Abstract In traditional systems of medicine, many plants have been documented to be useful for the treatment of various respiratory disorders including asthma. In the last two decades the use of medicinal plants and natural products has been increased dramatically all over the world. Current synthetic drugs used in pharmacotherapy of asthma are unable to act at all the stages and targets of asthma. However some herbal alternatives employed in asthma are proven to provide symptomatic relief and assist in the inhibition of disease progression also. The herbs have shown interesting results in various target specific biological activities such as bronchodilation, mast cell stabilization, anti-anaphylactic, anti-inflammatory, anti-spasmodyc, anti-allergic, immunomodulatory and inhibition of mediators such as leukotrienes, lipoxygenase, cyclooxygenase, platelet activating, phosphodiesterase and cytokine, in the treatment of asthma. This paper is an attempt to classify these pharmacological and clinical findings based on their possible mechanism of action reported. It also signifies the need for development of polyherbal formulations containing various herbs acting at particular sites of the physiological cascade of asthma for prophylaxis as well as for the treatment of asthma.

Keywords Asthma · Current therapy · Herbal therapy · Poly herbal formulations · Ayurvedic drugs · Medicinal plants

Introduction

According to the National Institute of Health (NIH), asthma is defined as a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role, in particular, mast cells, eosinophils, T-lymphocytes, neutrophils and epithelial cells (NIH 1997). Asthma is caused by a very complex interaction between inflammatory cells and mediators. Herbal approaches have regained their popularity, for the treatment of asthma, with their efficacy and safety aspects being supported by controlled clinical studies (Huntley and Ernst 2000). Ongoing worldwide research has also provided valuable clues regarding the precise mechanism of action of these herbal alternatives (Goyal et al. 2007).

Pharmacotherapy of bronchial asthma

In the past most clinicians managed asthma mainly according to the patient’s symptom. Asthma was regarded primarily as a problem of bronchospasm and measures to prevent or reverse bronchospasm comprised the mainstay of therapy. However, during early 1980s when asthma emerged as an inflammatory rather than primarily a bronchospastic disorder, the basic approach switched from control of symptoms to control of underlying airway inflammation (Barns 1989). According to guidelines of The National Asthma Education and Prevention Program’s
Bronchodilators

Bronchodilator drugs have an anti-bronchoconstrictor effect that may be demonstrated directly in vitro by drug-induced relaxation of precontracted airways (Barns et al. 1988).Bronchodilators promptly reverse airway obstruction in asthmatics. This action believed to be mediated by a direct effect on airway smooth muscle. However, additional pharmacologic effects on the other airway cells (such as capillary endothelium to reduce microvascular leakage and mast cells to reduce release of bronchoconstrictor mediators) may contribute to the overall reduction in airway narrowing. Only three types of bronchodilators are in current clinical use: β-adrenergic agonists, methylxanthines, and anticholinergics.

β-adrenergic agonists

Epinephrine has been used to treat asthma since the beginning of the 20th century. β Adrenergic agonists are most widely used and effective bronchodilators for the treatment of asthma. Bronchodilation is mediated by β₂ receptors; β₂ selective drugs (Salmeterol and Formotero) have been developed that have long duration of effect. β Adrenergic agonists lead to relaxation of bronchial smooth muscle that promote bronchodilation. Activation of adenylate cyclase increases the concentration of intracellular cyclic adenosine 3′, 5′-monophosphate (cAMP), leading to activation of specific cAMP-dependent protein kinases that cause relaxation. Relaxation may also be due to inhibition of myosin phosphorylation. β-adrenergic agonists reverse bronchoconstriction irrespective of the contractile agent. β₂-adrenergic agonists prevent release of mediators from a number of inflammatory cells in vitro (Church and Hiroy 1987). In addition, β adrenergic agonists increase mucus secretion from submucosal glands and ion transport across airway epithelium. These effects enhance mucociliary clearance caused by asthma (Pavia et al. 1980).

The inhaled route of administration is preferable to the oral route because adverse effects caused by systemic action of the drug are less and also because this route may be more effective. The inhaled drug reaches surface cells (e.g., mast cells or epithelial cells), which are less accessible to the orally administered drug.

Metaproterenol, terbutaline, albuterol, formoterol, bitolterol, salmeterol, and pirbuterol are the classic examples of selective β₂-adrenergic agonists.

β₂ agonists improve respiratory symptoms and exercise tolerance despite the small improvement in spirometric measurements. The long acting β-agonists decrease infection exacerbations as an additional potential benefit. Salmeterol has been shown to reduce adherence of bacteria such as H. influenzae to airway epithelial cells.

β₂ selective agents cause tachycardia and palpitation by reflex cardiac stimulation secondary to peripheral vasodilation. Muscle tremor is caused by stimulation of β₂ adrenergic receptors in skeletal muscle and is the primary adverse effect of albuterol and bitolterol. Transient hypokalemia may be induced by high dose of these agents.

Anticholinergics

Datura plants contain the muscarinic antagonist and were smoked for relief of asthma centuries ago. Now a days, atropine and ipratropium bromide are the most commonly available anticholinergics.

Antimuscarinic agents specifically antagonize muscarinic receptors. They inhibit reflex cholinergic bronchoconstriction and do not significantly block the direct effects of inflammatory mediators such as histamine and leukotrienes on bronchial smooth muscle and vessels. When given by inhalation, anticholinergics produce bronchodilation by competitively inhibiting cholinergic receptors in bronchial...
smooth muscle. This activity blocks acetylcholine with the net effect being a reduction in cyclic guanosine monophosphate (cGMP) that normally acts to constrict bronchial smooth muscle. Anticholinergic drugs usually are less effective as bronchodilators in asthmatic subjects than β adrenergic agonists. Nevertheless, they may have an additive effect with β adrenergic agonists.

