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Azadirachta Indica And Allergies: Investigation The Allergenic Potential Of Bioactive Compound

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Abstract: This study analyzes the medicinal importance and allergenic hazards of Azadirachta indica (neem), a plant that is widely used in traditional health practices like Ayurveda and Unani. Neem has been found to possess antimicrobial, anti-inflammatory, and immune-enhancing activities, which are attributed to bioactive compounds like azadirachtin, salannin, nimbin, flavonoids, and phenolic acids. Though beneficial, neem is potential allergen that can cause reactions, especially triggered by compounds like azadirachtin, leading to conditions such as contact dermatitis and respiratory trouble. The review highlights the importance of identifying allergenic compounds using techniques like chromatography and patch tests. It emphasizes the need for safer formulation and greater awareness among the public to counteract allergic risks while preserving neem's therapeutic advantages.

Keywords: Azadirachta indica, neem allergy, azadirachtin, contact dermatitis, hypersensitivity, phytoconstituents, neem oil, immune response, mast cell activation, oxidative stress, allergenic compounds, dermatological reactions, phytochemical analysis, traditional medicine, limonoids, flavonoids, histamine release, patch testing, safety assessment, bioactive compounds.

INTRODUCTION

Azadirachta indica or neem is a robust, evergreen tree native to India and widely naturalized in the tropical and subtropical regions all over the globe. Being a member of the Meliaceae family, to which mahogany also belongs, neem grows well in arid environments where annual rainfall ranges from 400 to 800 mm. Its introduction into various African countries, including Nigeria, Ghana, Ethiopia, Sudan, and Kenya, has also extended its range. The US National Academy of Sciences recognized neem's importance in 1992, labeling it a "tree for solving global problems." This "miracle tree" and "living pharmacy" has played a crucial role in traditional medical practices, including Ayurveda, Unani, and homeopathy, for centuries. Its various components like leaves, bark, fruit, flowers, oil, and gum have been applied in treating several disorders of human diseases like hypertension, diabetes, cardiovascular disease, and cancer.[2][3] The neem's bioactivity is attributable to its cell and molecular mechanisms encompassing the properties of scavenging free radicals, detoxifying, repair of DNA, immunomodulatory, and antiinflammatory actions. Extensive scientific studies were conducted as a result of the broad range of bioactive components present in neem.

The most significant phytochemical, azadirachtin, is a highly active triterpenoid comprising seven isomers (A-G) with azadirachtin E possessing the highest efficiency. Other biologically significant compounds present in neem include salannin, nimbin, meliantriol, volatile oils, flavonoids, alkaloids, phenolic compounds, carotenoids, steroids, and ketones. All of these compounds augment neem's medicinal efficiency, imparting antimicrobial, anti-inflammatory, and immunomodulatory effects. Because of its vast phytochemistry and pharmacological significance, neem remains a major field of study, focusing on its medicinal applications and potential allergenicity.[1]

Taxonomy:

Azadirachta indica resembles its relative, Melia azedarach. The term Azadirachta comes from the Persian word "azaddhirakt," which translates to "noble tree. " The taxonomic classification of neem is outlined as follows: [4]

- Kingdom: Plantae
- Subkingdom: Tracheobionta
- Superdivision: Spermatophyta
- Division: Magnoliophyta
- Class: Dicotyledons
- Subclass: Rosidae
- Order: Sapindales (formerly Rutales)
- Suborder: Sapindineae (formerly Rutinae)
- Family: Meliaceae
- Subfamily: Melioideae
- Tribe: Melieae
- Genus: Azadirachta
- Species: Azadirachta indica

Phytoonstituents:

The primary bioactive constituents identified in Azadirachta indica have been thoroughly examined. Girish and Shankara (2008) indicate that more than 135 compounds have been isolated from various parts of the neem tree. These can primarily be categorized into two groups: isoprenoids and non-isoprenoids. The isoprenoid category consists of diterpenoids and triterpenoids, including protomeliacins, limonoids, azadirone and its derivatives, genudin, vilarin-type compounds, and secomeliacins such as nimbin, salannin, and azadirachtin. Notably, azadirachtin, a crucial bioactive component of neem, has been synthesized in the laboratory quite recently, marking a significant achievement in the synthesis of natural products. Non-isoprenoids, on the other hand, encompass proteins, carbohydrates, sulfur compounds, polyphenolics such as flavonoids and their glycosides, dihydrochalcone, coumarin, tannins, aliphatic compounds, and phenolic acids. [2][7]

List of Phytoconstituents in Azadirachta Indica:

1. Azadirachtin[2]
   - Properties: Limonoid, bitter, insecticidal, antibacterial, antifungal.
   - Causes of Allergy: Skin irritation, contact dermatitis, respiratory allergies.
   - Mechanism of Action: Azadirachtin inhibits insect development but also may act as a sensitizer in humans, leading to immune hypersensitivity reactions.

