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Review on the efficiency of Neem (*Azadirachta indica*) as a pesticide and its pharmacological importance

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Abstract

Azadirachta indica (commonly known as neem) is one of the most valuable medicinal and agricultural plants because of its wide range of biological activities. For centuries, it has been used in traditional medicine as well as farming practices. In recent years, scientific studies have confirmed that neem contains several bioactive compounds with significant pesticidal and therapeutic potential. Among these compounds, azadirachtin has received the greatest attention due to its remarkable ability to control insect pests without causing major harm to beneficial organisms or the environment.

This review discusses the effectiveness of neem as a natural pesticide and highlights its growing importance in modern medicine. It explains how neem compounds interfere with insect growth, feeding behavior, and reproduction, making them useful alternatives to conventional chemical pesticides. In addition, the review summarizes the pharmacological activities of neem, including its anticancer, anti-inflammatory, antimicrobial, antiviral, antidiabetic, and antioxidant properties. The paper also examines current challenges such as poor bioavailability, variation in phytochemical composition, and difficulties in standardizing neem-based products. Finally, recent developments such as nano-formulations and advanced delivery systems are discussed as promising approaches for improving the effectiveness and stability of neem-derived products in both agriculture and healthcare.

Keywords: Azadirachta indica; Neem; Azadirachtin; Biopesticide; Phytochemicals; Pharmacological Activities; Anticancer Activity; Antimicrobial Activity; Sustainable Agriculture; Nano-formulations.

INTRODUCTION

Growing concerns about environmental pollution, pesticide resistance, and the harmful effects of synthetic chemicals have encouraged researchers to search for safer and more sustainable alternatives. Conventional pesticides, including organophosphates, carbamates, and pyrethroids, have played an important role in increasing crop production. However, their excessive and prolonged use has resulted in serious environmental problems, contamination of soil and water, development of resistant insect populations, and health risks for humans and animals. At the same time, pharmaceutical research is increasingly exploring plant-derived compounds as potential alternatives to synthetic drugs because many natural products possess multiple biological activities with comparatively lower toxicity (Saleem et al., 2018; Wylie & Merrell, 2022).

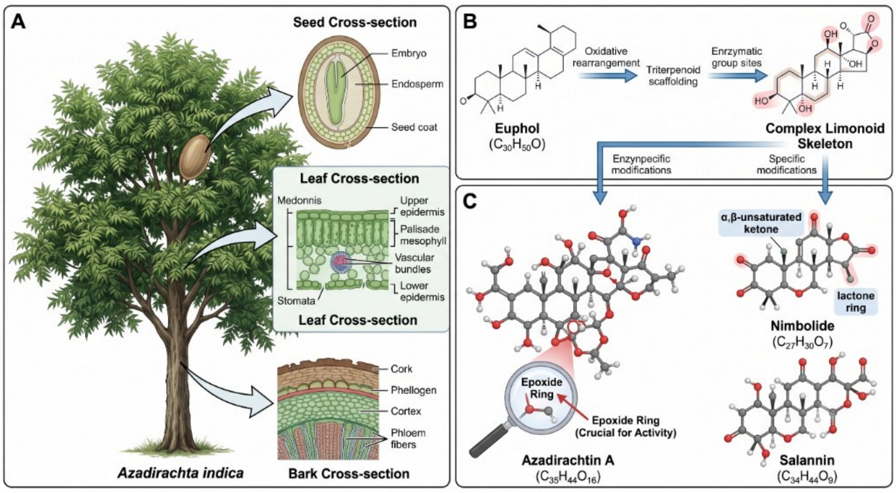
Among medicinal plants, *Azadirachta indica* (neem) has attracted considerable scientific interest. Native to the Indian subcontinent, neem has been widely used in Ayurveda and traditional medicine for centuries to treat infections, skin disorders, inflammation, and several other ailments. Farmers have also relied on different parts of the neem tree to protect crops from insect pests and plant diseases.

Unlike most synthetic pesticides that usually target a single biochemical pathway, neem contains a diverse mixture of biologically active compounds that affect multiple physiological processes simultaneously. This multi-target mode of action not only improves its effectiveness but also reduces the chances of insects developing resistance (Kilani-Morakchi et al., 2021). In addition to its agricultural applications, neem has demonstrated promising pharmacological activities, making it an important subject of research in medicine.

