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MANAGING ALLERGIC RHINITIS IN CHILDREN THROUGH AYURVEDIC HERBAL MEDICINES

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ABSTRACT: Allergic Rhinitis (AR) represents a common and serious health problem in pediatric age group in term of outpatient visit. The chronic nature of disease and its association with other comorbid conditions like asthma, eczema *etc*. has shown significant negative impact on quality of life, school performance and cognitive functioning in children which has influenced many parents to seek alternative therapies. Moreover there is a growing concern of long term use of dose related side effects of corticosteroids, antihistaminic *etc*. Considering etiopatho genesis of AR, Ayurvedic herbal drugs possessing properties of antihistaminic, mast cell stabilizer and immunomodulators, alone or in combination can show positive effects in relieving the symptoms of AR. Thus in this review paper, an attempt has been made in this direction to prepare a comprehensive list of herbal drugs with above aforementioned properties that can help in the management of AR in pediatric age group with better clinical efficacy and safety profile.

INTRODUCTION: Allergic Rhinitis (AR) is the most common allergic disease prevalent worldwide in children < 18 yrs. of age that generates an important healthcare burden in term of outpatient visit [1]. It is a major chronic disease of children due to its high prevalence, co morbidities and detrimental effect on quality of life, cognitive functioning and school performance [2]. The International study of Asthma and Allergies in Childhood (ISAAC) reports that the prevalence of AR in children and adolescents show great variability throughout the world, with average prevalence of 8.5% (range 1.8-20.4%) in 6 – 7 years old children and 14.6% (range1.4-33.3%) for 13 to 14 year old children [3].

Reports from India shows that 1 out of every 6 person has AR [4]. AR is achronic inflammatory disorder of the nasal mucosa induced by IgE mediated inflammation after allergen exposure characterized by presence of at least two of four nasal symptoms: nasal congestion, rhinorrhea, sneezing or itching present for > 1hr every day for > 2weeks; and often accompaniment with other symptoms like conjunctival irritation, impaired smell and postnasal drip [5]. Symptoms of AR are triggered by exposure to allergens including house dust mite, grass pollen, tree pollen, weed pollen, cockroaches, pets, rodents and smoke. Traditionally AR was classified on basis of symptoms occurring throughout the year or in relation to seasonal

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exposure to allergen as perennial or seasonal AR respectively.

However this classification has been revised by the Allergic Rhinitis and its impact on Asthma (ARIA) group based on duration and severity of symptoms according to its impact on quality of life and helps in the better approach of the treatment [6]. Patient experiencing symptoms fewer than four days per week or for fewer than four weeks at a time are classified as having intermittent rhinitis. Patient experiencing symptoms more than four days per week or more than four weeks at a time are classified as having persistent rhinitis. Severity of rhinitis is classified as mild or moderate to severe. Mild - when symptoms are present but are not interfering with quality of life; or more severe when symptoms are bad enough to interfere with quality of life. Factors that may lead to a more severe classification include exacerbation of coexisting asthma; sleep disturbance, impairment of daily activities, leisure and/or sport, impairment of school performance or work [6].

Need of Alternative Therapy: Studies over past decade have shown positive association of AR with many co-morbid conditions like conjunctivitis, pharyngitis, sinusitis, asthma, eczema, otitis media, obstructive sleep apnea, failure to thrive, behavioral disturbances, family disruption and adverse consequences for cognitive and school performance [7]. Treatment of AR begins with environmental controls to reduce allergen exposure. Pharmacological intervention is often required to control moderate to severe symptoms and includes; H1 receptor antagonist (anti histamines), decongestants, mast cell stabilizers, leukotriene receptor antagonists, corticosteroids and anti-cholinergic agents in oral or topical nasal formulations. Intranasal corticosteroids (INS) are considered to be a first line therapeutic option for the management of intermittent as well as persistent AR [8].

The safety of the above therapeutic options remains controversial. Corticosteroids are associated with long term and dose related systemic effects such as hypothalamic–pituitary–adrenal suppression, bone demineralization, growth retardation, and development of cataracts and glaucoma [9]. Considering the safety, compliance, cost effectiveness and reinforcement of negative impact on quality of life, there is growing concern among parents to seek alternative therapy for better clinical outcome of their children. So there is utmost need to search for alternative therapies with evidence based guidelines to yield better results in the treatment of AR. Ayurveda has a rich heritage of medicinal herbs that can be practiced effectively and safely in the management of AR in children.

