1. INTRODUCTION

From time immemorial, man depends on plants as medicine. From a historical perspective, it is evident that the fascination for plants is also as old as mankind itself. The plant kingdom represents a rich storehouse of organic compounds, many of which have been used for medicinal purposes and could serve as lead for the development of novel agents having good efficacy in various pathological disorders in the coming years.

Herbal medicines are being used by nearly about 80% of the world’s population, largely in developing countries for primary health care (Goldberg, 1994). Assessing the current status of health care system in adequacies of synthetic drugs is likely to be more glaring in the coming years. It has been reported that there has been an alarming increase in number of diseases and disorders caused by synthetic drugs, prompting a switch over to traditional herbal medicines (Ghule and Patil, 2001). Alternative system of medicine is a major component of health care globally and many healthcare providers and organizations are being forced to consider integrating them into their practice and treatment guideline (Muller and Clauson, 1997).

Herbs have always been the principal form of medicine in India and presently they are becoming popular throughout the world, as people strive to stay healthy in the face of chronic stress and pollution, and to treat illness with medicines that work in count with the body’s own defense (Perumalsamy et al., 1998). There is a widespread belief that green medicines are healthier and more harmless or safer than synthetic ones. Considerable research on pharmacognosy, chemistry, pharmacology and clinical therapeutics has been carried out on medicinal plants. Natural products, including plants, animals and minerals have been the basis of treatment of human diseases.

According to the World Health Organization (WHO), about three-quarters of the world population relies upon traditional remedies (mainly herbs) for the health care of its people. In fact, herbs/plants are the oldest friends of mankind. They not only provided food and shelter but also served the humanity to cure different ailments. The herbal medicine also sometime called as, traditional or natural medicine existed in one way or
another in different cultures/civilizations, such as Egyptians, Western, Chinese, Kampo (Japan), Siddha (South India), Ayurveda (North India), and Greco-Arab or Unani/Tibb (South Asia) (Gilani & Rahman, 2005).

Siddha and Ayurveda are the traditional Indian Medicinal System practiced for thousands of years. The current accepted modern medicine has gradually developed over the years by scientific and observational efforts of scientists. However, the basis of its development remains rooted in traditional medicine and therapies (Vishunakanta and Rana, 2008).

Siddha medicine is the oldest and the foremost of all other medical systems of the world. There were 18 important siddhars in olden days and they developed this system of medicine. Hence, it is called Siddha Medicine. The word Siddha comes from the word Siddhi which means an object to attain perfection or heavenly. Siddha science considers nature and man as essentially one. Nature is man and man is nature. According to Siddha medical science, the Universe originally consisted of atoms which contributed to the five basic elements, viz., earth, water, fire, air and sky which correspond to the five senses of the human body and they were the fundamentals of all the corporeal things in the world. The system is said to have emerged in antiquity, from the highly evolved consciousness of the Siddhars (Uttamarayan, 1992). The clarified intellect and heightened intuition of the Siddhars, resulting from their yogic powers, enabled them to explore the world around them and exploit its natural resources for the sake of humanity. Their findings on the characteristics of plants, metals, minerals and animal products and their knowledge of the properties of drugs, its purification, processing, fixing dosage, toxicity, antidote and clinical application, were preserved in the form of verses for the use of the posterity (Bharathathin siddha maruthugal seimurai kurippu nool, 1984).

Globally, there is a positive trend in favor of traditional and integrative health sciences both in research and practice. There are common approaches to drug discovery including use of chemical biology, serendipity, chemical synthesis, combinatorial chemistry and genomics. However, the innovative approaches involve ethnopharmacology, reverse pharmacology, holistic, systems biology and personalized medicine. Many recent studies suggest that entry barriers have fallen over time for new drug introductions (Di Masi & Paquette, 2004). The development histories of entrants to new drug classes suggest that development races better characterize new drug than does a
model of post hoc imitation. To resolve this impasse, pharmaceutical companies are now looking for true innovative approaches to drug discovery.

There is an increased demand in usage of alternative medicines including Siddha preparation around the world for treating various diseases. There are various types of Siddha preparation which includes Chooranam or Parpam. Chooranam is basically a single or compound herb given as such to the patients. However the amount of effectiveness and the safety of the Siddha formulation are under research so this system didn’t reach to community wise hence the system lacks.

**ASTHMA**

Asthma is a reversible obstructive disease of the lower airway. With asthma there is increasing airway obstruction caused by bronchospasm and bronchoconstriction, inflammation and edema of the lining of the bronchioles, and the production of thick mucus that can plug the airway (Dawson, 2007).

There are three types of asthma: (Hussain and Kumar, 2007)

1. **Extrinsic** (also referred to as allergic asthma and caused in response to an allergen such as pollen, dust, and animal dander).
2. **Intrinsic asthma** (also called non-allergic asthma and caused by chronic or recurrent respiratory infections, emotional upset, and exercise).
3. **Mixed asthma** (caused by both intrinsic and extrinsic factors).

