Journal of Ayurvedic and Herbal Medicine

Systematic Review

ISSN: 2454-5023
J. Ayu. Herb. Med.
2023; 9(1): 29-39
Received: 25-11-2022
Accepted: 06-03-2023

www.ayurvedjournal.com
DOI: 10.31254/jahm.2023.9106

Herbal remedies that can be used to treat type 1 hypersensitivity reactions associated with allergic rhinitis and asthma in Sri Lanka- A systematic review

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ABSTRACT

Background: Allergic rhinitis and asthma are common diseases of the immune system that negatively affect general health, quality of life, and social relationships. Many studies have been conducted to evaluate treatment options for these conditions, particularly using herbal remedies. Complementary alternative medicines are extensively used in the treatment of type 1 hypersensitivity-related allergic rhinitis and asthma. There is a dearth of scientific evidence even though the Sri Lankan population uses traditional medical treatments to effectively manage these conditions.

Aims and Objectives: To review the evidence-based recommendations for traditional natural plants with scientifically proven anti-allergic rhinitis and asthmatic activity in Sri Lanka. This review focuses on ten selected medicinal plants used by a traditional ayurvedic practitioner in Sri Lanka to treat allergic rhinitis and asthma. The selected 10 plants are: *Piper longum, Clerodendrum indicum, Clerodendrum serratum, Zingiber officinale, Piper nigrum, Allium cepa, Aegle marmelos, Vitex negundo, Coriendrum sativum*, and *Curcuma longa.*

Materials and Methods: Therefore, to provide evidence-based recommendations for these traditional natural plants used, a comprehensive literature survey was carried out using PubMed® (U.S. National Library of Medicine, USA), Google Scholar, and Hinary© (WHO, Switzerland). Studies released between 2006 and 2022 were incorporated after two rounds of evaluation and shortlisting; approximately 450 comprehensive database searches were used to find study articles. Then after evaluating the papers' titles and abstracts and evaluating the relevant complete texts for eligibility, the systematic review comprised 54 empirical investigations. It was carried out independently by two reviewers.

Results and Discussion: Herbal plant-based medications have several advantages: they are less expensive, have a long history of use, are better tolerated by patients, and have fewer or no side effects. These plants exert their anti-allergy effects by inhibiting various cytokines and interleukins and decreasing immunoglobulin levels. According to scientific evidence, *Clerodendrum indicum, Clerodendrum serratum, Piper longum, Piper nigrum, Zingiber officinale*, *Allium cepa*, and *Curcuma longa* are the most studied plants. The plants *Vitex negundo, Coriendrum sativum*, and *Clerodendrum indicum* have received the least amount of research of the selected ten plants.

Conclusion: These plants exert their anti-allergy effects by inhibiting various cytokines and interleukins and decreasing immunoglobulin levels. In addition, these essential herbal plants can be tested experimentally to treat these common type-1 hypersensitivities linked to allergic rhinitis and asthma.

Keywords: Allergic rhinitis, Asthma, Anti-allergic, Type 1 hypersensitivity, Herbal remedies.

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INTRODUCTION

The immune system is known as a composition of various cells and proteins that all together function to safeguard the human being from strangers and invading materials referred to as antigens, such as microorganisms, residue materials, or environmental things. However, some kind of change in this similar system can cause excessive immunological and inflammatory responses that produce unfavorable results, they are referred to as hypersensitive responses. hypersensitive reactions of types I, II, III, and IV are the four categories of hypersensitive responses [1]. Allergy symptoms are triggered by type 1 hypersensitive responses or sometimes type IV hypersensitive responses. Numerous people experience allergic reactions, which range in severity from a minor stage to severe, ultimately leading to a sudden demise. Which occur in inconvenient body locations and can sometimes vary depending on interpersonal variability factors [2].

The study indicated Allergy was the sixth most common chronic condition among United States communities, affecting more than 50 million Americans [3]. Over the past few decades, allergy problems

have become more common [4], which are generally associated with environmental exposure and lifestyle practices. Atopic allergy comes from the Greek word "atops," which means strange or out of place. However, from an epidemiologic and economic standpoint, allergic disorders, such as respiratory allergies, skin conditions, and adverse reactions to foods, medications, and antigens, showed a significant cost [5]. Bronchial allergies, based on the WAO White Book, a global association for allergy research [6] and Table 1 provides information on the prevalence of diseases around the world based on data from the International Study of Asthma and Allergies in Children (ISAAC) [2]. It's still not entirely understood why some people react violently to drugs that ought to be harmless, but it's been hypothesized that several sensitive genes and changes in the environment are too responsible.

Table 1: prevalence of allergic diseases

Allergic disorder	Prevalence %
Rhinoconjunctivities	Around 20 to 35
Prevalence of asthma	Among 10 and 20
Atopic eczema prevalence	20
Prevalence of urticaria	Around 15 to 20
Food allergy	Around 3 to 5
The hypersensitivity to insect venom	1

What is known as Type 1 hypersensitivity?

Type 1 hypersensitivity, commonly known as immediate hypersensitivity can be defined as mast cell and basophil degranulation is mediated by IgE, this shows that the release of antibodies against the antigen was mediated by immunoglobulin E (IgE). The result is the degranulation of the mast cells, which results in the discharge of inflammatory mediators including histamine [2].

When the body responds to infection with organisms, such as bacteria, viruses, or parasites [7], in type 1 hypersensitivity reactions, activation of mast cells results in the discharge of a specific type of mediators of inflammation. Other immune systevm cells like lymphocytes as well as neutrophils are drawn to the infection site as a result of the action of these mediators. According to infectious agents, mast cell degranulation takes place and is frequently brought on by the complement system's anaphylatoxins Complement factor 3A (C3a), and C5a (complement factor 5A) [8] as well as perhaps by the ligation of receptors for pattern recognition [9]. the antibody IgE-mediated activation is seen in type 1 hypersensitivities. The manner in which antigen-presenting dendritic cells and T cells (Thymus cells /lymphocytes) interact determines the type and potency of an immunological response. This critical event contributes to the balance of different types of T helper cell subpopulations. Such as Th1 (Type 1 T helper), Th2 (Type 2 T helper), Th9 (Type 9 T helper), Th17(Type 17 T helper), Th22 (Type 22 T helper), and so forth. As a result, if an acceptable immune response occurs, such interactions lead to selecting whether B cells (Bursa of Fabricius / lymphocyte) will also be encouraged to switch to IgE synthesis [10]. cytokines and interleukins are mostly linked to the formation of the IgE antibody. Such as IL-4 (interleukins), and IL-13, by the T helper cells (subpopulation) [11, 2].