The clinical manifestation of Allergic rhinitis closely resembles with Vataja Pratishyaya, a type of Pratishyaya (nasal catarrh/rhinitis/common cold) described under heading of Nasaroga (diseases of nose) which is characterized by stuffed and obstructed nose; thin nasal discharge; dryness of throat, palate and lips; pricking sensation in the temporal region; and hoarseness of voice [10].The Ayurveda approach is to potentiate the immune system in order to reduce the susceptibility towards the allergen and at the same time by providing symptomatic relief.

Review of Ayurvedic herbal drugs highlights that drugs possessing properties of antihistaminic, mast cell stabilizer and immunomodulators can serve as a mainstay of treatment for AR; for not only achieving control of symptoms but also to improve quality of life. Keeping this view in mind, herbal drugs are screened for their potential activity against above aforementioned properties.

MATERIAL AND METHODS: Various literatures available up to 31st march 2017 were searched using database like Pub med, Medline and Google scholar with key words – allergy rhinitis, antihistaminic herbs, anti-allergic herbs and mast cell stabilizer herbs. Screenings of herbs were limited to those described in Indian medicines or Ayurveda literature. Papers published in English language and peer reviewed journals were considered for present review paper.

Anti Allergic Herbs:

Clitoria ternatea: Ethanolic extract of *Clitoria ternatea* root (ECTR) at doses 100, 125 and 150 mg/kg i.p was evaluated for antihistaminic activity using clonidine and haloperidol induced catalepsy in mice. Investigation showed that chlorpheniramine maleate (CPM) and ECTR inhibit clonidine induced catalepsy significantly

(p<0.001) when compared to control group, while CPM and ECTR failed to inhibit haloperidol induced catalepsy [11]. In another study, ethanolic extract of *Clitoria ternatea* root (ECTR) at doses 100–150 mg/kg i.p. significantly decreased milk induced leukocytosis and eosinophilia, protects egg albumin induced degranulation of mast cells in mice and inhibits area of blue dye leakage in passive cutaneous anaphylaxis in rats[12].

Glycyrrhiza glabra– The effect of glycyrrhizin on immunity function in allergic rhinitis (AR) mice model was studied for prevention and therapy of AR. The AR mice model were induced by dripping ovalbumin in physiological saline (2 mg mL−1, 10 μL) into the bilateral nasal cavities using a micropipette. Mice were randomly divided into six groups: the normalcontrol, model, lycopene 20 mg /kg (as positive control drug) group, and glycyrrhizin 10, 20, 30 mg/kg groups. After the sensitization day 14, lycopene (20 mg/kg BW) andglycyrrhizin (10, 20 and 30 mg/kg bdwt.) were given orally for 20 days once a day. Mice inthe normal control and model groups were given saline orally once a day for 20 days. Results showed that glycyrrhizin treatment dose - dependently significantly reduced blood IgE, IL-4, IL-5, IL-6,nitrous oxide (NO), tumor necrosis factor-alpha (TNF-α) levels and nitrous oxide synthase(NOS) activity and enhanced blood IgA, IgG,IgM, IL-2 and IL-1 levels in ARmice. Glycyrrhizin treatment dose-dependently also significantly enhanced acetylcholinesterase (AchE) activity and reduced substance P (SP) level in peripheral blood andnasal mucosa of AR mice [13].

In another study, isolated components glycyrrhizin, 18 β-glycyrrhetinic acid, isoliquiritin, and liquiritigenin from licorice were evaluated both in vitro and in vivo for their anti-allergic effects such as anti-scratching behavior and IgE production-inhibitory activity. Liquiritigenin and 18β-glycyrrhetinicacid most potently inhibited the degranulation of RBL-2H3 cells induced by IgE with the antigen (DNP-HSA) and rat peritoneal mast cells induced by compound 48/80. Liquiritigenin and 18 β-glycyrrhetinic acid potently inhibited the passive cutaneous anaphylactic reaction as well as the scratching behavior in mice induced by compound 48/80. These components also inhibited the production of IgE in ovalbumin-induced asthma mice but liquiritigenin had little effect. The study concluded that the anti-allergic effects of licorice are mainly due to glycyrrhizin, 18 β-glycyrrhetinicacid and liquiritigeninwhich can relieve IgE-induced allergic diseases such as dermatitis and asthma [14].