This review provides a comprehensive overview of neem's phytochemical composition, its role as a natural pesticide, and its therapeutic potential. It also discusses the major challenges associated with the commercialization of neem-derived products and highlights future research directions that may enhance their applications in sustainable agriculture and healthcare.

2. Phytochemical Profiling of *Azadirachta indica*

The biological properties of neem are mainly attributed to its rich collection of naturally occurring secondary metabolites. More than 300 bioactive compounds have been identified from different parts of the neem tree, including its leaves, bark, roots, flowers, fruits, and seeds (Saleem et al., 2018). These compounds belong to several chemical groups, among which limonoids are considered the most important because they are responsible for many of neem's pesticidal and medicinal properties



2.1 Major Limonoids and their Structural Complexity

The most biologically potent compounds are highly oxygenated limonoids. The structural elucidation of these compounds reveals a core derived from a precursor steroid, euphol, undergoing extensive oxidation and rearrangement.

1. **Azadirachtin:** Azadirachtin is the most important and extensively studied bioactive compound present in neem. It is found mainly in the seed kernels, where its concentration ranges from approximately 0.2% to 0.6% of the seed weight. Several structural variants of azadirachtin have been identified, with Azadirachtin A being the most abundant and biologically active form (Kilani-Morakchi et al., 2021). Chemically, azadirachtin possesses a highly complex molecular structure containing multiple oxygen-containing functional groups, including epoxide, acetal, enol ether, and ester groups. These structural characteristics are largely responsible for its strong biological activity. However, they also make the compound highly

sensitive to heat, ultraviolet light, and alkaline conditions, limiting its long-term stability.

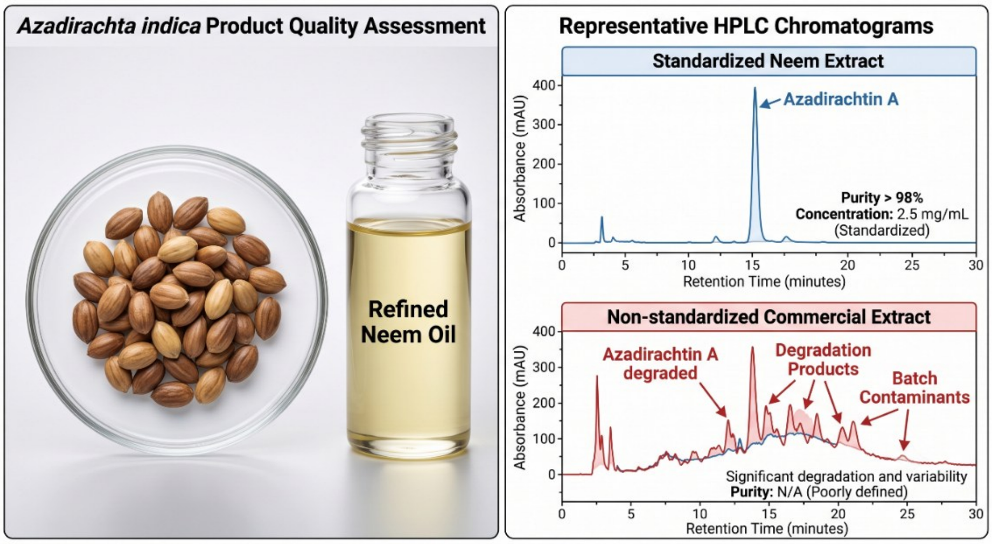
2. **Nimbin and Nimbidin:** Nimbin and nimbidin are other important limonoids present mainly in neem seed oil. Although they lack certain structural features found in azadirachtin, they exhibit significant medicinal properties. Numerous studies have demonstrated their anti-inflammatory, antipyretic, and antimicrobial activities. Nimbidin, in particular, represents one of the principal bitter constituents of neem seed oil and contributes substantially to its therapeutic value.

3. **Salannin:** Salannin is another biologically active limonoid known primarily for its insect-repellent and anti-feedant properties. Although it does not interfere with insect development as effectively as azadirachtin, it discourages insects from feeding on treated plants, thereby reducing crop damage.