2. Nimbin
   • Properties: Triterpenoid, anti-inflammatory, antifungal, antibacterial.
   • Causes of Allergy: Contact dermatitis, redness, itching.
   • Mechanism of Action: Nimbin has the potential to stimulate mast cells, leading to histamine release and inflammatory reactions.

3. Salannin
   • Properties: Limonoid, insect repellent, bitter taste.
   • Causes of Allergy: Skin rashes, eye irritation, asthma worsening.
   • Mechanism of Action: May act as a haptogen, forming antigenic complexes with skin proteins.

4. Gedunin
   • Properties: Limonoid, anti-malarial, anti-inflammatory.
   • Causes of Allergy: Respiratory irritation, dermatitis.
   • Mechanism of Action: Gedunin has the capacity to induce oxidative stress, initiating inflammatory pathways.

5. Nimbolide
   • Properties: Limonoid, cytotoxic, antioxidant, antibacterial.
   • Causes of Allergy: Contact dermatitis, urticaria.
   • Mechanism of Action: Stimulates cytokine release, leading to inflammation and hypersensitivity.

6. Quercetin
   • Properties: Flavonoid, antioxidant, anti-inflammatory.
   • Causes of Allergy: Cross-reactivity with pollen allergens, skin reactions.
   • Mechanism of Action: Alters immune response, possibly leading to uncontrolled histamine release.

7. Margosin
   • Properties: Limonoid, antibacterial, insecticidal.
   • Causes of Allergy: Eye irritation, rashes.
   • Mechanism of Action: Interacts with skin proteins, resulting in immune reactions.

8. Nimbidin
   • Properties: Triterpenoid, anti-inflammatory, antimicrobial.
   • Causes of Allergy: Eczema, contact dermatitis.
   • Mechanism of Action: May alter lipid metabolism, leading to inflammatory reactions.

9. Epicatechin
   • Properties: Flavonoid, antioxidant, antimicrobial.
   • Causes of Allergy: Gastrointestinal upset, skin irritation.
   • Mechanism of Action: May potentially induce mast cell activation, resulting in histamine release.

10. Kaempferol
    • Characteristics: A flavonoid that is antioxidant and anti-inflammatory.
    • Allergic Reactions: May cause skin irritation and hives.
    • Action Mechanism: Induces the action of immune cells, which can potentially induce hypersensitivity reactions.

11. Catechin
    • Characteristics: Flavonoid with antioxidant and antimicrobial activity.
    • Allergic Reactions: May cause dermatitis and oral ulcers.

• Action Mechanism: Interacts with immune cells, which can amplify inflammatory responses.

12. Rutin
    • Characteristics: A flavonoid with antioxidant and vascular protective properties.
    • Allergic Reactions: Linked to respiratory problems and skin rashes.
    • Action Mechanism: Modifies the behavior of mast cells, possibly resulting in more severe allergic reactions.

13. Gallic Acid
    • Characteristics: A phenolic acid with antioxidant and anti-inflammatory properties.
    • Allergic Reactions: May result in skin inflammation and redness.
    • Action Mechanism: Can cause oxidative stress, which stimulates immune cells.

14. Myricetin
    • Characteristics: A flavonoid with antioxidant and anti-inflammatory activities.
    • Allergic Reactions: Associated with respiratory irritation and skin rash.
    • Action Mechanism: Stimulates pro-inflammatory pathways that can result in hypersensitivity reactions.

15. Luteolin
    • Characteristics: A flavonoid known for its antioxidant and anti-inflammatory activities.
    • Allergic Reactions: May result in symptoms like itching, redness, and swelling.
    • Action Mechanism: Alters the balance of cytokines, leading to allergic inflammation.

Allergenic Properties of Major Compounds in Azadirachta indica (Neem)

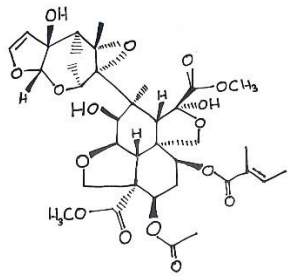
Azadirachta indica, or neem, is endowed with multiple bioactive compounds, such as azadirachtin, salannin, and nimbin. Although these constituents are responsible for the medicinal and pest-deterrent attributes of neem, they have been shown to induce allergic effects in sensitive people.

