7.6 percent in 2001. Asthma is known to affect people of all age groups including the elderly [5,8] and causes periodic "attacks" of shortness of breath, wheezing, cough, and chest tightness.

All age groups represent a growing clinical problem, within estimated prevalence between 6% and 14%. According to the World Health Organization (WHO, 2004), each year approximately 250,000 deaths are due to asthma [2]. Asthma is caused by various combinations of different factors such as (1) Environmental: allergens (e.g., house dust mites, animal fur and pollen), occupational irritants, tobacco, smoke, respiratory (viral) infections, strong emotional expressions and drugs (e.g. aspirin and beta blockers) and (2) Genetic

(inherited): usually occurs in children. The chances of developing asthma are increased if the patients' family members or relatives have asthma and other allergic conditions such as atopic dermatitis and hay fever.

Asthma exists as a chronic inflammatory disease worldwide albeit the extent of its prevalence and attack varies from one region to another depending upon the environmental and occupational factors. Some workers have reported the incidence of diagnosed asthma in many European countries to be varying in the range of 2.7-4%, England with 12% and US with 7.1% [9,10]. Peat., et al. [11] have indicated the prevalence of asthma in Australia by 9.5 to 17.9%. As against all these data regarding the prevalence of asthma in the different parts of the world, Tristan da Cunha exhibited about 56% of its population suffering from asthma, which might be genetically linked [2,12]. There is only limited data available on the asthma epidemiology from the developing world, including India. The overall burden of asthma in India is estimated at more than 15 million patients [2]. The mechanism of occurrence of asthma has been summarised in figure 1.

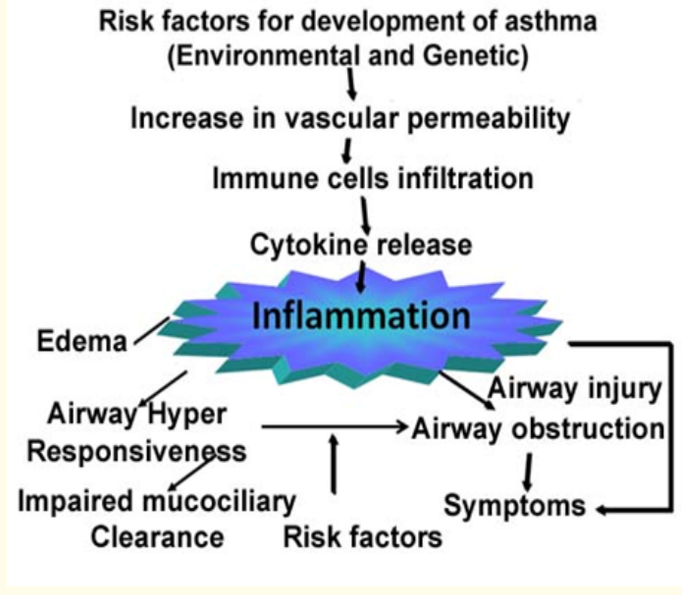

Figure 1: *The common mechanism of occurrence of asthma. Cascade of events are disolayed.*

The current therapeutic applications of many of the synthetic antiasthmatics have been found to be laced with the mild to severe side effects such as chronic trouble in sleeping, constipation, painful urination, dizziness dryness of mouth, aggressiveness, excessive sweating, accelerated heartbeat, anxiety, feeling faint, weakness, headache, hypertension, loss of appetite, skin de-pigmentation, depression, cramps in stomach, throat dryness etc. which may pose threat to the lives of the patients. Therefore, there is need to develop cost effective, safe and potential regimen to treat this disease. The chemicals derived from different plants have shown promises to offer a viable solution in these impediments of chemotherapy. The present review article deals with an updated account of asthma, factors associated to it, current drugs in practice and their side effects as well as the strategies to combat the disease.

Antiasthmatics in therapeutic applications

The medications for treatment of asthma are categorised into two groups: (1) The drugs used for quick relief from acute asthma. Quick-relief medications: they are used as needed for rapid, short-term symptom relief during an asthma attack. Types of quick-relief medications are: (a) Short-acting beta2 agonists: these inhaled, quick-relief bronchodilators act within minutes to rapidly ease symptoms during an asthma attack. Short-acting beta2 agonists can be taken using a portable, hand-held inhaler or a nebulizer. Examples are salbutamol and terbutaline. (b) Antimuscarinics: these inhaled antimuscarinics act quickly to immediately relax the airways, like other bronchodilators, making it easier to breathe. Examples are ipratropium and tiotropium. (c) Systemic corticosteroids: these systemic corticosteroids (i.e., oral and intravenous routes) relieve airway inflammation caused by severe asthma. However, due to serious side effects

when used long term, the systemic routes are used only on a short-term basis to treat severe asthma symptoms. Examples are prednisone and methyl prednisone. (d) Intravenous xanthine's: these xanthine's relax smooth muscle and to relieve bronchial spasm and are indicated for severe asthma attack. Example is aminophylline.

