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EFFICACY AND MECHANISMS OF MEDICINAL PLANTS AS IMMUNOTHERAPY IN TREATMENT OF ALLERGIC RHINITIS: A SYSTEMATIC REVIEW

Behzad Moradi ¹, Saeid Heidari-Soureshjani ², Majid Asadi-Samani ^{*3}, Qian Yang ⁴ and Ali Saeedi - Boroujeni ⁵

Lorestan University of Medical Sciences ¹, Lorestan, Iran.

Cellular and Molecular Research Center ², Student Research Committee ³, Shahrekord University of Medical Sciences, Shahrekord, Iran.

Institute of Pharmacy and Molecular Biotechnology ⁴, University of Heidelberg, Heidelberg, Germany.

Department of Immunology ⁵, School of Medicine, Jundishapur University of Medical Sciences, Ahvaz, Iran.

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Correspondence to Author:

Majid Asadi-Samani

Ph.D,
Medical Plants Research Center,
Shahrekord University of Medical
Sciences, Rahmatiyeh, Shahrekord,
Iran.


E-mail: biology_2011@yahoo.com

ABSTRACT: Allergic rhinitis is a common disease of immune system that negatively affects general health, quality of life, and social relationships. In the recent years, many studies have been conducted to discover novel treatments for this disease particularly using natural products. Here, we review findings of recent studies that harness medicinal plants and phytotherapies in oriental medicine that have effectively reduced allergic rhinitis complications. We also assess the use of medicinal plants and their derivatives in oriental medicine to treat allergic rhinitis. In addition, these agents have been reported to be used in combination with each other or separately as complementary therapies and even, in some cases, alternative therapies instead of chemical drugs. These plants display their anti-allergy effects through affecting immunoglobulin and inhibiting different cytokines and interleukins. Medicinal plants and traditional approaches can still offer new therapeutic alternatives to researchers and pharmacists so that these alternatives may further contribute to allergic rhinitis drug discovery.

INTRODUCTION: Allergic rhinitis, commonly are known as allergies or hay fever, is a type of inflammation in nose which occurs when the immune system overreacts to the allergens in the air. Allergy is the most common disorder of the immune system, and has affected around 20% of the population in US and Europe. The prevalence of allergy is growing worldwide.

Rhinitis influences quality of life due to associated complications ¹, such as mucosal edema, runny nose, itchy nose, sneezing, coughing, shortness of breath, and wheezing ². Rhinitis usually causes allergic conjunctivitis accompanied by itchy eyes. In addition to physical complications, certain psychiatric complications such as sleep disorders, anxiety, and cognitive disorders may develop due to rhinitis ³. Rhinitis is divided into two types: Allergic and nonallergic.

As the most common disorder of the immune system, allergic rhinitis may be seasonal or perennial. Plant allergens such as pollen are some of the causes of seasonal allergic rhinitis and dust mites, dust, mold, cockroaches, and animal proteins

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are some causes of perennial allergic rhinitis⁴. IgE production against the allergen and production of certain cytokines such as (IL-5) or interleukin 4 (IL-4) play a key role in the development of inflammation in nasal mucosa and ultimately the body's response to production of the mucus and allergic rhinitis symptoms⁵. Anti-histamines and corticosteroids, immunotherapy, and avoiding exposure to allergens are some of the treatments for allergic rhinitis⁵. Meanwhile, complementary therapies have a significant contribution in treating allergic rhinitis⁶ such that studies have shown that people commonly use medicinal plants and their compounds.

Despite availability of modern treatments, it is still common to trust the use of plants to treat rhinitis^{7,8}. However, the mechanism of medicinal plants used to treat allergic rhinitis is unknown. Natural products such as medicinal plants are one of most important resources for discovering new drugs⁹⁻¹⁵. Local people use them for prevention and treatment of various disorders¹⁶⁻²⁶. Also researchers have evaluated and confirmed their therapeutic properties²⁷⁻³¹. They can be used to produce more effective drugs if they are investigated in additional studies³²⁻³⁶. According to high prevalence of allergic rhinitis and its drug side effects and also growing use of plant-based compounds and drugs especially in East Asia, our aim is to investigate the findings of recent studies on the effects of medicinal plants and phyto-therapies in oriental medicine on immune system in treatments for allergic rhinitis.