Anticholinergic agent, ipratropium bromide, even when given in high doses, has no such detectable effect either on normal subjects or in patients with airway disease (Pavia et al. 1980). Ipratropium bromide has been shown to decrease the effectiveness of voluntary cough on clearing mucus from the airways, which may affect its role in the treatment of patients who have excessive mucus production. Ipratropium has a slower onset of action and a more prolonged bronchodilator effect compared with standard β2-agonists and has been considered to be less suitable for use on an as needed basis for immediate relief of bronchospasm.

The lack of systemic absorption of ipratropium greatly diminishes the anticholinergic side effects such as blurred vision, urinary retention, nausea, and tachycardia associated with atropine. A significant unwanted effect of inhaled ipratropium bromide is dryness of mouth and throat, bitter taste, cough and nausea. Nebulized ipratropium bromide may precipitate glaucoma in elderly patients because of its direct mydriatic effect on the eye. During sleep, ipratropium also has been shown to improve arterial oxygen saturation and sleep quality.

Tiotropium bromide is a long acting quaternary anticholinergic agent. Tiotropium in human lungs shows approximately 10 fold more potency than ipratropium and protects against cholinergic bronchoconstriction for greater than 24 h.

Methylxanthines

Methylxanthines such as theophylline are related to caffeine and have been used to treat asthma since 1930. The methylxanthines may produce bronchodilation through numerous mechanisms, including,

- inhibition of phosphodiesterase, thereby increasing cAMP levels
- inhibition of calcium ion influx into smooth muscle
- prostaglandin antagonism
- stimulation of endogenous catecholamines
- adenosine receptor antagonism
- Inhibition of release of mediators from mast cells and leukocytes.

Theophylline inhibits release of mediators from mast cells, increases mucociliary clearance, and prevents the development of micro vascular leakiness, as would an “anti-inflammatory” drug (Persson and Draco 1988). Theophylline also inhibits some functions of T lymphocytes, which may be relevant to control of chronic inflammation of the airway.

For nocturnal asthma, a single dose of slow release theophylline at bedtime often is effective. This has been demonstrated to reduce overnight declines in FEV1 and morning respiratory symptoms. Taken alone it increases exercise tolerance without improving spirometry tests.

Other theophylline salts, such as choline theophyllinate, offer no advantages over theophylline. The ethylenediamine component of aminophylline has been implicated in allergic reactions. Some derivates such as acepiphylline, diprophyl- line, and proxophylline, are less effective than theophylline (Weinberger 1984). The most common adverse effects are headache, nausea and vomiting, abdominal discomfort, and restlessness.

Anti-inflammatory drugs

Although the type of inflammatory responses may differ among diseases, inflammation is a common denominator of several lung diseases. Anti-inflammatory drugs suppress the inflammatory response by inhibiting infiltration and activation of inflammatory cells as well as their synthesis or release of mediators or effects of inflammatory mediators themselves.

Corticosteroids

Since asthma is viewed as a chronic inflammatory disease and inhaled corticosteroids are known to have low toxicity, they may be considered as first line therapy (Barns 1989). Prednisolone and dexamethasone were effective when they were given systematically to treat asthma but they had no anti-asthmatic activity when they were given by inhalation. Other corticosteroids e.g. beclomethasone dipropionate (BDP), betamethasone and budesonide, were effective in treating asthma when given by inhalation. The antiasthmatic potency of an inhaled steroid is approximately proportional to its potency as an anti-inflammatory agent.

Corticosteroids inhibit the release of arachidonic acid metabolites and platelet activating factor (PAF) from lungs and macrophages by enhancing the production of proteins called lipocortins. Thereby they inhibit the formation of prostaglandins and leukotrienes. These effects occur because of ability of steroid—receptor complex to be transported to the nucleus, where it initiates DNA transcription of specific mRNAs. Corticosteroids potentially inhibit the accumulation of neutrophils, inhibit secretion of human pulmonary macrophages of leukotrienes and prostaglan-
dins; inhibit formation of interleukins (ILs) such as IL-1, IL-2, IL-3 and IL-5, inhibit degranulation and adherence of eosinophils, reduce number of circulating T lymphocytes and formation of an IgE binding suppressive factor. Steroids prevent and reverse the increase in vascular permeability due to inflammatory mediators and may therefore lead to resolution of airway edema. Corticosteroids remain the most effective therapy available for asthma but the legitimate fear of their adverse effects makes using them difficult. Steroids potentiate the effects of β adrenergic agonists on bronchial smooth muscle (Barnes 1989). Methylprednisolone is given intravenously to patients with severe acute asthma. Inhaled steroids have no proven value in the management of acute asthma. Patients with chronic bronchitis occasionally respond to steroids, possibly because some have an element of undiagnosed asthma.

Corticosteroids inhibit release of ACTH and secretion of cortisol by a negative feed back effect on the pituitary gland. Adverse effects of corticosteroids include fluid retention, increased cell mass, increased appetite, weight gain, osteoporosis, capillary fragility, hypertension, peptic ulceration, diabetes, cataract, and psychosis (Dajani et al. 1981).

Anti-leukotrienes

Leukotrienes possess potent pro-inflammatory actions resulting in increased vascular permeability, mucus secretion and bronchial hyperresponsiveness. They are derived from the 5-lipoxygenase pathways in mast cells, eosinophils and macrophages. Anti-leukotrienes improve lung function and diminish symptoms, exacerbation rate and the need for rescue bronchodilator. These are drugs of choice in case of aspirin induced asthma, in which patients have high LTE4 levels in urine and nasal secretions and even higher after taking aspirin (Christie et al. 1992).