***Coccinia grandis*:** The ethanolic extract of *C. grandis* fruit (ECGF) at 100, 125 and 150 mg/kgi.p was evaluated for mast cell stabilizing, anti-anaphylactic and antihistaminic activity using egg albumin induced mast cell degranulation in mice; passive cutaneous anaphylaxis in rats and clonidine induced catalepsy in mice respectively. ECGF at (100-150 mg/kg, i.p.) significantly protected egg albumin induced degranulation of mast cells and caused reduction of blue dye leakage in passive cutaneous anaphylaxis in dose dependently. The treatment of ECGF also inhibited clonidine induced catalepsy in dose dependent manner [15].

***Crinum latifolium*:** The effect of glucan A and phosphatidyllycorine isolated from *Crinum latifolium* L. was studied on the rate of degranulation of mast cells of albino rats. Different combinations of glucan A and phosphatidyllycorine (5–20 and 5–10 μg/mL, respectively) *in vitro*, produced statistically significant protection against Tween 80-induced degranulation, as well as to sensitized mast cells challenged with an antigen (horse serum).The combination (10–20 mg/kg) when administered *in vivo* also provided protection against compound 48/80-induced degranulation of mast cells [16].

***Nyctanthes arbortristis*:** Petroleum ether, chloroform, ethyl acetate, ethanol and aqueous extracts of *N. arbortristis* bark (50 and 100 mg/kg, i.p.) were screened for mast cell stabilizing activity in mice and for bronchodilation property on smooth muscle preparation of guinea pig ileum (in vitro). The petroleum ether extract of *N. arbortristis* bark showed maximum protection against mast cell degranulation by clonidine and resistedcontraction induced by histamine better than other extracts[17].

***Myrica nagi*:** Ethyl acetate and water extract of M.nagi at doses of 100 mg/kg and200 mg/kg showed slightly better protection of mastcell degranulation (45-62%) than the standard drug prednisolone (65%) in egg albumin model. These

extractsalso showed better mast cell stabilizing activity (70-78%) than the standard drug (65%) when peritoneal mastcells are treated with compound 48/80[18].

***Picrorhiza kurroa*:** Picroliv, a standardized iridoid glycoside fraction from the root and rhizome of *Picrorhiza kurroa* at a dose of 25 mg/kg p.o. inhibited passive cutaneous anaphylaxis in mice (82%) and rats (50-85%) and protected mast cells from degranulation (60-80%) in a concentration-dependent manner. Its effect was also assessed in sensitized guinea pig ileum preparation in vitro (Schultz-Dale inhibition test) and in normal guinea pigs in vivo (Konzett-Rossler method). There was inhibition of the Schultz-Dale response in sensitized guinea pig ileum, but the bronchospasm induced by histamine could not be antagonized or prevented by Picroliv, indicating the absence of a direct post-synaptic histamine receptor blocking activity [19].

In another study, four weeks pretreatment with disodium cromoglycate (DSCG) and the powdered roots of the herb *Picrorhiza kurroa* Benth, rendered guinea pigs less sensitive to histamine when compared with appropriate controls. The bronchodilator effects of isoprenaline and adrenaline were found to be markedly enhanced. The severity and duration of the allergic bronchospasm was significantly less in animals pretreated with the two drugs. Furthermore, the total histamine content of the lung tissue in animals pretreated with DSCG and *P. kurroa* was significantly less than that in the untreated controls. The pretreatment was also found to exhibit inhibitory effect on the immunological release of histamine and slow reacting substances of anaphylaxis (SRS-A) from chopped lungs [20].

