MANAGEMENT OF ASTHMA BY HERBAL THERAPY WITH SPECIAL REFERENCE TO POLYHERBAL FORMULATION

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ABSTRACT
In traditional systems of medicine, various plants have been acknowledged to be useful for the treatment of different types of respiratory disorders including asthma. In few decades the use of medicinal plants has been increased dramatically throughout 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 are occupied a significant place in asthma are confirmed to provide symptomatic relief and support in the management of the disease. In case of asthma the herbal drugs have exhibited remarkable results in various target specific biological activities such as bronchodilation, mast cell stabilization, anti-inflammatory, anti-spasmodic, anti-allergic, anti-anaphylactic, immunomodulatory and inhibition of mediators such as leukotrienes, lipoxygenase, cyclooxygenase, platelet activating, phosphodiesterase, histamine, bradykinin, endothelin and cytokines, in the treatment of asthma. This current review is an attempt to accumulate pharmacological and clinical findings of the herbal drugs along with their mechanism used for the management of asthma. It also signifies the requirement for the development of polyherbal formulations containing a variety of herbs useful for the prophylaxis as well as treatment of asthma.

KEYWORDS: Asthma, Herbal therapy, Polyherbal, Traditional systems.

INTRODUCTION
Among several respiratory disorders affecting man, bronchial asthma is the most common one. Asthma is a chronic disease characterized by various airway obstruction, airway inflammation and bronchial hyper responsiveness[1]. These symptoms may be due to liberation of endogenous and intrinsic mediators like histamine, leukotrienes, bradykinin, prostaglandins, nitric oxide, platelet activating factors, chemokines and endothelin from mast cells during the allergic reactions and inflammation of the air passages in the lungs. It is also known that asthma can be triggered by various infections, dust, cold or warm air, exercise, emotion, perfumes, chemicals, various foods, tobacco smoke, genetics and histamine[2]. Nearly 8-10% of the world population...
suffering from bronchial asthma. Its increased prevalence, morbidity and mortality rates have documented the rising seriousness of asthma in the common population in the past 20 years.

Large number of anti-asthmatic drugs belonging to different classes such as $\alpha_2$ agonists (Ephedrine), corticosteroids (Hydrocortisone, Prednisolone), mast cell stabilizers (Sodium chromoglycate, Kitotifen), methylxanthines (Theophylline, Aminophylline), leucotriene antagonists (Montelukast, Zafirlukast) are widely used in the treatment of asthma. But they are not completely safe for long term use and hold some side effects like immune suppression, cardiac abnormalities, central nervous system depression, hyperglycemia etc. Muscle tremor and hypokalemia are the major adverse effects of $\beta_2$ agonists. Systemic corticosteroids have common side effects such as disturbance of adrenal function and immune suppression\[3\]. Therefore, there is a dreadful demand to identify a effective and safe remedy for the treatment of bronchial asthma. The traditional systems of medicine and the accessibility of a large array of medicinal plants in the universe have significantly facilitated the researchers to develop wholehearted interest in their screening, research and development\[4\]. Thus an attempt has been made to highlight the antiasthmatic medicinal plants in this review. The polyherbal formulations described in Ayurveda have been the basis of treatment of various human diseases including asthma. This present review gives more prominence on polyherbal formulations used for the management of asthma.

Evaluation of therapeutic effect of a polyherbal formulation in patients of asthma with different kind of temperament was carried out. In a clinical trial carried out in Ajmal Khan Tibbiya College hospital during 2000 to 2003, the therapeutic response of a polyherbal formulation of Barg-e-aroosa, Gul-e-Zoofah and Aslussoos, was found encouraging in patients having Balghami Mizaj(Phlegmatic temperament) while least response was observed in patients with saudavi Mizaj (Melancholic temperament). The study showed that the concept of ancient Unani scholars about asthma is true and scientific. Thus this polyherbal Formulation exhibited significant effect on patients with asthma and may be a better alternative to present conventional drugs used for the treatment of all kinds of asthma\[5\].

The antiasthmatic potential of a polyherbal formulation was evaluated using several experimental models. Adult Wistar albino rats were used for mast cell stabilization protocol. Acetylcholine and histamine-induced bronchospasm were conducted on guinea pigs. The results of the acetylcholine and histamine-induced bronchospasm showed bronchospasmolytic activity of polyherbal formulation at the dose of 300 mg/kg, p.o. The spasmodolytic effect was
characterized by prolongation of onset of bronchospasm and reduction of asphyxia as compared to control group. In the mast cell stabilization paradigm, compound 48/80 treatment produced 76% of mast cell degranulation. Polyherbal formulation at the concentration of 1, 10, and 100 μg/ml showed dose-dependent significant reduction in mast cell degranulation as compared to the compound 48/80-treated animals. The probable mechanism for the antiasthmatic action of the polyherbal formulation could be antihistaminic, anticholinergic and mast cell membrane stabilization[6].

Antiasthmatic activity of Zeal herbal granule was carried out against 48/80 induced mast cell degranulation. The percentage mast cell degranulation was calculated at different concentration levels such as 1, 10, 100 and 1000 µg/ml. Zeal herbal granule exhibited significant protection of rat mesenteric mast cells from disruption caused by compound 48/80. The tested herbal granule also displayed significant dose dependent effect in percentage mast cell degranulation at different dose levels in comparison to negative control. The study showed that the Zeal herbal granule has significant antiasthmatic activity[7].

