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Traditional Herbal Drug Approach used in the Treatment of Asthma: A Review

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Abstract
Asthma is a persistent inflammatory disease of the lower respiratory airway where the tracheobronchial smooth muscles of the lungs become tremendously narrow due to various causative agents like virus, allergens, exercise and become extremely responsive which leads to increase in secretions, mucosal oedema and mucus plugging. This results in repeating episodes of dyspnoea, wheezing, chest tightness, breathlessness, and coughing which might limit a person's ability to work and function depending on the time and intensity of the episode. WHO's assessment suggests that more than 339 million individuals had Asthma internationally and there were 417,918 deaths because of asthma worldwide in 2016. A review affirms that 1 out of every 10 Asthma patients are from India. Asthma can have various etiologies and types. The treatment involves Anticholinergics, corticosteroids, β_2 agonists, Xanthine drugs. These oral administration drugs are effective but come with their own respective side effects to some extent. Since ancient times the mankind has always turned to natural substances to cure various diseases and ailments. In a similar manner, Asthma treatment is also seeing new advances with the use of traditional herbal drugs from various plant sources. They work in various complex mechanisms and have very minimal side effects. This review deals with *Mangifera indica* and *Laurus nobilis* as treatment options for Asthma and the mechanism with which they work.

Keywords:
Asthma, *Mangifera indica*, Mangiferin, Vimang, *Laurus nobilis*, Magnolialide

Introduction

Asthma is characterized as an ongoing provocative sickness of the lower lung routes. Ongoing aggravation of the tracheobronchial smooth muscle (misrepresented aviation route restricting reaction to specific triggers, for example, infections, allergens, and exercise) is associated with hyper-responsiveness, which brings about restricting of air tubes frequently joined by expanded emission, mucosal oedema and bodily fluid stopping that prompts repetitive episodes of dyspnoea, wheezing, shortness of breath, chest snugness and additionally hacking and perhaps impediment of action that can shift after some time and in power.

Asthma is currently perceived to be basically provocative condition: irritation hidden hyper-reactivity. Numerous grown-ups, and a greater level of pediatric patients, have an unfavorably susceptible premise. Moreover, this sickness might be delegated a heterogeneous problem because of a confounded connection between hereditary inclination and ecological elements, as well as numerous connected qualities.

Causes of Asthma-

Asthma is a heterogeneous disease and involves multiple etiologies.

1. **Genetics-**

In 11 different populations, genome-wide linkage studies and case–control studies have revealed 18 genomic areas and over 100 genes linked to allergy and asthma. On the long arms of chromosomes 2, 5, 6, 12, and 13, there are reliably duplicated areas.

2. **Prenatal risk factors-**

Prenatal tobacco smoke

There is a dose–response relationship between prenatal mother smoking and early childhood wheeze, and there is a dose–response relationship between exposure and lower airway calibre.

Diet and nutrition

A higher intake of fish or fish oil during pregnancy has been linked to a lower risk of atopic disease (particularly eczema and atopic wheezing) up to the age of six years, according to several studies. Prenatal vitamin E and zinc levels have also been linked to a lower risk of wheeze development up to the age of five. There is an inverse relationship between maternal vitamin D levels and wheezing in early childhood, but no link between atopy or symptoms later in life.

Antibiotic use

The link between prenatal antibiotic treatment and the development of atopic disorder has been studied in two ways: as a dichotomous predictor (i.e., any antibiotic use) and as a continuous predictor (i.e., the number of antibiotic courses taken during pregnancy). Longitudinal cohort studies that looked at any antibiotic usage in early childhood found a higher risk of persistent wheeze and asthma, as well as a dose–response relationship between the number of antibiotic courses and the risk of wheeze or asthma.

Mode of delivery

Atopy was shown to be 2 to 3 times more prevalent in infants delivered by emergency caesarean section, but not in those delivered by elective caesarean section. Maternal stress and changes in the infant's gut microbiota linked with different techniques of delivery are two possible explanations for these findings.

3. **Risk factors in childhood-**

Phenotypes of Asthma

Transient wheeze, non-atopic wheezing, late onset wheezing, and persistent wheezing are all common characteristics in early childhood. The majority of children with persistent wheeze (who will later be diagnosed with asthma) had their first symptoms before the age of three. By 3 years they have abnormal lung function that persists to adulthood and by adolescence most have atopy. Among children with non-atopic and late-onset wheezing, some experience remission, whereas others experience persistent symptoms and atopy. Distinguishing among these different phenotypes in early childhood is critical to understanding the role of risk factors and their timing in early infancy.

Breastfeeding

The influence of breastfeeding on the risk of childhood atopy and asthma remains controversial. The following represents observational data accumulated to date. Some studies have shown protection, [5][6][7] whereas others have reported higher rates of allergy and asthma among breastfed children. [8][9]

In a longitudinal birth cohort study, breastfeeding was associated with a higher risk of atopic asthma in later childhood, with the greatest influence occurring among those with a maternal history of atopy. [8][9][10]

Lung function

Decreased airway calibre in infancy has been reported as a risk factor for transient wheezing, perhaps related to prenatal and postnatal exposure to environmental tobacco smoke. Furthermore, the presence of airways with decreased calibre has been associated with increased bronchial responsiveness and increased symptoms of wheeze. Several studies have suggested an association between reduced airway function in the first few weeks of life and asthma in later life.

Children with wheezing (and diagnosed asthma) persisting to adulthood have a fixed decrement in lung function as early as age 7 or 9 years.

Family Structure

Family size and the number and order of siblings may affect the risk of development of asthma. The hygiene hypothesis posits that exposure of an infant to a substantial number of infections and many types of bacteria stimulate the developing immune system toward non-asthmatic phenotypes. This may be exemplified in the real world by large family size, whereby later-born children in large families would be expected to be at lower risk of asthma than first-born children, because of exposure to their older siblings' infections. Although this theory has been supported by some studies of allergy prevalence, it has been partially refuted by recent studies of asthma prevalence suggesting that although large family size (more than 4 children) is associated with a decreased risk of asthma, birth order is not involved.

Antibiotic and Infection

The use of antibiotics has been associated with early wheezing and asthma in several studies.

Viral infections of the lower respiratory tract affect early childhood wheezing. Whether lower respiratory tract infection promotes sensitization to aeroallergens causing persistent asthma is controversial: childhood viral infections might be pathogenic in some children but protective in others. Infants of mothers with allergy or asthma have a relatively persistent maturational defect in Th1 cytokine synthesis in the first year of life which may play a role in the development of persistent or severe viral infections. Severe viral infection of the lower respiratory tract in genetically susceptible infants who are already sensitized to inhalant allergens may lead to deviation toward Th2 responses promoting asthma.

Exposure to environmental tobacco smoke

Postnatal exposure to environmental tobacco smoke, especially from maternal smoking has been consistently associated with respiratory symptoms of wheezing. Exposure to environmental tobacco smoke also consistently worsens asthma symptoms and is a risk factor for severe asthma.

Exposure to animals

Although several studies have demonstrated a lower risk of development of atopy and asthma with exposure to farm animals in early life, the findings of studies of the influence of exposure to domestic cats and dogs have been inconsistent. In some studies, exposure to cats was associated with a greater risk of allergic sensitization, whereas other studies showed a lower risk.

