HERBAL APPROACHES TO ASTHMA: A NEWER INSIGHT

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INTRODUCTION
Asthma afflicts approximately 53 million people across the world mostly in United States, France, Germany, Italy, Spain, United Kingdom and Japan. Epidemiological studies indicate that there is a global increase in the incidence, morbidity, and mortality caused by asthma despite an expanding repertoire of medications available for the treatment. Annual mortality in India as a result of complications arising from serious asthma attacks is reported to be more than 4000, although there are several recommendations and treatments being reported. The chronic inflammation is associated with airway obstruction and mucus production that leads to increased hyper-responsiveness of the airway resulting in recurrent episodes of wheezing, breathlessness, chest tightness, and cough, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or upon treatment. Many factors like goblet cell hyperplasia, goblet cells count and increased area of sub mucosal glands result in mucin hyper-production and decreased mucus clearance contribute to chronic airway inflammation, airway obstruction, and asthma exacerbation. The chronic airway inflammation of asthma is unique in a way that the airway wall is infiltrated by T-lymphocytes of the T-helper type-2 phenotype, eosinophils, macrophages/monocytes and mast cells.

Airway associated factors in pathophysiology of asthma
Bronchoconstriction
The dominant pathophysiological event leading to clinical symptoms is airway narrowing and a subsequent interference with airflow. In acute exacerbations of asthma, bronchial smooth muscle contraction (bronchoconstriction) occurs quickly to narrow the airways in response to exposure to a variety of stimuli including allergens or irritants. 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. Yet, no scientific pathological mechanism has been established. The pathophysiology has been presented in Fig. 1.

Fig. 1: Picture representing; A) the location of the lungs and airways in the body, B) a cross-section of a normal airway, and C) a cross-section of an airway during asthma symptoms.
Airway edema
Asthma becomes more persistent and inflammations more progressive, other factors further limit the airflow. These may include edema, inflammation, mucus hypersecretion and the formation of mucus plugs, as well as structural changes including hypertrophy and hyperplasia of the airway smooth muscle.\[^{11}\]

Airway hyper-responsiveness
The degree to which airway hyper-responsiveness can be defined by contractile responses to a challenge with methacholine in animals correlates with the clinical severity of asthma. The mechanisms influencing airway hyper-responsiveness are multiple and include inflammation, dysfunctional neuro-regulation and structural changes. Inflammation appears to be a major factor in determining the degree of airway hyper-responsiveness. Treatment directed toward reducing inflammation can reduce airway hyper-responsiveness and contribute to control of asthma.\[^{12}\]

Airway remodeling
In some patients, airflow limitation may be only partially reversible. Permanent structural changes can occur in the airway that is associated with a progressive loss of lung function and is not prevented by or fully reversible by current therapy.\[^{13}\] These structural changes can include thickening of the sub-basement membrane, sub-epithelial fibrosis, airway smooth muscle hypertrophy and hyperplasia, blood vessel proliferation and dilatation, and mucous gland hyperplasia and hypersecretion. Regulation of the repair and remodeling process is not well established, but both the processes of repair and its regulation are likely to be key events in explaining the persistent nature of the disease and limitations to a therapeutic response.\[^{14}\]

Inflammation holds a central role in the pathophysiology of asthma. The mechanistic pathophysiology has been presented in Fig. 2. Asthma occurrence due to airway inflammation is a result of interaction of many cell types and multiple mediators with the airways. These eventually result in the characteristic pathophysiological features of bronchial inflammation and airflow limitation leading to recurrent episodes of cough, wheeze, and shortness of breath.\[^{15}\] The processes by which these interactive events occur and lead to clinical asthma are still under investigation. Although, distinct phenotypes of asthma exist (e.g. intermittent, persistent, exercise-associated, aspirin-sensitive, or severe asthma), airway inflammation remains a consistent pattern. The pattern of airway inflammation in asthma, however, does not necessarily vary depending upon disease severity, persistence, and duration of disease. The cellular profile and the response of the structural cells in asthma are quite consistent.\[^{16}\]

![Fig. 2: Pathophysiology of asthma and sites of drug action. PAF- platelet activating factor; LTs- Leukotrienes; PGs- prostaglandins.](image)