The potency of an herbal drug formulation was evaluated for its efficacy in bronchial asthma by Singhal et al. Lung function test was performed before and after the treatment to evaluate the patients. Two parameters, peak expiratory flow rate and forced expiratory volume in one second after the treatment showed noticeable improvement with side effects of the test drugs[8].

A study was carried out to evaluate the usefulness of Bresol in the management of bronchial asthma and its adverse effects if any and to determine patient compliance by Manoj et al[9]. Patients were administered Bresol tablets at a dosage of two tablets twice daily for a period of 30 days in adults and one tablet twice daily for the same period in children in the age group of 12-18 years. They were evaluated on Days 0, 15 and 30 for subjective improvements in dyspnea, cough, wheezing, rhonchus, and tightness of the chest, difficulty in expectoration, rhinitis, sneezing, fever and paroxysmal nocturnal dyspnea. Results of the study showed a significant improvement in all the clinical parameters of asthma such as dyspnea, cough, wheezing, rhonchus, tightness of the chest, difficulty in expectoration, rhinitis, sneezing, fever and paroxysmal nocturnal dyspnea. None of the patients presented with any adverse effects. All the patients completed the treatment and compliance to the study drug was good without any dropouts. This indicates safety and efficacy of Bresol tablets in patients of bronchial asthma. Each Bresol tablet contain the extract of Curcuma longa, Ocimum sanctum, Adhatoda vasica,
Trikatu, Triphala, Embelia ribes, Cyperus rotundus, Cinnamomum zeylanicum, Elettaria cardamomum, Cinnamomum tamala and Mesua ferrea.

A study was aimed to formulate, standardise and evaluate the pharmacological activity of polyherbal capsule recommended as Antiasthamatic agent by Madheswari et al[10]. Selective combination of herbals in extract form which individually proven for their efficacy in asthmatic activity such as Adhatoda vasica, Tylophora asthmatica, Piper longum, Solanum trilobatum and Alpinia galanga were formulated as capsule. Raw materials, formulation development and finished capsule were standardized with improved formulation parameters. Granulation was done by wet granulation technique. The polyherbal capsule formulation was subjected to in-vivo evaluation for its antiasthmatic activity using histamine induced bronchospasm in guinea pigs. During acute toxicity study the polyherbal capsule was found to be safe up to 2000 mg/kg body weight. The polyherbal formulation was administered with a dose of 400 mg/kg showed that it was more significant than 200 mg/kg when compared with standard drug promethazine 300 mcg/kg. The Polyherbal formulation at a dose of 400 mg/kg showed maximum antiasthmatic activity.

Ethanolic extract of the aerial parts of Aerva lanta was prepared and studied at 100 μg/ml in the isolated goat tracheal chain preparation model to find out their antiasthmatic activity. The extract was studied at 30 and 60 mg/kg doses orally in clonidine induced catalepsy and mast cell degranulation in mice. The extract illustrated antiasthmatic activity[11].

Hydro alcoholic extract of leaves of Ageratum conyzoides was prepared by Tote et al[12]. The extract was subjected for its antihistaminic activity at the doses of 250, 500 and 1000 mg/kg by clonidine induced catalepsy in mice. The extracts displayed antihistaminic activity by inhibiting clonidine induced catalepsy in mice.

Amburana cearensis is a medicinal plant common to the Brazilian Northeastern “caatinga” (savannah) and popularly used in the treatment of respiratory tract diseases including asthma. The flavonoids isokaempferide isolated from trunk barks of A. cearensis showed significant relaxation of potassium chloride induced contraction on guinea pig trachea[13].

Asystasia gangetica is an important traditional plant used in the management of asthma. Hexane, ethylacetate and methanol extracts of the leaves of A. gangetica were prepared by Akah et al[14]. The extracts were subjected for antiasthmatic activity using guinea pig trachea, rat stomach strip, guinea pig ileal preparation and egg albumin-induced acute inflammation. The results indicated
that the extracts did not exhibit contractile or relaxant activity in isolated tissue preparations; however, they inhibited the contraction evoked by spasmogens.

*Bacopa monnieri* a widely used medicinal plant was selected to test its antiasthmatic activity by Samiulla et al\(^\text{[15]}\). Various solvent extracts of the leaves such as petroleum ether, chloroform, methanol and water were prepared and are tested at the dose of 10 μg/mL for mast cell stabilizing activity in rats. The result of the investigation observed that all the extracts significantly inhibit mast cell degranulation.

The gum resin of *B. serrata* is well known in the Indian Ayurvedic system of medicine as Salai guggal and contains boswellic acid as an important active principle which has been shown to inhibit leukotriene biosynthesis. In a six week, double blind, randomized clinical trial was conducted by Gupta et al\(^\text{[16]}\) in 1998 taking 80 adult patients with bronchial asthma. The effect of *B. serrata* gum resin was compared with placebo (lactose). The alcoholic extract of *B. serrata* roots containing boswellin, boswellic acids which inhibit LT biosynthesis and block synthesis of 5-HETE and LTB4.