Figure 1.Identifies the asthmatic pathway from both intrinsic and extrinsic stimulus. Extrinsic or allergic asthma causes the IgE inflammatory response (Galanter and Lazarus, 2008) with exposure; the IgE antibodies are produced and attach to mast cells in the lung. Re-exposure to the antigen causes them to bind to the IgE antibody, releasing histamine and other mast cell products (Ritter *et al.*, 2008). The release of these products causes bronchospasm, mucous membrane swelling, and excessive mucous production. Gas exchange is impaired, causing carbon dioxide to be trapped in the alveoli so that oxygen is unable to enter (Seth and Seth, 2009).
Figure 1: Asthmatic pathway from intrinsic and extrinsic stimulus
(Pazdernik and Kerecsen, 2009).
PATHOPHYSIOLOGY OF ASTHMA

In asthma, smooth muscle that surrounds the bronchi is hyper responsive to stimuli, and underlying inflammatory changes are present in the airways. Asthmatic stimuli include inhaled allergens, occupational allergens, and drugs or non-specific stimuli such as cold air, exercise, stress and pollution (Woodruff and Fahy, 2002). The stimuli cause asthmatic changes through several complex pathways (Figure 2). The possible mechanisms of these pathways include the following: (Rang and Dale, 2003)

- Immune reactions (type I hypersensitivity) and release of inflammatory mediators – the cross-linking of IgE by allergens causes mast cell degranulation, and release of histamine and powerful eosinophil and neutrophil chemotactic factors (Boyce, 2003). The mediators, viz. histamine, tryptase, LTC\textsubscript{4} and D\textsubscript{4}, and PGD\textsubscript{2}, when released enter through airway mucosa and stimulate mucosa and stimulate muscle contraction and vascular leakage, i.e. early asthmatic response. Re-exposure to allergen causes the synthesis and release of a variety of cytokines, viz. interleukin-4 (IL\textsubscript{4}) and IL\textsubscript{5}, granulocyte-macrophase colony-stimulating factor (GM-CSF), tumour necrosis factor (TNF), and tissue growth factor (TGF) from T cell and mast cells (Wenzel, 2003). These cytokines attract and activate eosinophils and neutrophils, which re-create eosinophil cationic protein, proteases, and platelet activating factor (PAF). These mediators cause edema, mucous hyper secretion, bronchoconstriction, and increase in bronchial activity associated with late asthmatic response (Bradding et al., 2006).

- An imbalance in airway smooth muscle tone involving the parasympathetic nerves (vagus), non-adrenergic non-cholinergic nerves and circulating noradrenalin that acts under normal circumstances to control airway diameter.

- Abnormal calcium flux across cell membranes, increasing smooth muscle contraction and must cell degranulation.

- Leaky tight junctions between bronchial epithelial cells allowing allergen access.
The above result in symptoms of wheezing, breathlessness and sometimes cough. In many people the asthmatic attack consists of two phases – an early-phase response and a late phase response (Dawson, 2007) (Figure 3).

**Early – Phase Response**

An early – phase response occurs on exposure to the eliciting stimulus. The response consists mainly of bronchospasm. Bronchodilators are effective in this phase (Ritter et al., 2008).

**Late – Phase Response**

Several hours later, the late-phase response occurs. This consists of bronchospasm, vasodilatation, edema and mucus secretion caused by inflammatory mediators released from eosinophils, platelets and other cells, and neuropeptides released by axon reflexes. Anti-inflammatory drug action is necessary for the prevention and/or treatment of this phase (Pazdernik and Kerecsen, 2009).
Figure 2: Pathogenesis and drug action in asthma (Dawson, 2007)
Seven hours after allergen challenge during the late phase response, eosinophils increase in sputum samples of asthmatics, and this is associated with the appearance of eosinophil- basophil progenitors, and eosinophilia in peripheral blood. Progenitor CD 34+ cells bear the IL-5 receptor (IL-5R) with increased responsiveness to IL-5 suggesting they are primed toward the development of eosinophils. IL-5 generated in the inflamed lung tissues in asthma acts hormonally on the bone marrow to increase the production of eosinophils. The presence of eosinophil progenitors and eosinophil growth factors IL-3, IL-5 and GM-CSF within the asthmatic lung indicates the potential of local eosinophil differentiation. The migration of eosinophils into the airways is initiated by local chemotactant factors. Many chemotactic substances act on eosinophils, including lipid mediators (LTB₄ and PAF), anaphylatoxins and chemokines (Macrophage inflammatory protein-1α, MIP-1α, macrophage-derived chemokine MDC, monocyte chemotactic protein-2 MCP-2, MCP-3, MCP-4, IL-8 and IL-16). The increased number of eosinophils in asthmatic patients is the combination of increased eosinophiliopoiesis and rate of egress from the bone marrow. The eosinophil recruitment results from the complex mechanisms
that involve interaction of adhesion molecules on the eosinophils with counter ligands on endothelial cells, extracellular matrix proteins and other tissue structures. Among these mechanisms are tethering and rolling on the endothelial surface, firm adhesion and transendothelial migration. The initial reversible tethering and rolling of eosinophils on the endothelium involve the formation of numerous weak reversible bonds between P-selectin and P-selectin glycoprotein ligand-1 and very late activation antigen-4 with vascular cell adhesion molecule-1 (Thomas and Warner, 1996). Preformed P-selectin is stored intracellularly in the Weibel-Palade bodies, from where it is mobilized to the endothelial surface by histamine and PAF. The tethering and rolling of eosinophils on the endothelium is followed by the activation step mediated by chemo attractants. Chemo attractants direct the migration of the tethered cells, involving crawling along the endothelium where chemokines are deposited in a solid phase, activation, diapedesis, and immigration into the tissue along a gradient of chemotactic signals. The activation results in up-regulation of \( \beta_2 \)-integrins and \( \beta_1 \)- integrin. \( \beta_2 \)-integrins bind to intracellular adhesion molecule-1 on endothelium whereas \( \beta_1 \)-integrin binds to vascular cell adhesion molecule – 1 resulting in the firm arrest that is critical for transmigration. RANTES induces transient activation of very late activation antigen – 4 increasing their adhesiveness to vascular cell adhesion molecule – 1, whereas MCP-3 stimulation results in conformational change of Mac-1 leading to increased ICAM-1 adhesion. IL-4 and IL-13 induce expression of VCAM-1, whereas TNF-\( \alpha \) and IL-1 induce expression of intracellular adhesion molecule-1 on the surface of endothelial cells. Binding of the chemokines (eotaxin, eotaxin 2, RANTES and MCP-3) to their G-protein-coupled receptors activates \( \text{Ca}^{2+} \) flux-induced polymerization and breakdown of actin leads to the formation and retraction of lamellipodia, which function like arms and legs of the migrating cells (Filipović and Cekić, 2001). Transendothelial migration also requires the function of matrix metalloprotease-9 that degrades type IV collagen, entactin, proteoglycans, and elastin, permitting eosinophil penetration through basement membrane. Eosinophils are richly endowed with matrix metalloprotease-9 in its precursor, with enzyme activation occurring when eosinophils adhere either to endothelial or epithelial cells (Foster et al., 2002). The extensive secretion of this enzyme with its capacity to degrade epithelial adhesion molecules, epithelial basement membrane collagen and proteoglycans acts as a component of the airways remodelling. After migration through the endothelium, eosinophils come into contact with extracellular
matrix proteins that are likely to play important roles in the regulation of eosinophil activation (Barry, 2004, 2005).