Sex and gender

Sex affects the development of asthma in a time-dependent manner. Before age 12, boys have more severe asthma than girls, with higher rates of admission to hospital so the incidence and prevalence of asthma are greater among boys than among girls. During teenage, greater incidence of asthma is observed among adolescent and young adult females and a greater proportion of males with remission of asthma. In adult females however, more severe asthma is seen than in males, with more hospital admissions, slower improvement, longer hospital stays and higher rates of readmission. Most authors have associated these changes with prevalence and severity of events during teenage, although mechanisms for differences between the sexes have not been established.

In childhood, airway hyper-responsiveness is more common and more severe among males; however, airway hyper-responsiveness increases in females during adolescence such that by adulthood it is both more common and more severe among adult women.

Types of asthma-

1. **Allergic asthma -**

Allergic (or atopic) asthma is asthma that is triggered by allergens like pollen, pets and dust mites.

2. **Seasonal asthma-**

Some people have asthma that only flares up at certain times of the year such as during hay fever season, or when it is cold.

While asthma is always a long-term condition, it is possible to be symptom-free when your triggers are not around. You might only need to take asthma medicines during the season when your asthma bothers you most and for a short time afterwards.

3. **Occupational asthma-**

Occupational asthma is asthma that is caused directly by the work you do. Occupational asthma is usually a type of allergic asthma. For example, if you work in coalfields you might be allergic to coal dust, or if you work in healthcare, the dust from latex gloves could trigger symptoms.

Occupational asthma is not the same as asthma that you already have which is made worse by a trigger at work.

4. **Exercise induced asthma-**

Some people without a diagnosis of asthma get asthma-like symptoms triggered only by exercise.

This is often called 'exercise-induced asthma', but a better term is 'exercise induced bronchoconstriction' (EIB). This is because the tightening and narrowing of the airways (bronchoconstriction) is not caused by having asthma. Exercise induced bronchoconstriction mostly affects elite athletes or people doing strenuous exercise in very cold conditions.

5. **Difficult asthma-**

Sometimes asthma is difficult to manage because of other health issues you have, including allergies. The signs of difficult asthma are:

- Asthma symptoms that do not go away even with high doses of asthma medicines.
- Needing to use your reliever inhaler three or more times a week – one of the warning signs of an asthma attack
- Frequent asthma attacks.

6. **Severe asthma-**

You're more likely to be diagnosed with severe asthma if:

- You've had more than two asthma attacks in the past year
- You have on going symptoms even though you've been taking higher doses of inhaled steroids, and have tried a long-acting bronchodilator or a preventer tablet (LTRA)
- You're using your blue reliever inhaler three or more times a week
- Other reasons for your symptoms have been ruled out by your doctor or specialist.

7. **Adult onset asthma-**

Some of the possible causes of adult onset asthma are:

- Occupational asthma: this accounts for 9-15% of adult onset asthma
- Smoking and second-hand smoking
- Obesity
- Female hormones: these can be linked to adult onset asthma and may be one of the reasons women are more likely than men to develop it
- Stressful life events.

8. **Childhood asthma-**

Some children diagnosed with asthma find it improves or disappears completely as they get older. This is known as childhood asthma.

Pathophysiology-

The key ecological components involved in asthma pathophysiology are sensitivity to different dust particles , pollen grains and may even be diet. Asthma triggers may likewise incorporate hypersensitive (e.g. house dust parasites,

cockroach buildup, creature dander, and dusts) and non-allergic (e.g. viral contaminations, subjection to tobacco smoke, cold air, work out) boost. These antigens are recognized by mast cells covered with IgE antibodies and influence T lymphocytes and eosinophils to deliver pro-inflammatory cytokines, for example, tumor necrosis factor-α (TNF-α), interleukins IL-2, IL-3, IL-4, IL-5, GM-CSF, prostaglandins, histamine, and leukotrienes. Exudate and oedema emerge because of the degranulation interaction, which increments vascular penetrability. This interaction is trailed by leukocyte movement to the tissue impacted by the inflammation through chemotaxis interceded by selectins and integrins. In this manner, the neutrophil movement to the site and the arrival of leukotrienes LTB4 prompt the enactment of type 2 cyclooxygenase (COX-2) and type 5 lipoxygenase (LOX-5), upgrading the outflow of the C3b opsonin that produces receptive oxygen species (ROS) and subsequently advancing cell oxidative pressure and pulmonary tissue injury.

Multiple other mechanisms engaged with asthma physiopathology are intake of certain medications, as well as respiratory infections, which advance an invulnerable reaction interceded by IgG antibodies. These cause escalation in inflammatory cells influx thus, releasing the mediators responsible for the damage.

Available treatments for asthma-

As asthma is a variable disease, treatment may need to be adjusted periodically in response to loss of control. All asthma patients should be enabled to play a functioning job in the administration of their illness. This can be achieved by giving patients a customized activity plan for infection the executives and by instructing the patient about the nature of the illness, the job of drugs, the significance of sticking to regulator treatment, and the proper utilization of inhaler gadgets. Some drugs associated with asthma therapy include based on

1. Pulmonary (the main administration route on asthma therapy) Oral or intravenous administration of class β2 agonist drugs (salbutamol, levalbuterol, terbutaline, and epinephrine)
2. Anticholinergics (ipratropium)
3.Corticosteroids (beclomethasone di- or monopropionate, ciclesonide, flunisolide, fluticasone propionate, mometasone furoate, triamcinolone acetonide, hydrocortisone, dexamethasone, budesonide, prednisone, prednisolone, and methylprednisolone)
4. Xanthine drugs (theophylline)

Among these, the β2 agonists are often the drugs of first choice. [3]

Herbal treatment-

The utilization of plant-based items for asthma treatment has been accounted for by the customary medication for more than 5000 years. Plant-inferred normal oils address the vitally regular items utilized on the reciprocal asthma treatment because of the presence of mixtures, for example, phenylpropanoids and mono-and sesquiterpenes as the major bioactive mixtures, which give their antifungal, antibacterial, anti-inflammatory and anaesthetic properties. Natural compounds studied for treatment of asthma-

1. ***Magnifera indica L extract-***

Magnifera indica is an important herb in the Ayurvedic and indigenous medical systems for over 4000 years. It is known by the common name mango. In India it is known by its various vernacular names, the most used ones are aam, ambiram, manga, mambalam and kaeri. [13]

Geographical source- Mangoes are believed to have originated from the region between north-western Myanmar, Bangladesh, and India. *M. indica* were domesticated separately in South Asia and Southeast Asia over centuries, resulting in two distinct genetic populations in modern mangoes – the "Indian type" and the "Southeast Asian type". Mangoes have since been introduced to other warm regions of the world.