Immunoglobulin E (IgE) antibodies that are specific to allergens are present in greater quantities in type 1 hypersensitivity. When exposed to allergens again, it can adhere to mast cells and trigger the release of histamine as well as other agents. This causative agent varies from person to person. It may consist of molds, animal dander, dust mites, pollens (from primarily entomophilous plants), dust mites and their excrement, and some foods [12]. Most patients suffer from various types of allergic symptoms which can occur in various organs.

Type 1 hypersensitivity reactions are pathophysiological reactions, allergens can cause various allergic disorders, such as allergic rhinitis and allergic asthma. However, this systematic review is based on allergic rhinitis and allergic asthma. Histamine, which increases vascular permeability and causes bronchoconstriction and vasodilatation in type 1 hypersensitivity, is released by degranulating mast cells [13]. Although allergic illnesses are most frequently connected with the IgE mast cell-driven pathway, type 1 hypersensitivity symptoms can also result from non-IgE mediated causes [14, 15].

Allergic rhinitis

The most widely scattered illness in Sri Lankan society, "Pinasa," can be found in all age groups. According to symptoms seen in modern medicine, the term pinasa employed in traditional medicine is identical to "Apinasa" in Ayurvedic medicine and allergic rhinitis in western medicine [16].

Sneezing is mostly brought on via mast cell mediated IgE cross-linking induced by allergens in the early stages of allergic rhinitis. However, because other patients are unresponsive to anti-IgE therapies, the allergen-IgE route may not have a specific purpose. Non-IgE allergic rhinitis symptoms are still unclear. However, the identification of allergic rhinitis depends on the existence of either systemic or regional (nasal) IgE antibodies to particular allergens as well as rhinitis symptoms such as sneezing, nasal discharge, and nasal clotting [17]. Non-allergic rhinitis is occasionally characterized or diagnosed in individuals with rhinitis who lack IgE that is specific to allergens, and the majority of the time, the triggering symptoms are unclear [18]. Though non-allergic rhinitis is not considered an allergic disease, infiltrating inflammatory cells, such as neutrophils, eosinophils, and mast cells, can trigger localized immune system activation, either innate or adaptive in some patients with non-allergic rhinitis [19]. Additionally, histamine is a key mediator of type 1 hypersensitivity and is linked to the signs and symptoms of the condition [20].

Allergic asthma

Asthma and allergic rhinitis are often well-known medical disorders that frequently coexist. Asthma is an airway disease including, airway narrowing, airway wall thickening, and increased mucous, characterized by an improvement in the tracheobronchial tree's receptivity to various stimuli. It causes to narrowing of the airway [21]. But sometimes it can be relieved naturally or by therapy. It is known as episodic disease clinically identified by dyspnea, cough, and wheezing. However, it can go from a severe stage to a fetal stage. According to the stimuli initiating asthma. There are three types of conditions are identified. Those are extrinsic (allergic, atopic) and intrinsic (idiosyncratic, non-atopic) and the third type is a mixed pattern [22].

The most prevalent form of asthma, known as atopic allergic asthma, typically attacks children or young adults. The majority of people who have allergic asthma also have rhinitis, urticarial, etc. [23]. Hypersensitivity to various types of "allergens" causes this. This hypersensitivity is caused by the inhalation of pollens, house dust, animal danders, molds, etc. [24]. occupational asthma can be also seen. These are increased IgE levels in the serum. IgE-mediated type 1 hypersensitivity reactions include an "acute immediate response" and a "late-phase reaction" [22].

Mucous hypersecretion, an increase in goblet cells, and secretory glands are examples of structural alterations in the airway that may indicate epithelial injury, subepithelial fibrosis, and an increase in airway smooth muscle [25, 26]. Coughing, wheezing, and shortness of breath are all considered to be clinical signs of asthma [27]. When an exacerbation is severe, cyanosis and the usage of supplementary muscles for breathing may be apparent[25]. To diagnose allergic-type 1 asthma and establish whether someone has allergic asthma, a skin prick test or quantifying a particular immunoglobulin E (IgE) is used[26].

Epidemiology of Allergic rhinitis and asthma

The prevalence of allergic rhinitis was reported as 15-25% in areas where, in the Americas, Asia, Europe, and Africa. Children, adolescents, and young adults were the age groups more affected and suffered from allergic rhinitis with correlations of asthma, sinusitis, conjunctivitis, and nasal polyposis [28]. Research studies have recorded that the prevalence of allergic rhinitis is about 21.4% among schoolchildren in the Western province of Sri Lanka, and among them, 44.4% of the population suffered from asthma [29]. Asthma has recently affected almost 350 million people worldwide and thinks about how the population will gradually expand to 400 million throughout the next 30 years. it has the highest morbidity and costs in the European Union, it expends 72.2 billion Euro annually on asthma patients [30].

In the world, allergic asthma is regarded as a disease that affects 5–16% of people, although asthma and allergic rhinitis are often co-occurring conditions, with ~19–38% of people with allergic rhinitis also having asthma [31].

Worldwide, the effects of allergic rhinitis and allergic asthma are a significant burden. However allergic asthma symptoms could be led to mild to severe stages. Western medicines only have the prevention method, not a cure. Therefore, to cure allergic disorders including allergic rhinitis and allergic asthma, people often turn to herbal medicines. For more than a thousand years, many illnesses have been treated in Sri Lanka using plants and items made from them [32]. More than 1400 plants native to Sri Lanka are utilized as medicines in traditional medicine. Additionally, a variety of herbs are widely utilized to treat pathological diseases linked to inflammation [32].