4. **Nimbolide:** Nimbolide is predominantly isolated from neem leaves and flowers. In recent years, it has gained considerable attention because of its strong anticancer activity. Research indicates that nimbolide can interfere with several signaling pathways involved in cancer progression, making it a promising candidate for future anticancer drug development (Liu et al., 2015; Wang et al., 2016).

2.2 Extraction and Standardization Challenges

The chemical lability of limonoids presents significant challenges. Azadirachtin is thermally unstable and highly sensitive to UV radiation and alkaline environments. Conventional Soxhlet extraction often leads to the thermal degradation of these thermolabile compounds.



3. Agricultural Efficacy: Neem as a Next-Generation Biopesticide

Neem has emerged as one of the most effective botanical pesticides because of its broad-spectrum activity against a wide range of agricultural pests. Unlike conventional synthetic pesticides, neem-based products not only control insect populations but also show activity against nematodes, fungi, and certain plant viruses. Studies have reported that neem is effective against more than 600 pest species while posing minimal risk to beneficial organisms such as pollinators, natural predators, birds, and mammals (Kilani-Morakchi et al., 2021). These characteristics make neem an environmentally friendly alternative for sustainable agriculture and an important component of Integrated Pest Management (IPM) programs.

3.1 Mechanisms of Insecticidal Action

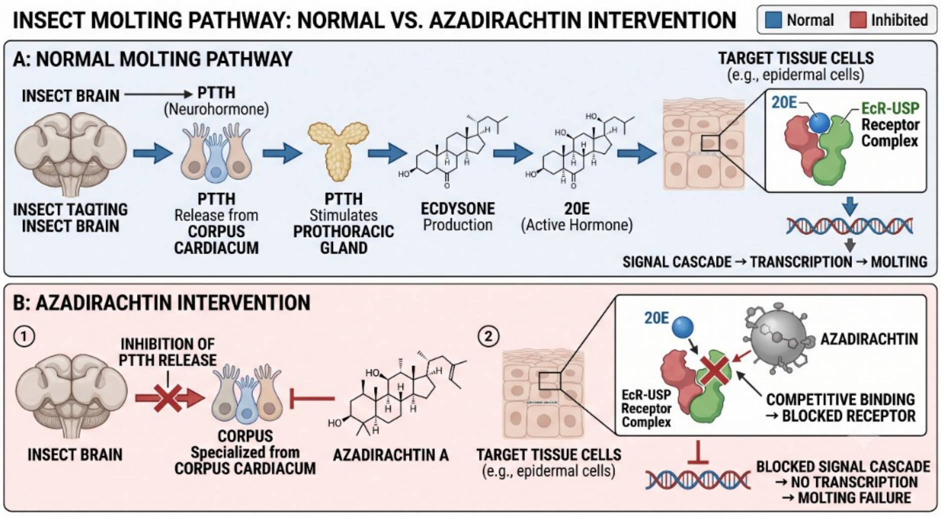
One of the major reasons for the success of neem as a biopesticide is its unique mode of action. Unlike most chemical pesticides that kill insects by attacking their nervous system, neem primarily affects the insect's growth, development, feeding behavior, and reproductive processes. Because it targets multiple physiological pathways simultaneously, the chances of insects developing resistance are considerably reduced.

3.1.1 Endocrine Disruption and Insect Growth Regulation (IGR)

The principal insecticidal compound in neem, azadirachtin, functions as an insect growth regulator by interfering with the hormonal system responsible for insect development.

Normally, insects require the molting hormone 20-hydroxyecdysone (20E) to shed their old exoskeleton and progress to the next developmental stage. Azadirachtin closely resembles the structure of ecdysone and competes for binding with the ecdysone receptor (EcR) and its partner protein, the ultraspiracle protein (USP). This interference blocks the hormonal signaling required for successful molting.

In addition to receptor inhibition, azadirachtin suppresses the release of prothoracicotropic hormone (PTTH) from the corpus cardiacum. Since PTTH stimulates the production of molting hormones, its inhibition further disrupts normal insect development. As a result, insects fail to molt properly, develop severe developmental abnormalities, experience unsuccessful pupation, and eventually die before reaching adulthood.