Taxonomy-
Kingdom : Plantae
Phylum : Mangoliophyta
Class : Mangoliopsida
Order : Sapindales
Family : Anacardiaceae
Genus : Mangifera
Species : Indica

Botanical description-
Tree- It is a large green fruit-tree, capable of growing to a height and crown width of about 30 metres (100 ft) and trunk circumference of more than 3.7 metres (12 ft).
Leaves- Leaves are 15–45 cm in length with variable sizes. *Magnifera indica* leaves possess different shapes (lanceolate, ovate-lanceolate, linear-oblong, roundish-oblong, oval, and oblong)
Flower- Red-yellow flowers appear at the end of winter and beginning of spring. Both male and female flowers are borne on same tree.
Fruit-The mango is an irregular, egg-shaped fruit which is a fleshy drupe. Mangos are typically 8–12 cm (3–5 in) long and greenish yellow in colour. Mango fruits are green when they are unripe. The interior flesh is bright orange and soft with a large, flat pit in the middle.
Seed- Seeds are ovoid or oblong-shaped covered with a hard endocarp having a woody fiber covering. It has a dicot seed.

Cultivation- The tree grows best in well-drained sandy loamy soil. Mango tree does not grow well in wet heavy soils. The optimal pH of the soil should be between 5.2 and 7.5. The climatic conditions have a significant role in the time of flowering of mangoes. In India, blooming begins in December in the South, in January in Bihar and Bengal, in February in eastern Uttar Pradesh, and in February-March in northern India. The duration of flowering is 20–25 days in Dashehari, while panicle emergence occurs in early December and flower opening is completed by February.

Ethnopharmacological Uses-
Various parts of plant are used as a dentrifrice, antiseptic, astringent, diaphoretic, stomachic, vermifuge, tonic, laxative and diuretic and to treat diarrhea, dysentery, anaemia, asthma, bronchitis, cough, hypertension, insomnia, rheumatism, toothache, leucorrhoea, haemorrhage and piles. All parts are used to treat abscesses, broken horn, rabid dog or jackal bite, tumour, snakebite, stings, dhatura poisoning, heat stroke, miscarriage, anthrax, blisters, wounds in the mouth, tympanitis, colic, diarrhoea, glossitis, indigestion, bacillosis, bloody dysentery, liver disorders, excessive urination, tetanus and asthma.
Ripe mango is known to be animate and refreshing. The juice is supportive tonic and utilized in heat stroke. The seeds are utilized in asthma and as an astringent. Vapours from the burning leaves are breathed in for alleviation from hiccups. The bark is astringent, it is used in diphtheria and rheumatism, and it is believed to possess a tonic action on mucus membrane. The gum is utilized in dressings for chapped feet and for scabies. It is additionally considered as anti-syphilis. Most parts of the tree are used medicinally and the bark also contains tannins, which are used for the purpose of dyeing. [17]

Phytochemistry-

The medicinal properties of *Magnifera* leaves make them a useful ingredient in traditional folk tea preparation, and to treat diabetes and respiratory diseases in Asian and African countries.

Phytochemicals present in *Magnifera* leaves can be broadly categorized as polyphenols, terpenoids, carbohydrates, sterols, carotenoids, vitamins, fatty acids, and amino acids. Mangiferin, gallic acid, catechins, quercetin, kaempferol, protocatechuic acid, ellagic acids, propyl and methyl gallate, rhamnetin, and anthocyanins are the major polyphenolic compounds found in *Magnifera indica*. Mangiferin is a well-known polyphenolic antioxidant and a glucosyl xanthone which has been extensively studied for its numerous biological properties. The quantities of different polyphenols in mango depend on the part and variety of mango.

1. Phytochemical Screening-

- Test for alkaloids-
  0.1 ml of *Magnifera* leaf extracts (prepared earlier in chloroform and ethanol separately) were added in test tubes and then 2 to 3 drops of Dragendoff's reagent was added. range red precipitate indicated the presence of alkaloids. [14]
- Test for flavonoids-
  4mg/ml of each extract was taken to which a piece of magnesium ribbon was added this was followed by concentrated HCl drop wise. A colour change ranging from orange to red indicated flavones while red to crimson indicated flavonoids. [15]
- Test for saponins-
  Half gram of the extract was dispensed in a test tube. 5ml of distilled water was added to the tubes and it was stirred vigorously. A persistent froth that lasts for about 15 min indicated the presence of saponins. [15]
- Test for steroids-
  Two milliliters of the extracts were taken into separate test tubes. The residues were dissolved in acetic anhydride and chloroform was then added. This was followed by the addition of concentrated sulfuric acid by the side of the test tubes using a pipette. A brown ring at the interface of the two liquids and a violet colour in the supernatant layer denoted the presence of steroids. [14]
- Test for tannins-
  From a large portion of each extract two millilitres of extract was diluted with distilled water in separate test tube and 2 to 3 drops of 5% ferric chloride ($FeCl_3$) solution was added. A green – black or blue colouration indicated the presence of tannins. [14]
- Test for glycosides-
  Ten milliliters of sulfuric acid (50% v/v) was added to 1 ml each of the *Magnifera* leaf extracts in separate test tubes. The mixtures were heated for 15 min. 10ml of Fehling's solution was added to tubes and the mixture boiled. A brick red precipitate indicated presence of glycosides. [15]
- Test for Terpenoids-
  To 0.5g of the plant extracts 2 ml of chloroform was added. Then 2 ml of concentrated sulfuric acid was added carefully and shaken gently. A reddish brown coloration of the interphase formation show positive results for the presence of terpenoids. [16]
- Test for phenols-
  Extracts were treated with few drops of ferric chloride solution. Formation of bluish-black colour indicates the presence of phenols. [15]

2. Quantification of Mangiferin-

By dissecting mango fruit into three parts, namely pulp, peel, and seed kernel, mangiferin content in both edible and non-edible parts of the mango fruit was characterized by 11 Chinese cultivars in the present study. Significant

difference in mangiferin content among different cultivars as well as different tissues of mango fruit was shown in the Table below. High mangiferin contents were found in the peel of mango cultivars such as LPM (7.49 mg/g DW), ZHM (7.34 mg/g DW), and seed kernel of ZHM (2.43 mg/g DW), XH-2 (1.04 mg/g DW), etc. Therefore, mango peel and seed kernel are good sources of mangiferin. The highest mangiferin content was found in the peel of Lvpimang (LPM) fruit (7.49 mg/g DW). [18]

Pharmacology-

Vimang is the brand name of formulations containing the stem bark aqueous extract of *Mangifera indica* L. (Anacardiaceae) traditionally used in Cuba for its anti-inflammatory, analgesic, antioxidant and immunomodulatory properties.

Mechanism of action of magniferin studied for asthma-

Mangifera indica L. extract (Vimang) and mangiferin reduce the airway inflammation and Th2 cytokines in murine model of allergic asthma-

Method-

Antigen sensitization, challenge, and treatments

The experimental schedule was based on a murine model of allergic asthma. Seven groups of ten mice were conformed. Six groups were intraperitoneally sensitized with 0.2 ml of saline solution containing 10 mg OVA (Chicken egg ovoalbumin) adsorbed on 2 mg aluminium hydroxide on days 0, 7 and 14. Seven days after the last intraperitoneal injection, the mice were subjected to aerosolized OVA (2%) inhalation for 30 min beginning on day 21 and continuing until day 24. Mice were placed in a plexiglass chamber (20 × 20 ×10 cm) and exposed to an aerosol generated from a nebulizer with an airflow rate of 7 l/min. Control group mice received intraperitoneal injections of 0.2 ml saline containing 2 mg aluminium hydroxide and were challenged with saline alone. To evaluate the protective effect, mice were orally treated with *Magnifera indica* L. extract (doses of 50, 100 or 250 mg/kg) or mangiferin (50 mg/kg) from days 0 to 24. Distilled water was used as vehicle and the extract and mangiferin were administered at a dose of 10 ml/kg. Dexamethasone (3 mg/kg) used as reference drug was orally administered only between days 18 and 24, and it was included as experimental control for the murine model, not for comparison with the extract or mangiferin.