Newer targets in Asthma therapy
The ongoing pharmacotherapeutic strategies to combat asthma have several limitations. There is no well-known and documented cure for asthma, moreover, very little evidences have been reported for the possibility of prevention in susceptible persons. Hence, patients continue to be at risk of symptoms and exacerbations. Mortality remains a severe problem. Importantly, the medications have been reported with adverse effects such as osteoporosis and dose associated growth impairment due to excessive use of steroids. New devices have been introduced to come up with immediate effects. In recent time, new understanding of the molecular pathology of asthma has identified several novel therapeutic targets.\[^{17}\]
Agents being tested in early phase clinical trials include antagonists of IgE, cytokines, adhesion molecules and transcription factors. Some of the targets are; TXA2 inhibitors (Serabenzast, domitroban and ozagrel) as a potent bronchoconstrictor, mucus producer and blood vessel permeability inducer and causes airway hyper responsiveness. TXA2 inhibitors BAYu3405 decrease the airways responsiveness to methacholine. Tachykinin receptor is also a newer target in asthmatic treatment. CP-96345 is known to be the first nonpeptidetachykinin receptor antagonist, which is also a potent NK1 receptor antagonist. Some examples of selective nonpeptide NK2 receptor inhibitors include SR 48968, GR 159897 and SR 144190, while, SR 142801 and SB 223412 are selective NK-3 receptor antagonists. Tryptase inhibitors inhibit both early and late reactions associated in asthma. APC-366 inhibited antigen induced late phase response and bronchial hyper-responsiveness. Lactoferrin disrupts the quaternary structure of trypptide, also attenuates antigen induced late response and bronchial hyper-responsiveness in allergic sheep.\[16\]

Targeting cytokines is one of the novel approaches in the treatment of asthma. Sch-55700 and SB-240563 (humanized anti-IL-5 monoclonal antibodies) reduce blood eosinophil count for several weeks and prevent eosinophils recruitment into the airways after allergen challenge in asthmatic patients. IL-5 signaling inhibitor, GCC-AP0341 inhibits IL-5 mediated survival of eosinophils. A range of chemokines (chemoattractantectoxin) are secreted by inflamed lung tissues thus attracting eosinophils. Eotaxin receptor blockers are being investigated for therapy, as eosinophils are believed to be major contributors to the pulmonary damage seen in asthma. Monoclonal antibody (7B11) for human CCR3 block the binding completely and signaling of CCR3 ligands, therefore inhibiting the chemotactic response of human eosinophils to all chemokines. Phosphodiesterase inhibitors also have shown to produce significant role in asthma. The potential effectiveness has been documented for isoenzyme-selective inhibitors of cyclic nucleotide phosphodiesterase in treatment of asthma. Some examples of phosphodiesterase inhibitors include benzaftenrine, zaprinast, rolipram, LAS- 31025, RP-73401, denbufylline, SB 207499, V11294A, CP-220 and roflumilast. Endothelin modulators inhibit the endothelin-converting enzyme (ECE), which mediates the synthesis of ET-1 from its precursor and via modeling the effects of ET-1 at the end organ level. Examples are BQ-123, SB-217242 and bosentan.\[19, 20\]

**Herbal drugs in Bronchial Asthma**

Globally, herbs are staging a comeback and herbal ‘renaissance’ is happening. The herbal products today represent safety in comparison to the synthetic molecules that are considered as unsafe to human and environment because of their side and adverse effects. Although herbs had been priced for their medicinal, flavouring and aromatic qualities for centuries, the synthetic products of the modern age have surpassed their importance. However, the blind dependence on synthetics is obsolete and people are returning to the naturals with a hope of safety and security.\[21\] More than 30% of the entire plant species are utilized for medicinal purposes. It has been estimated that in developed countries such as United States, plant drugs constitute as much as 25% of the total drugs, while in fast developing countries such as China and India, the contribution is as much as 80%. Thus, the economic importance of medicinal plants is much more to countries such as India than the rest of the world. These countries provide two third of the plants used in modern system of medicine and the health care system of rural population depend on indigenous systems of medicine.\[22\]

The first-hand information about the plants and plant parts used as traditional remedies against cough and asthmatic disorders was collected from tribal villages of Aravalli ranges of both the districts during 1999-2001. The data were collected by personal interviews with chieftains of different villages, elderly persons and traditional herbalists (Vaidyas) who have knowledge about the therapeutic values of wild plants in different illnesses. It has been presented in Table 4.

**Classification of anti-asthmatic herbs based on mechanism of action**

Some herbal alternatives employed in asthma are proven to provide symptomatic relief and assist in the inhibition of disease development as well. These herbs therefore have multifaceted roles to play in the management of asthma suggesting different sites of action within the body. Based on the possible mechanism of action reported, plant anti-asthmatics may be classified as shown in Tables 5-8.

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Name of plant</th>
<th>Part used/ extract/ fraction</th>
<th>Major chemical constituent(s)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Adhatodavasica_Nees</td>
<td>Leaves, Roots</td>
<td>Alkaloids</td>
<td>(23)</td>
</tr>
<tr>
<td>2</td>
<td>Albizia lebeck (Sareshca_rakat)</td>
<td>Stem bark/Aqueous</td>
<td>Saponins</td>
<td>(24)</td>
</tr>
<tr>
<td>3</td>
<td>Alstoniascholaris</td>
<td>Leaves/Aqueous</td>
<td>Ditamine, Echitamine and Echitenes</td>
<td>(25)</td>
</tr>
<tr>
<td>4</td>
<td>Artemisia caeulescens</td>
<td>Aerial parts/Butanol</td>
<td>Quercetin, isorhamnetin</td>
<td>(26)</td>
</tr>
<tr>
<td>5</td>
<td>Belamcanchachinenesis</td>
<td>Leaves/Ethanol</td>
<td>Tectorigenin</td>
<td>(27)</td>
</tr>
</tbody>
</table>
Table 6: Medicinal plants with mast cell stabilizing property