3.1.2 Anti-feedant and Repellent Properties

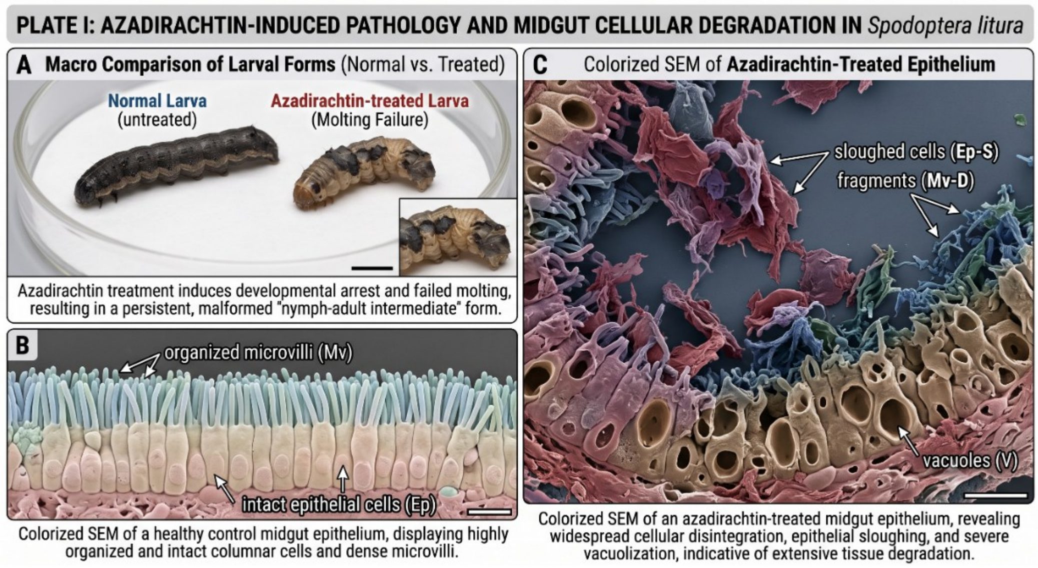
Apart from disrupting growth, neem strongly discourages insects from feeding on treated plants. This anti-feedant effect occurs through both immediate sensory responses and physiological changes after ingestion (Kilani-Morakchi et al., 2021).

Primary Anti-feedant Response

When insects come into contact with neem-treated plant surfaces, limonoids stimulate specialized deterrent receptors located within their mouthparts. Activation of these receptors sends inhibitory signals to the insect's feeding centers, causing insects to stop feeding almost immediately. As a result, crop damage is significantly reduced even before the insects die.

Secondary Anti-feedant Response

If insects consume neem-treated plant material, azadirachtin causes extensive damage to the digestive system. It induces programmed cell death (apoptosis) in the epithelial cells lining the insect midgut, decreases the secretion of digestive enzymes such as amylases, proteases, and lipases, and reduces gut movement. These physiological disturbances impair digestion, eventually leading to starvation and death.



3.1.3 Disruption of Fecundity and Reproduction

Even when neem does not immediately kill insects, exposure to low concentrations of azadirachtin can significantly reduce their reproductive capacity. In female insects, it suppresses vitellogenesis, the process responsible for producing yolk proteins necessary for egg development, by altering juvenile hormone levels. Consequently, fewer healthy eggs are produced.

In male insects, azadirachtin interferes with sperm production and decreases sperm motility, reducing fertility. These combined effects gradually suppress pest populations over successive generations, making neem an effective long-term pest management tool.

3.2 Resistance Management and Ecological Compatibility

One of the greatest advantages of neem-based pesticides is their ability to delay the development of insect resistance. Conventional synthetic insecticides generally act on a single biochemical target, allowing insects to develop resistance through relatively simple genetic mutations. In contrast, neem affects several biological processes simultaneously, including feeding, growth, molting, hormone regulation, and reproduction (Kilani-Morakchi et al., 2021).