Collection of bronchoalveolar lavage fluid (BALF) and blood

When the treatments and experimental schedule were completed (on day 25), the mice were bled via the retro orbital plexus and sera were separated by centrifugation at 3000 rpm for 10 min and kept at -70°C until analysis for OVA-specific IgE. Then, the mice were sacrificed using an overdose of sodium pentothal (100 mg/kg, i.p.). The trachea was cannulated and 0.5 ml of saline solution was used per lavage and repeated four times for each mouse. About 1.5 ml of BALF was recovered per mouse. The BALF was centrifuged (400g, 4°C, 10 min) and the supernatant was kept at -70°C until analysis for cytokines. The BALF cells were washed three times with phosphate buffered saline (PBS) and the pellet was re-suspended in 200 ml cold PBS. The total number of BALF cells was counted using a haemocytometer.

Histological examination and morphometry

After removal of BALF, lungs were isolated and prepared for histology study. They were slowly perfused with 10 ml PBS via the right ventricle, and then perfused with 4% paraformaldehyde and immersed in fixative solution overnight before being embedded in paraffin. Representative sections of lung were obtained by taking three 5-mm sections every 100 mm. Sections were stained with haematoxylin and eosin (H & E) and slides were evaluated by microscopy.

Inflammation was scored in a double-blind screen with two independent researchers who specialized in pathology. The degree of peribronchial and perivascular inflammation was evaluated by a subjective scale of 0–3 points, as described elsewhere. A value of 0 was assigned when no inflammation was detectable, a value of 1 indicated occasional cuffing with inflammatory cells, a value of 2 indicated that most bronchi or vessels were surrounded by a thin layer (one to five cells) of inflammatory cells and a value of 3 indicated that most bronchi or vessels were surrounded by a thick layer (more than five cells) of inflammatory cells.

Result-

The inflammatory lung response is one of the pathological features of bronchial asthma. Histological analysis of H & E stained lung tissue sections demonstrated a marked airway inflammation in OVA-sensitized/challenged mice (Figure a and b). This inflammation was qualitative and semi-quantitatively evaluated using an inflammation scores as described in the Materials and Methods section. We found marked peribronchial and perivascular inflammatory infiltrates in lung sections of OVA-sensitized/challenged mice compared with non-sensitized/challenged mice (Figure a and b), indicative of a significant inflammatory response induced by the experimental procedure. Figures c–f show the lung sections of treated mice, and the reduction of inflammation brought about by *Magnifera indica* extract, mangiferin and dexamethasone is evident. Only two representative pictures of *Magnifera indica* extract-treated mice are shown, corresponding to the lowest and highest doses. The inflammation score in non-treated groups was around 3, indicating a majority of bronchi and vessels surrounded by a thick layer with more than five inflammatory cells. This score was reduced to 2 or less when the mice were treated with the extract and mangiferin. The highest dose of the extract (250 mg/kg) and mangiferin (50 mg/kg) had similar effects to dexamethasone, used as positive control.

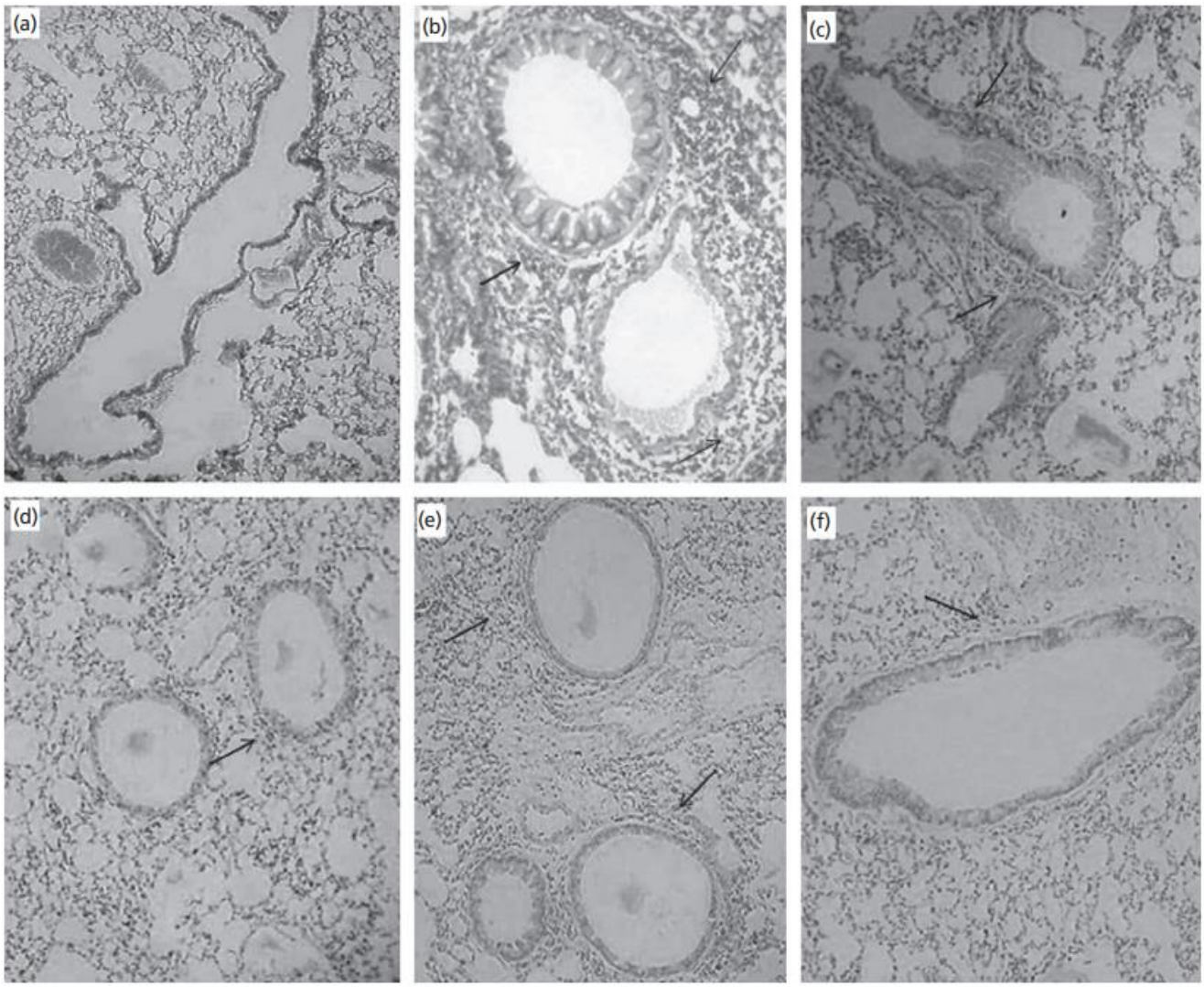


Figure 2 Qualitative evaluation of anti-inflammatory effects of *M. indica* extract and mangiferin on airway inflammation in mice pre-treated for 24 days. Histological study of lung sections (representative H&E-stained) from: (a) control group; Ovoalbumin (OVA)-sensitized/challenged groups treated with (b) saline solution (OVA group), (c) *M. indica* extract 50 mg/kg, (d) *M. indica* extract 250 mg/kg (e) Mangiferin 50 mg/kg (f) Dexamethasone 3 mg/kg. Objective lens × 100. Arrow indicates areas of inflammation. Only a representative picture is shown for each group; and for *M. indica* extract treatment only those corresponding to the lowest and highest doses are shown.