***Ziziphus jujube*:** Treatment with extract of *Z. jujuba* at all doses (250, 500 and 1000 mg/kg, orally) significantly prevented the milk-induced eosinophilia and compound 48/80 induced degranulation of mesenteric mast cells; decreased passive cutaneous and active anaphylactic reactions. In addition, extract of *Z. jujuba* inhibited acetylcholine as well as histamine induced tracheal chain contraction, antigen induced contraction of sensitized guinea pig ileum (Schultz-Dale inhibition test); and also exhibited free radicals scavenging activity *(in vitro*). The observed anti-allergic and anti-anaphylactic activity of extract of *Z. jujuba* may be largely through the stabilization of mast cells [21].

***Curcuma longa* -** An Ethyl acetate (AcOEt) extract from the rhizome of *Curcuma longa* L. has shown inhibitory actions on histamine release from rat mast cells in experimental models of allergy types I and IV. At a concentration of 50μg/ml, both the AcOEt extract and curcumin inhibited the histamine release induced by concanavalin A, and also suppressed the histamine release induced by compound 48/80, in the absence or presence of Ca^{2+} and that induced by A23187.

In the experiment of two stage models, they markedly reduced the histamine release when administered prior to and posterior to the addition of concanavalin A. The effect of the AcOEt extract on the inhibition of histamine release was somewhat stronger than that of curcumin. The findings suggested that AcOEt extract potently suppresses the histamine release probably through the blockage of the degranulation process following a rise in intracellular Ca^{2+} levels induced by the three types of histamine releasers, and the features of the actions of the AcOEt extract are similar to those of curcumin[22].

Sansevieria trifasciata: Ethanolic extract of *S. trifasciata* leaves (EEST) at 100 mg/kg and 200 mg/kg p.o inhibited milk-induced increased eosinophilia, leukocytosis, monocytes and neutrophils; prevented passive cutaneous and active anaphylactoid reactions; prevented compound 48/80 induced degranulation of sensitized mesenteric mast cells and inhibited histamine induced pedal edema formation significantly. EEST pretreatment inhibited Shultz–Dale reaction in guinea pig ileum and also elicited potent antioxidant activity [23].

***Benincasa hispida*:** The effects of an extract of *Benincasa hispida* on allergic inflammation were examined in terms of histamine and β-hexosaminidase release, serum IgE level and inflammatory cytokine level. The *B. hispida* extract inhibited the release of histamine and β-hexosaminidase, a degranulation marker, from rat basophilic leukemia cells (RBL-2H3).

When mice were first ovalbumin-challenged and then treated with *B. hispida* extract, there was a significant decrease in the IgE level in the mouse serum. The extract treatment reduced the serum IgE level prominently, compared with the ovalbumin-challenged mice. The extract also significantly reduced the TNF-α and IL-4 levels in the BAL fluid when challenged with antigen [24].

***Syzygium cumini*:** The study demonstrated an anti-allergic effect of *Syzygium cumini* and indicated that its anti-edematogenic effect is due to the inhibition of mast cell degranulation and of histamine and serotonin effects, whereas the inhibition of eosinophil accumulation in the allergic pleurisy model is probably due to an impairment of CCL11/eotaxin and IL-5 production. Oral administration of SC (25-100 mg/kg) in Swiss mice (20-25 g; N = 7/group) inhibited paw edema induced by compound 48/80 (50% inhibition, 100 mg/kg; $P \leq 0.05$) and, to a lesser extent, the allergic paw edema (23% inhibition, 100 mg/kg; $P \leq 0.05$). SC treatment also inhibited the edema induced by histamine (58% inhibition; $P \leq 0.05$) and 5-HT (52% inhibition; $P \leq 0.05$) but had no effect on platelet-aggregating factor-induced paw edema.

SC prevented mast cell degranulation and the consequent histamine release in Wistar rat (180-200 g; N = 7/group) peritoneal mast cells (50% inhibition, 1 µg/mL; $P \leq 0.05$) induced by compound 48/80. Pre-treatment of BALB/c mice (18-20 g; N = 7/group) with 100 mg/kg of the extract significantly inhibited eosinophil accumulation in allergic pleurisy (from 7.662 ± 1.524 to 1.89 ± 0.336 x 10^6/cavity; $P \leq 0.001$). This effect was related to the inhibition of IL-5 (from 70.9 ± 25.2 to 12.05 ± 7.165 pg/mL) and CCL11/ eotaxin levels (from 60.4 ± 8.54 to 32.8 ± 8.4 ng/mL) in pleural lavage fluid, using ELISA[25].