PATHOGENETIC ROLE OF MEDIATORS IN ASTHMA

The recruitment of eosinophils into bronchial mucosa in which allergic inflammation occurs is a critical contributor to the late asthmatic reaction of congestion and mucus hyper secretion (Thomas and Warner, 1996) (Figure 4). When these cells arrive they degranulate and perpetuate underlying airway inflammation (Filipović and Cekić, 2001).

Eosinophils are a rich source of cytotoxic proteins, lipid mediators, oxygen free radicals and cytokines. In asthmatic patients, after transendothelial migration, eosinophils transmigrate and adhere to bronchial epithelium where they degranulate and release substances (eosinophil cationic protein, major basic protein, eosinophil peroxidase and superoxide) which are toxic for epithelial cells (Foster et al., 2002). Damage and desquamation of cells, ciliostasis, and epithelial secretion manifest the toxicity to airway epithelium. Major basic protein is a selective, allosteric antagonist for M\textsubscript{2} muscarinic receptors (auto receptors) (Woodruff and Fahy, 2002).

The loss of M\textsubscript{2} muscarinic receptor function results in increased airway tone due to increased release of acetylcholine and potentiation of vagally mediated reflex bronchoconstriction and bronchial hyper responsiveness (Boyce, 2003). Major basic protein also stimulates histamine release from basophils and mast cells. Lipid bodies (intracellular lipid rich domains) are induced to be developed in the activated eosinophils, and are the sites for enhanced synthesis of both lypoxygenase and cyclooxygenase-derived eicosanoids. Eosinophils are capable of producing significant quantities of cysteinyi leukotrienes (especially LTC-4) (Wenzel, 2003). Cysteinyi leukotrienes contract airway smooth muscle (100-1000 fold more potent bronchoconstrictors than histamine), increase vascular permeability, stimulate mucus secretion, decrease mucocilliary clearance, stimulate eosinophil and neutrophil recruitment into the airways, stimulate smooth airway muscle proliferation and cause neuronal dysfunction (Barry, 2004, 2005).

Eosinophils have the potential to synthetize and release a number of cytokines and chemokines. Cytokines produced by eosinophils include the autocrine-eosinophil active growth factors (IL-3, IL-5, GM-CSF), immunoregulatory cytokines (IL-2, IL-4, IL-1,
TGF-β, IFN-γ), proinflammatory cytokines (IL-1, IL-6, TNF-α, IL-16) and chemokines (IL-8, MIP-1α, RANTES) (Puxeddu et al., 2005).

Transforming growth factor-β (TGF-β) is an immunoregulatory factor with a direct effect on growth of some cell types (stimulation on fibroblast growth and inhibition of epithelial cell growth) and up regulation of the synthesis of ECM proteins, inflammatory mediators and cytokines, making it an important factor in the remodelling process (Bradding et al., 2006).

Figure 4: Role of eosinophils in the late asthmatic reaction (Puxeddu et al., 2005).