Moreover, the inhibitory effect of *Magnifera indica* extract on eosinophil migration was studied but using a parasitic murine model of *Toxocara canis* infection which induces an IL-5-dependent systemic eosinophilia and mimics the features observed in asthma, such as high levels of serum IgE and airway inflammation.

We found a reduction of airway inflammation, Th2 cytokines production and IgE levels after treatment with *Magnifera indica* extract and mangiferin. These findings constitute the first pre-clinical report of the anti-inflammatory properties of *Magnifera indica* extract and mangiferin in a murine model of allergic asthma. [19]

Clinical trials conducted with Vimang capsule-

Two asthmatic patients were chosen. The patients were classified according to the Global Strategy for Asthma Management and Prevention (GINA, 2006).

Their clinical conditions were as follow:

1. Persistent Moderated Asthmatic Patient: 39 years old female. Standard treatment: salmeterol and fluticasone spray (Seretide® 25/50 µg) 3 puffs daily. Allergic potential: presence of animals, dust and perfumes. Symptoms included dry coughing and shortness of breath.
2. Persistent Severe Asthmatic Patient: 43 years-old male. Standard treatment: salmeterol and fluticasone spray (Seretide® 25/50 µg) 3 puffs daily. Allergic potential: dust. Symptoms included repetitive breath shortening and pronounced dry coughing.

Capsules: Vimang® capsules were prepared with 300 mg of dry extract obtained from a standard *Mangifera indica* L. stem bark. This extract was prepared by decoction with water for 1 h and then it was concentrated by evaporation and spray-dried to obtain a fine homogeneous brown powder with a particle size of 30–60 mm. (Nuñez-Sellés et al 2002). The lot used in the study was 200402-E from Novatec Laboratory (La Habana, Cuba). The quality control analysis showed more than 50% of total polyphenols, according to the established specification. Both patients received one capsule of Vimang®, 300 mg, every 8 h, during 3 months. Respiratory functional tests were done to both patients at times 0, 6 and 12 weeks of treatment as described. Blood samples were collected and the serum was obtained and stored at 20 ºC until the determination of IgE, ECP and MMP-9.

Experiments conducted-

1. Measurement of Force Expiration Volume in one second (FEV1)
2. Determination of serum total IgE and ECP
3. Determination of enzymatic activity of MMP-9

Result-

Serum concentrations of total IgE and ECP were reduced and FEV1 values were improved in both patients after Vimang® treatment. MMP-9 activity in blood serum was also reduced.

Table- Blood serum concentrations of IgE and ECP, MMP-9 activity and FEV1 values in asthmatic patients after Vimang® treatment.

Time (weeks)	IgE (kU/l)	ECP (ng/ml)	FEV1			
			Pre	Chg (%)	Post	Chg (%
A. Persistent moderated asthmatic patient						
0	1369	51.6	1.75	-	1.78	-
6	1174	40.4	2.23*	27	2.10	18
12	740	29.8	2.62*	50	2.23	25
B. Persistent severe asthmatic patient						
0	422	62.9	2.16	-	2.50	-
6	368	41.8	2.39 *	11	2.49	0
12	290	30.7	2.62*	21	2.74	10

* Represents the improvement of patients FEV1 with respect to the initial values. Chg- Change respect time 0. Pre and Post- values pre- and post-aerosol improved equal or superior than 10% compared to 0, 6 and 12 weeks of treatment.

The patient with persistent moderated asthma did not show any of the allergic symptoms as above described (to see Materials and Methods) during the 3 months of treatment with Vimang® capsules. On the other hand, the patient with persistent severe asthma didn't have acute symptoms during the treatment and he took only salbutamol at the

second and fifth weeks, one time each. Significantly, the steroids never were consumed by neither the two patients during the three months of treatment. No adverse events were reported during the treatment.

Inference-

Experimental studies in mice (discussed previously) have demonstrated the capacity of Vimang® to reduce IgE and IL-5 production, and the maturation and migration of eosinophils which support the described clinical results. Also, Vimang® has about 50% of polyphenols in its composition, and they are reported that possess in vivo anti-allergic activity. [20]

2. *Laurus nobilis L.*

Bay leaf (*Laurus nobilis*) is an evergreen perennial shrub that belongs to the laurel family (*Lauraceae*). It has been used for 1000 years, and it is an essential ingredient in cooking and in many traditional practices. *Laurus nobilis* is known by different names. In Urdu it is known as teejh pat. In English it is known as bay leaf or sweet bay. In Arabic it is known as waraq ghaar. In German it is known as lorbeer. In Greek it is known as dafni. In hindi it is known as tej patta

Geographical source-

The genus *Laurus* has a range of 24,00 to 25,00 species, and their varieties are native to the Southern Mediterranean region, the subtropics and tropics of Eastern Asia, South and North America, the Balkans, and Asia Minor. In Meghalaya, bay leaf unit production ranges from 30 to 70 kg per tree per year, but in Nepal, the average range is 13 kg of the dry leaves. About 900 tons of bay leaf are produced in Udaipur district, and 2100 tons are exported by Nepal to India. Bay is widely growing in the following countries: India, Pakistan, other Southeast Asian countries, some Pacific islands, Australia, around the coast of the Mediterranean and Southern Europe, Greece, Portugal, France, Turkey, Spain, Algeria, Morocco, Belgium, Central America, Mexico, Southern United States, and the Canary Islands.[21]

Taxonomy-

Kingdom: Plantae
Phylum: Spermatophyta
Class: Dicotyledonae
Order: Laurales
Family: Lauraceae
Genus: Laurus
Species: Nobilis

Botanical Description-

Tree- It is a multibranched, deciduous shrub having height up to 6e8 m and diameter up to 15e40 cm with smooth, thin, and brown bark containing a shady crown.

Leaves- Leaves are alternate, lanceolate, and bipinnate compounds with smooth or sharp margins 29e30 cm long containing 24 leaflets that are lanceolate, 4.8e4.9 cm long, and 1.7e1.8 cm wide with 0.5 cm long petiole.

Flower- Flowers are ebracteate, four-lobed, white, scented, and small, having eight to 12 male stamens and two to four female staminoids.

Fruit- Fruit is 10e15 mm, in small clusters, ovoid, thin pericarp enclosing spinach-green seeds and black when ripe.

Cultivation-

Bay leaf is grown in different ecologic and climatic conditions. Wet, sandy soil that has a large quantity of water or some moist atmospheric conditions close to the ocean shore is optimum and the best conditions for rapid luxuriant growth. In warmer weather leaves may burn, therefore partial sun shade well-drained sandy soil that has some moisture and a pH range of 4.5e8.2 are preferred.