***Albizia lebbeck*:** 50 – 300mg/kg of *Albizia lebbeck* (AL) extract and 50 mg/kg of catechin were administered to mice to evaluate the mast cell stabilization and estimation of histamine elevation in the plasma. AL at different concentrations has got potent mast cell stabilizing property and the IC_{50} value of AL was found to be 85µg/ml. This inhibitory potential of catechin from AL is due to modulation of two important effector's functions, histamine release and cytokine expression of antigen -IgE activated mast cells [26]. Successive chloroform, methanol and water extracts of bark and leaves of *AL* were tested for its *in vitro* mast cell stabilizing effect against compound 48/80. Methanolic extract of leaf and methanolic and water extracts of bark shown maximum activity comparable to that of disodium chromoglycate [27].

In another study, the extract from the bark of AL was investigated on histamine H_1receptor (H1R) and histidine decarboxylase (HDC) gene expression using toluene - 2,4-diisocyanate (TDI) sensitized allergy model rats and HeLa cells expressing endogenous H1R. Administration of the AL extract significantly decreased the numbers of sneezing and nasal rubbing. Pretreatment with the AL extract suppressed TDI-induced H1R and HDC mRNA elevations as well as [3H] mepyramine binding, HDC activity, and histamine content in the nasal mucosa. AL extract also suppressed TDI-induced up-regulation of IL-4, IL-5, and IL-13 mRNA. In HeLa cells, AL extract suppressed phorbol-12-myristate-13-acetate - or histamine-induced up-regulation of H1R mRNA.

The study shows that AL alleviated nasal symptoms by inhibiting histamine signaling in TDI-sensitized rats through suppression of H1R and HDC gene transcriptions [28]. *In vitro* effects of AL and DCG on the degranulation rate of the sensitized mast cells were also studied. The results show that AL has a significant cromoglycate like action on the mast cells and inhibits the early processes of sensitization and synthesis of reaginic-type antibodies. If AL is administered during the first week of sensitization it markedly inhibits the early sensitizing processes while given during the second week it suppresses antibody production during the period of drug administration [29].

***Centella asiatica*:** Study demonstrated anti-pruritic and anti-inflammatory effect of *Centella asiatica* extract in rats and anti-allergic *in vitro* using sheep (*Capra hircus*) serum method and compound 48/80 induced mast cell degranulation method, compared with standard drug ketotifenfumarate [30].

***Smilax glabra*:** An anti-allergic activity of crude extracts and pure isolated flavonoid compounds from SG was investigated *in vitro* by determination of inhibitory effect on antigen-induced release of β-

hexosaminidase from RBL-2H3 cells. The 95% and 50% ethanolic extracts of SG showed remarkably high anti-allergic activity, with IC_{50} values of5.74+2.44 and 23.54+4.75 μg/ml, much higher activity than that for Ketotifen (IC_{50} 58.90 μM). The water extract had negligible activity (IC_{50}>100 μg/ml). The two isolated flavonols Engeletin and Astilbin showed weak anti-allergic activity, IC_{50} values 97.46+2.04 and >100 μg/ml, respectively. The 95% and 50% ethanolic extracts of SG showed strong anti-allergic activity, but two flavonol constituents did not show any significant anti-allergic activity. The findings suggested that a combination of effects of various phytochemicals in crude extracts used in traditional medicine are responsible for the purported anti-allergic activity of SG herbal preparations [31].

***Ocimum sanctum*:** Mast cell stabilizing activity of *Ocimum sanctum* leaves was studied in twenty-eight albino rats sensitized by injecting subcutaneously 0.5 ml of horse serum along with 0.5 ml of triple antigen containing 20,000 million Bordetella pertussis organisms. Treatment was given with *Ocimum sanctum* ethanolic extract and flavonoid fraction and standard for 14 days. In the unsensitized rats, 12.55% of the mesenteric mast cells were in the process of degranulation.