Western treatment methods for allergic rhinitis and asthmatic activities are well documented. Consideration of allergic rhinitis (locally known as Pinasa), as a western treatment method, the most effective treatment is Intranasal corticosteroids, which act as the first-line therapy for persistent symptoms affecting the day-to-day quality of life. Second-line treatments such as antihistamines are required for more severe cases that don't respond to intranasal corticosteroids, leukotriene receptor antagonists, decongestants like Cromolyn, as well as alternative treatments such as nasal irrigation [33]. Subcutaneous or sublingual immunotherapy might be given to a patient with allergic asthma if standard treatments are ineffective at controlling their symptoms [33]. When it comes to anti-allergic asthmatic treatments, it is recently treated and it is depending on the stage, with bronchodilators, as an illustration, consider long-acting beta-agonists, long-acting muscarinic antagonists, or anti-inflammatory medications. Theophylline, leukotriene modifiers, oral or inhaled corticosteroids, and anti-IgE treatment are a few examples [34]. Unfortunately, some asthmatics do not react to these types of therapies, and long-term steroids have reported many side effects. Therefore, novel and more effective drugs with minimum adverse effects are needed. Therefore, many patients are interested in natural herbal remedies.

There is a huge demand for herbal medicines globally, and there is an interest in researching the unknown active ingredients in herbal plants that exhibit allergic asthma and rhinitis. Several kinds of literature document the herbal plants that can be used to treat allergic asthma and rhinitis, and the literature suggests knowledge is scarce on most herbal preparations. Among the countries that abundance of herbal plants, a tropical country like Sri Lanka pursues herbal plants for their various properties. However, herbal plant products remain a suitable source for novel lead molecules in the light of the future for the effective and helpful development of medicines for allergic diseases.

On such a background, this article is aimed at providing an overview of the available herbal plants in Sri Lanka that have been proven scientifically effective in the treatment of allergenic asthma and rhinitis. An attempt has taken to explore the possible treatment options using natural herbal treatments to treat allergic asthma and allergic rhinitis.

METHODOLOGY

An interview was conducted with a traditional ayurvedic practitioner from Welimada, Sri Lanka, regarding his practices and treatments for the management of asthma and allergic rhinitis. Ten plants were provided by the traditional ayurvedic practitioner. The anonymity of the practitioner was maintained upon his request

A literature survey on herbal remedies that can be used to treat type 1 hypersensitivity reactions associated with allergic rhinitis and asthma was conducted in the databases listed below: PubMed ® (U.S. National Library of Medicine, USA) (United States of America), Google Scholar, and Hinary © (WHO, Switzerland) (World Health Organization) using the following keywords, Allergic rhinitis, Asthma, Anti-allergic, Type 1 hypersensitivity, Herbal remedies. Additionally, each plant was screened for "anti-allergic characteristics" activity to identify other mechanisms and modes of action that were not explicitly included in the list of key terms. The review included studies published between 2006 and 2022 after two steps of evaluation and shortlisting; A comprehensive database search yielded over 450 research publications. The systematic review includes 54 empirical studies after screening the themes and abstracts of the publications and reviewing the relevant complete texts for eligibility. This information proves that previously obtained results were from the research articles. The results were restricted to peer-reviewed research articles written and published in English. while conference proceedings and communications were excluded. The search method was carried out

independently by two reviewers, and the final collection of papers to be included in the review was decided through several consensus processes. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) flow diagram and the checklist are attached as supplementary documents.

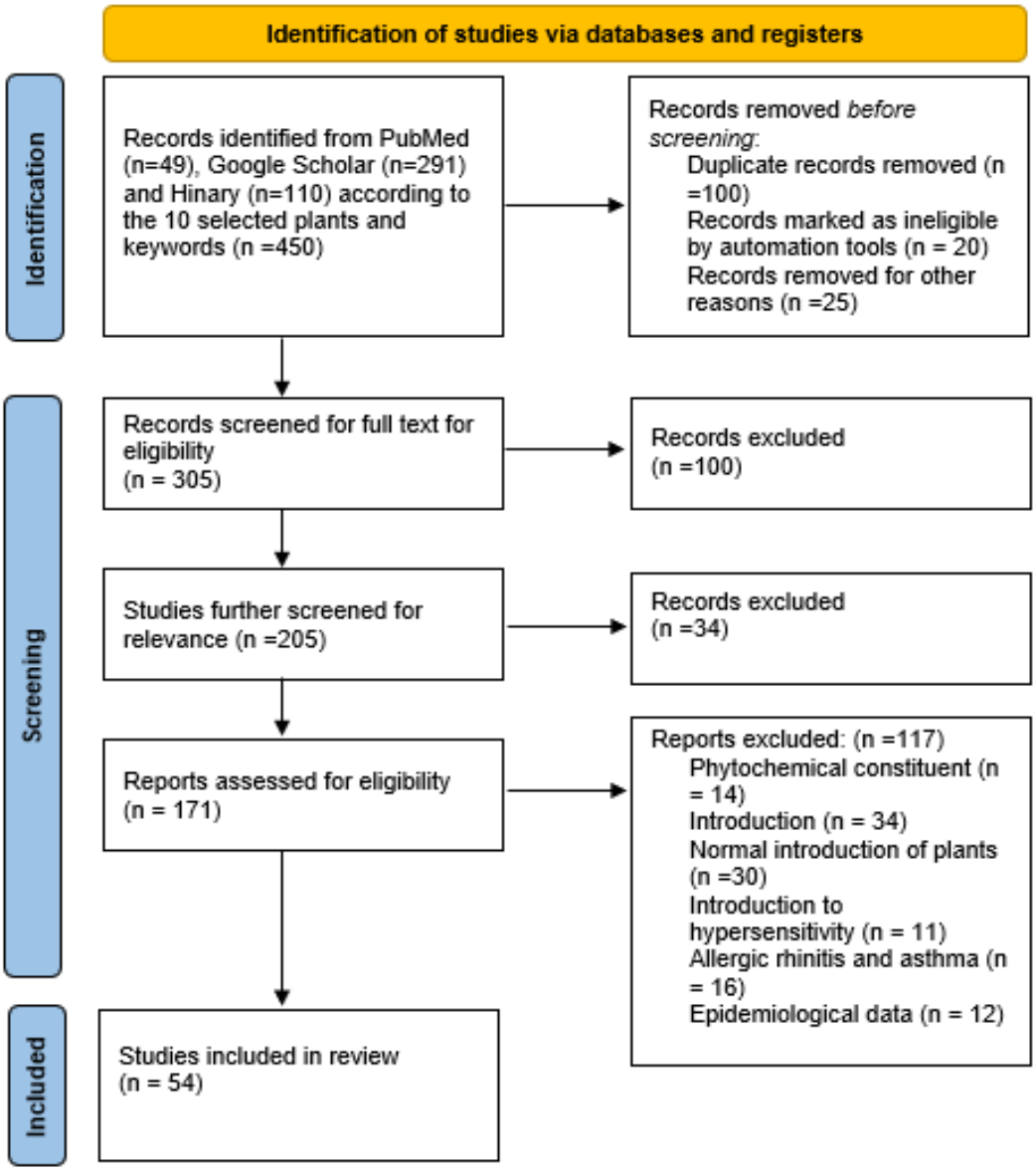

Figure 1: Systematic review flow chart

RESULTS

The authors seek to give evidence to close the gap in scientific understanding regarding the traditional usage of certain herbs in Sri Lanka for the treatment of asthmatic and allergic rhinitis-related type 1 hypersensitivity responses.

