

LAMIACEAE, MEDICINAL POTENTIAL & ANTI-ALLERGENIC DEVELOPMENTS

Sanika Datar, Marc Teitelbaum, Inglemoor High School Kenmore, Washington, United States, sanikadatar@gmail.com

ABSTRACT

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<http://www.ayimi.org.info@ayimi.org>

Recently, allergic disorders have become a prevalent global epidemic affecting millions of people who experience asthma, allergies, and medication hypersensitivities. Medicinal plants such as Lamiaceae, commonly known as mint, are proving to be much more effective in treating the problem as they contain natural anti-allergenic compounds that act as anti-inflammatory agents to reduce and prevent cascading allergic reactions. This research paper will demonstrate how this plant's properties work, medicinal uses, and provide up-to-date research about the phytoconstituents from the Lamiaceae family and anti-allergenic activity.

Key Words : *Lamiaceae, Allergic reaction, IgE, anti-histamines, anti-allergenic compound*

1. Introduction

Allergies are the immune system's reaction to foreign substances in the body. These reactions can have a wide range of severity, from a runny nose and coughing, to anaphylaxis, a life-threatening reaction. The typically harmless foreign substances that cause these reactions are called allergens and can be found in dust, pets, pollen, food, and some medicines. Allergies can affect anyone and are generally more common in children. People whose family had allergies have a genetic tendency to develop allergies, and this is known as atopy [1]. When atopic people are exposed to the allergen, the immune system has a reaction, it over reacts by producing antibodies that attack the allergen, and this can cause allergic inflammation.

2. Significance of Allergies

The prevalence of allergies are increasing worldwide, and becoming more severe and complex. Allergies are the 6th leading cause of chronic illness in the U.S., costing an excess of \$18 billion annually. More than 50 million people in the U.S. alone experience various types of allergies each year. In the U.S. asthma affects more than 24 million people, food allergies affect about 32 million people, and seasonal allergic rhinitis, or hay fever, affects about 24 million people [1]. In addition, data published from the 2014 National Health Interview Survey shows that 8.4% of US children under age 18 suffered from hay fever, 10% from respiratory allergies, 5.4% from food allergies, and 11.6% from skin allergies [2].

A major cause of allergies, other than genetics, is environmental conditions. Climate change and pollution contribute to people's health declining and increasing allergies. Health care costs are also high in many places, making it hard for people to get tested and the right medicines they need, making it harder to solve this worldwide issue. Allergies have many effects on individual people, including economic troubles, interruptions in quality of life, and possibly death. Allergies can prevent people from partaking in certain activities and can increase risks for other medical health problems.

3. Immunological Response

Common allergic reactions are linked to an antibody the body produces, called immunoglobulin E (IgE) [3]. The

purpose of antibodies in our immune system is to help remove any foreign substances that invade our body. Everyone produces IgE antibodies but allergic people produce much larger quantities of it. Each IgE is very specific, which is the reason people can be allergic to one substance, yet not another. A person becomes sensitized when exposed to an allergen, causing B cells, a specific type of white blood cell, to produce IgE antibodies and release them in the blood. Some of the IgE attach themselves, using the high-affinity IgE receptor, FcεRI, to the surface of allergy-specific cells called mast cells and basophils, which are filled with grains containing allergic mediators [3].

All of these cells cause allergic symptoms by releasing the mediators stored in them. Repeated exposure to the allergen leads to an immediate reaction, triggered by cross-linking of the IgE, which is the binding to allergens, also called Activation, and results in rapid release of the allergic mediators, and this process is called degranulation [4].

Other white blood cells called T-cells drive a delayed and prolonged inflammatory reaction that can be seen hours later with itching, swelling, and other visible symptoms. These phases in the allergic reaction can be classified as immediate and late. The immediate responses are triggered by fast mast cell degranulation, and the late responses are caused by other inflammatory cells like eosinophils (also used in the immediate responses), neutrophils, and lymphocytes being attracted to the site because of chemotactic factors released by the mast cells, and producing more mediators [3].

4. Current Treatments, Downsides & Limitations

There are three main treatment options once it is known that a person has an allergy: avoiding the allergen, going through immunotherapy, or most commonly, taking medicine. Lastly, epinephrine is used during a severe reaction called anaphylactic shock and stimulates the adrenal glands and increases the rate and force of the heartbeat. [5] Despite all of the benefits that the three main treatment options provide, there are arguably many more downsides and limitations to them as well. In order to avoid the allergen, the allergy triggers need to be identified so they can be avoided. This is often not a viable option if the allergen is present in many places and in large amounts. It's

also unwise to avoid medications in the hopes that the allergen won't be encountered, which could cause a serious reaction.