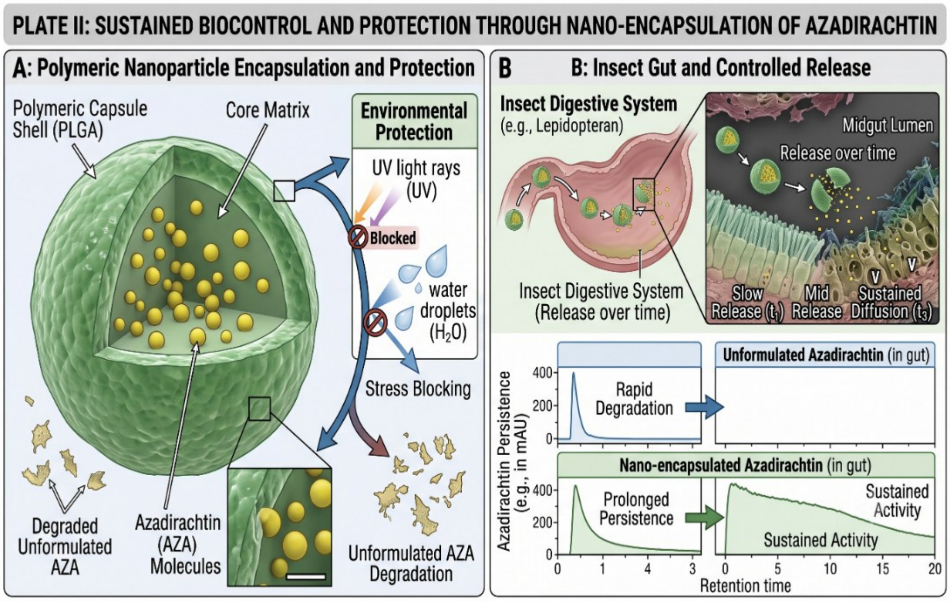
Because insects would need multiple genetic adaptations to overcome all these effects at once, the probability of resistance developing is considerably lower. This characteristic makes neem particularly valuable in Integrated Pest Management programs, where long-term pest control and resistance management are essential objectives.

Neem is also environmentally compatible. Most of its active compounds break down rapidly under sunlight and through microbial activity in soil, preventing long-term accumulation in the environment. Consequently, neem leaves very little toxic residue on harvested crops and is widely accepted for use in organic farming systems.

Another important advantage is its relatively low toxicity toward non-target organisms. Research indicates that recommended agricultural doses of azadirachtin have minimal harmful effects on honey bees (*Apis mellifera*), beneficial predatory insects, birds, and other vertebrates. This selective toxicity distinguishes neem from many broad-spectrum chemical pesticides that often eliminate beneficial insects along with pests.

3.3 Nano-formulations: Overcoming Environmental Lability

The primary limitation of neem in agriculture is its rapid photodegradation and poor aqueous solubility. Recent advancements in nanotechnology are resolving these issues (Kilani-Morakchi et al., 2021). Nano emulsions, polymeric nanoparticles, and solid lipid nanoparticles encapsulating azadirachtin provide protection against UV irradiation and control the release rate of the active ingredient.



4. Pharmacological and Therapeutic Importance

In addition to its well-established role in agriculture, *Azadirachta indica* has gained significant attention in modern medicine because of its wide range of therapeutic properties. Different parts of the neem tree contain numerous bioactive compounds that exhibit anticancer, anti-inflammatory, antimicrobial, antiviral, antidiabetic, antioxidant, and antiparasitic activities (Saleem et al., 2018). Unlike many conventional drugs that target a single biological pathway, neem contains multiple phytochemicals capable of acting on several molecular targets simultaneously. This multi-target approach has made neem an important focus of research for the treatment and prevention of complex diseases such as cancer, diabetes, chronic inflammatory disorders, and infectious diseases.