**Eosinophils**

![Diagram showing the role of eosinophils in asthma](image)

- **Crystalloid granule proteins**: -Core: MBP, -Matrix: EPO, ECP, EDN
- **Lipid mediators**: -LTC4, LTB4, 5-HETE, -PGE1, PGE2, TxB2, -PAF
- **Cytokines and Chemokines**: -IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, -IL-8, IL-10, IL-12, IL-16, GM-CGF, -RANTES, TGF-β, TGF-α, MCP-1, MIP-1α

- **Increased mucus secretion**
- **Increased vascular permeability**
- **Increased adhesion molecules expression**
- **Bronchoconstriction**
- **Eosinophil and Neutrophil chemotaxis**

- **Increased Eosinophil survival**
- **Increased adhesion molecules expression**
- **Sustained inflammation**
- **Eosinophil and Neutrophil chemotaxis**
- **Airway wall remodelling**

**INFLAMMATORY COMPONENT**

The inflammatory features of asthma consist of a dense inflammatory infiltrate in which eosinophils, mast cells, and CD4 + helper T lymphocytes predominate (Hogg, 1993). Neutrophilic infiltration also arises during asthma exacerbations (Fahy et al., 1995) and in the late response to allergen challenge. Dendritic cells seem to be the key cells for antigen presentation in asthma (Jahnsen et al., 2001). Antigens then cause cross-linking of Ig E and as a consequence mast cells are activated and degranulate. Mast
cells are important in the acute airway responses to allergens and may also contribute to remodeling in chronic asthma (Williams and Galli, 2000).

A defining characteristic of asthma is the presence of many activated eosinophils (Lee et al., 2001) which are thought to contribute to airway epithelial damage by release of products such as eosinophil major basic protein. However, the central role for eosinophils as effector cells in asthma has been challenged. Administration of antibodies against interleukin 5 to patients with asthma greatly reduces systemic and sputum eosinophilia, but has a negligible effect on airflow and airway hyper-responsiveness (Leckie et al., 2000). Similarly, administration of interleukin 12, which drives differentiation of T cells to a Th1 rather than a Th2 phenotype, reduced eosinophil numbers, but not airway responsiveness in patients with asthma (Bryan et al., 2000). The role of T lymphocytes is less controversial. T lymphocytes play an important role in the airway inflammation. T-helper lymphocytes differentiate into two main phenotypes, Th1 and Th2, which produce distinct profiles of cytokines and chemokines (Grunig et al., 1998). Th1 cells produce interferon, whereas Th2 cells produce interleukin 4, 5, and 13. Th2 cells are potent stimulators of Ig E production from B lymphocytes. Results of studies (Tournoy et al., 2001) in mice have suggested that Th2 cytokines have key roles, and results of bronchoscopic lavage studies (Walker et al., 1992) in human beings have shown increased concentrations of these cytokines.

Inflammatory cells are recruited into the airways by chemokines, which exert some degree of selectivity in the cells they attract. Eosinophil chemotactants include eotaxin, interleukin 5, RANTES (i.e., regulated by activation, normal T-cell expressed and secreted), and monocyte chemotactant proteins 3 and 4, whereas neutrophils are recruited mainly by interleukin 8 (Lukacs et al., 1999). These chemokines are produced by inflammatory and structural cells such as airway smooth muscle cells and airway epithelium (Johnson and Knox, 1997; Folkerts and Nijkamp, 1998). Inflammatory cells bind to adhesion molecules on bronchial vessel endothelium and subsequently undergo a process of transmigration into the airway interstitium (Hellewell, 1999). Airway cells also release survival factors, such as granulocyte macrophage colony stimulating factor (GM-CSF), which extend the life of inflammatory cells at the site of inflammation (Turlej et al., 2001).
REMODELING COMPONENT

Acute inflammatory diseases usually resolve with repair processes restoring normal structure and function. In chronic asthma, this process becomes disturbed and ineffective repair leads to remodeling involving several structures (Elias et al., 1999). Epithelial damage and loss of its protective barrier function exposes the deeper airway structures to environmental insults, and both inflammatory and structural cells produce several growth factors that lead to angiogenesis, proliferation of smooth muscle in the airway, thickening of basement membranes, and fibrosis (Elias et al., 1999). The increase in the mass of smooth muscles in the airway increases bronchial responsiveness by increasing force in response to bronchoconstrictor stimuli and by reduction of the airway’s diameter (Knox, 1994). Important cytokines and enzymes during the remodeling process include transforming growth factor, epidermal growth factor, and matrix metalloproteinases.

STATUS

Asthma affects 7% of the total population and approx 300 million worldwide. During attacks (exacerbations), the smooth muscle cells in the bronchi constrict, and the airways become inflamed and swollen with difficulty in breathing. Asthma causes 4,000 deaths a year in the US alone. Attacks can be prevented by avoiding triggering factors and by drug treatment (Prasad et al., 2009). With the projected increase in the proportion of the world's population that is urban from 45% to 59% in 2025, there is likely to be a marked increase in the number of asthmatics worldwide over the next two decades. It is estimated that there may be an additional 100 million persons with asthma by 2025 (Masoli et al., 2003). Asthma is thought to affect about 3% of the population in most countries. The highest prevalence (almost 30%) is found in New Zealand. The prevalence in a number of countries falls in the range of 10%–17% (Murthy and Sastry, 2005).