Another treatment option is immunotherapy. The two types are allergy shots and sublingual immunotherapy (SLIT) [6]. Allergy shots are a series of injections of purified allergen extracts increasing in dose over time (usually a few years). The person gradually becomes less sensitive to that allergen because by gradually increasing the doses, the immune system is able to build up a tolerance to that allergen. Allergy shots slow down and reduce the production of the IgE antibody. Sublingual immunotherapy can be used for pollen allergies, and involves small doses of an allergen, in the form of a tablet, placed under the tongue, improving tolerance to the substance and reducing symptoms without using injections. This occurs because the allergen from the tablet crosses the mucous membranes in a matter of minutes and are captured by tolerogenic dendritic cells and are processed as small peptides. Through the lymphatic system, an immune response occurs and results in an early decrease in mast cell and basophil degranulation.

These immunotherapy methods can also have limitations. Allergy shots are generally limited to working for pollen, pets, dust, bees, and asthma allergies, but don't work well for allergies to food, medicines, feathers, or for hives or eczema. These shots can also cause redness, swelling, or irritation at the injection site, and there is also potential for a severe allergic reaction. Sublingual immunotherapy's most common side effects include itching and mild swelling inside the mouth, which can last up to an hour, and is experienced by one-quarter of people in SLIT therapy. Medications are used in allergy treatments are in table (1).

Table 1: Medications currently used in allergy treatments & limitations

Type of Allergy Med	Medication examples (brand name active ingredient)	Mechanism of Action	Uses	Limitations
Anti-histamines	Brendyl (diphenhydramine) Clar-Trimeton (chlorpheniramine) Allegra (fexofenadine hydrochloride) Claritin (loratadine)	Block histamine, a chemical compound that triggers allergic symptoms such as inflammation when it binds to certain receptors in the body	Decrease the effects of histamine at certain cell receptors, and help with congestion, sneezing, itching, nasal swelling, rives, skin rashes, and itchy and watery eyes	Common: drowsiness, dry mouth, nose, and throat, and headaches Example: Allegra can cause common side effects and some more serious side effects include hives, rashes, itching, trouble breathing or swallowing, and inflammation
Mast-cell stabilizers [7]	Nasacrom (sodium cromoglycate)	Inhibits release of histamines and allergic mediators (from mast cells); blocks mast-cell degranulation → also stabilizes mast cell membrane; A main mechanism: blocking the IgE-regulated calcium channels	Alleviates asthma & many allergic conditions (inhalers, oral solutions, and eye drops form)	Example: Commonly used sodium cromoglycate, can cause headaches, muscle aches, and diarrhea.
Corticosteroids [8]	Dexamethasone (tablet) Hydrocortisone (topical cream) Methylprednisolone (tablet) Prednisone (oral)	Suppress the inflammatory genes activated in chronic inflammatory diseases, by: 1) reversing "histone acetylation" of activated inflammatory genes through "binding of liganded glucocorticoid receptors (GR) to coactivators 2) recruitment of histone deacetylase-2 (HDAC2) to the activated transcription complex" [9]	Can be used in various forms: Nasal corticosteroids - nasal sprays that help with nasal allergies corticosteroid creams or ointments - help typically with itches and rashes; oral corticosteroids - can be prescribed to prevent swelling or severe allergic reactions	Various forms of use enhances the potential for adverse effects for certain medications. Long term use of corticosteroids in general can cause: increased appetite and weight gain, acne, thinned skin (easy bruising), increased risk of infections, mood changes and swings, depression, diabetes, high blood pressure, osteoporosis, and withdrawal symptoms.
Leukotriene modifiers [3]	Leukotriene receptor antagonists: Zafirlukast (Accolate) Montelukast (Singulair) Leukotriene synthesis inhibitor: Zileuton (Zyflo)	Act by blocking 5-lipoxygenase activity and are either leukotriene receptor antagonists (block the effects of leukotrienes), or leukotriene synthesis inhibitors (prevents the body from making leukotrienes)	Asthma medication	Risks: Some leukotriene modifiers can cause liver damage