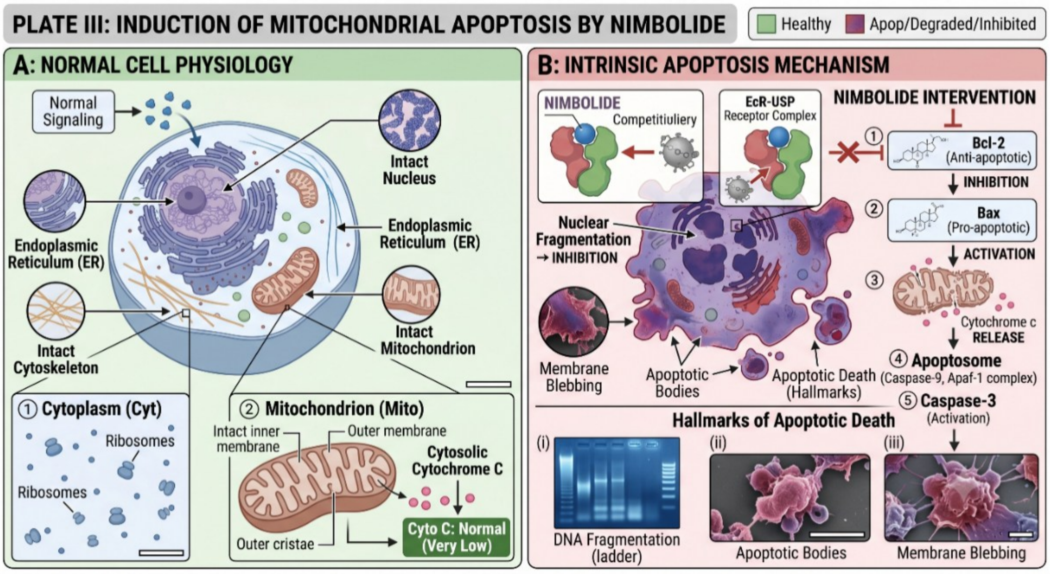
4.1 Anticancer and Chemopreventive Efficacy

Among the various medicinal properties of neem, its anticancer activity has attracted considerable scientific interest. Several studies have demonstrated that neem-derived compounds can inhibit the growth of cancer cells through multiple mechanisms while causing comparatively less damage to normal cells. One of the most promising compounds is **nimbolide**, a triterpenoid predominantly isolated from neem leaves. Research suggests that nimbolide possesses significant chemotherapeutic potential because it interferes with several signaling pathways involved in cancer progression (Wang et al., 2016).

4.1.1 Induction of Apoptosis and Cell Cycle Arrest

Neem shows strong anticancer activity mainly by triggering apoptosis, the body's natural process of removing damaged or abnormal cells. Since cancer cells often avoid this process and continue growing uncontrollably, neem compounds help restore normal cell death.

Studies on breast (MCF-7), prostate (PC-3), and cervical (HeLa) cancer cells have shown that nimbolide activates both intrinsic and extrinsic apoptotic pathways (Liu et al., 2015; Wang et al., 2016). It increases the levels of pro-apoptotic proteins such as **Bax** and **Bad** while reducing anti-apoptotic proteins like **Bcl-2** and **Bcl-xL**. These changes damage the mitochondrial membrane, release cytochrome c, and activate caspase enzymes, leading to the controlled destruction of cancer cells. Nimbolide also slows cancer progression by arresting the cell cycle and preventing further cell division.



4.1.2 Inhibition of Angiogenesis and Metastasis

Tumor metastasis requires angiogenesis and the degradation of the extracellular matrix. Neem leaf extract suppresses the expression of Vascular Endothelial Growth Factor (VEGF) and its receptor (VEGFR), thereby starving the tumor of blood supply. Additionally, nimbolide inhibits the activity of Matrix Metalloproteinases (MMP-2 and MMP-9). Mechanistically, this is largely mediated by the inhibition of the Nuclear Factor-kappa B pathway, a master regulator of inflammation and metastasis (Liu et al., 2015; Wang et al., 2016).

4.2 Anti-inflammatory and Immunomodulatory Activity

Chronic inflammation is associated with the development of several diseases, including arthritis, diabetes, cardiovascular disorders, autoimmune diseases, and certain cancers. Neem contains several compounds, particularly **nimbidin**, that exhibit potent anti-inflammatory activity comparable to some commonly used non-steroidal anti-inflammatory drugs (NSAIDs) (Saleem et al., 2018).

Neem extracts reduce inflammation by suppressing the production of important pro-inflammatory cytokines such as **Tumor Necrosis Factor-alpha (TNF-α)**, **Interleukin-1 beta (IL-1β)**, and **Interleukin-6 (IL-6)**. These signaling molecules normally stimulate inflammatory responses during infection or tissue injury, but excessive production contributes to chronic inflammatory disorders.