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Name of plant</th>
<th>Part used/ extract/fraction</th>
<th>Major chemical constituent(s)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Achyranthes aspera</td>
<td>Aerial parts/Aqueous</td>
<td>Oleanolic acid</td>
<td>[28]</td>
</tr>
<tr>
<td>2</td>
<td>Allium cepa</td>
<td>Bulb/Juice</td>
<td>α and β unsaturated Thiosulphinates</td>
<td>[29]</td>
</tr>
<tr>
<td>3</td>
<td>Aquillaria agallocha</td>
<td>Stem/Aqueous extract</td>
<td>Triterpenoids</td>
<td>[30]</td>
</tr>
<tr>
<td>4</td>
<td>Azadiracthaindica</td>
<td>Leaves/Juice</td>
<td>Nimbin, nimbinine, Nimbandiol, quercetin</td>
<td>[31]</td>
</tr>
<tr>
<td>5</td>
<td>Bacopamonniera</td>
<td>Leaves/Ethanol</td>
<td>Bacosides, Alkaloids, Glycosides</td>
<td>[32]</td>
</tr>
</tbody>
</table>

Table 7: Medicinal plants with anti-allergic property

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Name of plant</th>
<th>Part used/ extract/fraction</th>
<th>Major chemical constituent(s)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Adhatodavasica</td>
<td>Leaves/Methanol</td>
<td>Vaxicinol, vasicine</td>
<td>[33], [34]</td>
</tr>
<tr>
<td>2</td>
<td>Albizzialebbeck</td>
<td>Stem bark/Aqueous</td>
<td>Saponins</td>
<td>[35], [36]</td>
</tr>
<tr>
<td>3</td>
<td>Asiasarumsieboldi</td>
<td>Roots/Methanol</td>
<td>Methylheugenol, gamma-asarone, Elemicin, Asarinin</td>
<td>[37]</td>
</tr>
<tr>
<td>4</td>
<td>Camellasinesis</td>
<td>Leaves</td>
<td>Flavanoids</td>
<td>[38]</td>
</tr>
<tr>
<td>5</td>
<td>Citrus unshiu</td>
<td>Peels</td>
<td>Flavanoids</td>
<td>[39]</td>
</tr>
</tbody>
</table>

Table 8: Medicinal plants with anti-inflammatory property

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Name of plant</th>
<th>Part used/ extract/fraction</th>
<th>Major chemical constituent(s)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Asystasiagangetica</td>
<td>Leaves/Methanol, Ethyl Acetate</td>
<td>Isoflavone glycoside, dalhorrin</td>
<td>[40]</td>
</tr>
<tr>
<td>2</td>
<td>Aloe vera Tourn. ex Linn. (Liliaceae)</td>
<td>Leaves/Aqueous, Chloroform and ethanol</td>
<td>Anthraquinones, sterols, saponins and carbohydrates</td>
<td>[41]</td>
</tr>
<tr>
<td>3</td>
<td>Bryoniaalaciniosa</td>
<td>Leaves/chloroform extract</td>
<td>Flavanoids</td>
<td>[42]</td>
</tr>
<tr>
<td>4</td>
<td>Calotropis procera</td>
<td>Latex</td>
<td>α-amyrin, β-amyrinalotropin (Triterpenoid)</td>
<td>[43]</td>
</tr>
<tr>
<td>5</td>
<td>Curcuma longa</td>
<td>Rhizomes</td>
<td>Tumerones, curcuminoinds</td>
<td>[44]</td>
</tr>
</tbody>
</table>

CONCLUSION
Asthma is an increasingly prevalent pathological condition worldwide. Herbal approaches have regained their popularity, with their efficacy and safety aspects being supported by controlled clinical studies. The herbal approaches have offered effective results. The herbs have shown promising results in various target specific biological activities such as bronchodilation, mast cell stabilization, anti-anaphylactic, anti-inflammatory, anti-spasmodic, anti-allergic, immunomodulatory and inhibition of mediators such as leukotrienes, lipoxigenase, cyclooxygenase, platelet activation, phosphodiesterase and cytokine in the treatment of asthma. The ongoing research has provided some relevant and valuable evidences regarding the mechanistic approach of these herbal alternatives. Conclusively, these herbal medication or natural derived drugs could overcome the adverse effects in comparison to synthetic molecules.

Conflict of interest
Authors have declared no conflict of interest.

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35. Acharya S, Yanpallewar S, Singh R. A preliminary study on the effect of Azadirchaitandica on