*Cassia sophera* is used traditionally for treatment of asthma and bronchitis. Chloroform, ethyl acetate and ethanol fractions isolated from ethanol extract of the leaves of *C. sophera* by Nagore et al\(^\text{[17]}\). The isolated compounds possesses significant antiasthmatic activity in carrageenan induced paw edema, histamine induced bronchoconstriction, clonidine and haloperidol induced catalepsy, milk induced leukocytosis and eosinophilia and passive paw anaphylaxis animal models at doses 250, 500 and 750 mg/kg and this activity may be due to the presence of flavonoids.

*Casuarina equisetifolia* is an evergreen tree possesses variety of pharmacological activities. The methanol extract of wood and bark were prepared and tested for their antihistaminic activity by inhibiting the histamine induced contraction of trachea (10-80 μg/ml), clonidine induced catalepsy and mast cell degranulation at the doses 100 mg/kg by Aher et al\(^\text{[18]}\). The extract exhibited significant antihistaminic activity by these models.

*Clerodendrum serratum* known as bharangi in Ayurveda, ethanol extract of roots of *C. serratum* showed antiasthmatic activity using isolated goat tracheal chain preparation, clonidine induced catalepsy, milk induced leucocytosis and eosinophilia in mice at different doses such as 50, 100 and 200 mg/kg\(^\text{[19]}\).

*Crinum glaucum* is popular in Yoruba of South West Nigeria. Traditional medicine practitioners reported it as an effective remedy in the relief of cough, asthma and convulsions. The aqueous
extract of *C. glaucum* acquire antiallergic activity at 100-400 mg/kg body weight by reduction in area of dye leakage in passive cutaneous anaphylactic reaction, protecting degranulation of mast cell and histamine induced bronchoconstriction in the guinea pig.[20]

*Curculigo orchioides* is a small herbal plant widely distributed in different countries of the world such as India, China, Malaya and Japan. Alcoholic extract of *C. orchioides* rhizomes at doses 100-400 mg/kg showed mast cell stabilizing and antihistaminic activity on compound 48/80-induced mast cell degranulation and systemic anaphylaxis. It also inhibited histamine induced contraction in goat trachea, guinea pig ileum and bronchoconstriction in guinea pigs; egg albumin induced passive paw anaphylaxis in rats; milk induced leucocytosis and eosinophilia; clonidine induced catalepsy in mice.[21]

*Eclipta alba* is famous for its traditional uses. The ethanol extract was prepared and tested for its antianaphylactic and antihistaminic activities. The ethanol extract showed significant antianaphylactic and antihistaminic activity at 250 and 500 mg/kg on compound 48/80-induced degranulation of mast cell, egg albumin induced passive cutaneous and paw anaphylaxis; bronchoalveolar lavage study on guinea pig trachea and determination of histamine.[22]

*Euphorbia hirta* popularly known as asthma weed, which is an herbaceous wild plant which grows in the hotter parts of India. Ethanol extract of whole aerial part of the plant was prepared and tested from lower to higher concentrations i.e., 100-1000 mg/kg showed antihistaminic and antiallergic activity by inhibiting the passive cutaneous anaphylaxis and paw anaphylaxis reaction; protection of mast cell from degranulation.[23]

The antiasthmatic activity of Ayurvedic polyherbal formulation each 20 ml contains, extracts of *Swertia chirata*, *Azadirachata indica*, *Terminalia chebula*, *Terminalia belerica*, *Emblica officinalis*, *Trichosanthes cucumerina*, *Adhatoda vasica*, *Tinospora cordifolia*, *Fumaria parviflora*, *Eclipta alba* each 731 mg. Antiasthmatic mechanism of using propranolol, which antagonized relaxant effect of polyherbal formulation on histamine induced contraction, showed the activity through goat tracheal β receptor activation. This gives antiasthmatic potential of this polyherbal formulation.[24]

*Momordica dioica* is a climbing creeper plant. Its fruits and leaves are traditionally used as medicinal agent of asthma, leprosy, bronchitis and fever. Methanol and aqueous extract of pulp possesses antihistaminic activity by inhibiting clonidine induced catalepsy in mice at the dose of 50 mg/kg.[25]
Aqueous extract of ripe olives possesses antiasthmatic activity by inhibiting clonidine induced peritoneal mast cell degranulation in rats and catalepsy in mice at doses 4 and 8 mg/kg and also by protecting histamine induced contraction of goat trachea and guinea pig ileum at concentration of 100 μg/mL\[26\].

*Piper betel* is traditionally used to cure cough, cold, pruritis, asthma and rheumatism. Ethanol and aqueous extract of the leaves at doses 100 and 200 mg/kg possesses antiasthmatic activity on histamine induced bronchoconstriction in guinea pig and histamine induced dose dependent contraction of guinea pig tracheal chain and isolated guinea pig ileum preparation\[27\].

Ethanol and aqueous extracts of whole plant *Striga orobanchioides* showed antihistaminic and mast cell stabilizing activity by inhibiting histamine induced contractions of the guinea pig ileum at the concentration 2.5-25 μg/ml in a dose associated manner and inhibiting degranulation of mast cells at 100 and 200 mg/kg\[28\].