At the molecular level, neem inhibits the activity of **Cyclooxygenase-2 (COX-2)** and **inducible Nitric Oxide Synthase (iNOS)**. These enzymes are responsible for producing prostaglandins and nitric oxide, two important mediators of inflammation. By reducing their production, neem helps decrease swelling, pain, and tissue damage associated with chronic inflammatory conditions.

In addition to suppressing inflammation, neem has immunomodulatory properties that help regulate immune system activity. Rather than simply suppressing immune responses, neem appears to promote a balanced immune reaction, making it potentially useful for managing inflammatory and autoimmune disorders.

4.3 Antidiabetic and Metabolic Regulation

The hypoglycaemic effects of neem have been documented for centuries, and modern endocrinological research validates these claims (Saleem et al., 2018). The mechanism of action is multifactorial:

1. Insulin Secretagogue Activity: Aqueous extracts of neem leaves stimulate the pancreatic cells, enhancing the secretion of insulin.

2. Peripheral Glucose Uptake: Neem improves insulin sensitivity in skeletal muscle and adipose tissue. It facilitates the translocation of GLUT4 transporters to the cell membrane by activating the PI3K/Akt signalling pathway.

3. Inhibition of Carbohydrate Digesting Enzymes: Neem extracts act as competitive inhibitors for intestinal glucosidase and amylase, retarding the digestion of complex carbohydrates.

4.4 Antimicrobial, Antiviral, and Antiparasitic Properties

***Antibacterial:** Neem oil and leaf extracts show potent bactericidal activity against both Gram-positive (*Staphylococcus aureus*, including MRSA) and Gram-negative (*Escherichia coli*, *Pseudomonas aeruginosa*) bacteria (Wylie & Merrell, 2022).

*** Antiviral:** Neem leaf extract has demonstrated efficacy in inhibiting the replication of DNA and RNA viruses, including Dengue virus, Herpes Simplex Virus (HSV), and Coxsackievirus (Wylie & Merrell, 2022).

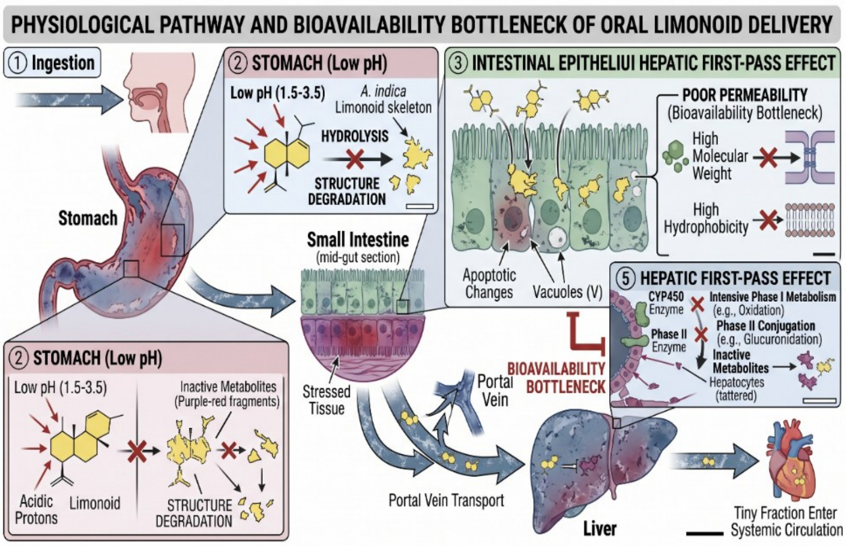
*** Antimalarial:** Gedunin exhibits high antiplasmodial activity against *Plasmodium falciparum*. It appears to disrupt the parasite's redox balance and inhibit the maturation of the parasite in the human erythrocyte phase.

5. Pharmacokinetics, Toxicity, and Safety Profile

Although neem has demonstrated remarkable potential in both agriculture and medicine, its successful application depends not only on its biological activity but also on its pharmacokinetic properties and safety profile. Understanding how neem compounds are absorbed, distributed, metabolized, and eliminated is essential before they can be widely used in clinical practice. Similarly, evaluating their toxicological effects helps ensure their safe use in humans and animals (Braga et al., 2021).