Sri Lankan plants that can be used to treat allergic rhinitis and asthma

Sri Lanka is one of the most biologically diverse countries in the Asian region, as a tropical nation, Sri Lanka is home to numerous native, tropical forests and herbaceous flora, among them in Sri Lanka's lengthy tradition of using natural plant treatments, several herbs have been employed. Sri Lanka has more than 3000 plant species, and majorities of them are used in the conventional system of medicine in Sri Lanka [35]. In Sri Lanka, between 60% and 70% of the rural population primarily receives basic healthcare via indigenous medical systems [36], and also Sri Lanka has a long heritage of using herbal treatments in Ayurveda, Unani, and Siddha traditions. Though there is valuable knowledge of traditional herbal remedies, still they have not been researched by the scientific community.

A literature survey on Herbal remedies that can be used to treat type 1 hypersensitivity reactions associated with allergic rhinitis and asthma was conducted using popular databases, and results were categorized according to the respective topics including Allergic rhinitis, and allergic asthma for the selected ten plants. Figure 2 depicts the families of the plants.

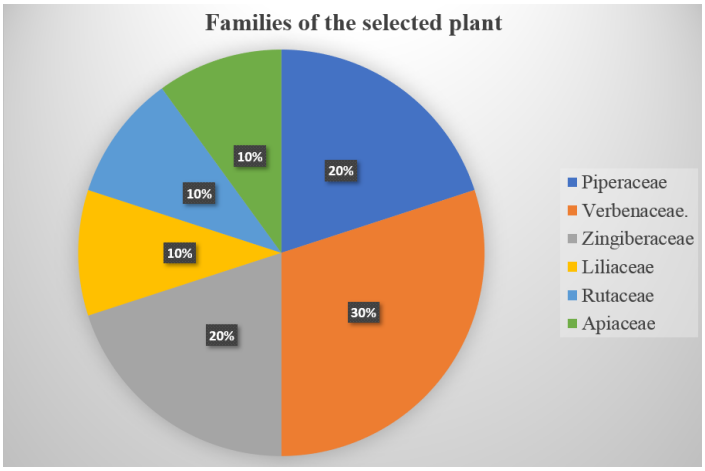

Figure 2: Families of the selected plants

Piper longum (Thippili)

Piper longum (belongs to the family Piperaceae), commonly known as Long Pepper or "Thippili" (in Sinhalese), is widely used to treat type 1 hypersensitivity reactions, a study was investigated using fruits of *Piper longum*, for their allergic-resistance activity in β-hexosaminidase in the RBL-2H3 (rat basophilic leukemia) cells using IgE (immunoglobulin E) sensitization [37]. In vitro study was conducted using a basophilic leukemia cell line from rats (RBL-3H3) for allergic rhinitis and allergic asthma (37). Additionally, a study suggested allergic-resistance properties in vitro studies [37]. This plant contains a variety of active ingredients, including Essential oils, Alkaloids, glycosides, Flavonoids, and longumosides [38, 39]. A study was conducted to assess antihistaminic activity using the ileum of the Guinea pig (in vitro), histamine-induced bronchospasm in Guinea pigs, and catalepsy in mice (In-vitro) in opposition to petroleum ether, alcohol, and mixture made from long-paper fruits [40]. Leukocytosis produced by milk in mice and anaphylaxis in rats (in vitro) was used to determine its anti-allergic activity. [40]. Most effective drugs for asthma are mostly steroidal. Phytochemical constituent of *piper longum* reviled the presence of steroids other than other constituents [40] and confirmed anti-asthmatic activity. Anti-rhinitis, and other uses.

Clerodendrum indicum (Sirithekku)

Conventional herbs with phytochemical Compositions have been utilized as drugs to treat a variety of ailments. [41]. Such a traditional plant named "Sirithekku" in Sinhala, known as *Clerodendrum indicum* belongs to the family Verbenaceae. The roots & leaves of *Clerodendrum indicum* are used in many recipes in Ayurveda for different kinds of ailments[42]. This plant can be used to treat asthma, bronchitis, inflammations, fever, and more. Leaves are used for fever and hiccoughs. As its major active constituents, sapogenins are present in the root bark and leaves composed of flavonoids and phenolic acids[42]. Since ancient days this plant is used as an anti-asthmatic agent in a traditional system. In vivo anti-asthmatic study was evaluated using biochemical parameters, WBC (White Blood Cell) count and Eosinophil count in BALF (Broncho Alveolar Lavage Fluid), IgE antibody concentration in blood serum, and histopathology of lungs were carried out using, Female Albino Wister rats[42]. According to the study on acute oral toxicity, *Clerodendrum Indicum* extract did not demonstrate a significant hazardous impact until a dose of 2000mg/kg. It was evaluated against asthma caused by ovalbumin in experimental rats with the dose of 400mg/kg (1/5 of LD_{50}) (Median Lethal Dose) and 200mg/kg(1/10 of LD_{50}) for respective extract [42]. Kits for sandwich ELISA (Enzyme-Linked Immunosorbent Assay) were used to determine serum IgE levels. In in vivo anti-asthmatic activity, test drugs have revealed a considerable reduction in inflammatory markers such as concentration of IgE antibodies, Absolute eosinophil count in BALF, and total leukocyte count in the BALF, and. Extract-treated animal groups showed good results with $p< 0.0001$ when compared with asthmatic groups [42]. The results showed that the hydroalcoholic extract of the plant showed anti-asthmatic properties. As the active phytochemicals, Alkaloids, Flavonoids, Terpenoids, and Tannins were found[42].