Azadirachtin: This compound of limonoids is found in the seeds and leaves of neem and is recognized as possessing high allergenicity. Despite common application in herbal medicines and farming, the allergy-inducing property of azadirachtin has gained prominence in recent years while stressing the importance of thorough knowledge of its nature and its impact on health.[3]

Common Allergic Reactions to Azadirachtin

• **Skin Irritation:** Rashes, itchiness, and allergic dermatitis can result from contact with neem oil or azadirachtin-containing insecticides.
• **Respiratory Symptoms:** Inhalation of neem oil vapors or dust can induce asthma-like reactions characterized by wheezing and shortness of breath.
• **Eye Symptoms:** Eye redness, swelling, and irritation are caused by direct contact with azadirachtin-containing products.[3]

Structure of azadirachtin:



Molecular Formula: $C_{35}H_{44}O_{16}$

Molecular Weight: 720.7 g/mol

Clinical Case: Neem Oil Airborne Allergic Contact Dermatitis

Case Overview

A 58-year-old male patient with a history of psoriasis, treated topically with emollients and corticosteroids, appeared with severe lid irritation, hyperemia, and edema after 24 hours of using his own neem oil mixture fumigations in his garden. His prior use of neem oil also benefited his psoriasis, although repeated usage manifested as allergic reaction, leading him to stop their use and revert to normal subsequent to the settling of symptoms. Patch test identified a vigorous positive response to neem oil, whereas control subjects were negative for irritant dermatitis. The patient demonstrated eczematous responses that were delayed when challenged again.[6]

Discussion and Treatment

Neem oil contains more than 140 bioactive compounds, which can behave as allergens. Allergic reactions can result from these sensitizers triggering immune responses in hypersensitive users. The patient was asked to totally discontinue neem oil, and antihistamines and topical corticosteroids successfully settled his symptoms in a week's time. The case emphasizes the importance of patient history, patch testing, and formulation studies in the diagnosis of allergies related to neem. Further studies have to be undertaken to identify the exact allergens in neem oil.

Diagnosing Azadirachtin-Induced Allergy

Diagnosis of an allergy to azadirachtin requires a careful clinical history, patch testing, and laboratory studies. Allergic contact dermatitis was established by positive patch test results in neem oil. The patient's medical history of previous application of neem oil for psoriasis was crucial in establishing the allergy.

Results:

- The acid layer is bright greenish yellow in color, and the chloroform layer is red in color, which shows the presence of terpenoids.[6]

Evaluation parameters for Azadirachtin:

1. FT-IR Spectroscopy: Determines functional groups and structural changes.
2. HPLC (High-Performance Liquid Chromatography): Determines the quantity of Azadirachtin.
3. Mass Spectrometry: Confirms the molecular structure of Azadirachtin.
4. Nuclear Magnetic Resonance (NMR) Spectroscopy: Determines molecular structure and purity.
5. Chromatographic Techniques: Separates, identifies, and determines the quantity of Azadirachtin in neem oil.
6. Spectrophotometric Methods: Determines the quantity of Azadirachtin in neem oil.
7. Biological Assays: Determines the insecticidal and antimicrobial activity of Azadirachtin.
8. Toxicity Studies: Assesses the toxicity and safety of Azadirachtin in various formulations.[5]

Conclusion:

Azadirachta indica or neem is well known to have medicinal as well as agronomic uses due to its highly bioactive nature. Although neem's pharmacological properties are well established, this review identifies its ability to cause allergic responses in vulnerable populations. Major phytoconstituents like azadirachtin, salannin, nimbin, and other flavonoids possess immunomodulatory and antimicrobial activities but also have the capability to cause contact dermatitis, respiratory irritation, and systemic hypersensitivity reactions.

The documented case studies and diagnostic evaluations, including patch testing and biochemical assessments, underscore the need for increased awareness of neem-induced allergies. As neem-based products continue to gain popularity in traditional medicine and industry, understanding their allergenic potential becomes imperative. Future research should focus on elucidating the molecular pathways through which neem compounds interact with the immune system, identifying specific allergens, and developing safer formulations.

By appreciating both the medicinal and allergenic properties of neem, this research demands a balancing act in its utilization, where the vulnerable are adequately informed and its medicinal properties are maximized.[8][9][10]

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