Search strategy and Study design: As a main medical database in English language, Pubmed was searched using the following keywords: ethno-medicinal plants, ethnobotanical study, ethnopharmacology, phytotherapy, herbal treatments, and allergic rhinitis or respiratory allergy to retrieve relevant publications from 2010 until November, 2016. The data was collected independently by two authors. By using the above search terms, 546 articles, of which 58 articles were duplicates, were retrieved. After evaluation of the titles and abstracts of the retrieved articles, 35 articles that devoted to the effects of medicinal plants on allergic rhinitis were selected. Only articles with accessible full text in English language were selected for more evaluation.

Accordingly, twenty-one articles were included in the final analysis.

Phytotherapies of allergic rhinitis: Around two thirds of children with allergic rhinitis in Taiwan used Chinese traditional drugs. Xin-Yi-Qing-Fei-Tang (magnolia flower lung-clearing decoction) is one of the plant-based compounds that are used to treat allergic rhinitis in China and Taiwan⁸. A study was conducted to compare Traditional Chinese Medicine (TCM) and other oriental medicine with reference to insurance files of patients with allergic rhinitis, and found that certain plants such as Xin-Yi-Qing-Fei-Tang, Shau Ching Long Tang, Shin Yee San, Tsang Err San, Jel Girng, Yu Shing Tsao, Bai Zu, and Opium derivatives have various effects to treat allergic rhinitis compared to therapies in western medicine³⁷. Also some plants such as Baizhi (*Radix angelicae*), Jiangzhi (*Ginger juice*), Xixin (*Radix et rhizama Asari*), Yanhusuo (*Corydalis*), Gansui (*Radix kansui*), and Baijiezi (*Brassica alba* Boiss) are used to conduct acupuncture. Administration of these plants in traditional manners alongside acupuncture can decrease allergic rhinitis symptoms³⁸. In addition, the effects of Zhi Gan Sui (*Kansui radix*), Rengong She Xiang (*Moschus artificus*), Xi Xin (*Asari radix et rhizama*), Yan Hu Suo (*Corydalis rhizoma*), and Bai Jie Zi (*Sinapis semen*) were investigated in combination with acupuncture.

The findings demonstrated that the symptoms and the rate of taking medications decreased after completion of treatment with this method³⁹. According to a method called Sanfu herbal patch, a collection of medicinal plants such as *Semen sinapis*, *Radix kansui*, *Herbaasari*, *Rhizoma corydalis*, and *Ephedra sinica* were applied to certain acupoints. Use of herbal patches, according to this method, was reported to be effective in treating allergic rhinitis because treatment with this method not only decreased nasal symptoms but also improved quality of life⁴⁰.

Scutellaria baicalensis and Eleutherococcus senticosus: Zhang et al., investigated *S. baicalensis* and *E. senticosus* for treatment of allergic rhinitis. After examining nasal mucosa tissues, they reported that these plants could modulate lipid mediators (PGD₂, histamine, and IL-5). In

addition, the synergistic effect of the two plants was greater than their effects when they were independently administered. Besides that, combination of the two plants inhibited pro-inflammatory, and Th1-, Th2-, and Th17-derived cytokines⁴¹.

***Nigella sativa*:** The effect of black cumin (*Nigella sativa*) essential oil, which is from family Ranunculaceae, was investigated on allergic rhinitis. This oil was found to decrease nasal mucosal eosinophil and exert optimal effects on stuffy, itchy, and runny nose. In addition, this plant can relieve sneezing attacks, turbinate hypertrophy, and mucosal pallor⁴².

***Caffeoylx anthiazonoside*:** *Caffeoylx anthiazonoside* is a derivative of *Xanthium strumarium* L. The effects of this compound on allergic rhinitis were investigated in rats. This study demonstrated that *caffeoylx anthiazonoside* could decrease and regulate serum IgE levels and nasal symptoms due to rhinitis⁴³.

***Silymarin*:** *Silymarin* is a flavonoid derived from the seed of a medicinal plant named *Silybum marianum*. *Silymarin*'s effects were investigated on human. A study on 94 patients with allergic rhinitis demonstrated that *silymarin* could reduce allergic indices (serum IgE, interferon-gamma, IL-4, and IL-5) and the severity of allergic rhinitis symptoms⁴⁴.

Phytoglycoprotein: Phytoglycoprotein is a derivative of *Zanthoxylum piperitum* DC fruit. This compound suppresses histamine (the most important mediator in incidence of Type 1 hypersensitivity), IL-4, and IgE. Phytoglycoprotein decreased degranulation of the mast cells as well as inflammation factors both *in vitro* and in mice with allergic rhinitis⁴⁵.