Clerodendrum serratum (Kan henda)

The anti-allergic and anti-inflammatory activity and effect on bronchial hyperreactivity were evaluated using both steam and roots of the *clerodendrum serratum*. The plant is known as "Kan henda" in Sinhala and belongs to the family Verbenaceae [43]. According to the findings, a low dosage (LD) of clerodendrum root and a higher dosage (HD) of the stem have 23% of anti-inflammatory and 21% of anti-allergic activity comparable to Dexamethasone (21%). Large doses of root extract, however, demonstrated 35% of anti-allergic and 44% of anti-inflammatory efficacy. The anti-allergic action of low dosage of the stem is low (8.6%). As a result of the research, the root of *clerodendrum serratum* is far more efficient than the stem. [44]. Another study was conducted using in vitro & in vivo investigations, and the findings showed in the model systems, the medication possesses histamine antagonistic qualities and significant mast cell stabilization and spasmolytic effect. Early diagnosis and treatment using plant extract provided 80% and 86% prevention from histamine-caused bronchoconstriction activities in guinea pigs, respectively, including 27.8% and 36.1% improvement in well before time (same to the slandered medications) [45] antagonistic to histamine, medicines on the ileum of guinea pigs indicated particular medication decrease the smooth muscle constriction in a dose-dependent pattern [45]. Increased plant extraction concentration with the maximum histamine dose (1.6g) revealed the highest inhibition (99.78%) at 50mg dosage [45]. Smooth muscle constriction caused by medicines in an organ bath before the addition of histamine revealed also that the drug possesses preventative-type antagonism [45]. *Clerodendrum serratum* is utilized in indigenous medicine to manage respiratory conditions, especially asthma, and it was used to prepare several formulas [46], anti-asthmatic, anti-histaminic, anti-allergic, and mast cell stabilization activity was evaluated. As an antihistaminic activity, an alcoholic fraction of *clerodendrum serratum* root was identified to cause bronchoconstriction, and it was prevented with anti-histaminic medications. The drug was identified as it blocks histamine-mediated constrictions of guinea pigs' tracheal preparations without harming the cholinergic response. This allergenic bronchoconstriction activity was found in separated guinea pig lungs that had been exposed to compound 48/80 and were identified as it stopped after continuous perfusion of the fraction of the plant. Therefore in vivo, root extract use every day has been demonstrated to sensitize guinea pigs and step-by-step induced protection against anaphylaxis, anti-allergic, and anti-asthmatic activities of the plant [46].

Higher (180 mg/kg) and lower (90 mg/kg) dosages were used in vivo of plant aqueous and root extract were determined by milk-caused leukocytosis in rodents and egg albumin-caused asthmatic in guinea pigs. These results indicated that the use of *clerodendrum serratum* roots (180mg/kg) is suitable for inflammatory and allergic illnesses like asthma [44]. The alcoholic extract also showed anti-asthmatic properties by restricting inflammatory mediators due to cyclooxygenase (cox) inhibition, including histamine, prostaglandin, and serotonin [47]. Several in vivo and in vitro accurate models in guinea pigs and mice have proven the antiasthmatic capabilities of *clerodendrum serratum* roots [48, 49]. In Vivo and in Vitro anti-asthmatic activity was conducted using mice and goat tracheal chain preparation [50], In vivo study, was conducted using Wister albino rats to evaluate treatment for asthma and allergic rhinitis [42, 51]. As the phytochemical constituents of the *clerodendrum serratum* Terpenoids, sterols, iridoids, phenylpropanoids, flavonoids, and carbohydrates were documented [46].

Zingiber officinale (Inguru)

Allergic rhinitis (AR) and asthma are worldwide health problems and plants are one form of alternative treatment. *Zingiber officinale*, a member of the *Zingiberaceae* family, is primarily employed in spicy meals, and rhizomes are utilized as a major part of the plant. Several investigations have found the ginger extract to have promising anti-allergic and anti-inflammatory properties [52]. As the main pungent compound, it has been discovered to include 6-shogaol, 6-gingerol, 8-gingerol, and 10-gingerol [53]. In rat basophilic leukemia (RAT-2H3) cells, the ethanolic extract of ginger and isolated components including 6-gingerol and 6- shogaol showed good anti-allergic efficacy by reducing allergic reactions with having respective IC50 (Half maximal inhibitory concentration) readings of 12.93 ± 1.28 µg/ml, 18.30 ± 3.38µg/ml (62.16 µM), and 0.28 ± 0.11 µg / ml (1.01 µg) [37]. In an in vivo experiment, 50µM 6-gingerol suppressed the generation of Th2 cytokines (IL-4, IL-10, and IL-13) as well as Th1 cytokines (Interferon-gamma) in splenic cells exposed to ovalbumin (OVA). other than that six- gingerol, compared to the control group, there was a significant decrease in mast cells and histamine in the rat peritoneum as well as a latent cutaneous anaphylactic reaction. [54]. Other than that, an in vitro study was investigated utilizing a cell line from a mouse macrophage leukemia (RAW 246.7) to evaluate the anti-allergic and anti-inflammatory effects of an ethanolic ginger extract [52]. A Vitro study was conducted [including, RTPCR (Real-Time Polymerase Chain Reaction), gel electrophoresis, ELIZA, and Lung histopathology] using mice to evaluate anti-allergic airway inflammation properties, hematoxylin, and Eosin (H&E) and PAS staining were used to examine the histology of lung tissue (Periodic Acid Schiff). They discovered that ethanol and aqueous extracts considerably decreased goblet cell hyperplasia (0.83±0.17 and 1.0 ±0.26), inflammatory cells infiltration in airways (0.67 ±0.33 and 1.0 ± 0.37), and edema with vascular obstruction (1.0 ± 0.26 and 1.2 ± 0.17) [55], both extracts reduced the Th2 driven immune response, and they noticed a considerable reduction in the total and differential count of neutrophils and eosinophils [55]. Therefore, according to the literature, Zingiber officinale can be used to treat asthma and allergic rhinitis. As the major phytochemical constituents, Gingerol, Shogaol, Polyphenols, Terpenes, Lipids, Organic acids, and Essential oils (Zingiberene, α- Farnesene, Bisabolene,α- Curcumene, and β- Sesquiphellandrene) were documented [56].