There are only a few studies from India on field epidemiology of asthma. In a study conducted more than 30 years ago, prevalence of asthma was reported as 2.78% in an urban population aged 30-49 years. It was also reported in the same study that the prevalence in morbidity surveys of Government employees and their families in Delhi was 1.8% (Aggarwal et al., 2006). According to the National Family Health Survey-2 (NFHS-2) report the estimated prevalence of asthma in India is 2468 per 100,000 persons. The prevalence was higher in rural than in urban areas. The prevalence among males was
slightly higher than among females. Among those below 15 years of age, asthma was seen in 950 per 100,000 persons. The prevalence of asthma in adult males (18 years and above) during 1995–97 was 3.94% in urban and 3.99% in rural areas. In females of the same age group, the prevalence was 1.27% in urban as well as rural areas. Increasing in prevalence is associated with spreading urbanization, exposure to domestic mites, vehicle exhausts, smoking, allergens and family history (Murthy and Sastry, 2005).

**DIAGNOSIS AND ASSESSMENT**

Ascertainment of whether asthma is present is usually straightforward, and is based on a characteristic history and variability in lung function. In young children it can take some time to ascertain whether the child has persistent asthma rather than wheezy bronchitis (Stolley and Schinnar, 1978). In older patients, distinguishing severe chronic asthma from COPD can be difficult and the two disorders sometimes merge in those who have smoked cigarettes. Asthma can also be diagnosed incorrectly, especially in patients with inappropriate hyperventilation, dysfunction of the vocal cords, or obstruction of the upper airway. Diagnosis of asthma still relies on demonstration of variability (measurement of asthma severity) in lung function over time or improvement after a bronchodilator, prednisolone, or high-dose inhaled corticosteroid. Such variability can be measured with spirometry in the clinic or by regular peak flow measurements at home. Demonstration of bronchoconstriction after vigorous exercise can be useful in young people, whereas an increase in blood eosinophils could point to asthma in older patients. Other features associated with asthma, such as non-specific bronchial hyper responsiveness to agents such as methacholine, are not specific enough to be a useful diagnostic test. The essential treatment for asthma includes oxygen, nebulised 2 agonists, and oral or intravenous corticosteroids to patients.

**MANAGEMENT**

A patient might have poorly controlled asthma due to poor management, severe asthma, or both. Poor compliance with treatment, especially inhaled corticosteroids, continues to be an important cause of poor asthma control and much effort is needed to ensure that patients understand why prophylactic treatment needs to be taken regularly and the dangers of poor compliance (Rona, 2000). Several developments have contributed to better asthma management including development of guidelines (The British Guidelines on Asthma Management, 1997), better of peak-flow meters, and recognition
of the need to improve patient education. Patients with asthma should be advised strongly not to smoke and to lose weight, if overweight, since these measures improve asthma control (Stenius-Aarniala et al., 2000). Inactivated influenza vaccine is recommended and is safe in patients with asthma (The American Lung Association Asthma Clinical Research Centers, 2001).

**PHARMACOTHERAPY**

Drugs should be given by inhalation when possible so that the same beneficial effect can be achieved with a much smaller dose, thus causing lower systemic drug concentrations and fewer systemic adverse effects (Haahtela et al., 1994). Over the past two decades, many groups have tried to develop new types of drug for asthma, but only the leukotriene modifiers are on the market. Most asthma guidelines include a stepwise approach to asthma treatment, which ranges from $\beta$-agonists alone for very mild intermittent asthma to oral corticosteroids for severe chronic asthma (Pauwels et al., 1997). A schematic hierarchy of the drugs considered most appropriate for different levels of asthma severity is shown in Figure 5. Treatment should be determined by symptoms, exacerbations, and lung function. There is some controversy about inhaled corticosteroids, which are very effective at suppressing inflammation in asthma. Symptoms and airway obstruction usually reappear when the drugs are discontinued (O’Byrne et al., 2001).
Inhaled Corticosteroids

Inhaled corticosteroids are the cornerstone of treatment for asthma. They are especially helpful in patients with mild or moderate asthma, improving lung function, and reducing symptoms and exacerbations (Haahtela et al., 1994) and they have been shown to reduce readmissions for asthma (Blais et al., 1998) and asthma deaths (Suissa et al., 2000). Inhaled corticosteroids are recommended for all patients requiring more than one puff a day from their β-agonist inhaler. However, there are two limitations of inhaled corticosteroids. First, although small doses of an inhaled corticosteroid are very effective, the added benefit from higher doses is limited. Doubling (Greening et al., 1994) or quadrupling (Pauwels et al., 1997) the dose of an inhaled corticosteroid can improve asthma control, but it is usually better to add in a long-acting β-agonist. Second, long-term high doses of inhaled corticosteroids can cause systemic adverse effects, including reduced bone mineral density (Wong et al., 2000) which is likely to predispose patients to osteoporotic fractures as they get older, and an increase in cataracts (Cumming et al., 1997) and glaucoma (Garbe et al., 1997). Since inhaled corticosteroids reduce the need
for oral corticosteroids, which have many more adverse effects, the goal of treatment is to
give the minimum dose of inhaled corticosteroid to maintain good control.

Most patients with asthma can be managed on a low dose, which will produce
maximum or near maximum benefit with minimum risk of long-term adverse effects
(Figure 6). Fluticasone is twice as potent as beclometasone and budesonide. The dose of
corticosteroids vary depending on the severity of asthma but will rarely be above 800 µg
beclometasone or budesonide a day (equivalent to 400 µg of fluticasone a day) and
usually preferred less than 400 µg a day (equivalent to 200 µg fluticasone a day) for most
of patients.