Biminne: This Chinese formulation consists of two active compounds to treat allergic rhinitis, namely icariin and *astragalus saponin* I. Investigating the effect of biminne on mice with allergic rhinitis indicated that this compound suppressed splenocyte proliferation and regulated the secretion of cytokines, IL-4, IL-5, and INF-gamma⁴⁶.

So-Cheong-Ryong-Tang (SCRT): SCRT is a Korean herbal formulation to treat allergic rhinitis.

Study of SCRT's effect on allergic rhinitis in mice demonstrated its efficacy in decreasing allergic rhinitis symptoms such as sneezing, runny nose, and infiltrated nasal eosinophils. This finding is attributed to the suppression of serum IgE, OVA-specific IgE, and OVA-specific IgG1 levels and increased OVA-specific IgG2 a level. In addition, SCRT causes decrease in the expression of Th2 cytokine, which is considered as a main target in IL-4 immunotherapy⁴⁷.

Cure-allergic-rhinitis syrup: Cure-allergic-rhinitis syrup is a Chinese herbal formula. The effects of cure-allergic-rhinitis syrup and Yu-ping-feng San on allergic rhinitis on a number of students were compared. According to the results, both formulations relieved the symptoms and improved quality of life among the patients under treatment, but the indices improved significantly only in cure-allergic-rhinitis syrup-treated group⁴⁸.

Chinese allergic rhinitis nose drops: This herbal formulation consists of certain plants such as *Herba Centipedae*, *Radix Glycyrrhizae*, *Radix Paeoniae Alba*, *Floz Ionicerae*, *Radix Scutellariae*, *Radix Platcodi*, *Herba menthae*, *Fructus Zizyphi Jujubae*, *Pericarpium citri reticulatae*, *Rhizoma coptidis*, and *Radix ledebouriellas* and is used as nose drop. A study demonstrated that this nose drop could decrease allergic rhinitis symptoms and therefore improve the patient's quality of life⁴⁹.

KOB extracts: KOB extracts is a polyherbal medicine consisting of *Saposhnikovia divaricata*, *Atractylodes macrocephala*, *Astragalus membranaceus*, *Scutellaria baicalensis* and *Ostericum koreanum*. A study demonstrated that combination of pseudoephedrine and KOB extracts could be a suitable treatment for allergic rhinitis⁵⁰.

KOB03: KOB03 is a herbal formulation consisting of *Scutellariae radix*, *Osterici radix*, *Astragali radix*, and *Saposhnikovia radix*. This formulation was investigated *in vivo* and was found to decrease allergic rhinitis symptoms via suppressing certain cytokines such as TNF-a, IL-1b, IL-6 and IL-8 with anti-inflammatory effects⁵¹.

A Chinese herbal formulation: This formulation consists of Xin-yi-san, Xiang-sha-liu- jun-zi-tang, and Xiao-qing-longtang that is used to treat allergic rhinitis and asthma. A study indicated that HLA-

DR expression on dendritic cells was suppressed after treatment with this herbal formulation. In addition, CD4(+) T cells increased production of their IL10, and the production of TNF-alpha decreased⁵².

Qu Feng Xuan Bi Formula: Qu Feng Xuan Bi is a herbal formulation consisting of *Radix glycyrrhizae preparata*, *Radix glycyrrhizae*, *Pheretima*, *Allium macrostemon* Bunge, *Paeonia sterniana* Fletcher in Journ, *Divaricate saposchnikovia* root and *Astragalus membranaceus* (Fisch) Bunge. Aqueous extract of this formulation can decrease recruitment of eosinophils in the lung, increase IL-4 concentration in broncho-alveolar lavage fluid, and increase the expression of STAT-3, JAK-1, and C-Jun in nasal tissues⁴¹.

BiRyuChe-bang (BRC): BRC is a Korean formulation that is used to treat allergic rhinitis. This blend is made by combining pine oil, lavender oil, and eucalyptus oil and can decrease the levels of IL-6 and TNF-alpha. Besides that, BRC suppresses histamine, mRNA expressions of TNF-alpha, IL-6, and IL8, and the activation of NF-kappaB in a human mast cell line (HMC-1). Therefore, this formulation can be used to treat mast cell-mediated allergic and inflammatory responses⁵³.