Medications are used as a treatment to help reduce immune system reaction and alleviate symptoms. This can include prescriptions as well as over-the-counter medicines. Some of the most widely used medicines include antihistamines, mast-cell stabilizers, corticosteroids, and leukotriene inhibitors [3]. Currently, allergy medicines are generally helpful for allergic reactions, however, they only help with short-term symptoms, and don't usually provide long-term effects or

help cure the allergy. Due to this, an alternative should be explored for these medications. In addition, some medicines' effects only come into play days later, which can cause allergic discomfort until that time. Many medications are required to be taken multiple times a day and long-term use can cause many adverse effects, and may even worsen the condition. Most medications, if not all, have some sort of side effects and can be expressed differently in different people. As seen in Figure 1, the mechanism of action in current allergy medications create unnatural imbalances and lead to side effects in patients (Fig. 1).



Fig.1: Current Limitations and Downsides of Allergy Treatments (Created with BioRender.com)

Medicinal plants are being considered as a positive replacement to general medicines as it provides similar effects and benefits, but is often safer and healthier since it's natural. As many as 80% of people globally rely on herbal medicinal products for healthcare needs [10]. Herbal medicines include plant products that can be ingested as well as topical products that come from plants. Also, new drug discoveries and developments are being made as interest in herbal medicine increases. In fact, many drugs used nowadays include ingredients derived from medicinal plants. This is because plant-based chemicals are being seen as safe and more effective than synthesized chemicals. The versatility and effectiveness of natural treatments are causing herbal medications to become increasingly used worldwide, and one plant family that has been shown to have these potential benefits is Lamiaceae.

The plant family Lamiaceae has 236 genera and over 7,000 species, the largest family of the order, Lamiales [3]. Lamiaceae can be found nearly worldwide, and is known for its species' fragrant leaves and attractive flowers. Lamiaceae is usually found in dry, rock, woodland, or grassland habitats along forest margins and in fynbos. Some popular plants in this family include lavender, basil, mint, rosemary, sage, oregano, catnip, and thyme. Humans use these herb plants for flavor, fragrance, or its wide range of medicinal properties.

5. Uses of Lamiaceae

Lamiaceae has been known to be effective in alleviating conditions like exhaustion, weakness, depression, memory enhancement, circulation improvement, strengthening of fragile blood vessels, skin allergies, and asthma. Certain plants like Lamiaceae possess phytochemicals with anti-allergenic properties. These phytochemicals include flavonoids, terpenoids, and additional essential oils. The flavonoids within Lamiaceae plants are known for their antioxidant and anti-inflammatory properties, and have been shown to play a role in the treatment of various health conditions, including allergies and asthma. Terpenoids are responsible for the characteristic aromas of many plants in the Lamiaceae family. They also have anti-inflammatory and anti-allergenic properties, and they have been found to be effective in the treatment of various skin conditions. The other essential oils in the Lamiaceae plants have

phytochemicals that obtain similar properties to flavonoids and terpenoids.

These bioactive compounds have various mechanisms of action to combat the mediators or immune system involved in the inflammatory cascades or allergic reaction pathways, and these can be used as medicine for allergic symptoms [3]. For example, flavonoids have been shown to inhibit the release of histamine, a key mediator involved in the development of allergic symptoms. They also have been found to modulate the immune system and reduce the production of pro-inflammatory cytokines, which play a role in the development of allergies and other inflammatory conditions. Additionally, the essential oils present in Lamiaceae plants have been found to have a relaxing effect on the airways, which can help to relieve symptoms of asthma and other respiratory conditions.

6. Lamiaceae Studies

Prior research has been conducted to look into the potential benefits of Lamiaceae in allergic responses. These studies encompass the different mechanisms of actions that alter the immune response. Some of these studies have investigated the mechanisms of action of Lamiaceae species in modulating immune responses, particularly in suppressing IgE levels and IgE-mast cell cross-linking. The in-vivo studies highlighted in table 2 elucidate the therapeutic effect of Lamiaceae species in treating allergies by reducing passive cutaneous anaphylaxis and decreasing mortality due to anaphylactic shock-induced bronchospasm. In these studies, different Lamiaceae species, including *Mentha arvensis*, *Mosla dianthera*, and *Perilla frutescens*, have been shown to have a suppressive effect on IgE levels and the reaction to allergens. The usage of Lamiaceae plant is in table (2).