In the sensitized untreated rats, 80.90% of the mesenteric mast cells degranulated when challenged with the antigen. Prednisolone used as reference standard was found to inhibit degranulation of mast cells to an extent of 72.25%. The ethanolic extract at 100 and 200 mg/kg body weight inhibited degranulation of mast cells to an extent of 62.44 and 67.24%, respectively. The isolated flavonoidal fraction of *Ocimum sanctum* at 75 and 150 mg/kg body weight inhibited degranulation of mast cell to an extent of 54.62 and 60.48% respectively [32].

Similarly another study reported anti-anaphylactic, antihistaminic and mast cell stabilization activity of *Ocimum sanctum* leaf extracton various experimental models (wistar rats and Duncan Hartley guinea pigs). The anti-anaphylactic activity was evaluated in rats by using the active anaphylaxis model; mast cell stabilization activity by *ex vivo* challenge of antigen in sensitized rat intestinal mesenteries; and antihistaminic activity in guinea pigs using histamine - induced bronchospasm where pre convulsive dyspnea was used as an end point following exposure to histamine aerosol [33].

***Cassia alata*:** Anti-allergic activity of hydroalcoholic extract of *Cassia alata* along with its two components rhein and kaempferol was evaluated using *in vivo* mast cell stabilization assay and inhibitory effect on lipoxygenase (LOX) enzyme was evaluated *in vitro*. The hydroalcoholic extract of *Cassia alata* significantly inhibited mast cell degranulation at 200 mg/kg dose. Both chemical constituents rhein and kaempferol also showed potent (>76%) inhibition of mast-cell degranulation at 5 mg/kg. Extract and rhein inhibited LOX enzyme with IC_{50} values of 90.2 and 3.9 μg/mL, respectively, whereas kaempferol was inactive. Results suggest that *Cassia alata* or its active constituents could be potential alternative treatment for allergic diseases [34].

***Tinospora cordifolia*:** The effect of an aqueous extract of *Tinospora cordifolia* (Willd.) Miers(TC) stem was investigated on mast cell mediated allergic reactions *in vivo* and *in vitro* and studied for its possible mechanismin the treatment of acute and chronic allergic disorders. TC (125 to 1000 mg/kg) dose-dependently inhibited compound 48/80 induced lethality in rats, histamine induced paw edema in mice and histamine induced bronchial asthma in guinea pigs. TC significantly ($p < 0.001$) inhibited the cutaneous anaphylaxis reaction activated by histamine in a rat model and compound 48/80 induced ear swelling response in mice. TC (2.5-160 μg/mL) also showed significant ($p < 0.001$) inhibition of histamine induced contraction of guinea-pig ileum *in vitro* implying the H_1 antihistamine activity. TC(0.01 to 10 mg/mL) significantly ($p < 0.001$) inhibited the histamine release from rat peritoneal mast cells activated by compound 48/80.

In addition, TC (0.01 to 10 mg/mL) significantly ($p < 0.001$) inhibited the secretion of tumor necrosis factor-α (TNF-α) in antidinitrophenyl (DNP) IgE-stimulated rat peritoneal mast cells. The level of cAMP in RPMC transiently and significantly increased compared with that of control cells when TC was incubated with mast cells. TC (0.01 to 10 mg/mL) showed concentration-dependent inhibition in compound 48/80 induced reactive

oxygen species (ROS) generation. In addition, TC decreased intracellular calcium levels of activated mast cells [35].

In another study, the efficacy of *Tinospora cordifolia* (TC) extract in patients of AR was assessed in a randomized double blind placebo controlled trial. Seventy-five patients were randomly given either TC or placebo for 8 weeks. They were clinically examined and Hb%, TLC, DLC and nasal smear was done. At the end of trial baseline investigations were repeated, drug decoded and results analyzed. With TC treatment 100% relief was reported from sneezing in 83% patients, in 69% from nasal discharge, in 61% from nasal obstruction and in 71% from nasal pruritus. In placebo group, there was no relief in 79% from sneezing, in 84.8% from nasal discharge, in 83% from nasal obstruction, and in 88% from nasal pruritus. The difference between TC and placebo groups was highly significant. After TC, eosinophil and neutrophil count decreased and goblet cells were absent in nasal smear. After placebo, decrease in eosinophil and neutrophil count was marginal and goblet cells were present. TC significantly decreased all symptoms of allergic rhinitis [36].