Ethnopharmacological Uses-

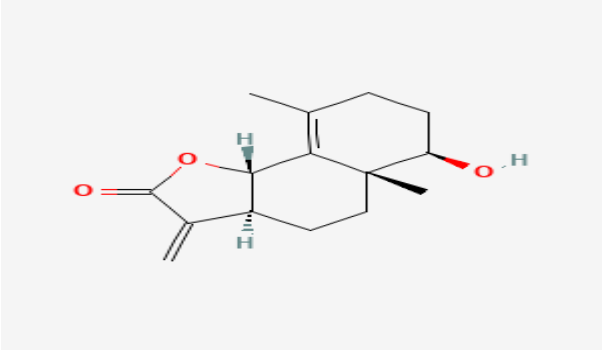
Bay is full of antioxidants and is a good source of minerals and dietary fibers. It complements food flavor, and bay tea is used to treat stomachaches, clear up mucus in the lungs, colds, and sore throat. Poultice of bay leaves is used for the treatment of rheumatism and neuralgia. To treat headache, leaf of bay is kept in a nostril or under the headbands to relieve this pain. Traditionally, it has been used for the treatment of gastrointestinal problems such as impaired digestion, flatulence, eructation, and epigastric bloating and used as diuretic and has many analgesic effect. Leaves are used for the treatment of skin rashes, earaches, and rheumatism. The essential oil of Bay is used in the cosmetic industry for soaps, perfumes, prepared foods, beverages, and dental products. Leaves and bark are used in treatment of rheumatism, nausea, vomiting, fever, anemia, body odor, diarrhea, and colic due to having astringent, aromatic, stimulant, and carminative qualities. Seeds mixed with honey or sugars are used in cough and dysentery in children. Bay leaves having antidiarrheal, antiinflammatory, and antidiabetic activity are used for the improvement of the immune system. Antioxidants such as vitamin C, vitamin E, and carotenoids are used in many dietary sources and are used to lower blood cholesterol and uric acid level.

Fresh, mature leaves are used to treat blood dysentery, inflammation, and congestion of kidney. Bay leaf is also used to treat arthritis, headache, fungal diseases, anorexia, colds, cataracts, diarrhea, colic ulcer, appetizer, neuralgia, and digestive stimulant traditionally.

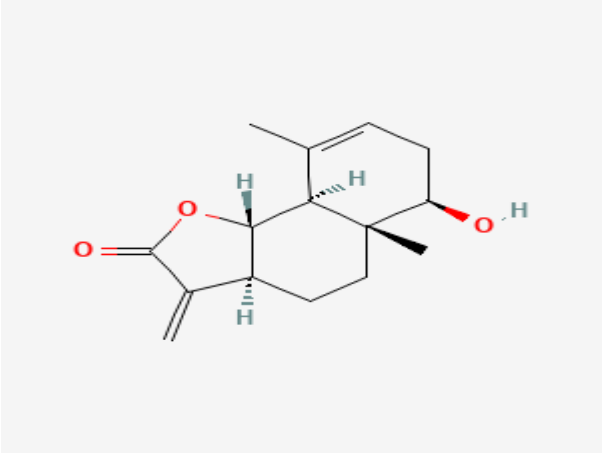
Phytochemisty-

Bay leaf has a sharp and bitter taste. The difference in fragrance and aroma is due to the presence of essential oils in leaves and other parts of the plant. It has flavonoids, tannins, eugenol, citric acid, carbohydrate, steroids, alkaloids, tri terpenoids, and essential oils. Antioxidant properties were discovered in the extract of bay leaf to have phenolic compounds.

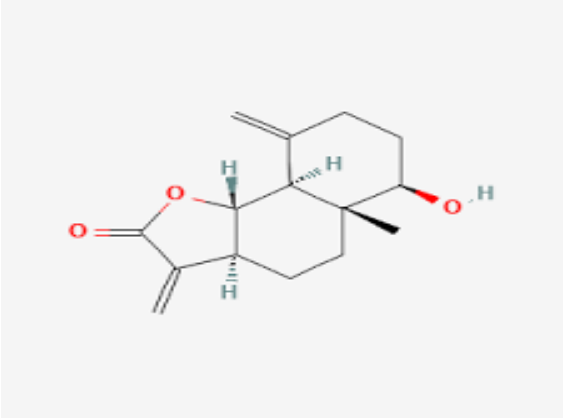
1. Structure-



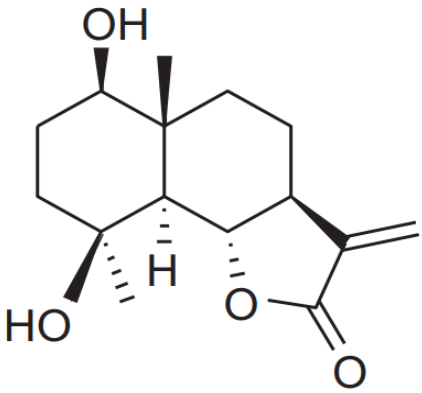
Magnolialide



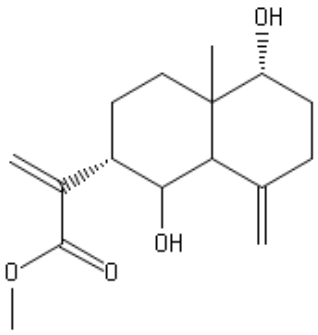
Santamarine



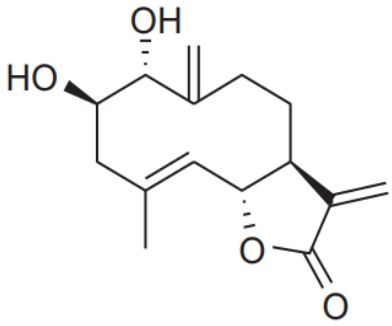
Reynosin



3aS,5aR,6R,9S,9aS,9bS)-6,9-dihydroxy5a,9-dimethyl-3-methylidene3a,4,5,6,7,8,9a,9boctahydrobenzo[g][1]benzofuran-2-one



Baynol C



Lucentolide

2. Phytochemical Screening-

Bay leaves were air dried and coarsely powdered. 10g of the dried powder were soaked separately into 100ml of ethanol and distilled water and shaken occasionally well for five hours and kept undisturbed for 24 hours and 48 hours respectively. The extracts collected was then concentrated in a water bath to obtain a thick mass of the respective extract.

- Test for Phenols-
  The extracts were treated with few drops of 5% (w/v) glacial acetic acid followed by 5% (w/v) $NaNO_2$ solution. Formation of muddy brown colour indicated the presence of phenols.
- Test for tannins-
  The extracts were treated separately with few drops of $FeCl_3$ solution. Formation of blackish precipitate indicated presence of tannins.
- Test for flavonoids-
  To 1-2ml of all the extracts add a small piece of magnesium paper and add a few drops of conc. HCl carefully along the walls of the tube. Appearance of red colour indicated the presence of flavonoids.
- Test for sterols-
  To 1-2ml of all extracts, a few drops of acetic anhydride solution was added. To this mixture a few drops of conc. H_2SO_4 was added carefully along the walls of the test tube. Formation of reddish brown ring at the junction of two layers indicated the presence of sterols.
- Test for saponins-
  5ml of each extract is taken in a test tube and shaken vigorously to obtain a stable froth. To this frothing solution 5-6 drops of olive oil was added. Formation of an emulsion indicated the presence of saponins.