Leukotriene modifiers are drugs that modify the response of these mediators of inflammation by one of the four ways (Drazen 1997).

a) Cysteinyl LT receptor inhibitors

C-LTs promote eosinophil influx, bronchospasm and mucus hypersecretion, all are considered hallmarks of asthma. C-LT receptor inhibitors antagonize or inhibit leukotrienes predominantly LTD4. These agents inhibit phospholipases, prostaglandins, leukotrienes, and IL-1 synthesis. Probilukast and Iralukast belong to this class (Drazen 1997; Florenani and Rennard 1999).

b) 5-lipoxygenase inhibitors

They prevent the formation of leukotrienes by blocking a 5-lipoxygenase pathway in their synthesis. Zileuton, ZD-2138, ABt-761 belongs to this class (Florenani and Rennard 1999).

c) 5-lipoxygenase activating protein (FLAP) inhibitors

MK-0591 and MK-886 attenuated the early and late asthmatic response following antigen challenge but not the attendant increase in airway responsiveness to spasmogens (Diamant et al. 1995).

d) Leukotrienes receptor antagonists

Montelukast, Zafirlukast, Pranlukast are selective and high affinity LT1 antagonists (Adcock and Matthews 1998).

Zileuton has shown efficacy in exercise-induced asthma, aspirin induced bronchospasm and following chronic administration, an improvement in pulmonary function (FEV1) and a reduction in oral and inhaled corticosteroid use (Tamaoki et al. 1997). Furthermore, in a small study, zileuton attenuated both airway and blood eosinophilia in nocturnal asthmatics (Wenzel et al. 1995).

Zafirlukast has been demonstrated to attenuate the acute airway obstructive response to allergen and exercise challenge and to improve chronic asthma control both objectively (FEV1, nocturnal awakenings, β-agonist use) and subjectively.

Montelukast has been shown to block the early and late response to allergen challenge following single dosing, to improve FEV1 in both children (6–14 years) and adults and to protect against the development of exercise induced bronchoconstriction in both children and adults. Tolerance to the bronchoprotective effects of montelukast in attenuating exercise-induced bronchospasm does not develop following at least 12 weeks of therapy.

Pranlukast increases FEV1 within 1 h of dosing, improves patient summary symptom and nighttime asthma scores and reduces the use of rescue bronchodilators. In patients with moderate persistent asthma, it prevents exacerbations of asthma during reduction of high dose inhaled corticosteroids therapy (Tamaoki et al. 1997).

Mediator release inhibitors

Cromolyn sodium

Cromolyn Sodium (Sodium cromoglycate) is a derivative of khellin, an Egyptian herbal remedy. Cromolyn inhibited the release of mediators by allergen in passively sensitized animal and human lung preparations (Cox 1967). Cromolyn was classified as mast cell stabilizer. Cromolyn has variable inhibitory actions on other inflammatory cells including macrophages and eosinophils that may participate in allergic inflammation. In vivo cromolyn can block both the early response that may be mediated by mast cells to allergens and the late response and bronchial hyper responsiveness (Cockcroft and Murdock 1987). Cromolyn Sodium is used for prophylactic treatment and consequently needs to be taken regularly. It is the first choice anti-
inflammatory drug for children because it has few adverse effects (Bernstein 1985). Cromolyn sodium is classified as an antiallergic drug because it appears to have a specific effect on allergy based inflammation. Several other drugs also may be included in this category.

Nedocromil sodium is a new drug used for prophylaxis. It has a similar pharmacologic profile of activity to cromolyn, is more potent in various tests, and may have a longer duration of action. Ketotifen also is described as a drug to be used for prophylaxis against asthma.

Newer targets in asthma therapy

The current pharmacotherapeutic approaches to asthma have several limitations. First, there is no known asthma cure and little evidence that prevention is possible in susceptible persons. Hence, patients continue to be at risk of symptoms and exacerbations. Mortality remains a severe problem. Finally, the medications have adverse effects. There is even some evidence, albeit conflicting, that cataract formation, osteoporosis and growth impairment, as associated with systemic glucocorticoids, may arise from topical steroids, depending on dosages used. New inhalation devices and new generation beta-agonists are available. At the same time, new understanding of the molecular pathology of asthma has identified several novel therapeutic targets. Agents being tested in early phase clinical trials include antagonists of IgE, cytokines, adhesion molecules and transcription factors.

TXA2 inhibitors

TXA2 is a potent bronchoconstrictor, mucus producer and blood vessel permeability inducer and causes airway hyper responsiveness. Serabenast, dimotitran and ozagrel are the