*Sphaeranthus indicus* is a medicinally important plant used as folk medicine. The ethanol extract at the doses of 150, 300 mg/kg and its ethyl acetate extract at the dose of 100, 150 and 300 mg/kg demonstrated slightly better protection against sheep serum and compound 48/80-induced mast cell degranulation than the standard drug ketotifen. This exhibited it antiasthmatic potency\[29\].

*In vitro* anti-asthmatic activity of the fruit extracts of *Sapindus mukorossi* and *Piper nigrum* was studied by using acetylcholine induced contraction of goat tracheal chain preparation model of bronchial asthma. Significant decrease in acetylcholine induced contraction of goat trachea was observed in the presence of aqueous extract of fruits of these above two plants. Thus the study revealed that the aqueous extract of fruits of these two plants has good antiasthmatic activity\[30\].

The effect of ethanol extract of bark of *Cordia subcordata* at 25, 50, 100 mg/kg doses orally in the isolated goat tracheal chain preparation, passive paw anaphylaxis in rat was studied by Selvi et al\[31\]. The extract showed significant dose-dependent antiasthmatic activity in all these models. It was observed that ethanol extract inhibits contraction produced by histamine in the isolated goat tracheal chain preparation. The study revealed that *Cordia subcordata* extract exhibits significant percentage decreased contraction at concentration 80 μg/ml in goat tracheal chain preparation. Similarly there was significant inhibition in rat paw edema at the dose 50 mg/kg of ethanol extract of bark of *Cordia subcordata*, in all time intervals when percentage inhibition was calculated but more specific effect was seen at 3hour interval time. Paw edema volume also significantly decreased in all time intervals at this dose only.
Anti-asthma herbal medicine intervention (ASHMITM), a combination of three traditional Chinese medicinal herbs developed by Bolleddula et al\textsuperscript{[32]}, has confirmed its effectiveness in both mouse models of allergic asthma and a double-blind placebo-controlled clinical trial in patients with asthma. The study was designed to determine if the anti-inflammatory effects of individual herbal constituents of ASHMITM exhibited synergy. Effects of ASHMI and its components aqueous extracts of Lingzhi (\textit{Ganoderma lucidum}), Kushen (\textit{Sophora flavescens}) and Gancao (\textit{Glycyrrhiza uralensis}), on Th2 cytokine secretion by murine memory Th2 cells (D10.G4.1) and eotaxin-1 secretion by human lung fibroblast (HLF-1) cells were determined by measuring levels in culture supernatants by enzyme linked immunosorbent assay. Potential synergistic effects were determined by computing interaction indices from concentration-effect curve parameters. Individual Lingzhi, Kushen and Gancao extracts and ASHMI (the combination of individual extracts) inhibited production of interleukin IL-4 and IL-5 by murine memory Th2 cells and eotaxin-1 production by HLF-1 cells. By comparing the interaction index values they found that constituents in ASHMITM synergistically inhibited eotaxin-1 production as well as Th2 cytokine production.

\textit{Pistacia integerrima} belongs to family Anacardiaceae is popularly known as Karkatakashringi in Ayurveda and in the Indian traditional medicine it is used as a folk medicine in the treatment of allergies, asthma, coughs etc. A study was conducted to find out the activity of aqueous extract of the galls against the mast cell stabilization in rats, histamine-induced bronchospasm in guinea pigs and spasmolytic activity in isolated guinea pig tracheal chain preparation. The extract was subjected to phytochemical screening and found to contain essential oils, volatile oils, tannins, phenolics, flavonoids, carbohydrates and resinous matters. The rats were pretreated with the extract (27 and 54 mg/kg p.o.) and the antiasthmatic effect was compared with that of Prednisolone (10 mg/kg p.o.) on disruption rate of actively sensitized mesenteric mast cells of albino rats when challenged with antigen (horse serum along with triple antigen vaccine) and the extract (23.25 and 46.50 mg/kg p.o.) and the antiasthmatic effect was compared with that of Ketotifen (1 mg/kg p.o.) on histamine aerosol-induced bronchospasm in guinea pigs. The results underlined that the aqueous extract of \textit{P. integerrima} galls treatment for ten days resulted in significant effect on disruption rate of actively sensitized mesenteric mast cells of albino rats when challenged with antigen and significant protection against histamine aerosol-induced bronchospasm in guinea pigs and showed the spasmolytic activity against histamine induced contractions in isolated guinea pig tracheal chain preparation. Antiasthmatic activity of aqueous
extract of *Pistacia integerrima* galls may be possibly due to the membrane stabilizing potential, suppression of antibody production and inhibition of antigen induced histamine release\[^{33}\].