**Figure 6: Relation between beneficial and adverse effects with increasing doses of
inhaled corticosteroids**

(X=dose at which maximum benefit is achieved with minimum side effects)

(Tattersfield *et al.*, 2002).

**Agonists**

Short-acting β-agonists such as salbutamol and terbutaline are very effective in
prevention of exercise-induced asthma and for relieving acute attacks of asthma. They do
not provide benefit when given regularly (Drazen *et al.*, 1996) and are debatable, as some
patients can even deteriorate (Sears et al., 1990). Patients should therefore take short-acting β-agonists only as required. By contrast with short acting β-agonists, regular use of the long-acting β-agonists, salmeterol and formoterol, improves asthma control and reduces asthma exacerbations (Taylor et al., 1998). Both drugs are effective for longer than 12 h and should be taken twice daily. The main clinical difference between the two drugs is that formoterol has a rapid onset of action, similar to that of salbutamol, raising the possibility that formoterol could be used for symptom control in addition to regular administration. Asthma control was better with formoterol when compared with terbutaline for relief of asthma (Tattersfield et al., 2001) and it is now licensed for up to 72 μg a day. Thus, these drugs are now introduced at an earlier point in asthma management—i.e., for patients who remain symptomatic despite 400–800 μg of an inhaled corticosteroid. Both long-acting β-agonists can be given in combination with an inhaled corticosteroid which improves patient compliance.

**Theophylline, Ipratropium, Cromoglycate and Nedocromil**

Theophylline is effective in asthma and has some anti-inflammatory activity (Sullivan et al., 1994). It is less effective than the long acting - agonists (Fjellbirkeland et al., 1994) however, and its narrow therapeutic window and interactions with other drugs make it a less attractive option. More selective phosphodiesterase inhibitors have been developed (Torphy, 1998) but have not yet shown clear benefit over theophylline. Ipratropium and oxtropium are also effective bronchodilators but usually add little in patients with stable asthma who are already taking a β-agonist. Sodium cromoglicate and nedocromil have also been used in mild to moderate asthma therapy.

**Prednisolone and Steroid-Sparing Drugs**

Oral corticosteroids cause much morbidity and patients on long-term oral steroids need careful assessment to be sure that such treatment is necessary. For those who require prednisolone, prophylaxis against osteoporosis needs to be considered, ideally with a measure of bone mineral density. Bisphosphonates and hormone replacement therapy decrease the loss of bone mineral density seen with oral corticosteroids (Dawson-Hughes, 2001). Some immunosuppressive drugs (methotrexate, ciclosporin, and gold) reduce oral steroid requirements in patients with severe asthma (Hill, 1995; Lynch & McCune, 1997).

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NEW DRUG THERAPY FOR ASThma

Leukotriene modifiers consist of the lipoxygenase inhibitors such as zileuton, and the leukotriene antagonists such as montelukast and zafirlukast. The drugs are given orally and a single drug can therefore treat both rhinitis and asthma. Both types of drug are effective in patients with mild or moderate asthma (Horwitz et al., 1998). Leukotriene antagonists cause some bronchodilatation within an hour of administration (Reiss et al., 1997) and results of long term studies (Barnes and Miller, 2000) have shown a reduction in symptoms and exacerbations. Both drugs have shown efficacy when added to an inhaled corticosteroid (Horwitz et al., 1998). Montelukast was ineffective when added to other treatment in a pragmatic study of patients with more severe asthma (Robinson et al., 2001). Leukotriene antagonists should theoretically be useful in aspirin-induced asthma, but their effectiveness in these patients has been limited (Dahlen et al., 1998). Churg-Strauss syndrome has occurred in association with use of the leukotriene antagonists, but whether it is due to a direct drug effect or unmasking of the syndrome as inhaled or oral corticosteroids are reduced is still uncertain (Stirling and Chung, 1999; Tuggey and Hosker, 2000).

Drugs That May Be Promising in Near Future

The suggestion that the anti-inflammatory effects of corticosteroids are due to gene silencing (transrepression), whereas the adverse effects are due to gene activation (transactivation) (Newton, 2000) has led to interest in dissociated steroids that have only transrepression properties and should therefore have fewer adverse effects. Dissociated steroids produced unwanted effects on bone in animals, however, suggesting that some of their adverse effects are linked to transrepression (Belvisi et al., 2001). The role of glucocorticoid receptor polymorphisms in determining the response to corticosteroids is also being investigated (Huizenga et al., 1998) as is whether long-acting β-agonists enhance the anti-inflammatory effects of corticosteroids in vivo as shown in vitro (Knox et al., 2001). Increased understanding of the role of various cytokines and chemokines and the imbalance between Th1 and Th2 cells in asthma raises the possibility of interventions at different sites in the inflammatory cascade (Stirling and Chung, 2000) Some improvements in asthma control have been seen in early studies of soluble interleukin 4 receptors (Borish et al., 1999) and selective Th2 cytokine inhibitors (Tamaoki et al., 2000). Clinical studies of humanised monoclonal antibodies to Ig E,
CD4+ cells, and interleukins 4 and 5 are under way. Antibodies to Ig E caused a large reduction in circulating free Ig E without major safety problems (Milgrom et al., 1999). The first large-scale clinical study (Milgrom et al., 1999) with an Ig E monoclonal antibody, omalizumab, in selected patients showed some clinical benefit and it enabled the dose of inhaled corticosteroid to be reduced. The effects of antibodies to interleukin 5 (Leckie et al., 2001) and interleukin 12 (Bryan et al., 2000) on clinical features of asthma have been disappointing. The need for regular injections to administer monoclonal antibodies is likely to restrict their role to patients with troublesome asthma. The completion of the human genome project is likely to fuel a new and important period of research into asthma therapy.