### Table 1 Bronchodilators

| Sr. No | Name of plant                   | Part used/extract/fraction     | Major chemical constituent(s)                  | Reference                              |
|--------|--------------------------------|--------------------------------|-----------------------------------------------|----------------------------------------|
| 1.     | *Adhatoda vasica* Nees          | Leaves, Roots                  | Alkaloids                                     | Paliwa et al. 2000                     |
| 2.     | *Albizia lebbeck* (Sareesha _ rakt) | Stem bark/Aqueous              | Saponins                                      | Tripathi and Das 1977                  |
| 3.     | *Alstonia scholari*             | Leaves/Ethanol                 | Ditamine, Echitamine and Echitamines          | Channa et al. 2003                     |
| 4.     | *Artemisia caerulescens*        | Aerial parts/Butanol           | Quercetin, isorhamnetin                       | Moran et al. 1989                      |
| 5.     | *Belamcanda chinensis*          | Leaves/Ethanol                 | Tectorigenin                                  | Singh and Agrawal 1990                 |
| 6.     | *Benincasa hispida*             | Fruits/Methanol                | Triterpenes, Glycosides, Sterols              | Kumar and Ramu 2002                    |
| 7.     | *Cissampelos sympodielix*       | Leaves and root bark/Aqueous   | waritine, α-bisbenzylisoquinoline alkaloid     | Thomas et al. 1995, 1997; Cortes et al. 1995 |
| 8.     | *Clerodendron serratum*         | Stem bark/Aqueous              | Phenolic glycoside                            | Gupta 1968; Gupta and Tripathi 1973    |
| 9.     | *Coleus forskholi*              | Roots                          | Forskolin (Diterpenoid)                      | Marone et al. 1987                     |
| 10.    | *Elaeocarpus sphericus*         | Fruits/Aqueous, Pet-ether, Benzene, Acetone and ethanol | Glycoside, Steroids, Alkaloid, Flavanoids | Singh et al. 2000                      |
| 11.    | *Galpinia glauca*               | Aerial/Alcohol extract/Ethyl-acetate | Tetragalloyquinic acid, Quercetin | Campos et al. 2001                     |
| 12.    | *Gardenia latifolia*            | Bark                           | Saponins                                      | Gupta 1974                             |
| 13.    | *Ginko biloba*                  | Leaves                         | Ginkgolides                                  | Puglisi et al. 1988                    |
| 14.    | *Mikania glomerata*             | Leaves/Aqueous, hydroalcohol   | Coumarin                                      | Soares de Moura et al. 2002            |
| 15.    | *Lepidium sativum*              | Seeds/Ethanol fractions        | Alkaloids, Flavanoids                         | Mali et al. 2008                       |
| 16.    | *Ocimum sanctum*                | Leaves/Ethanol                 | Myrcenol, Nerol, Eugenol                     | Singh and Agrawal 1991                 |
| 17.    | *Passiflora incarnata*          | Leaves/Methanol                | Alkaloids                                     | Dhawan et al. 2003                     |
| 18.    | *Pavetta crassipes*             | Leaves/Aqueous                 | Flavanoids, tannins, antraquinones            | Amos et al. 1998                       |
| 19.    | *Picrorrhiza kurroa*            | Roots/                         | Androislin                                    | Stuppern et al. 1991                   |
| 20.    | *Sarcostemma brevistigma*       | Twigs/Alkaloidal fraction      | Bregenin                                      | Saraf and Patwardhan 1988b             |
| 21.    | *Tephrosia purpurea*            | Aerial parts/Ethanol extract    | Flavanoids, Tephrosin                         | Gokhale et al. 2000                    |
| 22.    | *Tylophora indica*              | Leaves/Alkaloidal fraction     | Tylophorine                                   | Nayampalli et al. 1986                 |
| 23.    | *Vitex negundo*                 | Leaves/Ethanol                 | Casticin, isoorientin Chrysophenol D, Luteolinc Acetic acid (CA) and Rosmarinic acid | Nair and Saraf 1995                     |
| 24.    | *Rosmarinus officinalis*        | Shrub/Aqueous                  | Ephedrine                                    | Aqel 1991                              |
| 25.    | *Ephedra sinica*                | Stems                          | Ephedrine                                    | Akiba et al. 1979                      |
| 26.    | *Gleditsia sinensis Lam.*       | Leaves/Decocitions             |                                              | Dai et al. 2002                        |
examples of these TXA2 synthetase inhibitors. Ozagrel reduced cough sensitivity to capsaicin and bronchoconstriction due to acetaldehyde. TXA2 antagonists BAY u3405 produced a modest decrease in airways responsiveness to methacholine following 2 weeks treatment in asthmatics.

Tachykinin receptor antagonists

The first nonpeptide tachykinin receptor antagonist was CP-96345, which is a potent NK1 receptor antagonist. SR

| Sr No | Name of plant            | Part used/extract/fraction | Major chemical constituent(s)                                | Reference                  |
|-------|---------------------------|----------------------------|-------------------------------------------------------------|----------------------------|
| 1.    | Achyranthes aspera        | Aerial parts/Aqeous        | Oleanolic acid                                              | Agrawal and Mehta 2005     |
| 2.    | Albizia lebbeck           | Stem bark/Aqueous          | Saponins                                                    | Tripathi et al. 1979       |
| 3.    | Allium cepa               | Bulbs/Juice                | α and β unsaturated Thiophosphinates                       | Johri et al. 1985          |
| 4.    | Aquilaria agallocha       | Stem/Aqueous extract       | Triterpenoids                                               | Kim et al. 1997            |
| 5.    | Azadirachta indica        | Leaves/Juice               | Nimbin, nimbinine, Nimbandiol, quercetin                    | Acharya et al. 2003        |
| 6.    | Bacopa monniera           | Leaves/Ethanol             | Bacosides, Alkaloids, Glycosides                           | Samiulla et al. 2001       |
| 7.    | Bidens parviflora         | Aerial parts               | Glycosides                                                  | Wang et al. 2001           |
| 8.    | Calotropis proceras       | Latex                      | α-amyrin,β-amyrin calotropin (Triterpenoid)                 | Kumar and Basu 1994        |
| 9.    | Cassia alata              | Leaves/Ethanol             | Anthraquinones, Flavanoids                                 | Palanichamy et al. 1991    |
| 10.   | Cassia obtusifolia        | Seeds/Glycosidal fraction  | Anthraquinones, Betulinic acid                              | Kitanaka et al. 1998       |
| 11.   | Cassia tansia             | Seeds                      | Gentio biosides                                             | Kanno et al. 1999          |
| 12.   | Cedrus deodara            | Wood oil                   | Himacholol                                                  | Shinde et al. 1999         |
| 13.   | Citrus unshiu             | Peels/                     | Flavanoids                                                  | Kim et al. 1999            |
| 14.   | Clerodendron serratum     | Bark/Aqueous               | Phenolic glycoside                                          | Gupta 1968                 |
| 15.   | Cnidium monnieri          | Fruits/Ethanol             | Osthol                                                      | Chen et al. 1988           |
| 16.   | Coleus forskohlii         | Roots                      | Forskolin (diterpenoid)                                    | Marone et al. 1987         |
| 17.   | Crinum glaucum            | Leaves/Aqueous             | Alkaloids, lycorine, crinamine                              | Okpo and Adeyemi 2002      |
| 18.   | Curcuma longa             | Rhizome                    | Tumorones, curcuminoids                                    | Ammon and Wahl 1991        |
| 19.   | Drymaria cordata          | Methanol extracts          |                                                            |                            |
| 20.   | Elaeocarpus spatharicus   | Fruits/Aqueous, Pet-ether, Benzene, Acetone and ethanol | Glycoside, Steroids, Alkaloid, Flavanoids  | Singh et al. 2000          |
| 21.   | Gleditsia sinensis        | Fruits/Ethanol             | Saponins                                                    | Dai et al. 2002            |
| 22.   | Impatiens textori         | Flowers/Ethanolic          | Apigenin, uteolin, chrysoeriol                              | Ishiguro et al. 2000       |
| 23.   | Inula racemosa            | Roots/Alcohol              | Inulolide-a new Sesquiterpen lactone                       | Srivastava et al. 1999     |
| 24.   | Magnolia officinalis      | Bark/Aqueous               | Honokiol, Magnolol                                          | Shin et al. 2001b          |
| 25.   | Mentha piperita           | Leaves                     | Flavanoidal glycosides                                     | Inoue et al. 2002          |
| 26.   | Ocimum sanctum            | Leaves/Aqueous             | Myrcenol, Nerol, Eugenol                                   | Sen 1993                   |
| 27.   | Picrorrhiza kurroa         | Roots/                     | Androsin                                                    | Stuppner et al. 1991       |
| 28.   | Solanum xanthocarpum      | Roots/Alkaloid fraction    | Solasodine                                                  | Chitravanashi et al. 1990  |
| 29.   | Striga orobanchioid       | Aerial parts/Ethanol       |                                                            |                            |
| 30.   | Tephrosia purpurea        | Aerial parts/Ethanol extract | Flavanoids, Tephrosin                                     | Gokhale et al. 2000        |
| 31.   | Terminalia chebula        | Fruits/Aqueous             | Ellagic acid, Tannins Chebulagic acid                       | Shin et al. 2001a          |
| 32.   | Tinospora cordifolia      | Stem/Aqueous               | Tinosporin                                                  | Nayampalli et al. 1986     |
| 33.   | Tylophora asthmatica      | Leaves/Alkaloidal          | Tylophorine                                                 | Geetha et al. 1991         |
| 34.   | Vitex negundo             | Leaves/Ethanol             | Casticin, isoorientin Chrysophenol D, Luteolin              | Nair et al. 1994           |
of tryptase, also attenuates antigen induced late response and bronchial hyperresponsiveness in allergic sheep.