Nigella sativa: Total of 152 patients with allergic diseases (allergic rhinitis, bronchial asthma, atopic eczema) were treated with *Nigella sativa* oil, given in capsules at a dose of 40 to 80 mg/kg/day. The patients scored the subjective severity of target symptoms using a predefined scale. The laboratory parameters assessed were IgE, eosinophil count, endogenous cortisol in plasma and urine, ACTH, triglycerides, total cholesterol, LDL and HDL cholesterol and lymphocyte subpopulations. The score of subjective feeling decreased over the course of treatment with black seed oil in all four studies. A slight decrease in plasma triglycerides and a discrete increase in HDL cholesterol occurred while the lymphocyte subpopulations, endogenous cortisol levels and ACTH release remained unchanged. *Nigella sativa* oil proved to be an effective adjuvant for the treatment of allergic diseases [37].

***Momordica dioica*:** Petroleum ether, ethyl acetate, methanol and aqueous extracts of *Momordica dioica* seed were evaluated for anti-allergic (200 mg/kg i.p.) and analgesic activity (dose dependent 50 mg/kg and 100 mg/kg) activity in mice. Methanol extract of *M. dioica* seed shows more significant anti-allergic activity ($p<0.01$) as compared to other extracts in all three models of milk induced leukocytosis, milk induced eosinophilia and differential leukocytes count in mice. In dose dependent analgesic activity petroleum ether and methanol extracts gives significant hot plate activity ($p<0.05$, $p<0.01$) and in acetic acid induced writhing test significantly ($p<0.01$) reduced the number of writhing [38].

Sphaeranthus indicus: Ethanol extract of *S. indicus* at the doses of 150 mg/kg and 300 mg/kg and ethyl acetate extract at the dose of 100 mg/kg, 150 mg/kg and 300 mg/kg showed slightly better protection of mast cell degranulation (77–86%) than the standard drug ketotifen (75%) in the sheep serum model. These extracts also showed better mast cell stabilizing activity (77–88%) than the standard drug (69%) when peritoneal mast cells are treated with compound 48/80[39].

Aristolochia indica: The ethanol extract (300 mg/kg) and petroleum ether extract of *Aristolochia indica*(100 mg/kg) were found to inhibit mast cell degranulation significantly equivalent to that of standard drug ketotifen (69%) by compound 48/80 model. In sheep serum model the ethanol extracts (150 and 300 mg/kg) and petroleum ether extract of *A. indica* (100 mg/kg) showed good mast cell stabilizing activity (66-67%). Ethanol extract at 150 mg/kg showed 70% reduction of rat paw edema and also significantly reduced the scratching response [40].

***Vitex negundo*:** The anti-asthmatic activity of ethanolic extract (AE), petroleum ether (PF), aqueous (AF) and ethyl acetate (EAF) extracted from leaves of *V. negundo* were evaluated by various experimental models like mast cell degranulation by compound 48/80, passive cutaneous anaphylaxis, and egg-albumin induced asthma. Dexamethasone (5mg/kg) was used as a reference standard. AE, EAF and AF showed significant protection of rat mesenteric mast cells from disruption caused by compound48/80.

Animals treated with AE, EAF, and AF showed significantly lesser the amount of dye leakage as compared to control animals at the site of

heterologous antibody injection. Animals treated with AE, EAF, and AF showed significantly lesser the amount of eosinophils, serum bicarbonate level and lung body weight ratio and significantly higher tidalvolume as compared to untreated, egg-albumin sensitized animals. The study concludes that AE, EAF, and AF of leaves of *V. negundo* are found to be effective in stabilization of mast cells, inhibitory effects on immediate hypersensitivity reactions and anti-eosinophilic activity appear to be involved in its mode of action [41].

***Bauhinia variegate*:** *Bauhinia variegata* stem bark extracts (400 mg/kg) significantly protected mast cell from degranulation (71.18%) and reduced the mortality (50%) when compared to standard drug disodium cromoglycate (DSCG) used in the study [42].

***Solanum nigrum*:** Petroleum ether, ethanol and aqueous extracts of *S. nigrum* berries (50, 100 and 200 mg/kg, i.p.) were screened for its anti-allergic properties *in vitro*. The petroleum ether extract of *S. nigrum* berries inhibited clonidine-induced catalepsy significantly but not haloperidol-induced catalepsy. It also inhibited increased leukocyte and eosinophil count due to milk allergen and showed maximum protection against mast cell degranulation by clonidine. Petroleum ether extracts resisted contraction induced by histamine better than other extracts [43].