**Drawbacks of Modern Medicines in Asthma Treatment**

Despite the availability of a wide range of drugs for the treatment of asthma, the relief offered by them is mainly symptomatic. Moreover, the side effects of these drugs are also quite disturbing. Hence, a continuous search is ongoing to identify effective and safe remedies to treat bronchial asthma. Therefore, it is necessary to look for new solutions to manage this health problem. Although many drugs and interventions are available to manage asthma, in most instances these are expensive for a developing country like India and have several adverse effects. India is a country with a vast reserve of natural resources and a rich history of traditional medicine (Grover and Vats, 2001). Although the contribution of modern synthetic medicine for elevating the human sufferings cannot be under-estimated, equally true is the fact that most of them leave unwanted harmful side/toxic effects on the human system disturbing the basic physiology. During the last three decades or so, there has been serious realization of these problems associated with synthetic drugs and as a result the world has started exploring the herbs as agents of therapy which, apart from being comparatively economical and easily available, are relatively free from the hazardous side effects, toxicity and development of resistance towards causative organisms. This does not mean that plants are hundred percent safe but in-depth review of literature and scientific work is still required in the field of medicinal plants regarding assessment of heavy metals and presence of toxins to call them safe Indian Medicinal Plants (Prasad et al., 2009).

Among several respiratory diseases affecting man, bronchial asthma is the most common disabling syndrome. Nearly 7–10% of the world population suffers from
bronchial asthma. Asthma is characterized by various airway obstruction, airway eosinophilic inflammation and bronchial hyper responsiveness (Djukanovic et al., 1990) and is a global health problem that results from a complex interplay between genetic and environmental factors (Philip, 2003). Despite the availability of a wide range of drugs, the relief offered by them is mainly symptomatic and short lived. Moreover, the side effects of these drugs are instigates scientists to identify effective and safe remedies to treat bronchial asthma (Govindan et al., 1999).

Conventional antiasthmatic compounds such as sodium cromolyn and sodium cromoglycate is one of the examples of the lead prepared from the analogs of the naturally occurring furanchromone khellin (visammin), found in Ammi visnaga Lam (Cox et al., 1970). Explanation of the chemical constituents of the plants and pharmacological screening will thus provide us the basis for developing new life saving drugs. Avoidance of allergens can be helpful for patients with specific allergen sensitivities. Complementary approaches to treatment, such as Yoga, help some patients, but overall, the effect seems to be small (Kleijnen et al., 1991; Lewith, 1998).

In the light of above background, the present study was aimed to screen Indian medicinal plants and their combinations in the form of polyherbal formulations for the potential anti-asthmatic activity and synergistic effects of these combinations.
Table No.1: List of some medicinal plants traditionally claimed to have potential anti-asthmatic activity (Prasad et al., 2009)

<table>
<thead>
<tr>
<th>S.No</th>
<th>Common Name</th>
<th>Botanical Source</th>
<th>Family</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Kuppi</td>
<td><em>Acalypha indica</em></td>
<td>Euphorbiaceae</td>
</tr>
<tr>
<td>2.</td>
<td>Sweet Flag</td>
<td><em>Acorus calamus</em></td>
<td>Araceae</td>
</tr>
<tr>
<td>3.</td>
<td>Golden apple/ Bael</td>
<td><em>Aegle marmelos</em></td>
<td>Rutaceae</td>
</tr>
<tr>
<td>4.</td>
<td>Onion</td>
<td><em>Allium cepa</em></td>
<td>Liliaceae</td>
</tr>
<tr>
<td>5.</td>
<td>Kalmegh</td>
<td><em>Andrographis paniculata</em></td>
<td>Acanthaceae</td>
</tr>
<tr>
<td>6.</td>
<td>Indian olibanum tree</td>
<td><em>Boswellia serrata</em></td>
<td>Brusseraceae</td>
</tr>
<tr>
<td>7.</td>
<td>Bhang</td>
<td><em>Cannabis sativa</em></td>
<td>Cannabaceae</td>
</tr>
<tr>
<td>8.</td>
<td>Bharnagi</td>
<td><em>Clerodendrum serratum</em></td>
<td>Verbenaceae</td>
</tr>
<tr>
<td>9.</td>
<td>Jeera</td>
<td><em>Cuminum cyminum</em></td>
<td>Umbelliferae</td>
</tr>
<tr>
<td>10.</td>
<td>Thorn apple</td>
<td><em>Datura metel</em></td>
<td>Solanaceae</td>
</tr>
<tr>
<td>11.</td>
<td>Liquorice</td>
<td><em>Glycyrrhiza glabra</em></td>
<td>Fabaceae</td>
</tr>
<tr>
<td>12.</td>
<td>Pushkarmoola</td>
<td><em>Inula racemosa</em></td>
<td>Asteraceae</td>
</tr>
<tr>
<td>13.</td>
<td>Jatamansi</td>
<td><em>Nardostachys jatamansi</em></td>
<td>Valerianaceae</td>
</tr>
<tr>
<td>14.</td>
<td>Anisu</td>
<td><em>Pimpinella anism</em></td>
<td>Umbelliferaceae</td>
</tr>
<tr>
<td>15.</td>
<td>Pippali</td>
<td><em>Piper longum</em></td>
<td>Piperaceae</td>
</tr>
<tr>
<td>16.</td>
<td>Plantain</td>
<td><em>Plantago major</em></td>
<td>Plantaginaceae</td>
</tr>
<tr>
<td>17.</td>
<td>Brinjal</td>
<td><em>Solanum melongena</em></td>
<td>Solanaceae</td>
</tr>
<tr>
<td>18.</td>
<td>Vibhitaki</td>
<td><em>Terminalia bekerja</em></td>
<td>Combretaceae</td>
</tr>
<tr>
<td>19.</td>
<td>Guduchi</td>
<td><em>Tinospora cordifolia</em></td>
<td>Menispermaceae</td>
</tr>
<tr>
<td>20.</td>
<td>Ginger</td>
<td><em>Zingiber officinale</em></td>
<td>Zingiberaceae</td>
</tr>
</tbody>
</table>
Table No.2: List of some existing Siddha traditional formulation claimed to have potential anti-asthmatic activity (Bharathathin siddha maruthugal seemurai kurippu nool, 1984).