Piper nigrum (Gammiris)

p. nigrum L., belongs to the family Piperaceae, also called black paper in English and "Gammiris" in Sinhalese. It has more than 1000 species, grows in regions in the tropics and subtropics, and is native to southern India, although recently worldwide distribution can see. Vietnam, Ceylon, Malaysia, Indonesia, and Brazil are just a few examples [57]. Also, *p. nigrum* consists of oleoresins, alkaloids, and essential oils, the alkaloids piperidine, piperine, piperidine, and chavicine are found in *P. nigrum*. The additional primary constituents, steroids, terpenes, lignans, flavones, and alkamides are present. recently, in the volatile oils of black paper, 46 constituents have been discovered [57]. In vivo study was conducted using mice, and ovalbumin (OVA)-induced allergic rhinitis in mice was created, *piper nigrum* fruit extract was studied for its anti-allergic and anti-inflammatory effects (PNE). The extract, when taken orally, reduced allergy responses in the nose such as sneezing and rubbing in the early stage of allergic rhinitis [58]. Fruit extract and PNE decreased inflammatory cell aggregation in both the Nasal Lavage Fluid (NALF) and nasal tissue, particularly with eosinophils in the NALF [58]. Other than that, fruit extract inhibited the beginning of signal transducer and activator of transcription 3 (STAT3) and NFkBp65 activation (Nuclear Factor Kappa B 65) cytoplasm signaling and which increased the production of the anti-inflammatory Th 1 cytokine and restrained the generation of the pro-inflammatory Th 2 and Th 17 cytokines [58]. Another study revealed the outcomes of *P. nigrum*'s ethanolic extract (PNE) on airway inflammatory activity in mice with asthma (female BALB/c) model in allergic asthmatic mice triggered by OVA; they analyzed the number of immune cells and cytokine production in lung tissue, in addition, bronchoalveolar lavage fluid (BALF); the serum level of histamine, total IgE, anti-OVA IgE, anti-OVA IgG1, and histological structure [59]. 200mg/kg oral intake of PNE showed, a reduction of the rise in the number of inflammatory cells; control of the consistency of production of Th1, Th2, and Th17 cytokines and T regulatory cells, especially, GATA3 expression was restricted (GATA Binding Protein 3), IL-4, IL-6, IL-1β, RORγt (Orphan nuclear receptor gamma associated with a retinoic acid receptor), IL-17A, TNF- α (Tumour Necrosis Factor Alpha) and elevated the secretion of IL-10. INF-γ (Interferon-gamma) in both the BALF and the lung homogenate [59]. As well as it showed, that PNE defeated the entire IgE count, anti- OVA IgE count, anti- OVA IgG_1 count, and discharge of histamine in serum; not only were histological signs of fibrosis and invasion of inflammatory cells improved in PNE-treated animals; PNE also reduced allergic reactions by preventing rat peritoneal mast cell degranulation [(59)]. This evidence suggested that PNE has the potential to treat the treatment of allergic rhinitis and asthma. As the major phytochemical constituents Alkaloids, steroids, sterols, Cardiac glycosides, essential oil, Anthraglycosides, Anthraquinones, coumarins, Arbutin, Flavonoids, and bitter principles were documented [60].

Allium cepa (Rathu loonu)

The Liliaceae family member *Allium cepa* plants all over the globe and has been utilized as a food additive [61]; is a monocot plant that grows as a bulbous perennial or biennial; *A. cepa* in English known as "Onion" and "Rathu- loonu" in Sinhala. Onion has been identified as that contains different kinds of medicinal properties from ancient times

[62]. Conventionally used medication as the treatment of illnesses such as asthma, bronchitis-related cough, inflammatory disorders, swelling because of insect bites, and more [63]. As well as previous studies showed, that several pharmacological effects of *A. cepa*, including anti-hypersensitive, decreasing cholesterol in the blood, function as a hyperglycemic, neuroprotective, anticonvulsant, preventing the release of histamine and the oxidative and inflammatory processes in asthma, stimulating the immune system and help to reduce the osteoporosis, etc. [64, 63]. The evidence from the literature demonstrated that using onions as a medication may use to prevent asthma attacks [63]. animal experiments in vivo showed, that *Allium cepa*'s water-based extract can reduce inflammation of the lung and neutrophil, eosinophil, and lymphocyte count [62]. The study revealed methanolic extract showed a decreasing level of inflammatory markers (e.g.: IL – 5 and IL – 13) and peroxidation of eosinophils, extract also loosens up the smooth muscle of the trachea [65]. The introduction of the plant extract to the asthmatic rats revealed a considerable reduction in tracheal activity to methacholine and a reduction of total white blood cells and PLA2 (phospholipases A2) levels in comparison to the group of asthmatics who are not receiving treatment [66]. Antioxidant and immunomodulation activities of *A. cepa* were determined in asthma-induced rats by reducing immunoglobulin E (IgE), NO_2 (Nitrogen dioxide), nitrate, MDA, and IL-4 levels However, increased SOD, CAT, and IFN-γ levels and IFN-γ/IL-4 ratio [61]. Therefore, the study indicated that *A. cepa* contains anti-asthmatic activities by a decrease in oxidative indicators including MDA and inflammatory indices [eg: NF-κB, PGD2, leukotrienes, and GM-CSF (Granulocyte-Macrophage Colony Stimulating Factor)], increasing antioxidants such SOD (Superoxide dismutase), and inhibition of Th2 cytokine production (eg: IL-4 and IL-13) because of the flavonoids (eg: quercetin) [67, 63].

The effects of applying an extract of Allium cepa to the nasal passages to treat allergic rhinitis were assessed. Ova was administered intraperitoneally to sensitize BALB/c mice, and their nasal sensitization was assessed with OVA in the presence or absence of onion extract. And a study revealed surface administration of onion extract extensively lower levels of OVA-specific IgE and allergic responses. The study concluded that topical administration of onion extract greatly lessens allergic inflammatory reactions and allergic rhinitis symptoms in a mouse allergy model [68].

As the phytochemical constituent of *Allium cepa* including thiosulphates, quercetin, and phenolic acids. Basic phytochemical investigations have shown that onion contains steroids, essential oils, phytoestrogens, vitamins, minerals, water, carbohydrates, proteins, vegetal hormone, lectin, etc. [63].