Cytokine inhibitors

One of the novel approaches for the treatment of asthma is to target cytokines and develop cytokine modulators as drugs. Two humanized anti-IL-5 monoclonal antibodies, Sch-55700 and SB-240563 reduced blood eosinophil count for several weeks and prevented eosinophils recruitment into the airways after allergen challenge in asthmatic patients. IL-5 signaling inhibitor GCC-AP0341 inhibited IL-5 mediated survival of eosinophils. IL-4 receptor antibodies inhibited allergen induced airway hyperresponsiveness, goblet cell metaplasia and pulmonary eosinophilia in a murine model.

Chemokine inhibitors

A variety of chemokines, one of which is the chemo-attractant eotaxin, are secreted by inflamed lung tissue thereby attracting eosinophils. Eotaxin receptor blockers are being investigated, as eosinophils are believed to be major contributors to the pulmonary damage seen in asthma. Monoclonal antibody (7B11) for human CCR3 has shown to completely block the binding and signaling of the known CCR3 ligands, thus blocking the chemotactic response of human eosinophils to all chemokines.

Adhesion molecule antagonists

Interactions of eosinophils with intra cellular adhesion molecule-1 (ICAM-1) are thought to be necessary for eosinophils recruitment into airways. Antibodies to ICAM-1

Table 3 Anti-allergics

| Sr. No. | Name of plant       | Part used/extract/fraction          | Major chemical constituent(s)                                  | Reference                     |
|---------|---------------------|-------------------------------------|----------------------------------------------------------------|--------------------------------|
| 1.      | Adhatoda vasica     | Leaves/Methanol                     | Vasicinol, vasicine                                           | Muller et al. 1993; Kumar Suresh 1979 |
| 2.      | Albizzia lebbeck    | Stem bark/Aqueous                    | Saponins                                                      | Baruah et al. 1997; Suresh et al. 1981 |
| 3.      | Alisma orientale    | Rhizomes/Aqueous, Methanol          | Alisol B monoacetate, Alismaketones-B 23-acetate and –C 23-acetate | Kubo et al. 1997 |
| 4.      | Aquillaria agallocha| Stem/Aqueous extract                | Triterpenoids                                                 | Kim et al. 1997             |
| 5.      | Asiasarum sieboldi  | Roots/Methanol                      | Methyl Eugeneol, gamma-asarone, Elemicin, Asarinin            | Hashimoto et al. 1994        |
| 6.      | Camellia sinensis   | Leaves                              | Flavanoids                                                    | Suzuki et al. 2000           |
| 7.      | Centipedea minima   | Aerial parts                        | Flavanoids, Pseudoguainolide, sesquiterpene lactones         | Wu et al. 1985              |
| 8.      | Citrus unshiu       | Peels/                              | Flavanoids                                                    | Kim et al. 1999              |
| 9.      | Cnidium monnieri    | Fruits/Ethanol                      | Osthol                                                        | Matsuda et al. 2002          |
| 10.     | Crinum glaucum      | Leaves/Aqueous                      | Alkaloids, lycorine, crinamne                                 | Okpo and Adeyemi 2002        |
| 11.     | Curcuma longa       | Rhizomes                            | Curcumin and tetrahydrocurcumin                              | Suzuki et al. 2000           |
| 12.     | Dalbergia odorifera | Heart Wood                          | Flavanoids, Tannins                                          | Chan et al. 1998             |
| 13.     | Desmodium adscendens| Aqueous                            | Triterpenoid Saponin                                         | Addy 1989                    |
| 14.     | Galphimia glauca    | Aerial/Alcohol extract/Ethyl-acetate| Tetragalloylquinic acid, Quercetin                            | Neszmelyi et al. 1993        |
| 15.     | Ginko biloba        | Leaves                              | Ginkgolides                                                   | Touvay et al. 1985           |
| 16.     | Gleditsia sinensis  | Fruits/Ethanol                      | Saponins                                                      | Dai et al. 2002              |
| 17.     | Hydrangea macrophylla| Leaves                           | Glycosides                                                    | Matsuda et al. 1999          |
| 18.     | Inula racemosa      | Roots/Alcohol                       | Inulolide-a new Sesquiterpene lactone                        | Srivastava et al. 1999       |
| 19.     | Magnolia officinalis| Bark/Aqueous                        | Honokiol, Magnolol                                           | Shin et al. 2001b            |
| 20.     | Sarcostemma brevistigma| Twigs/Alkaloidal fraction        | Bregenin                                                     | Saraf and Patwardhan 1988a   |
| 21.     | Solanum xanthocarpum| Roots/Alkaloidal fraction           | Solasodine                                                    | Chitravanshi et al. 1990     |
| 22.     | Terminalia chebula  | Fruits/Aqueous                      | Ellagic acid, Tannins Chebulagic acid                        | Shin et al. 2001a            |
| 23.     | Vitex negundo       | Leaves/Ethanol                      | Casticin, isoorientin Chrysophenol D, Luteolin                | Nair and Saraf 1995          |
### Table 4 Anti-inflammatory agents