Drugs to treat long-term asthma are so often used in prophylactic measures. Long-term asthma controlling medications help reduce the extent of airways inflammation and help prevent attacks of asthma. The drugs used in such condition are: (a) The corticosteroids such as fluticasone and budesonide are used in inhalers. They most effectively prevent the asthmatic attack. In order to get maximum benefit of this medication, their use for several days to weeks is recommended. (b) The long-acting β2 agonists such as salmeterol and formoterol are used as inhaled medications. Although they help open the airways, they may increase the risk of a severe asthma attack as shown by some researchers. In order to minimise this risk, these medications are recommended to be used in combination with an inhaled corticosteroid. (c) The leukotriene inhibitors such as montelukast and zafirlukast act against inflammatory asthma. These medications when taken before exercise or exposure to allergen or to cold air help reduce the chances of occurrence of bronchoconstriction. (d) The xanthene's such as theophylline offer two-fold actions: relaxation of the bronchial muscle thereby providing relief from bronchial spasm and anti-inflammatory effects. (e) Mast cell stabilizers such as Alfetamine, Azelastine, Bepotastine, Cromoglicic acid, Epinastine, Ketotifen, Lodoxamide, Nedocromil, Olopatadine are used to prevent attack of asthma. (f) Phosphodiesterase type-4 (PDE4) inhibitor (PDE4) inhibitors such as Apremilast, CC-1088, Cilomilast, Crisaborole, Development of analogs of thalidomide, Drotaverine, Etazolate, Filaminast, Glaucine, HT-0712, Ibudilast, Luteolin, Mesembrenone, Mesembrine, Pentoxifylline, Piclamilast, Propentofylline, Roflumilast, Rolipram, and RPL-554 block the degradative actions of PDE4. In addition, some antihistaminics and antimuscarinics are being prescribed to the patients for the relief from bronchoconstriction and other respiratory disorders. The estimated comparative daily dosages for inhaled glucocorticosteroids are presented in table 1. The physical forms, mechanisms of actions and the dosage of some antiasthmatics are summarised in table 2.

Drugs	Low Daily Dose (μg)		Medium Daily Dose (μg)		High Daily Dose (μg)	
	Adult	Child	Adult	Child	Adult	Child
Beclomethasone-CFC	200-500	100-250	500-1000	250-500	> 1000	> 500
Budesonide-DPI	200-600	100-200	250-500	200-400	> 1000	> 600
Budesonide-Neb	NA	250-500	NA	500-1000	NA	>1000
Flunisolde	100- 250	100-200	1000-2000	750-1250	> 2000	> 1250
Mometasone	200- 400	NA	400- 800	NA	> 800	NA
Triamcinolone acetonide	400- 1000	400-800	1000-2000	800-1200	> 2000	> 1200

Table 1: *Estimated daily dosages for inhaled glucocorticosteroids*

NA: Not Available. Reference: [13].

Adverse effects of the antiasthmatics

Many antiasthmatics currently in practice to treat the asthma patients are reported to exert mild to severe side effects depending on the conditions of the disease, patients' health status, the dose and duration of the medication. A summary of most of these drugs, their mechanism of action and the adverse effects due to their applications are presented in table 3.

Herbal antiasthmatic drugs

The complementary and alternative medicines have always been a preferred choice to treat those chronic diseases which need application of synthetic drugs usually for longer durations as these compounds so often induce adverse effects in the patients posing a threat to chemotherapy. Out of 45000 plant species available in India, there are many plants reported to possess medicinal values. Some of them have been evaluated for their efficacy against asthma as they potentially exhibit antiasthmatic, antihistaminic, anticholinergic and antiallergic activities [29].