Table 2: Lamiaceae Plants Used in In-Vivo Studies

Specimen	Assay Extract	Application & Concentration	Observation & Results
OVA-sensitized mice [11]	N/A	N/A	<ul style="list-style-type: none"> Essential oil of <i>Mentha arvensis</i> significantly decreased the serum IgE level Identification of three compounds in the essential oil: menthol, menthone, and 1,8-cineole, with particularly large percentage contents of menthol
Mice sensitized with compound 48/80 and anti-DNP IgE [12]	Aqueous extract of <i>Mosla dianthera</i>	Intraperitoneal pretreatment of 1-1,000 mg/kg	<ul style="list-style-type: none"> Reduction in passive cutaneous anaphylaxis (PCA) reaction Effectively reduced mortality (41%) due to anaphylactic shock-induced bronchospasm in tested subjects with a significant drop in IgE level
Mice injected with anti-ovalbumin serum [13]	Isolated rosmarinic acid from leaves of <i>Perilla frutescens</i>	N/A	<ul style="list-style-type: none"> <i>Perilla</i> extract significantly suppressed the PCA-reaction, which was brought about by rosmarinic acid <ul style="list-style-type: none"> anti-allergic titer of rosmarinic acid was 8 folds higher than the conventional anti-allergic drug tranilast, where 19 mg/kg of rosmarinic acid was sufficient to achieve an equivalent PCA reaction suppression as 150 mg/kg of tranilast (an anti-allergic drug)
BALB/c mice sensitized intraperitoneally and challenged with ovalbumin (OVA) [14]	Water & ethanol extracts of <i>Perilla frutescens</i> leaves	Each group of mice was tube-feeding with 0 (control), 80 µg (PWL), or 320 µg (PWH) water extracts or 80 µg (PEL) or 320 µg (PEH) ethanol extracts of perilla leaves daily for 3 weeks	<ul style="list-style-type: none"> OVA-specific IL-5 and IL-13 secretions from OVA-stimulated splenocytes were significantly suppressed in the ethanol extract groups PIEL and PEH Serum level of anti-OVA IgE tended to be lower in the PEH group Inflammatory mediators, such as cotaxin and histamine, and total cells, particularly eosinophils in bronchoalveolar lavage fluid (BALF), were also decreased in the PIEL and the PEH groups PEL and the PEH groups had significantly lower methacholine-induced hyperresponsiveness (AHR) Conclusion: Ethanol extracts, rather than water extract, of perilla leaves could significantly suppress Th2 responses and airway inflammation in allergic murine model of asthma

These studies show the progress the scientific community has made towards research towards Lamiaceae, but there are next steps needing to be taken and future directions that can be explored. In studies where multiple compounds were shown to cause anti-allergenic activity, it's important to isolate the primary compound that contributed to this, and perform experiments that show its potential as herbal

medicine. Some experimental studies could also focus on the prospective of including compounds from multiple plant species in a medication. It is also essential to obtain research related to toxicology studies for Lamiaceae. Lamiaceae used as a medication would clearly be plant-based, therefore providing a more sustainable option.

7. Additional Benefits of Manufactured Lamiaceae

Currently, large-scale drug production is known to have negative impacts on the environment due to the large number of medications being produced. A research project by Laximnarayan, Duse, Watal et al published in *The Lancet* in November 2013 shows that "contamination of water sources with antimicrobial drugs (combined with mass misuse of antibiotics and poor sanitation) has had grave consequences in India, where an estimated 58,000 new-borns die from multidrug-resistant infections every year". Pharma pollution affects people and animals who live near production plants because water and food sources can be contaminated with waste products from the pharma. [15] Plant-based medications could reduce environmental effects such as pollution and would be more sustainable for the environment in the long-term. Further analysis will be needed to determine positive outcomes of plant-based manufacturing.

Specifically, green manufacturing with Lamiaceae is a much more ethical and sustainable option for mass producing allergy medication, and would be a better alternative for the wellbeing of the planet as well as the benefits it offers to individual people, as an allergy medication. The use of plant-based products can be more beneficial because they have fewer toxic byproducts that often find themselves polluting streams, rivers, and communities nearby during the drug's manufacturing. Plant-based drug manufacturing has been shown to produce much lower levels of greenhouse gas emissions as demonstrated in US biotech Amgen's biomanufacturing plant where 69% less carbon emissions are produced compared to a traditional manufacturing facility. [16] As described in this paper, current allergy medications have many limitations as well as downsides related to their sustainability. Lamiaceae is an important alternative to consider and further research will be able to prove its effectiveness.