Abrus precatorius: Ethanolic extract of *A. precatorius* leaves (EAPL) at doses 100, 125, 150 mg/kg i.p were evaluated for antihistaminic activity using clonidine and haloperidol induced catalepsy in mice. Finding of investigation showed that chlorpheniramine maleate (CPM) and EAPL inhibit clonidine induced catalepsy significantly $p < 0.001$ when compared to control group while CPM failed to inhibit haloperidol induced catalepsy. The study concludes antihistaminic activity of EAPL [44].

Poly herbal Formulation: (1) HK-07 polyherbal formulation containing the extracts of *Curcuma longa, Zingiber officinale, Piper longum, Emblica officinalis, Terminalia belerica, Ocimum sanctum, Adhatoda vasica,* and*Cyperus rotundus* was studied for anti-anaphylactic, antihistaminic and mast cell stabilization activity in experimental animals. The anti-anaphylactic activity was investigated in rats using the active anaphylaxis model. The effect on mast cell stabilization was performed by *ex vivo* challenge of antigen in sensitized rat intestinal mesenteries. Antihistaminic activity was studied in guinea pigs using histamine-induced bronchospasm where preconvulsive dyspnea was used as an end point following exposure to histamine aerosol. Treatment with HK-07 at 125, 250, and 500 mg/kg, p.o. showed significant reduction in signs and severity of symptoms ($p<0.05$), onset ($p<0.001$) and mortality rate ($p<0.05$) following anaphylactic shock-induced bronchospasm. HK-07 also significantly reduced the serum IgE levels ($P <0.001$) in animals compared to untreated controls. Treatment of sensitized animals with HK-07 at 500 mg/kg, p.o. for 2 weeks resulted in a significant reduction in the number of disrupted mast cells ($P <0.001$) when challenged with an antigen (horse serum). HK-07 significantly prolonged the latent period of convulsion ($P <0.008$) as compared to control following exposure of guinea pigs to histamine aerosol. The findings reveals that the antihistaminic and anti-anaphylactic activity of HK-07 may be due to the mast cell stabilizing potential, suppression of IgE and inhibition of release of inflammatory mediators [45].

(2) *Bharangyadi*, a polyherbal compound having Bharangi (*Clerodendrum serratum*), Sati (*Hedychium spicatum*) and Pushkarmoola (*Inulara cemosa*) was evaluated for anti histaminic, mast cell stabilizer and bronchodilator effect through various *in-vitro* and *in-vivo* experimental models. Ethanolic extract of *Bharangyadi* at the doses 500 and 1000 μg/ml protected from compound 48/80-evoked degranulation ($p< 0.01$) in dose dependent manner. Pre-treatment with *Bharangyadi* extract showed 80% & 86% protection from histamine induced broncho constriction in guinea pigs with 27.8% and 36.1% increase in pre-convulsion time (equal to standard drug). Screening of Histamine antagonism activity on guinea pig ileum showed that drug reduces the smooth muscle contraction in dose dependent manner. Increasing concentration of *Bharangyadi* extract with maximum dose of histamine (1.6μg) showed maximum inhibition at the dose of 50mg (99.78%). Inhibition of smooth muscle contraction by addition of drug in organ bath before adding histamine showed that drug has preventive type antagonism [46].

CONCLUSION: Allergic rhinitis is a common health problem present worldwide in pediatric age group. Due to its chronic nature and association with other co morbid conditions like asthma, otitis media etc., has shown significant negative impact on quality of life, cognitive functioning and school performance in children if not treated properly. There is growing worldwide interest in Ayurvedic herbal medicines among parents to seek alternative therapy for their children for better clinical efficacy and safety profile. Several experimental studies reported in this review paper has shown positive effects on ameliorating allergic manifestation. The paper concludes that herbal drugs with anti histaminic, mast cell stabilizer and immmunomodulator properties alone or in combination can achieve better clinical outcome in the management of AR. Further clinical studies are required to support or refute the hypothesis presented in this article.

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