Aegle marmelos (Beli)

One species in the Rutaceae family is the *Aegle marmelos*. Sri Lankan natives are called “Beli” in Sinhala. They are mostly utilized as an old and contemporary traditional cure for the treatment of various ailments. They originate and are commonly grown in specific regions of southeast and south Asian countries. Anti-allergy [69], anti-inflammatory, antipyretic, analgesic, antioxidant, antifungal, antiviral, hypoglycemic, and antidiabetic [69], anti-histamine, antiproliferative properties are examples of pharmacological activities [70], as well as the antiasthma, and immunomodulatory activities were documented. As an active compound, the Marmin of coumarin is separated from *Aegle marmelos* [69]. A rat basophilic leukemia (RBL- 2H3) cell line and rat peritoneal mast cells (RPMCs) in vivo study were carried out. An HPLC fluorometric method was used to detect histamine release from these cells. The research discovered that marmin can inhibit the amount of histamine released by the DNP24- BSA-induced (Dinitrophenylated bovine serum albumin) RPMCs and RBL-2H3 cell line, thapsigargin, or ionomycin. Marin also suppressed the Ca^{+2} (Calcium ion) influx brought on by thapsigargin on the RBL-2H3 cell line. According to these results, the histamine released from the mast cells was weakly inhibited by marmin [69]. In vivo study showed that marmin prevents guinea pig tracheal smooth muscle from contracting, particularly through interacting with the histamine receptor, preventing mast cell histamine release, preventing intracellular Ca^{+2} release from the storage, and preventing Ca^{+2} inflow through voltage-dependent Ca^{+2} channels [70]. Another study was carried out using the compound Zeorin and Dustaninn on histamine produced by the RBL-2H3 cells [71]. According to the kinds of literature *Aegle marmelos* can use to treat allergic rhinitis and allergic asthma. As the active phytochemical constituents, alkaloids, coumarins, seed oil, and polysaccharide were contained [72], Other than that, marmenol, marmin, marmelosin, marmelide, psoralen, alloimperatorin, rutaretin and many more [73].

Vitex negundo (Nika)

The species *Vitex negundo* is a 2–5 m tall, upright, fragrant shrub tree of the Verbenaceae family, widely distributed in southwest Asia. Additionally, it has historically been used to treat cancer, inflammatory diseases, oxidative stress, hyperglycemia [74], and allergic disorders. As the phytochemical constituents flavonoids, phenolic acids, essential oils, iridoids, triterpenes, and pagans are found in the leaves, and they have analgesic, anti-inflammatory, antihistamine, antioxidant, hepatoprotective, and antibacterial properties [74]. In vivo study was conducted, and the effect of a subfraction of the plant was tested on hyperresponsiveness of the bronchi and bicarbonate level in the serum using egg albumin-induced asthma in guinea pigs. Aqueous fraction showed considerably lesser bicarbonate level in the serum, and lower eosinophil count when compared with untreated sensitized animals. And histopathology of lungs in animals pretreated with aqueous sub-fraction (200mg/kg) indicated normal airway, bronchoalveolar space, and blood vessels. Therefore, it reveals the plant contained anti-eosinophilic activity. Therefore, it can be suggested to treatment of allergic rhinitis and asthma [75]. Anti-asthmatic properties of different kinds of leaf extracts were tested on different test modals Such include mast cell degradation by compound 48/80, anaphylaxis, and egg albumin-induced asthma. As a standard medication, dexamethasone (5mg/kg) was employed, and also ethanolic extract (AE), ethyl acetate extract (EAF) and aqueous extract (AF) demonstrated that compound 48/80 protects rat mesenteric mast cells against depletion. Also, animals given AE, EAF, and AF demonstrated considerable reduction of eosinophils, bicarbonate concentrations in serum, comparison to untreated, egg albumin sensitized mice, had a considerably larger tidal capacity and lung body weight ratio; and the study was demonstrated *Vitex negundo* effective in mast cell stabilization, inhibition of anti-eosinophilic activity and rapid hypersensitivity reactions [76] and it has an anti-asthmatic activity [77]. Therefore, the literature is evident vitex negundo can be used to treat allergic rhinitis and asthma. Phytochemical investigations on vitex negundo revealed the presence

of flavonoids, lignans, terpenoids, and volatile oil, fatty acids, steroids from different parts of the plant [78].

Coriendrum sativum (Koththamalli)

The plant *coriendrum sativum* categorized under the family Apiaceae, in Sri Lanka known as "Koththamalli", is a medicinal herbal plant. It is used to treat sore throat, nosebleeds, cough, allergies, urethritis, urinary tract infection, rash, burns, hay fever, and more [79]. All parts of the plant are edible, but the dried seeds and the fresh leaves are the most common parts, which are used to treat respiratory, digestive, and urinary diseases [79], and they contained many pharmacological properties [79]. A clinical trial was conducted using the case, control groups; all groups pointed to routine treatment methods such as nasoflow spray, cetirizine, allergen avoidance, and daily nasal washing. The case group also pointed towards treatment with *Coriandrum sativum* fruit extract (spray some coriander three to four times a day with 10 to 15 drops); after that, during the first, third, and seventh days, each participant was instructed to complete a survey on their disease symptoms; results showed that from the third day onward, signs and symptoms became considerably less severe in comparison to the control group ($p<0.05$); rhinorrhea, conjunctivitis with itchy eyes symptoms were noticeably less severe in the case group on day seven comparison to the individuals in the control group ($p<0.05$); as a result, the effects of evident fruit extracts may be effective and even therapeutic for those with asthma and allergic rhinitis [80]. And also, literature revealed seeds contained saponins, tannins, and cardenolides; the investigation of essential oils using gas chromatography-mass spectroscopy found 49 components including linalool, other than that γ-terpinene, decanal, geranyl acetate, α-pinene and limonene [81].