5.1 Bioavailability and Pharmacokinetics

The therapeutic potential of neem's major bioactive compounds, particularly azadirachtin and nimbolide, is limited by several pharmacokinetic challenges. These compounds have poor water solubility, are absorbed inefficiently in the gastrointestinal tract, and undergo rapid first-pass metabolism in the liver (Wang et al., 2016). As a result, when administered orally, only a small proportion of these triterpenoids reaches the bloodstream in an active form, leading to very low bioavailability and reduced therapeutic effectiveness.



5.2 Toxicological Assessment

Neem is generally considered safe for human consumption at moderate doses; however, it is not devoid of toxicity when misused (Braga et al., 2021).

Acute Toxicity: Aqueous leaf extracts exhibit a high margin of safety with an typically exceeding 5,000 mg/kg in murine models (Braga et al., 2021).

Reproductive Toxicity and Contraceptive Use: Traditional medicine has utilized neem oil as a vaginal spermicide and abortifacient. Consequently, systemic oral administration of concentrated neem extracts is contraindicated in pregnant women and those attempting to conceive.

Hepatotoxicity and Nephrotoxicity: High-dose, prolonged administration of crude neem extracts has shown mild, reversible elevations in liver transaminases (ALT, AST) in animal models (Braga et al., 2021).

6. Results and Discussion

6.1 Synthesis of Agricultural Efficacy Findings

A rigorous critical synthesis of empirical literature confirms that *Azadirachta indica* derivatives, specifically those enriched with azadirachtin A, offer unmatched advantages within integrated pest management (IPM) systems (Kilani-Morakchi et al., 2021). The quantitative evaluation of historical and current field trials indicates that botanical formulations containing standardized concentrations of azadirachtin (1,000 to 10,000 ppm) consistently achieve pest population reduction rates between 75% and 92% across various orders.

The primary driver of this high efficacy is the non-neurotoxic, poly-targeted mode of action. This multi-targeted mechanism radically attenuates the selection pressure for resistance mutations compared to synthetic neurotoxins (e.g., neonicotinoids).

6.2 Synthesis of Pharmacological and Therapeutic Data

From a pharmacological perspective, secondary metabolites isolated from *A. indica*—most notably nimbolide and gedunin—demonstrate significant therapeutic activity across oncological, inflammatory, and metabolic pathways (Saleem et al., 2018; Wang et al., 2016).

In oncology, nimbolide shows high cytotoxic potency against carcinoma lines. Mechanistic evaluations validate that this cytotoxicity operates via dual actions: (1) Direct suppression of the pathway, downregulating downstream anti-apoptotic gene networks (Wang et al., 2016), and (2) generation of reactive oxygen species that trigger mitochondrial outer membrane permeabilization, leading to cytochrome release and caspase activation (Liu et al., 2015).

6.3 Translational Bottlenecks and Critical Evaluation

Despite robust preclinical data, translational success into clinical therapeutics and standard agronomic practices remains hindered by three key challenges.

Phytochemical Heterogeneity and Standardization Deficits (addressed in Section 2.2) require comprehensive bio-fingerprinting via. Pharmacokinetic Limitations (addressed in Section 5.1) confirm that pure limonoids exhibit rapid hepatic first-pass metabolism, making oral bioavailability a major bottleneck (Wang et al., 2016). Finally, Safety and Toxicological Boundaries require strict warnings regarding spermicidal and anti-implantation activities (Braga et al., 2021).

6.4 Strategic Directions for Future Research

To bridge the gap between empirical discovery and industrial implementation, future research must focus on three core areas. Synthetic Biology must be leveraged to engineering host organisms for sustainable, high-yield bioproduction of complex limonoids (Veitch et al., 2007). Targeted Nano-Delivery systems (addressed in Section 3.3) must be refined to protect active ingredients and enhance tissue targeting. Finally, there is a glaring deficit in rigorous, Phase II/III human clinical trials; moving beyond murine models is mandatory to establish definitive pharmacodynamics, safe therapeutic windows, and clinically relevant dosing protocols for standardized neem formulations.

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