- Test for anthraquinone-
  1-2ml of the extract was mixed with equal volumes of benzene and then about 1ml of 10% ammonia solution was added. Formation of red colour on addition of ammonia indicated presence of anthraquinones.
- Test for quinones-
  The extracts were treated separately with alcoholic KOH solution. Appearance of colours ranging from red to blue indicated presence of quinone.
- Test for terpenoids-
  To 1-2ml of all extracts 1% HCl was added and allowed to stand for 5-6 hours. Later these extracts were treated with 1ml Trim-Hill reagent (solution of 10ml of acetic acid, 1ml of 0.2% Copper sulphate in water and 0.5ml conc. H_2SO_4) and heated in a boiling water bath for 5-10mins. Formation of bluish-green colour indicated presence of terpenoids.
- Test for carbohydrate-
  2-3 drops of molisch reagent was added to the extracts and mixed well. To this, a few drops of conc. H_2SO_4 was added carefully. Formation of reddish purple coloured ring at the junction of two layers indicated the presence of carbohydrate. [22]

Pharmacology-

Type I hypersensitivity responses have been implicated in the cause of several diseases including allergic asthma and atopic dermatitis. These responses are characteristically associated with immunoglobulin E (IgE) and mast cells play a crucial role in the development of IgE-mediated hypersensitivity reactions. Mast cells possess a high-affinity IgE receptor that binds to IgE. In type I hypersensitivity reactions, allergen interacts with mast cellbound IgE and activates cells by cross-linking IgE–FcεRI complexes. The activation of mast cells following the engagement of IgE–FcεRI complex by antigens results in a process called degranulation, and the activated mast cells release preformed molecules from its cytoplasmic granules, such as histamines, proteoglycans, serine proteases, and β-hexosaminidase, which are capable of inducing bronchoconstriction, mucus secretion, and mucosal edema, all features of asthma. Degranulation of mast cells with the resulting release of histamine and β-hexosaminidase elicits the production of cytokines including interleukin (IL)-4, which activates pre-T helper (pre-Th) cells and transforms into T helper 2 (Th2) cells, and the overexpression of the IL-4 affects Th2 differentiation and IgE class switch. IL-4 levels are elevated in patients with severe asthma and atopic dermatitis, and this increase in the IL-4 levels also correlates with the severity of these diseases.
Mechanism of action studied opted was evaluation of the compounds from *Laurus nobilis* L. on immunoglobulin E (IgE)-mediated type I hypersensitivity responses.

Method-

To prepare a sample, 1.5 kg of the leaves of *Laurus nobilis* L. was air-dried and were extracted repeatedly with CH_2Cl_2 and MeOH. The combined filtrates were evaporated under reduced pressure using a rotary vacuum evaporator to yield a dark green gum (dry weight, 270 g) which was stored in the dark at -20°C until use. The extract was partitioned between n-hexane (dry weight, 57.8 g) and MeOH/H2O (9:1) (dry weight, 196.3 g), then the latter was repartitioned between H_2O (dry weight, 116.8 g) and $CHCl_3$ (dry weight, 67.8 g). The inhibition of mast cell degranulation was performed and bioactivity-guided fractionation procedure was performed to obtain seven isolates, the $CHCl_3$ fraction was subjected to silica normal-phase vacuum flash chromatography with n-hexane and ethyl acetate gradients (elution order: n-hexane, n-hexane/EtOAc (9:1-3:7), EtOAc, acetone) and finally MeOH. The sub-fraction (970.0 mg) eluted with n-hexane/ EtOAc (1:1) mixture was subjected to semi-preparative high performance liquid chromatography (HPLC). The final purification of compound was accomplished by HPLC to yield 9.0 mg and 112.8 mg of **magnolialide**, **santamarine.** The sub-fraction (1220.0 mg) eluted with nhexane/EtOAc (4:6) mixture

was subjected to semi-preparative HPLC, then further purified by HPLC to yield 183.6 mg, 41.2 mg, and 100.6 mg of **reynosin**, **baynol C**, and **11,13-dehydrosantonin** respectively. Finally, the sub-fraction (381.1 mg) eluted with n-hexane/ EtOAc (3:7) mixture was subjected to semi-preparative HPLC, then further purified by HPLC to yield 20.6 mg of **(3aS,5aR,6R,9S,9aS,9bS)-6,9-dihydroxy-5a,9-dimethyl3-methylidene-3a,4,5,6,7,8,9a,9b-octahydrobenzo[g][1]benzofuran2-one** and 140.7 mg of **lucentolide.**

Cytotoxic effects of 7 compounds were determined after 24 h of treatment in RBL-2H3 cells using the MTT assay at various concentrations up to 100 μM

In this experiment, baynol C and lucentolide revealed relatively strong cytotoxic effects at a concentration of 100 μM, whereas magnolialide revealed a relatively weak cytotoxic effect, and the other compounds showed a little or non-cytotoxic. A positive control compound doxorubicin revealed a cytotoxic effect with an IC50 value of 29.2 μM. The degranulation of RBL-2H3 mast cells, after sensitization with anti-DNP IgE and reaction with DNP-HSA, was evaluated by measuring the activity of β-hexosaminidase released.

Result-

Treatment with magnolialide inhibited the release of β-hexosaminidase with an IC50 value of 20.2 μM, and mast cell stabilizers, cromoglycate and ketotifen, used as positive control compounds, revealed IC50 values of 74.3 and 58.4 μM, respectively. The effect of magnolialide on the release of IL-4 was determined by measuring the IL-4 concentration in the cultured medium by using the ELISA kit. Magnolialide inhibited the IL-4 release with an IC50 value of 18.1 μM; the positive control compounds, cromoglycate and ketotifen, also inhibited IL-4 release with IC50 values of 7.4 and 15.2 μM, respectively. In addition, the effect on the expression of IL-4 mRNA was investigated. Magnolialide reduced the IL-4 mRNA expression with an IC50 value of 15.7 μM, cromoglycate with an IC50 value of 8.1 μM, and ketotifen with an IC50 value of 19.4 μM.

n addition, the inhibitory effect of magnolialide on IL-5-stimulated Y16 cell proliferation was examined and inhibition was also observed in a dose dependent manner. The IC50 values of magnolialide and of the positive control compound tyrphostin AG490 were 18.4 μM and 24.9 μM, respectively.