8. Conclusion

In conclusion, allergic disorders have become a major global health concern, with millions of people suffering from asthma, food allergies, allergic rhinitis, and medication hypersensitivities. While traditional medicines may not be as effective, natural products derived from medicinal plants, such as the Lamiaceae family, have been found to contain anti-allergenic compounds. The research provided in this paper has shown that Lamiaceae plants have been proven to target IgE responses in the allergy cascade and act as anti-inflammatory agents, reducing allergic reactions. This paper has highlighted the properties, medicinal uses, and up-to-date research on the phytoconstituents and anti-allergenic activity of the Lamiaceae family, and their potential use as a natural alternative in the treatment of allergies. However, additional research needs to be done in a clinical setting in order to explore Lamiaceae's use as a viable option to replace current allergy medications.

References

- 1] "Facts and Stats - 50 Million Americans Have Allergies:

- Acaai Patient.” ACAAI Public Website, American College of Allergy, Asthma & Immunology, 16 Sept. 2022.
- [2] Clements, Julie. “Spring Time Ailments and Their ICD-10 Codes.” Outsource Strategies International, 10 Nov. 2022.
- [3] Sim, Lee Yen, et al. “Lamiaceae: An Insight on Their Anti-Allergic Potential and Its Mechanisms of Action.” *Frontiers*, Frontiers, 24 May 2019, doi:10.3389/fphar.2019.00677
- [4] Bax, Heather J et al. “Cytokinergic IgE Action in Mast Cell Activation.” *Frontiers in immunology* vol. 3 229. 6 Aug. 2012, doi:10.3389/fimmu.2012.00229
- [5] “Allergies and the Immune System.” *Allergies and the Immune System* | Johns Hopkins Medicine, 8 Aug. 2021.
- [6] “Slit: Allergy Treatment.” ACAAI Public Website, 15 Apr. 2022.
- [7] “Mast Cell Stabilizer.” Wikipedia, Wikimedia Foundation, 23 Nov. 2022.
- [8] Rahim, Nur Amira et al. “Anti-Allergic Rhinitis Effects of Medicinal Plants and Their Bioactive Metabolites via Suppression of the Immune System: A Mechanistic Review.” *Frontiers in pharmacology* vol. 12 660083. 13 Apr. 2021, doi:10.3389/fphar.2021.660083
- [9] Barnes, Peter J. “How corticosteroids control inflammation: Quintiles Prize Lecture 2005.” *British journal of pharmacology* vol. 148,3 (2006): 245-54. doi:10.1038/sj.bjp.0706736
- [10] Ekor, Martins. “The growing use of herbal medicines: issues relating to adverse reactions and challenges in monitoring safety.” *Frontiers in pharmacology* vol. 4 177. 10 Jan. 2014, doi:10.3389/fphar.2013.00177
- [11] Sharma, S., Rasal, V. P., Patil, P. A., Joshi, R. K. (2018). *Mentha arvensis* essential oil suppressed airway changes induced by histamine and ovalbumin in experimental animals. *Nat. Prod. Res.* 32, 468–472. doi: 10.1080/14786419.2017.1311891
- [12] Lee, D. H., Kim, S. H., Eun, J. S., Shin, T. Y. (2006). *Mosla dianthera* inhibits mast cell-mediated allergic reactions through the inhibition of histamine release and inflammatory cytokine production. *Toxicol. Appl. Pharmacol.* 216, 479–484. doi: 10.1016/j.taap.2006.06.007
- [13] Makino, T., Furuta, Y., Wakushima, H., Fujii, H., Saito, K., Kano, Y. (2003). Anti-allergic effect of *Perilla frutescens* and its active constituents. *Phytother. Res.* 17, 240–243. doi: 10.1002/ptr.1115
- [14] Miaw-Ling Chen, Chi-Heng Wu, Li-Shiuan Hung, Bi-Fong Lin, “Ethanol Extract of *Perilla frutescens* Suppresses Allergen-Specific Th2 Responses and Alleviates Airway Inflammation and Hyperreactivity in Ovalbumin-Sensitized Murine Model of Asthma”, *Evidence-Based Complementary and Alternative Medicine*, vol. 2015, Article ID 324265, 8 pages, 2015. <https://doi.org/10.1155/2015/324265>
- [15] Nawrat, Allie. “Pharma and the Environment: Pollution Continues despite Public Pressure.” *Pharmaceutical Technology*, 14 Feb. 2022
- [16] “Green Buildings.” Amgen, Inc.