A study was carried out by Iyekowa et al\[^{34}\] to evaluate the antiasthmatic activity of methanolic extract obtained from *Portulaca oleracea*. Bronchial asthma was induced in guinea pigs using 10% histamine dihydrochloride. Chlorpheniramine (8 mg/kg), saline (5 ml/kg) and the methanolic extract of *P. oleracea* (40, 60 and 80 mg/kg) were administered orally for 30 min prior to their exposure to histamine aerosol. Disponea was not seen in all the guinea pigs treated with chlorpheniramine, but was observed in all the guinea pigs treated with saline and a concentration of the extract (80 mg/kg) at the 3\(^{rd}\) and 5\(^{th}\) minutes. Guinea pigs which were administered with the other concentrations of extract (60 and 40 mg/kg) exhibited peak disponea of 80 and 60% at the 4\(^{th}\) and 6\(^{th}\) minute of exposure to histamine aerosols respectively. The results obtained from the study suggested that methanolic extract of *P. oleracea* has an insignificant bronchodilatory activity against histamine aerosols.

An study was carried out by using three different polyherbal formulations (Formulation 1, 2 and 3) by Patil and Burande\[^{35}\]. The formulations were prepared as per the standard formulas of Ayurvedic proprietary medicines and were tested for their antiasthmatic potency using passive paw anaphylaxis in rats and histamine induced bronchoconstriction in guinea pigs. Three different doses of each formulation i.e. 1000, 1500 and 2000 mg/kg were used during the study. The result of the study showed that formulation 1 was found to be most effective and it showed significant delay in the latency of dyspnea as compared to other two formulas. It also showed dose dependent effects suggesting that the preparation is devoid of any interaction or side effects even at large doses. The formulation 1 has not only delayed the latency but this ability was sustained for a longer duration of time. The increased duration may be attributed to the synergistic combinations of phytoconstituents.

Kristin et al\[^{36}\] evaluated the safety and tolerability of a polyherbal formulation i.e., ASHMI derived from a Traditional Chinese Medicine in adults subjects with allergic asthma. Randomized, double-blind, placebo-controlled, dose escalation, phase- I trial was done under the United States Food and Drug Administration Investigational New Drug title. Subjects received one of three doses of ASHMI or placebo: 600 mg (2 capsules); 1200 mg (4 capsules); or 1800 mg (6 capsules) twice daily for 1 week. Four ASHMI and 2 placebo subjects were treated at each dose level. Subjects continued to use their conventional asthma medications for the duration of the study. In this study, ASHMI appeared to be safe and well tolerated.
Ethanolic extract of leaves of *Hiptage benghalensis* was prepared and converted into formulated dosage forms. Formulated dosage forms then subjected to evaluation of production quality by different methods stated as per official compendia. The evaluated formulation were then subjected to check for its efficacy by using experimental animal model like histamine and Ach induced bronchoconstriction in guinea pigs. The formulated dosage forms exhibited significant protection from histamine and Acetylcholine induced bronchospasm when compared to control group and is comparable to crude extract of *Hiptage benghalensis* and marketed antiasthmatic product[37].

An herbal compound formulation Pentapala-04 prepared from five medicinal plants namely, *Adhatoda vasica*, *Ocimum sanctum*, *Coleus aromaticus*, *Glycyrrhiza glabra* and *Alpiania galangal*. The effect of “Pentapala-04” on ova albumin and aluminium hydroxide induced lung damage in albino wistar rats was investigated. The rats were divided into three groups of four animals each. Group I, II and III serves as control, toxic and post treatment group respectively. The results showed that there was increased level of lipid peroxidation and decreased level of antioxidants in toxic group animals. But the levels of antioxidant enzymes were restored in post-treated groups of animals, which might be due to the ability of Pentapala-04 to scavenge the reactive oxygen species. Thus they demonstrated that ‘pentapala-04’ prevents ova albumin and aluminum hydroxide induced oxidative stress, lung injury and inflammatory changes and can be used as an antiasthmatic drug[38].

Shirishadi is an Ayurvedic polyherbal preparation used in Indian traditional medicine for the treatment of Asthma and allergic disorders. The pharmacodynamic properties of ethanolic extract of Shirishadi compound was evaluated on experimental model for its antihistaminic property against H₁ receptor and mast cell stabilizing property by Kajaria et al[39]. Significant increase in preconvulsion time was observed on pretreatment with Shirishadi compound when the guinea pigs were exposed to histamine. Demonstration of graded dose response of histamine and its competitive antagonism on isolated perfused guinea pig ileum showed that it has specific antagonism. The increasing dose of Shirishadi showed the Tachyphylaxis and receptor protection response. Polyherbal formulation (500 μg and 1000 μg/ml) showed dose dependent significant reduction in mast cell degranulation as compared to the compound 48/80 treated animals. The result showed that the compound has antiasthmatic property by virtue of its bronchodilator, anti-histaminic and mast cell stabilizing effect.
The aqueous ethanol extracts of various traditional herbs like *Adhatoda vasica*, *Acorus calamus*, *Glycyrrhiza glabra*, *Ocimum sanctum*, *Tylophora asthmatica*, *Piper longum* and *Solanum xanthocarpum* was evaluated for its antihistaminic activity by the inhibition of histamine induced contractions on the guinea pig ileum. The results showed that the formulated cough syrup inhibited histamine induced contractions of guinea pig ileum at 2.5 to 25 μg/ml concentrations in a dose dependent manner and also significantly inhibited degranulation of mast cells\cite{40}.