| Sr.No. | Name of plant          | Part used/extract/fraction          | Major chemical constituent(s)                                      | Reference                  |
|--------|------------------------|-------------------------------------|------------------------------------------------------------------|----------------------------|
| 1.     | Asystasia gangetica    | Leaves/Methanol, Ethyl Acetate      | Isoflavone glycoside, dalhorinin                                  | Akah et al. 2003           |
| 2.     | Aloe vera Tourn.ex Linn. (Liliaceae) | Leaves/Aqueous, Chloroform and ethanol | Anthraquinones, sterols, saponins and carbohydrate              | Vazquez et al. 1996        |
| 3.     | Bryonia laciniosa      | Leaves/chloroform extract           | Flavonoids                                                       | Gupta et al. 2003          |
| 4.     | Calotropis procera     | Latex                               | α-amyrin, β-amyrin calotropin (Triterpenoid)                     | Kumar and Basu 1994        |
| 5.     | Cinnamomum Zeylanicum  | oil                                 | Eugenol, cinnamic aldehyde and α-terpeniol.                     |                            |
| 6.     | Curcuma longa          | Rhizomes                            | Tumerones, curcuminoids                                          | Ammon and Wahl 1991        |
| 7.     | Dalbergia odorifera    | Heart Wood                          | Flavanoids, Tannins                                              | Chan et al. 1998           |
| 8.     | Elaeocarpus sphericus  | Fruits/Aqueous, Pet-ether, Benzene, Acetone and ethanol | Glycoside, Steroids, Alkaloid, Flavanoids                      | Singh et al. 2000          |
| 9.     | Nelsiona canescens     | Leaf/ethanol extract                | Flavonoids                                                       | Owoyele et al. 2005        |
| 10.    | Indigofera tinctoria   | Whole plant/methanol                | Polyphenols                                                      | Oli et al. 2005            |
| 11.    | Butea frondosa Koen.   | Leaves/Aqueous                      | Flavonoid, glycosides, proteins and amino acids.                 | Mengi and Deshpande 1999   |
| 12.    | Ocimum sanctum         | Leaves/Aqueous                      | Myrenol, Nerol, Eugenol                                          | Singh and Agrawal 1991     |
| 13.    | Ophiopogon japonicus   | Root/aqueous extract                | Ruscogenin and ophiopogonin D                                    | Kou et al. 2005            |
| 14.    | Pavetta crassipes      | Leaves/Aqueous                      | Flavanoids, tannins, anthisraquinones                           | Amos et al. 1998           |
| 15.    | Tylophora asthmatica   | Leaves/Alkaloidal                   | Tylophorine                                                      | Manez et al. 1990          |

### Table 5 Anti-spasmodic agents

| Sr. No. | Name of plant          | Part used/extract/fraction          | Major chemical constituent(s)                                      | Reference                  |
|---------|------------------------|-------------------------------------|------------------------------------------------------------------|----------------------------|
| 1.      | Aegle marmelos         | Leaves/Ethanol                      | Aegelin, Aegelemine,Aegeline                                     | Arul et al. 2004           |
| 2.      | Asiasarum sieboldi     | Roots/Methanol                      | Methyleugenol, gamma-asarone, Elemicin, Asarinin                 | Hashimoto et al. 1994      |
| 3.      | Asystasia gangetica    | Leaves/Methanol, Ethyl acetate      | Isoflavone glycoside, dalhorinin                                  | Akah et al. 2003           |
| 4.      | Bacopa monniera        | Leaves/Ethanolic                    | Bacosides, Alkaloids,Glycosides                                  | Dar and Channa 1997; Channa et al. 2003 |
| 5.      | Belamcanda chinensis   | Leaves/Ethanol                      | Tectorigenin                                                     | Singh and Agrawal 1990     |
| 6.      | Cissampelos glaberrina | Leaves, Root Bark/Aqueous           | Warifice, α-bisbenzylisoquinoline alkaloid                       | Thomas et al. 1995; Cortes et al. 1995 |
| 7.      | Clerodendron serratum  | Stem bark/Aqueous                   | Phenolic glycoside                                               | Gupta 1968                 |
| 8.      | Cnidium monnieri       | Fruits/Ethanol                      | Osthol                                                           | Chen et al. 1988           |
| 9.      | Coleus forskohlii      | Roots                               | Forskolin (diterpenoid)                                         | Marone et al. 1987         |
| 10.     | Crinum glaucum         | Leaves/Aqueous                      | Alkaloids, lycorine, crinamine                                   | Okpo and Adeyeme 2002      |
| 11.     | Drymis winteri         | Bark                                | Terpene                                                          | Sayah et al. 1998          |
| 12.     | Ferula ovina           | Aerial parts/Ethanol                | Carvacrol, alpha-pinene, geranyl isovalerate and geranyl propionate | Khalil et al. 1990         |
| 13.     | Ferula sinica          | Roots/Ethanol                       | Resins                                                           | Aqel et al. 1991           |
| 14.     | Pavetta crassipes      | Leaves/Aqueous                      | Flavanoids, tannins, anthisraquinones                           | Amos et al. 1998           |
| 15.     | Saussurea leppa         | Alkaloidal fraction                 | Sesquiterpene lactone, Terpenoids                               | Dutta et al. 1968          |
| 16.     | Striga orbanchioids    | Aerial parts/Ethanol                | ??                                                               | Harish et al. 2001         |
| 17.     | Thymus vulgaris        | Ethanol                             | Flavanones                                                       | Meister et al. 1999        |
| 18.     | Tylophora asthmatica   | Leaves/Alkaloidal                   | Tylophorine                                                      | Hananath and Shyamalakumari 1975; Udapa et al. 1991 |
Phosphodiesterase inhibitors