Curcuma longa (Kaha)

Curcuma longa is a medicinal plant, which belongs to the family Zingiberaceae. It has several names, turmeric in English and Sri Lankan natives called "Kaha". Widely grows in Asia and tropical countries. *C. longa* roots (rhizomes) have been used as a major medication for many purposes, including respiratory tract illness [82] and, specifically as the treatment of asthmatic diseases [82]. Golden yellow color is naturally present, because of the curcuminoids, with a curcumin content of 75-81%, a demethoxycurcumin content of 15-19%, and a bisdemethoxycurcumin content of 2.2-6.66% [82], and a previous study indicated that the composition of curcuminoids is most effective than the single compounds [82]. Curcumin showed several kinds of biological activities, such as anti-allergic, anti-inflammatory, antibacterial, antiviral, antifungal, and more [83] previous evidence showed curcumin help to modulate the nuclear factor kappa-B (NF-B) activation, effective inhibition of phosphorylation and decline of NF-B inhibitor alpha, blocking of phosphorylation of I – κBα kinase, and suppression of inflammatory reactions and cytokine release [82]. This evidence suggests curcumin is an effective treatment for many inflammatory diseases, especially including asthma., and curcumin can be used to control inflammation and hyper-responsiveness in, In-vivo animal models [82]. It was studied in an in vivo experiment utilizing a guinea pig model of ovalbumin-induced allergic rhinitis, and the frequency of sneezing and rubbing were two symptoms of allergic rhinitis that were studied. Biochemical modifications such as serum IgE, IL – 4, and Nitric oxide in nasal lavage and eosinophil peroxidase activity were determined in allergic rhinitis (AR); and results indicate that the treatment with 200mg/Kg of curcumin considerably reduced the symptoms, including the frequency of sneezing and rubbing, as well as the reduction of nasal congestion and eye lacrimation [83]. And also, curcumin improved the histopathological reactions and prevented significantly elevated serum IgE, IL-4, NO (Nitrogen Oxide), and eosinophil peroxidase [83]. Curcumin demonstrated immunomodulatory properties, including the inhibition of IL-4, IL-8, and tumor necrosis factor α and the rise in IL-10 production. therefore it showed curcumin improves nasal ventilation and modulates the patient's immune response who are suffering from AR [84]. Another study investigated the antioxidant impact of curcumin in an experimental rat modal of AR.; it revealed curcumin increases antioxidant enzymes and decreases oxidative stress in AR [85]. The activity of curcumin was determined using ovalbumin-induced AR mouse and found the activity of allergen-induced inflammatory mediators are released like IgE specific to OVA, histamine, and cytokines of inflammation, and curcumin was proven to improve AR complaints, prevent nasal mucosal histopathological changes, lower levels of histamine, OVA-specific IgE, and TNF α were found in experimental animals [86]. And curcumin reduced cytokines production, like IL-1β, IL-6, TNF α, and IL-8 and also curcumin inhibited PMA (Phorbol 12 myristate 13 acetate)– induced p- ERK (Extracellular Signal Regulated Kinase), p-p38, p-JNK, p- Iκ-Bα, and NF -κB [86]; and an in vivo investigation was carried out to assess the effects of curcumin on the Notch 1-GATA3 signaling cascade in mice with allergic asthma during acute airway inflammation [87]; these evidence suggest *Curcuma longa* has anti-allergic effect against allergic rhinitis and asthma. As a major phytochemical compound, curcuminoids, and sesquiterpenes were named. Curcumin is the primary curcuminoid; essential oils, essential oils' principal ingredients were α phellandrene, 1,8- cineole, α-zingiberene, β- sesquiphellandrene, ar-turmerone, α- turmerone and β turmerone [88].

CONCLUSION

The plants included in this article have a wide range of medicinal properties, including those that can treat allergic rhinitis and asthma. These plants are frequently used in combination with other plant sources as polyherbal formulae in Sri Lankan traditional medicine to manage type 1 sensitivity linked with asthma and allergic rhinitis. Combinatorial approaches maximize the synergistic effect of all plants, hence increasing the treatment's effectiveness and minimizing negative effects. According to the literature, numerous studies have been conducted to determine whether herbal remedies are effective in treating allergic rhinitis and asthma.

Sri Lanka has a wide number of herbs that may be utilized to treat hypersensitivity conditions, including allergic rhinitis and asthma. Animal models and a lengthy history of use revealed that the herbs possessed potent anti-allergy capabilities.

In conclusion, the plants used by traditional medicinal practitioners already have scientific evidence, which is not communicated well to the general public and the practitioners. According to scientific evidence, the most researched plants are *Clerodendrum Indicum*, *Clerodendrum serratum*, *Piper longum*, *Piper nigrum*, *Zingiber officinale*, *Allium cepa,* and *Curcuma longa*. In addition, there were many in-vivo studies on *Clerodendrum serratum*, *Allium cepa*, and

Curcuma longa. The least researched plants are *Vitex negundo*, *Coriandrum sativum*, and *Aegle marmelos*.

Many studies have reported the common phytochemical compounds from the reviewed plants, for example, essential oils, alkaloids, glycosides, flavonoids, and other substances. Few plants have demonstrated significant scientific evidence, which may be due to the presence of active phytochemicals such as terpenoids, sterols, iridoids, phenylpropanoids, flavonoids, and carbohydrates from *Clerodendrum serratum*, gingerols, shogaol, polyphenols, terpenes, lipids, organic acids, essential oils from *Zingiber officinale*, quercetin, thiosulphinates, phenolic acids, carbohydrates, proteins, vegetal hormones, leptin, steroids, essential oils, phytoestrogens, vitamins, minerals, etc. from *Allium cepa*, curcuminoids from *Curcuma longa*.

Although some plants have been classified as anti-allergies, their functionality, anti-allergic mechanism, or the chemicals that project the anti-allergic rhinitis and anti-asthmatic activity have not yet been extensively studied. To develop effective drugs and treatment regimens against allergic rhinitis and asthma that are linked to type 1 hypersensitivity, the fundamental mechanisms of anti-allergic activities should be focused on. Also, there is a current need to explore these essential herbal plants' hidden medicinal anti-allergic properties and utilize their rich value in medicinal preparations to address these typical type 1 hypersensitivity conditions linked to allergic rhinitis and asthma.

Author contributions

H.D.T. Madhuranga conceptualized and drafted the manuscript and conduct the systematic review process, and he was a major contributor. P.J. Wijekumar supported the systematic review process. D.N.A.W. Samarakoon was a major contributor in editing and revising and substantively reviewed the draft. The final manuscript was read by all authors and got their approval.

Acknowledgment

Not applicable.

Conflicts of Interest

The author reports no conflicts of interest in this work.

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HOW TO CITE THIS ARTICLE

Madhuranga HDT, PWijekumar PJ, Samarakoon DNAW. Herbal remedies that can be used to treat type 1 hypersensitivity reactions associated with allergic rhinitis and asthma in Sri Lanka- A systematic review. J Ayu Herb Med 2023;9(1):29-39. DOI: 10.31254/jahm.2023.9106