Xin-yi-san: This herbal formulation consists of roots of *Asarum heterotropeoides* rhizoma of *Ligusticum sinense* Oliv, Benth. et Hook, flower of *Magnolia liliflora* Desr, dried roots of *Angelica dahurica* roots of *Saposhnikovia divaricata* Chischk, rhizomas of *Ligusticum wallichii* Franch, dried rhizomas of *Cimicifuga foetida* L, rhizomas of *Akebia quinata* Decne and roots and rhizome of *Glycyrrhiza uralensis* Fisch. It was demonstrated that this herbal formulation could reduce the complications of perennial allergic rhinitis through

exerting immunomodulatory effects such that it caused suppression of IgE and increased production of sICAM-1, IL-8, and IL-10⁵⁴.

Acupoint herbal patching: As a herbal drug, acupoint consists of *Sinapis semen*, *Euphorbiae kansui* Radix, *Corydalis rhizoma*, *Asari Herba* Cum Radice and is used, as pulverized, to treat allergic rhinitis. This formulation can decrease the serum levels of IgE (T-IgE) and eosinophile cationic protein and improve the patients' quality of life and social relationships⁵⁵.

According to the evidence, the medicinal plants, their derivatives, and several herbal formulations in oriental medicine are used to treat allergic rhinitis and, via different action mechanisms, lead to decrease in the symptoms or even treatment of this disease.

Action mechanisms: Allergic rhinitis is regarded due to an imbalanced Th1/Th2 cell-mediated response. Different parts of innate and adaptive immune system play part in the pathogenesis of allergic diseases particularly allergic rhinitis. The plants used to treat allergic rhinitis in oriental medicine can decrease allergic responses, through affecting most pathways involved in induction of allergic responses, and therefore decrease the symptoms of allergic rhinitis and even display therapeutic properties (Table 1) such that the plants investigated in the cited studies were found to display anti-allergy properties through modulating the immune system reaction to allergens via inhibiting release or activity of mast cell mediators such as histamine, inhibiting inflammatory activity using their anti-inflammatory compounds, lowering and regulating IgE serum level, and lowering the activity of lymphocytes, particularly Th2 and TFH, and macrophages³².

TABLE 1: THE ROLE OF PHYTOTHERAPY ON DIFFERENT CONSTITUENTS OF INNATE AND ADAPTIVE IMMUNE SYSTEM IN THE PATHOLOGICAL PROCESS OF ALLERGIC DISEASES

Constituents	Constituents' roles and their actions	Therapeutic approach in modern medicine	Phytotherapy (Modulatory and effective plants)
Antibody IgE	One of the most important constituents in incidence of response immediately hypersensitivity and responsible for sensitizing mast cells; IL-4 and IL-13 play a key role in producing it.	Monoclonal antibody against IL-4, and shared part of IL-4 and IL-13; Decreasing production of IgE and increasing IgG4 against desensitizing allergen	So-Cheong-Ryong-Tang <i>Caffeoyl xanthazonoside</i> Phytoglycoprotein Xin-yi-san Acupoint herbal patching Sanfu herbal patch

	Atopic people produce large amounts of IgE in response to environmental allergens.		
Follicular helper T(TFH)	In lymphoid organs, TFH contribute to producing IgE-producing plasma cells in the lymph and express TH2 cytokines	-	-
Th2 cells	Migrating to the sites possibly exposed to the allergen in tissue and initiating executive phase of inflammation and allergic responses	-	So-Cheong-Ryong-Tang <i>Scutellaria baicalensis</i> and <i>Eleutherococcus senticosus</i>
Innate lymphoid cells (ILCs) Type 2	Producing involved cytokines in allergy such as IL-13 and IL-5 (It was demonstrated to play a role in airway inflammation in animal models)	-	-
MAST cells, basophils, neutrophils, and eosinophils	Effector cells involved in allergic responses through producing and secreting different cytokines, biogenic aminos, and lipid mediators	-	<i>Nigella sativa</i> <i>Scutellaria baicalensis</i> and <i>Eleutherococcus senticosus</i> Qu Feng Xuan Bi Formula
Dendritic cells	Playing a key role in differentiating Th1 and Th2 cells, maintaining immune system hemostasis, and Treg;	-	Xiao-qing-longtang
Cytokines	Cells as well as a main source of the cytokines involved in allergy. IL-4 and IL-13 are responsible for differentiating and stimulating different types of the cells involved in allergy.	-	Silymarin Phytoglycoprotein (24kDa) Biminne KOB03
Treg	TSLP disease exacerbation IL-10 significant improvement in the disease course TNF exacerbation of inflammatory, presentations due to allergic used Treg dysfunction was reported in different allergic diseases including respiratory ones such as asthma and rhinitis.	Different methods to improve the function of these important cells in maintaining studied immune responses.	<i>Scutellaria baicalensis</i> and <i>Eleutherococcus senticosus</i> Qu Feng Xuan Bi Formula BiRyuChe-bang (BRC Xin-yi-san -
Breg	Breg cells play key role particularly in preventing production of excessive amounts of IgE.	As a target to improve the conditions of patients with allergies are under investigation.	-