Gohil et al\cite{41} evaluated novel poly herbal formulations (PHE and LM-02) for asthma and related conditions. The individual herbs were evaluated for their standard specification according to the Ayurvedic Pharmacopoeia of India. PHE and LM-02 (an oral aerosol spray prepared from PHE) were studied against allergen-induced bronchospasm using guinea pigs. The bronchospasm studies indicated that these polyherbal formulations possess good bronchodilatory activity and LM-02 produced better bronchodilatory effect than PHE. PHE and LM-02 might be considered as cheaper and safer alternative for the treatment of bronchial asthma and related conditions.

The marine alga is always an important source of drugs and many useful drugs are directly belonging to the marine sources. The marine algae *Sargassum wightii* have many pharmacological activities. The antiasthmatic activity of leaf of *Sargassum wightii* and *Adiantum capillus* was studied by Swaroop et al\cite{42}. Ethanolic extracts of leaf of *Sargassum wightii* and *Adiantum capillus* were prepared and the antiasthmatic activity was evaluated by experimental models like histamine aerosol induced asthma in guinea pig. Animals treated with these extracts showed significantly prolonged the latent period of convulsions as compared to control animals when exposure of histamine aerosol. The histamine produced bronchial constriction in animal model in histamine chamber. The ethanolic extract *Adiantum capillus* was more effective comparatively to ethanolic extract *Sargassum wightii*.

A polyherbal preparation was set up by Tulsiani et al\cite{43} with multi directing mechanisms targeting on Asthma. The herbs used for the polyherbal preparation was *Glycyrrhiza glabra*, *Allium cepa* and *Clerodendrum serratum*. The preparation at 200 and 400 mg/kg were evaluated for anti asthmatic activity. These herbs have expectorant, anti oxidant and anti inflammatory, antihistaminic effects respectively which are in turn useful parameters against asthma. Guinea pig tracheal chain proved helpful for evaluation of the efficacy of the preparation as compared to other marketed Ayurvedic and allopathic medications. Also Broncho Alveolar Lavage fluid was observed for eosinophilic and macrophage count estimation. Airway hyper responsiveness in response to Methacholine administration proved beneficial for the study. This was further
supported by lung tissue histology. Bronchial muscle relaxation was seen as well as inflammation due to free radicals and cytokines exhibited a marked decline which displayed the antiasthmatic potency of the polyherbal preparation.

A study was conducted by Shyamlal et al\textsuperscript{[44]}, 63 patients were administered with Shirishavaleha (Herbal Ayurvedic Confection) at the dose of 10 g twice daily for 4 weeks with lukewarm water. The results were assessed in terms of clinical recovery, symptomatic relief and pulmonary function improvement. The effect of the treatment was assessed based on subjective and objective parameters. A significant increase in PEFR, Hb and considerable decrease in absolute eosinophil count (AEC) and E.S.R. were observed. From the study conducted, it was found that 21.15% (10) cases has shown marked improvement, 50.00% (26) cases shown moderate improvement, 19.23% (10) cases shown mild improvement and 11.54% (06) of patients remained unchanged. 11 cases were dropped out from the trial. The study revealed that current herbal formulation can be used as an effective drug in bronchial asthma.

An investigation was undertaken by Kalpana et al\textsuperscript{[45]} to evaluate the bronchodilator and anti-anaphylactic activity of the stem bark of \textit{Myrica sapida}. Experimental models studied were acetylcholine induced bronchospasm in guinea pigs, egg albumin induced anaphylaxis in guinea pigs, \textit{in vitro} studies on tracheal strip of egg albumin sensitized guinea pigs. Treatment with ethanolic extract of \textit{M. sapida}, (75 mg/kg, orally) resulted in significant protection against acetylcholine aerosol induced bronchospasm and allergen induced anaphylaxis in guinea pigs. The extract of \textit{M. sapida} prevented the potentiation of responses and also produced a decrease in pD\textsubscript{2} value of histamine and acetylcholine in guinea pig tracheal strip. These results suggested that \textit{M. sapida} possesses bronchodilator activity, has potent inhibitory effect on immediate hypersensitivity reactions and decreases bronchial hyper responsiveness.

A clinical trial was conducted to detect the effect of an Ayurvedic herbal formulation Shatyadi churna with and without Pranayama in the management of childhood asthma (Tamaka Shwasa) by Aman et al\textsuperscript{[46]}. After reaching to the diagnosis, patients were randomly distributed to three groups, viz. Group-A received Shatyadi churna with warm water, Group-B received the same with Pranayama and Group-C received the Placebo (Glucose in the dose of 2 gm in capsule form) with Pranayama. The duration of the trial was two months and the patients were examined after a gap of 15 days. The follow up period was of one month. The subjective and objective parameters were measured before and after treatment in each group. The result of the Shatyadi churna along with Pranayama was found to be highly significant in the study.
In-vitro and in-vivo safety and anti-asthmatic activity of stem bark extracts of *Prunus africana* and *Warburgia ugandensis* against induced asthma in BALB/c mice was studied by Karani et al.\[^47^\] Efficacy against induced asthma was determined by assaying heart blood serum for ovalbumin specific immunoglobulin E (IgE) antibodies and quantification of eosinophil proportion in Bronchoalveolar lavage fluid (BALF). Eight sensitized groups were used, 2 were controls, 3 were treated with *P. africana* extract and 3 with *W. ugandensis*; each treatment group received one dose concentration of 125, 250 or 500 mg/kg body weight of either plant extracts. The results showed that *P. africana* and *W. ugandensis* stem bark extracts have anti-asthmatic property.