<table>
<thead>
<tr>
<th>S.No</th>
<th>Name of the Formulation</th>
<th>Uses</th>
<th>Dosage/Per day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Adathodai nei</td>
<td>Erumal, Suvasam, Kasam, Elai.</td>
<td>5ml / tds</td>
</tr>
<tr>
<td>2.</td>
<td>Kasthuri karuppu</td>
<td>Erumal, Eraippu, Saali</td>
<td>65mg / bd</td>
</tr>
<tr>
<td>3.</td>
<td>Kasthuri mathirai</td>
<td>Suvasam, Kabha noigal</td>
<td>1 / tds</td>
</tr>
<tr>
<td>4.</td>
<td>Muthu chippi parpam</td>
<td>Erumal, Eraippu, Kasam</td>
<td>65mg / tds</td>
</tr>
<tr>
<td>5.</td>
<td>Muthu parpam</td>
<td>Erumal, Eraippu, Kasam</td>
<td>65mg / tds</td>
</tr>
<tr>
<td>6.</td>
<td>Nellikai legiyam</td>
<td>Kabha noigal</td>
<td>5gm / bd</td>
</tr>
<tr>
<td>7.</td>
<td>Pachai kapoora mathirai</td>
<td>Kabham 96</td>
<td>1tab / tds</td>
</tr>
<tr>
<td>8.</td>
<td>Pavana kadukai</td>
<td>Erumal, Suvasam</td>
<td>One slice / tds</td>
</tr>
<tr>
<td>9.</td>
<td>Poorana chandrothayam</td>
<td>Erumal, Elai.</td>
<td>65mg / tds</td>
</tr>
<tr>
<td>10.</td>
<td>Sivanar amirtham</td>
<td>Eraippu Erumal 5, Iyam 20</td>
<td>65mg / tds</td>
</tr>
<tr>
<td>11.</td>
<td>Suvasa koodoori mathirai</td>
<td>Eraippu Erumal, Erumal, Kasam</td>
<td>1 tab / tds</td>
</tr>
<tr>
<td>12.</td>
<td>Thalaga chendooram</td>
<td>Kasam</td>
<td>4mg / tds</td>
</tr>
<tr>
<td>13.</td>
<td>Thalaga kattu</td>
<td>Kabha suram, Sanni</td>
<td>4mg / tds</td>
</tr>
<tr>
<td>14.</td>
<td>Thalaga parpam</td>
<td>Erumal, Mandhara kasam, Elai.</td>
<td>4mg / tds</td>
</tr>
<tr>
<td>15.</td>
<td>Thalagakaruppu</td>
<td>Kasam, Eraippu Erumal, Elai.</td>
<td>4mg / tds</td>
</tr>
<tr>
<td>16.</td>
<td>Thalisathi chooranam</td>
<td>Kabham 96, Erumal.</td>
<td>1gm / tds</td>
</tr>
<tr>
<td>17.</td>
<td>Thalisathi vadagam</td>
<td>Kabham</td>
<td>2 / tds</td>
</tr>
<tr>
<td>18.</td>
<td>Thipilli rasayanam</td>
<td>Kabham 96, Natpatta erumal,</td>
<td>2gm / tds</td>
</tr>
<tr>
<td>19.</td>
<td>Thoothuvalai nei</td>
<td>Eumal, Mandhara kasam</td>
<td>5ml / tds</td>
</tr>
<tr>
<td>20.</td>
<td>Velli parpam</td>
<td>Elai, Erumal, Kabham 96.</td>
<td>65mg / tds</td>
</tr>
</tbody>
</table>
Aim and Objectives