Drugs	Doses	Physical forms	Target of action	References
Isoprealine, Isoetharin	0.25 to 0.5 mL diluted in 1 mL of sterile water or saline or 0.68 mg (2 puffs)	Aerosols, inhalers, oral	β_2-agonists, Stimulates both β1 and β2 adrenergic receptors	[14]
Theophylline	Healthy Nonsmoking Adult: 10 mg/kg/day. Healthy Adult Smoker: 16 mg/kg/day. Patient with congestive heart failure: 5 mg/kg/day.	Tablet, oral	Inhibition of phosphodiesterase (PDE)3, inhibition of PDE4 and activation of histone deacetylases	[15]
Anticholinergics	15–30 mg four times per day.	Tablet, oral	Acts through muscarinic receptor (M), modulates airway, muscle tone, mucus gland secretion, and various parameters of inflammation and remodeling.	[16]
Ketotifen	Adults and children 3 years of age and olde: 1 milligram (mg) (1 tablet or 5mL of syrup), twice daily	Tablet/syrup oral	Non-competitive histamine antagonist (H1-receptor) and mast cell stabilizer, Inhibition of the release of mediators from mast cells involved in hypersensitivity reactions	[17]
Systematic corticosteroid				
Prednisone (Short acting, less active)	1 to 2 mg/kg daily (maximum 50 mg/d)	Tablet, oral	Inhibit the inflammatory response and chemotaxis,inhibition of LTB4 release	[18]
Dexamethasone (Long acting, more active)	0.3 to 0.6 mg/kg daily	Tablet, oral	Inhibition of LTB4 release	[19]
Leukotriene	800 μg daily	Tablet, oral	Inflammatory lipid mediators	[19]
Xanthine	150 mg twice daily to 300 and later 450 mg twice daily depending on the patient's tolerance	Tablet, oral	Not clear, cyclic nucleotide phosphodiesterase (PDE) inhibitors	[20]
Antimuscarinics	2.5 mcg (2 inhalations of 1.25 mcg) orally once a day	Aerosols, inhalers, oral	They block muscarinic acetylcholine receptors	[21]
Tiotropium	2 inhalations (34 mcg) orally four times a day	Aerosols, inhalers, oral		[22]
Iprotropium	500 mcg three or four times a day	Aerosols, inhalers, oral	Anticholinergic (parasympatholytic) agent, blocks the muscarinic receptors of acetylcholine	[23]
Beta 2 agonists for long term Arformoterol inhalation	15 mcg inhaled by nebulisation twice daily 30 mcg daily	Aerosols, inhalers, oral	Beta 2 agonists for long term	[24]
Formoterol	12 mcg inhalation capsule twice a day	Aerosols, inhalers, oral	Long-acting selective $beta_2$-adrenergic receptor agonist ($beta_2$-agonist), inhibits release of mast cell mediators i.e. histamine and leukotrienes, from the human lung.	[25]
Salmeterol	50 mcg (1 inhalation) orally twice a day,	Aerosols, inhalers, oral	a long acting beta2-adrenoceptor agonist (LABA), Binds to a specific exo-site domain of the beta 2-receptor protein to produce continuous stimulation of the active site of the receptor	[26]

Table 2: *The antiasthmatics, physical forms, mechanisms of actions and their dosage.*