To determine the prevalence and pattern of use of complementary therapies in adults treated for asthma in primary care in Singapore and the demographic and clinical factors associated with their use a study was designed by Ng et al.\[^48^\] Five primary care clinics in Singapore were selected for the study. Adult patients with asthma received a structured questionnaire interview and clinical assessment that included demographic and clinical variables (clinical status, patient’s knowledge, self-care and healthcare-seeking behaviour and spirometric measurements) and detailed information on CAM use in the past one year. CAM use in the past year was reported by 27.2%, including animal food products (12.3%), herbs (10.3%), herbal-based proprietary medicines (3.2%) and acupuncture or reflexology (1%). The use of CAM was significantly associated with Chinese ethnicity, longer disease duration, moderate and severe persistent asthma, lack of positive response to treatment in the past year, higher patient knowledge score, and multiple sources of care providers. The use of CAM is highly prevalent in Asian patients treated for asthma in primary care and was associated with cultural and clinical factors reflecting a need to improve care.

A study was aimed by Gerda et al.\[^49^\] to investigate the potential anti-inflammatory and immune-modulating properties of *S. aethiopicus* in vitro. The dried and powdered *S. aethiopicus* plant material was extracted with organic solvents. The dried extracts were screened in vitro in the transcription response, NF-κB and a cytokine assay. Significant activity was observed for the extracts of the plant in these assays. This study provided that *S. aethiopicus* has anti-inflammatory and immune-suppressing properties in vitro. These findings supported its effectiveness against allergic asthma.

*Adhatoda vasica* have been used for the treatment of Shvasa roga in the traditional system and its antiasthmatic property also revealed by various studies in recent years. Polyherbal formulation
(containing mainly the ethanolic extract of *Adhatoda vasica, Clerodendrum serratum, Curcuma longa, Solanum xanthocarpum* and *Piper longum*) was evaluated against compound 48/80-induced mast cell degranulation as well as triple antigen-induced anaphylaxis in rats and results suggested anti-anaphylactic and mast cell stabilizing property by Gohil et al\(^{[50]}\).

The ethanolic extract of aerial parts of *Aerva lanata* was prepared and studied for its antiasthmatic activity by Deepak et al\(^{[51]}\). The extracts exhibited significant dose dependent antiasthmatic activity as revealed by its mast cell stabilization and inhibited the clonidine induced catalepsy when evaluated in the isolated goat tracheal chain preparation model and *in-vivo* model using clonidine-induced catalepsy, mast cell degranulation in mice.

Methanolic extract of the stem barks of *Ailanthus excelsa* was prepared and evaluated *in-vivo* and *in-vitro* screening models in Guinea pigs and revealed dose-dependent antiasthmatic activity by Kumar et al\(^{[52]}\).

*Inula racemosa* root extract was prepared by Gautam et al\(^{[53]}\). The dried extract was subjected for its antiasthmatic activity by using suitable animal models. The results of the study revealed antiasthmatic activity as noticed by antagonistic effect on histamine induced contraction, milk-induced eosinophilia and leukocytosis and protection against mast cell degranulation.

Methanolic extract of dried whole plant of *Leucas aspera* was prepared and screened for its possible antiasthmatic activity by using different animal models by Limbasiya et al\(^{[54]}\). The results of the study revealed the antiasthmatic activity *in-vivo* models like histamine induced bronchospasm in guinea pigs, passive paw anaphylaxis in rats and milk induced eosinophilia mice and *in vitro* model like mesentric mast cell degranulation by egg albumin etc.

Aerial parts of *Onosma bracteatum* showed antiasthmatic potential by decreasing the infiltration of inflammatory mediators, inhibiting histamine release and decreasing airway inflammation *in vivo* and *in vitro* experimental models\(^{[55]}\).

The aqueous extract of *Piper nigrum* fruits was prepared and studied for its anti-asthmatic potential by Parganiha et al\(^{[56]}\). The aqueous extract significantly inhibited acetylcholine induced bronchoconstriction of isolated goat trachea which revealed its anti-asthmatic potential of the fruits of *Piper nigrum*.

Ethanol extract of *Woodfordia fruticosa* dried flower showed bronchoprotective, bronchodilatory and anti-inflammatory activity against experimental asthma induced by the combination of histamine and acetylcholine aerosol in guinea pigs\(^{[57]}\).
The ethanol extract of the leaves of *Alstonia scholaris* inhibited the spontaneous movements of rabbit jejunum and contractile effects of acetylcholine and histamine on guinea-pig ileum. The extract also displayed marked reduction of barium chloride-, potassium chloride- and calcium chloride-induced contraction on guinea pig ileum and pulmonary artery, implying a direct interference of plant extract with the influx of calcium ions into cells. On the other hand, the extract has no noticeable effect on mobilization of intracellular calcium. These results coupled with the *in vivo* effects of ethanol extract make known that the *Alstonia scholaris* leaves possessed broncho-vasodilatory activity mediated presumably by prostaglandins, calcium antagonism and endothelium-derived relaxing factor\cite{58}.