Thus, magnolialide significantly inhibited IgEmediated degranulation from RBL-2H3 mast cells. No significant toxicity was observed at the range of concentrations tested in this experiment. [23]

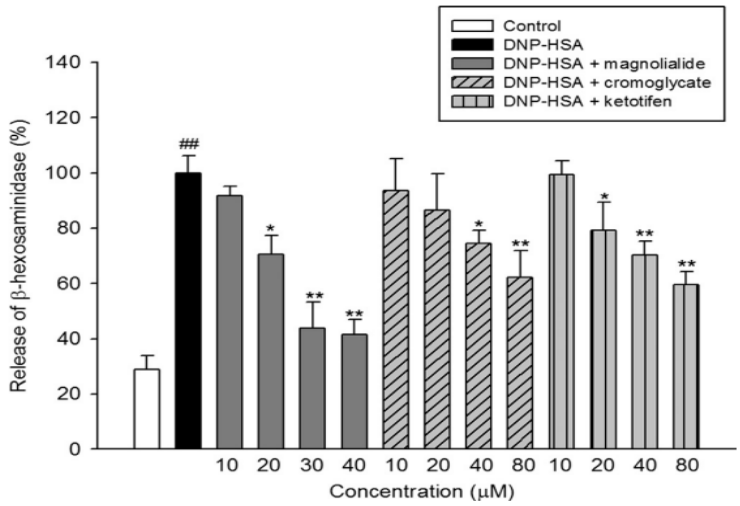


Fig. 4. Inhibitory effects of magnolialide on β-hexosaminidase release from RBL-2H3 cells. Values measured from cells treated with anti-DNP IgE and DNP-HSA were considered to represent 100% of degranulation. Cells were treated with magnolialide or positive control compounds (cromoglycate and ketotifen) for 20 min followed by DNP-HSA for an hour. Data represent the mean ± S.D. of three independent experiments; $^{\#\#}p < 0.01$, compared with control group (anti-DNP IgE treatment alone); $^{*}p < 0.05$ and $^{**}p < 0.01$, compared with anti-DNP IgE and DNP-HSA treatment, respectively.

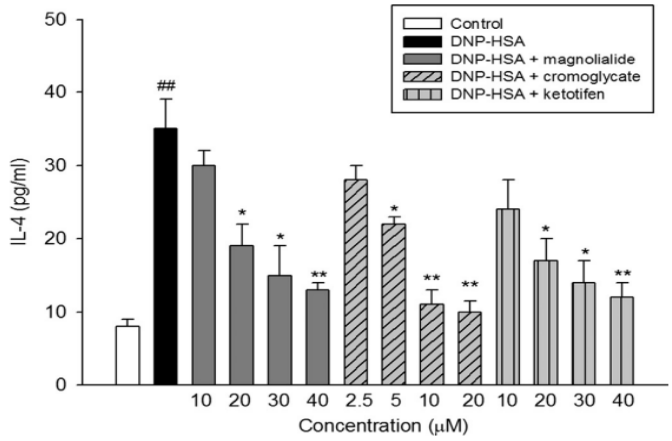


Fig. 5. Inhibitory effect of magnolialide on IL-4 release from RBL-2H3 cells. Cells were treated with magnolialide or positive control compounds (cromoglycate and ketotifen) for 3 h followed by DNP-HSA for 2 h. The release of IL-4 was measured by ELISA as described in materials and methods. Data represent the mean ± S.D. of three independent experiments; $^{\#\#}p < 0.05$, compared with control group (anti-DNP IgE treatment alone); $^{*}p < 0.05$ and $^{**}p < 0.01$, compared with anti-DNP IgE and DNP-HSA treatment, respectively.

Side effects-

Bay leaf might interfere with blood sugar control and may not be safe to use during diabetes. Bay leaf might slow down the central nervous system (CNS). There is a concern that it might slow down the CNS too much when combined with anesthesia and other medications used during and after surgery. It is recommended to stop using bay leaf as a medicine at least 2 weeks before a scheduled surgery.

Conclusion

Natural products have been extensively used as a complementary treatment for asthma therapy. Studies concerning these products have aimed at investigating their activity as a matrix of compounds to complement or replace current asthma treatment, while others aim at isolating compounds to generate new medicines based on synthetic drugs of natural origin. Historically, natural products have contributed tremendously to the development of marketable medicines to the treatment of several diseases. The evaluation of their therapeutic activities and identification and isolation of their bioactive molecules allowed not only their clinical use, but also the discovery of the pharmacophore groups and the radicals responsible for their toxicity or their biopharmaceutics aspects. In fact, based on such studies, it is possible to perform structural or delivery changes on these compounds that would increase their safety or would be able to module their half-life allowing to target them to specific action sites. This review shows the experimental studies that identified the antiasthma activity of different natural sources along with the molecules responsible for that. Plants were found to be the major source of products used by the folk medicine to treat asthma, since they are a renewable source of easy access. Also, due to their variety of secondary metabolites, plants are able to promote antiasthma activity mainly due to their anti-inflammatory and bronchodilator properties. This study reveals that flavonoids, phenolic acids, and terpenoids are the main elucidated compounds able to promote the attenuation of asthma symptoms. On the other hand, a lack of scientific reports regarding the pharmaceutical activity of natural products from animal and microorganism sources has limited their use. However, these products still represent an important source of bioactive compounds able to be used on asthma treatments.

The current asthma treatment is of high cost and has many side effects, which compromises the patient treatment compliance. Literature reports show that asthma treatment can be improved using natural products to complement the traditional drugs, since those products are of low cost and biocompatible and show reduced side effects. [

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TABLE 1: MANGIFERIN CONTENT IN DIFFERENT FRUIT TISSUES OF 11 CHINESE MANGO CULTIVATORS

Cultivators	**Mangiferin content (mg/g DW)**		
	Peel	**Pulp**	**Seed Kernel**
GF	0.23±0.03	N.D	0.38±0.02
GR-265	3.76±0.63	0.004±0.001	0.63±0.06
JHM	0.16±0.05	N.D	0.89±0.05
LPM	7.49±0.14	0.012±0.003	0.67±0.02
LXM	3.93±1.48	N.D	0.33±0.03
MQS	1.91±0.33	0.20±0.07	0.14±0.01
SLLK811	0.52±0.09	N.D	0.50±0.05
TN-1	0.04±0.01	N.D	0.62±0.02
XH-2	0.67±0.36	0.008±0.002	1.04±0.14
YX-1	0.13±0.10	N.D	0.21±0.005
ZHM	7.34±0.13	0.002±0.0002	2.43±0.10

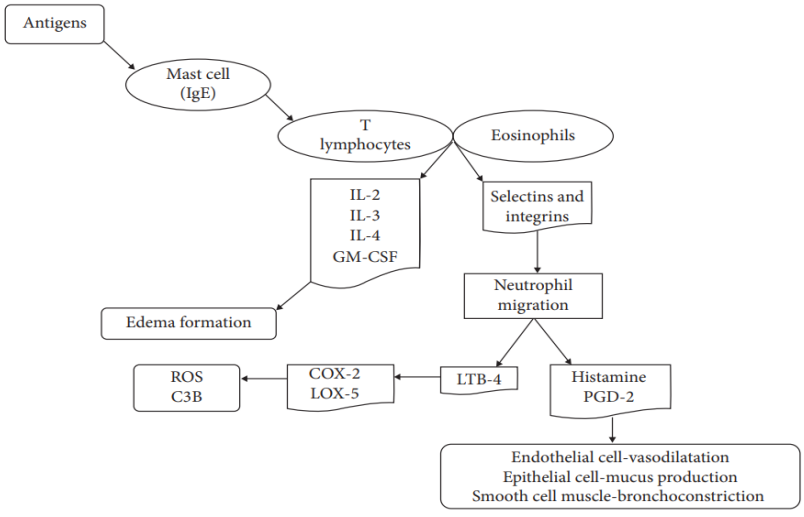

Fig.1: Pathophysiology of Asthma