Antiasthmatics	Mechanism of action	Adverse effects	References
Isoprenaline	It acts as a potent β-receptor agonist	Tachycardia	[27]
Salbutamol	It increases cAMP production by activating adenylate cyclase	Muscle tremors (dose related), palpitation, restlessness, nervousness, throat irritation and ankle edema	[27-29]
Theophylline	It acts via inhibition of phosphodiesterase (PDE)3 and PDE4 and activation of histone deacetylases.	Convulsions, diuresis, dyspepsia, insomnia, shock, hypotension, restlessness, tremors, vomiting, palpitation,	[27-29]
Anticholinergics	They competitively inhibit binding of acetylcholine with either muscuranic or nicotinic acetylcholine receptors	Cardiovascular collapse with respiratory depression, convulsions and coma (in severe poisoning), dry mouth, photophobia, palpitation	[27-29]
Ketotifen	It inhibits cAMP phosphodiesterase and the release of mediators from mast cells, acts as a non-competitive histamine antagonist (H1-receptor).	Sedation, dizziness, dry mouth, nausea and weight gain	[27-29]
Corticosteroids	They suppress the chronic airway inflammation and cause upregulation of inflammatory genes by proinflammatory transcription factors, such as nuclear factor-κB and activator protein-1.	Delayed healing of wounds, hyperglycemia, muscular weakness, susceptibility to infection, osteoporosis, growth retardation, psychiatric disturbances.	[27-29]
Inhaled corticosteroids (For long Term Asthma Control)	Act as most effective preventers. Examples: fluticasone and budesonide.	Fungal infection of the mouth or throat may develop a hoarse voice.	[27-29]
Systemic corticosteroids	Through oral and intravenous routes, they relieve airway inflammation caused by severe asthma. Examples: prednisone and methylprednisone	Fragile bones, High blood pressure, Diabetes,Weight gain,Cataracts and glaucoma,Thinning of the skin,Easy bruising, Muscle weakness	[27-29]
Leukotriene Inhibitors (For long Term Asthma Control)	They act against inflammatory components of asthma, provide protection against bronchoconstriction, Examples: montelukast and zafirlukast.	Abdominal pain, Thirst, Headache Hyperkinesia (in young children)	[27-29]
$Beta_2$ agonists (For long Term Asthma Control)	These are inhaled; act as quick-relief bronchodilators. Short-acting $beta_2$ agonists (used as inhaler or a nebulizer. Examples: salbutamol, terbutaline. The long-acting $beta_2$ agonists are salmeterol and formoterol	Fine tremor (particularly in the hands), Nervous tension, Headache, Muscle cramps, Palpitation	[27-29]
Antimuscarinics	The inhaled antimuscarinics act quickly like other bronchodilators, making it easier to breathe. Examples are ipratropium and tiotropium	Dry mouth, Gastro-intestinal motility disorder (including constipation and diarrhoea), Cough, Headache	[27-29]
Xanthines (Long Term asthma Control)	Xanthines relax smooth muscle and relieve bronchial spasm during severe asthma attack such as aminophylline. For long term asthma control theophylline (methyl xanthine) is used.	Nausea, vomiting, Gastric irritation, Diarrhoea, Palpitation, Tachycardia, Arrhythmias, Headache, Insomnia	[27-29]

Table 3: *The antiasthmatic drugs, targets of their actions and side effects.*

Several plants and plant-based compounds have been investigated for their potential to treat asthma and they have been found to be safe and cost effective. Among many plant-based chemicals analysed, the saponins have been reported to exhibit strong antiasthmatic property. The saponins from *C. Serratum, C. latifolia* and *Albizzia lebbeck* were found to display anti-allergic, bronchodialating and immunomodulatory activities [30]. The bronchoconstriction in asthma has been reported to be cured by use of the alcoholic extract of *Tylophora indica* or by chewing of *T. indica* leaves for about a week [31]. The antihistaminic and antiallergic properties of the extracts of T. *Bellerica, O. sanctum* and *Ocimum sanctum* have been demonstrated. In addition, the plant extracts from *Tinospora cordifolia, Balsamodendron mukul* and *Curcuma longa* have been found to possess anti-inflammatory activity. The anti-inflammatory activity of *C. longa* has been found to be mediated through inhibitory effects of the principles isolated from this plant on the activities of hyaluronidase, activated

proteases and some enzymes involved in prostaglandin synthesis. An Ayurvedic preparation constituting *Boswellia serrata, Curcuma longa* and *Withania somnifera* has been reported to markedly decrease the intensity of pain and morning stiffness [29,30,32] A list of some plant-based principles, sources and their antiasthmatic properties is presented in table 4.