In addition, serum levels of eosinophile cationic protein ⁵⁵ and OVA-specific IgG1 ⁵⁶, several interleukins, biogenic aminos, and interferon-gamma were reported to decrease after administration with medicinal plants or their compounds ^{44, 53}. Besides that, anti-allergy medicinal plants affect chloride channel-3 and suppress secretion of MCP-1 and CIC-3, which play an important role in chemo attraction of the leukocytes to the sites of allergic responses and especially pathological process of allergic rhinitis, as well as VCAM-1 in the epithelial mucus and

therefore controls inflammatory responses ⁵⁶. Aside from the above mentioned, disturbing differentiation balance between Th2 lymphocyte and Th1 lymphocyte and their cytokines is one of the most important mechanisms of allergic diseases. Recovering such balance is one of the targets of new treatments for allergic rhinitis.

Investigating the action mechanisms of the plants used at acupoints indicated that acupoint herbal plaster improved allergic inflammation via maintaining an appropriate balance between Th1

and Th2 cells and therefore inhibited the secretion of cytokines GM-CSF, IL-3, IFN- γ , and IL-2 by Th1 cells and that of IL-3, GM-CSF, IL-13, IL-10, IL-5, and IL-4 by Th2 cells^{57, 58}. These cytokines contribute to activation of JAK-STAT (regulator of activity of histamine mediators). For example, IL-13, which is one of the lymphocytes of Th2 and produces ILC2, plays a key role in exacerbating inflammatory response such that humanized monoclonal antibody against the fixed part of IL-13 was found to be greatly effective in improving allergy. A study demonstrated that plant-based compounds induced anti-inflammatory and anti-allergy effects through down regulating IL-13 via JAK-STAT pathway⁵⁷. Actually medicinal plants through several mechanisms can prevent the allergic rhinitis (**Fig. 1**).

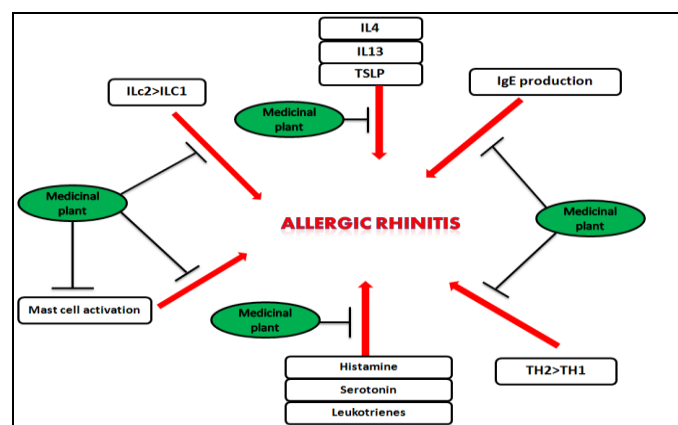


FIG. 1: THE MECHANISMS OF MEDICINAL PLANTS IN AMELIORATING ALLERGIC RHINITIS

Meanwhile, it is noteworthy that allergic responses to the medicinal plants used to treat allergic rhinitis are likely to exacerbate the conditions of patients with allergic rhinitis, because in people with allergies, incidence of allergic responses is more likely and therefore necessary measures to stop taking the herbal drug should be taken into account⁵⁹.

CONCLUSION: Nowadays, with the raised level of public health, infectious diseases have declined but instead allergic diseases have become a main health issue of the community. Meanwhile, growing research is being conducted to develop new treatments based on a more in-depth understanding of the immunologic mechanisms of allergic diseases. Recovering hemostatic immune responses is the main feature of these treatments. In this regard, medicinal plants should not be

disregarded because they are a rich source of compounds some of which have not yet been identified. The medicinal plants, used in oriental medicine and in different ways, induce anti-allergy effects through affecting immunoglobulins and inhibiting different cytokines and interleukins. These plants also prevent inflammation in nose and respiratory tract through exerting anti-inflammatory effects. The plants used in oriental medicine, especially Chinese medicine, can, in combination or separately, be used as complementary and even, in some cases, alternative treatment to chemical drugs. Altogether, this review confirms the value of a great number of medicinal plants used in oriental medicine to treat allergic rhinitis, which can represent a rich source for drug discovery in the future.

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