Considerable interest has been generated in the potential utility of isoenzyme-selective inhibitors of cyclic nucleotide phosphodiesterase (PDE) in the treatment of asthma and other inflammatory disorders. The scientific foundation for this interest is based upon two fundamental principles. First, inhibition of PDE activity increases the cellular content of two key second messengers, cAMP and cGMP, thereby activating specific protein phosphorylation cascades that elicit a variety of functional responses. Increases in cAMP content suppress a broad array of functions in inflammatory and immune cells. Both cAMP and cGMP mediate bronchodilation. PDE3 inhibitor enoxamine was shown to decrease lung resistance and increase compliance in patients with decompensated chronic pulmonary disease. Benzafentrine administered to normal volunteers by inhalation produced bronchodilation. Zaprinast is PDE5 inhibitor; it reduced exercise-induced bronchoconstriction but not histamine-induced bronchoconstriction. Most of the work now is focused on selectively targeting PDE4, primarily because inhibitors of this isoenzyme family have a notably appealing therapeutic profile; broad-spectrum anti-inflammatory activity coupled with additional bronchodilatory and neuromodulatory action. Rolipram, LAS-31025, RP-73401 and denbufylline are selective PDE4 inhibitors. SB 207499, VII294A, CP-220 and roflumilast are PDE4 inhibitors with less gastrointestinal side effects.

Endothelin modulators

There are two approaches for ET-1 directed therapeutics- (1) Inhibitors of endothelin-converting enzyme (ECE), which mediates the synthesis of ET-1 from its precursor; (2) Receptor antagonists of the effects of ET-1 at the end organ level. These agents reverse and/or prevent the increase in pulmonary artery pressure and vascular remodeling elicited by acute or chronic hypoxia. Examples are BQ-123, SB-217242 and bosentan.

Herbal drugs in bronchial asthma

Many Ayurvedic plants have been described to be useful in the treatment of various bronchial disorders including

### Table 6 Miscellaneous agents

| Sr No | Name of plant          | Part used/extract/fraction | Major chemical constituent(s)                              | Reference                  |
|-------|------------------------|----------------------------|------------------------------------------------------------|----------------------------|
| 1.    | **Lipoxygenase inhibitors** |                           |                                                            |                            |
| 1.    | Allium cepa            | Bulbs/Juice                | α and β unsaturated Thiosulphinates                        | Bayer et al. 1989          |
| 2.    | Boswellia serrata      | Gum resin/Ethanol          | Forskolin (diterpenoid)                                    | Ammon et al. 1991          |
| 3.    | Coleus forskohlii      | Roots                      | B-sitosterol, quercetin and dihydroquercetin                | Delporte et al. 2005       |
| 4.    | Prunus pyrifolia       | Whole plant/methanol       |                                                            |                            |
|       | **Platelet Activating Factor (PAF) inhibitors** |                       |                                                            |                            |
| 1.    | Allium cepa            | Bulbs/Juice                | α and β unsaturated Thiosulphinates                        | Dorsch et al. 1987         |
| 2.    | Galphimia glauca       | Aerial/Alcohol extract/Ethyl-acetate | Tetragalloylquinic acid, Quercetin | Neszmelyi et al. 1993     |
| 3.    | Impatiens textori      | Flowers/Ethanol            | Apigenin, uteolin, chrysoeriol                             | Ueda et al. 2003           |
| 4.    | Picrorrhiza kurroa      | Roots/                     | Androsin                                                   | Stuppner et al. 1991       |
|       | **Cyclooxygenase inhibitor** |                       |                                                            |                            |
| 1.    | Allium cepa            | Bulbs/Juice                | α and β unsaturated Thiosulphinates                        | Bayer et al. 1989          |
| 2.    | Magnolia obovate       | Stem bark                  | Magnolol and honokiol                                     | Lee et al. 2005            |
| 3.    | Crataegus pionatifida  | Fruit                      | Flavanoids                                                 | Kao et al. 2005            |
|       | **Interleukins (ILs) biosynthesis inhibitors** |                       |                                                            |                            |
| 1.    | Calocedrus formosana   | Bark/alcohol               | Sugiol                                                     | Chao et al. 2005           |
| 2.    | Nidularium procerum    | Leaves/Aqueous extract     |                                                            | Vieira-de-Abreu et al. 2005|
| 3.    | Waltheria indica       | Whole plant/               | flavonoids                                                 | Rao et al. 2005            |
| 4.    | Mahonia aquifolium Nutt. Berberidaceae | Stem bark/hydroalcohol extract | Polysaccharides Protoberberine and bisbenzylisoquinoline (BBI) alkaloids berbamine, tetrandrine | Kostalova et al. 2001     |
|       | **Leukotriene biosynthesis inhibitors** |                       |                                                            |                            |
| 1.    | Nigella sativa         | Seeds oil                  | Thymoquinone (TQ)                                         | El Gazzar et al. 2006      |
bronchial asthma (Kumar Suresh 1979). The use of medicinal plants and natural products increased dramatically in the last two decades in all over the world. More than 400 medicinal plant species have been used ethanopharmacologically and traditionally to treat the symptoms of asthmatic and allergic disorders worldwide.