Phytochemical	Plant Source	Function	Reference
Saponin	*Clerodendron serratum, Gardenia turgida, Albizzia lebbeck, Solanum xanthocarpum, Ocimum sanctum, Tylophora indica*	Antiallergic activity in the lung tissues, potentiate broncho-dilator beta-adrenergic activity, Inhibition of broncho-constriction, prevention of bronchospasm	[32-35]
Khellin (a naturally occurring chromone)	*Amni visnaga*	Bronchodialator	[36]
Ethanol extract	*Aerva lanta*	Antiasthmatic activity	[37,38]
Hydroalcoholic extract	*Ageratum conyzoides*	Antiasthmatic activity	[29]
Aqueous extract	Argemone mexicana	Antistress activity	[29]
Extract in hexane, ethylacetate and methanol	*Asystasia gangetica*	Inhibition of spamogen mediated contraction	[29]
Extracts in petroleum ether, chloroform, methanol and water	*Bacopa monnieri*	Inhibits mast cells degranulation	[39]
Extracts in chloroform, ethylacetate, ethanol	*Cassia sophera*	Antiasthmatic, antibronchitis	[40]
Extract in Methanol	*Casuarina equisetifolia*	Antihistaminic activity	[29]
Extract in ethanol	*Eclipta alba*	Antihistaminic activity	[29]
Extract in ethanol	*Clerodendrum serratum*	Antiasthmatic, antiinflammatory	[41]
Extract in ethanol	*Euphorbia hirta*	Protection of mast cells from degranulation	[42]
Extracts in Ethyl acetate, ethanol and aqueous	*Ficus bengalensisis*	Antihistaminic activity	[29]
Extract in ethanol	*Cnidium monnieri*	Antiallergic activity	[29]
Aqueous extract	*Crinum glaucum*	Protection of mast cells from degranulation	[43]
Alcoholic extract	*Curculigo orchioides*	Antiallergic	[44]
Ethanolic extract	*Hemidesmus indicus*	Antiasthmatic	[39]
Aqueous Extract	*Amburana cearensis*	Antiasthmatic	[29]
Petroleum ether	*Nyctanthes arbortristis*	Antihistaminic	[45]
Extract in ethanol, ethyl- acetate, n-butanol, methanol	*Lepidium sativum*	Antihistaminic	[29]
Aqueous extract of ripe olives	*Olea europea*	Antihistaminic	[46]
Extarcts in ethyl acetate	*M. spicata*	Antihistaminic	[29]
Ethanolic extract of arial part	*Phymatodes scolopendria*	Antihistaminic	[47]
Methanolic and aqueous extract	*Momordica dioica*	Antihistaminic	[29]
Ethanolic and aqueous extract	*Piper betel*	Antihistaminic	[48]
Ethanolic and aqueous extract	*Striga orobanchioides*	Antihistaminic	[49]
Methanolic extract	*Mucuna pruriens*	Protection of mast cells from degranulation	[29]
Ethanolic extract of arial part	*Myrica esculenta*	Antiasthmatic	[45]
Ethanolic extract	*Sphaeranthus indicus*	Protection of mast cells from degranulation	[50]
Extract in petroleum ether, chloroform and methanol	*Cynodon dactylon*	Protection of mast cells from degranulation	[51]

Table 4: *Plant based molecules and their antiasthmatic properties.*

Future prospects of development of more potential antiasthmatics using new targets

In addition to the use of once-daily drugs, the application of combination inhalers containing corticosteroid and a long-acting β2-agonist have been found to be highly effective against asthma. However, there is a pressing need to investigate more effective therapies for patients suffering from severe asthma, who do not get controlled by current therapies. New treatments in development for asthma include inhibitors of the proinflammatory enzymes, such as PDE4, p38 mitogen-activated kinase and nuclear-factor-κB activating kinase (IKK2) (Barnes, 2004). Other specific approaches towards development of new antiasthmatics are exploring molecules which could act like inhibitors of chemokine receptors (present on the eosinophils and T lymphocytes), and of mast cells. The quest for search of an efficient vaccine against asthma could be another strategy which may help switch back the patients' immune system to normal, though it may have its own demerits, which could be investigated further. Currently, the anti-inflammatory agents for bronchial asthma under development are drugs affecting lipid mediators. Currently the researchers are putting efforts to investigate different immunomodulators, immunopotentiators and immunosuppressors in addition to various prostaglandin (PG) D2 antagonists as well as the inhibitors of leukotriene and thromboxane A2 [52] as the strategies to effectively control asthma. Pelaia., *et al.* [53] had also suggested three significant strategies to control asthma (1) repurposing of the existing antiasthmatics, (2) exploring new compounds which could potentially control the complex network of proinflammatory mediators involved in disease pathogenesis (cytokines, chemokines, and adhesion molecules) and (3) immunotherapeutic strategy to block the unbalanced Th2 responses [54].

Conclusion

The extensive literature search indicates that there is an urgent need to find effective and safe antiasthmatics to cure the disease thereby to improve the health of patients. The future strategies to develop new chemotherapeutics against asthma may include medications to optimize lung function; bronchial thermoplasty, and the compounds/regimen which may target specific inflammatory cells or receptors of inflammatory mediators. It may also involve targeted therapies based on the clinical (phenotype) or new biological (endotype) tools leading to the development of personalised medicine. Simultaneously, various plant based principles isolated from different plant species may be explored to develop them as potential antiasthmatics with almost no adverse effects.

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Conflict of Interests

The authors declare that they do not have any conflict of interests.

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