Andrographolide is traditional Chinese herbal medicines possessed a strong anti-inflammatory activity and has the potential to be used in allergic lung inflammation. Andrographolide could inhibit extensive infiltration of inflammatory cells in lung and decrease airway hyper reactivity. Andrographolide could inhibit NFkB expression in lung and suppress NF-kB translocation from the cytoplasm to the nucleus of airway epithelial cells. Results bring in the anti-inflammatory mechanisms of Andrographolide are associated with NF-kB expression in lung and suppress NF-kB translocation from the cytoplasm to the nucleus of airway epithelial cells\cite{59}.

*Euphorbia lunulata* belongs to family Euphorbiaceae is found in the southeast of China. The whole plants of *E. lanulata* have yielded kaempferol, quercetin, kaempferol 3-O-L-rhamnoside, quercetin 3-O-L-hamnoside, 6,7-dihydroxycoumarin and maoyancaosu. It has long been used as a traditional crude drug for the treatment of bronchial asthma and chronic bronchitis\cite{60}.

*Gingko biloba* is one of the most extensively used herbal medications in Europe. Standardized extract of *Gingko biloba* (EGb), is sold under several different brand names: Ginkgobil, Rokan, Tanakan, Tebonin and Kaveri. Ginkgo’s active ingredient, ginkgolide, antagonizes Platelet Activating Factor (PAF) and may decrease airway inflammation. Ginkgo is also a commanding antioxidant. Although *Gingko biloba* has a long history and a reasonable biochemical rationale, one small pilot study has evaluated its effectiveness as an asthma remedy. That study found that it has protective action against exercise-induced bronchospasm; it also decreased participants’ reactivity to house dust mite antigen\cite{61}.

Gyokuheifusan (GHS) is a usual formulation of Traditional Chinese Medicine (TCM) that is usually prescribed to prevent or treat respiratory tract diseases, such as respiratory infection and bronchial asthma. GHS down-regulates the over-production of IgE and IL-4 via a significant and persistent increase of IFN-g. Yang et al found that *Astragalus* root (a core material of GHS)
reduced the secretion of IL-4 by regulating the shift of Th$_1$ to Th$_2$, and the total IgE produced by B cells decreased accordingly. GHS is commonly used to care for respiratory diseases in clinical practice in oriental countries$^{[62]}$.

The anti-asthmatic activity of the extract of dried and fresh leaves, and the volatile and fixed oils of *Ocimum sanctum* was evaluated against histamine and acetylcholine induced pre-convulsive dyspnea (PCD) in guinea pigs. The extract of fresh leaves, volatile oil extracted from fresh leaves and fixed oil from the seeds significantly protected the guinea pigs against histamine and acetylcholine-induced PCD which showed its anti-asthmatic activity$^{[63]}$.

The fruits of *Piper longum* contain volatile oil, resin, alkaloids, piperine and piperlonguminine, a waxy alkaloid Nisobutyldeca-trans-2-trans-4-dienamide and a terpenoid substance. The fruit successfully reduce passive cutaneous anaphylaxis in rats and protect guinea pigs against antigen induced bronchospasm; a 30% protection of mast cells was observed in an *in vitro* study by Dahanukar et al$^{[64]}$.

The powdered rhizome of *Hedychium spicatum* given in divided doses of 10gm to 25 patients with recurrent paroxysmal attacks of dyspnoea for 4 weeks (Bronchial asthma), completely relieved dyspnoea, cough and restlessness in all patients. The bronchi completely disappeared in 36% of the patients. The mean R/R was reduced by 25% and the vital capacity increased by 20%. The mean absolute count also decreased by 55.6%$^{[65,66]}$.

**CONCLUSION**

Plants have always plays a commendable source of drugs; as a matter of fact many of the currently available drugs in the market were derived either directly or indirectly from them. In the last few decades, research has been focused on scientific evaluation and standardization of traditional drugs of plant origin for their safety, efficacy and potency. More than 80% of populations in the developing countries are using traditional medicines for their primary health care. Over the past few decades, there have been significant scientific advances leading to improved understanding and management of asthma. The current systems of conventional therapy do not cure the disorder but can control the symptoms. Thus there is a need to walk around safe alternative therapies, such as herbal medicines, so that they can be successfully incorporated along with conventional therapy to provide utmost benefits to the patients suffering from asthma. The research for alternate remedies for asthma will continue all over the world as the disease acquire several challenges not only to the physician but also to the researchers. Inadequate numbers of clinical trials have been conducted till date. Further studies in this track
are to be expected to result in novel additions to modern therapeutics. The present review highlighted need for more research in effectiveness of herbal medicine in bronchial asthma. As a large number of experimental studies have documented the presence of antiasthmatic properties in various medicinal plants, there is budding for discovering new compounds helpful in the management of asthma. Attempt should be made to develop polyherbal formulations which contain various herbs valuable for prophylaxis as well as for the treatment of asthma.

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