Classification of antiasthmatic 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 antiasthmatics may be classified as shown in tables (Tables 1, 2, 3, 4, 5, 6, 7 and 8).

**Conclusion**

Herbal approaches have regained their popularity, with their efficacy and safety aspects being supported by controlled clinical studies. The herbal approaches have offered effective mast cell stabilizers like sodium cromolyn and sodium cromoglycate developed from khellin and antileukotriene products like—boswellic acids. Ongoing re-

### Table 7 Antianaphylactic drugs

| Sr. No. | Name of plant   | Part used/extract/fraction | Major chemical constituent(s)                      | Reference                  |
|---------|-----------------|----------------------------|----------------------------------------------------|----------------------------|
| 1.      | *Xanthii fructus* | Whole plant/Aqueous         | Saponin, flavones, Caflfic acid, 1,4-dicaffeoylquinic acid, sesquiterpene lactones | Hong et al. 2003          |
| 2.      | *Lycopus lucidus* | Whole plant/Aqueous         | Betulinic acid, pentacyclic Triterpenes             | Shin et al. 2005          |
| 3.      | *Poncirus trifoliata* | Fruit/Aqueous               | Flavonoids                                         | Kim et al. 1999           |
| 4.      | *Trichopus zeylanicus* | Leaves/butanol              | Lipopolysaccharides/Glycolipopolysaccharides       | Subramonian et al. 1999   |
| 5.      | *Cryptotympana atrata* | Whole plant/Aqueous         | Oleaneolic acid                                     | Shin et al. 1999          |
| 6.      | *Striga orobanchioides* | Whole plant/Aqueous, ethanolic | Flavonoids, apigenin and luteolin                   | Harish et al. 2001        |
| 7.      | *Crumum glaucum* | Bulbs/Aqueous               | Alkaloids                                          | Okpo and Adeyemi 2002     |
| 8.      | *Acanthopanax senticosus* | Stem/Aqueous                | Acanthoside A, B & C, Chiisanoside, Senticoside, Saponin, flavones, | Yi et al. 2002            |
| 9.      | *Syzygium aromaticum* | Flower bud/Aqueous          | Flavanoids                                         | Shin et al. 2001a         |
| 10.     | *Terminalia chebula* | Fruit/Aqueous               | Tannins                                            | Shin et al. 2000          |
| 11.     | *Vitex rotundifolia* | Fruit/Aqueous               | Flavonoids                                         | Shin et al. 2000          |

### Table 8 Immunomodulatory drugs

| Sr. No. | Name of plant    | Part used/extract/fraction | Major chemical constituent(s)                      | Reference                  |
|---------|------------------|-----------------------------|----------------------------------------------------|----------------------------|
| 1.      | *Picrohiza scrophularisflora* | Rhizomes/Pet. ether, Diethyl ether and methanol | Apocynin, androsin and picroside II | Smit et al. 2000          |
| 2.      | *Trichilia glabra* | Leaf/Aqueous                | Polysaccharides                                    | Benancia et al. 2000      |
| 3.      | *Cedrela tubiflora* | Leaf/Aqueous                | Gallic acid, polysaccharides                        | Benancia et al. 1995      |
| 4.      | *Ipomoea carnea*  | Leaf/Aqueous                | Nortropane alkaloids, calystegines β2              | Huesa et al. 2003         |
| 5.      | *Withania somnifera* | Coded extracts              | Glycolipids                                         | Rasool and Varalakshmi 2006 |
| 6.      | *Clausena excuata* | Wood/Aqueous                | Phenolic compounds, furanocoumarins, flavanoids and carbazole alkaloid | Manosroi et al. 2005     |
| 7.      | *Magnifera indica* | Bark/Alcohol, ether         | Magniferin                                         | Makare et al. 2001        |
| 8.      | *Cleome viscosa*  | Aerial parts/Aqueous, ethanolic | Alkaloids, saponins                                | Tiwari et al. 2003        |
| 9.      | *Plantago ovata*  | Seeds/Aqueous               | Polysaccharides glycosides                         | Rezaiepoor et al. 2000    |
| 10.     | *Typhae angustifolia* | Pollen/ethanol             | Phenolic compounds, flavones Triterpenes And β-sitosterol | Qin and Sun 2005          |
| 11.     | *Angelica sinensis* | Roots/Aqueous and ethanolic | Polysaccharides                                    | Yang et al. 2006          |
| 12.     | *Boerhaavia diffusa* | Roots/ethanol               | Alkaloids                                          | Mungantiwar et al. 1999   |
| 13.     | *Tephrosia purpurea* | Aerial parts/Ethanol        | Flavanoids                                         | Damre et al. 2003         |
search worldwide has provided valuable clues regarding the precise mechanism of action of these herbal alternatives and these herbs, have shown interesting 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 viz., leukotrienes, lipooxygenase, cyclooxygenase, platelet activating, phosphodiesterase and cytokine, in the treatment of asthma.

Some herbal alternatives employed in these traditions are proven to provide symptomatic relief and assist in the inhibition of disease development as well. In nutshell, attempt should be made to develop polyherbal formulations which contain various herbs acting at particular sites of the pathophysiological cascade of asthma for prophylaxis as well as for the treatment of asthma and subsequent clinical studies on them.

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