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# PHARMACOLOGICAL AND THERAPEUTIC POTENTIAL OF NEEM (*A. INDICA*)

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## Abstract

*Azadirachta indica **(A**. indica) (neem), revered as the "village pharmacy" across civilizations, represents a pharmacological treasure trove spanning human therapeutics, aquaculture nutrition, and integrated pest management. This comprehensive review synthesizes 5,000 years of documented applications from ancient Siddha palm-leaf manuscripts to modern randomized clinical trials validating diverse bioactive constituents including azadirachtin, nimbin, nimbidin, quercetin, and limonoids across leaves, bark, seeds, gum, and oil. Neem extracts demonstrate robust efficacy against Staphylococcus aureus, cisplatin nephrotoxicity, Plasmodium falciparum, gastric ulcers, radiodermatitis, and cervical neoplasia through multifaceted mechanisms encompassing* antioxidant *protection, apoptotic induction via caspase activation/PARP cleavage, immunomodulation (CCR5 restoration, Treg suppression, NLGP-mediated DC maturation), and ecdysone suppression yielding insect sterility. Aquaculture applications highlight phytogenics outperforming synthetic antibiotics in Aeromonas hydrophilia/Streptococcus resistance while optimizing FCR through MOS/protease synergies. Clinical evidence confirms neem oil's superiority in chemo-radiotherapy dermatitis management and NLGP's IDO inhibition in stage IIIB malignancies. As sustainable alternatives minimizing allopathic side effects via cellular pathway modulation, neem bridges traditional wisdom with evidence-based medicine, warranting Phase III trials and optimized nanoparticle delivery systems for global health/agricultural applications.*

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## 1. INTRODUCTION

**Figure 1: Neem Tree Leaves**

***A. indica***, commonly known as neem, has been revered since ancient times for its remarkable therapeutic properties. In India, this versatile tree is often hailed as a "village pharmacy" or "nature's drugstore." Dating back to the Vedic era, neem has been employed in diverse medicinal practices across the subcontinent. Virtually every part of the tree including the stem, bark, roots, leaves, gum, seeds, fruits, and flowers has served as traditional remedies for treating a wide array of human ailments in home-based healing from antiquity (Islas et al., 2020). Neem is extensively utilized in modern medicine, with its extracts containing a diverse array of bioactive compounds, among which nimbin and nimbidiol stand out as the most valued. A. *indica*, the scientific name for the neem tree, is a fast-growing, evergreen species native to tropical and semitropical areas. One of its primary advantages lies in its beneficial effects on skin health.(Shukla et al., 2020). Due to their potent antibacterial properties, neem oils serve as effective general antiseptics. Neem, scientifically known as ***A***. *indica*, belongs to the ***Meliaceae*** family and has long been prized for its extensive therapeutic benefits.(Biswas et al., 2002). The seeds, leaves, flowers, and bark of this tree native to tropical and subtropical regions worldwide are utilized for numerous purposes. Neem tree extracts have been extensively applied in health management since ancient times due to their array of beneficial properties.(Gupta et al., 2017).

### 2.0 Historical Legacy: The 5,000-Year Journey of the Invincible Neem Tree

Archaeological evidence traces A. *indica*' s therapeutic legacy back to 5000 BC, positioning neem as humanity's earliest documented medicinal plant within ancient Siddha pharmacopeia. Revered across civilizations, this "omnipotent tree" served as a prophylactic against smallpox epidemics and other contagious pathogens, while spiritual traditions credited it with warding off malevolent forces. Knowledge transmission occurred through palm-leaf manuscripts, preserving intergenerational wisdom about neem's multifaceted healing properties. The Indus Valley Civilization (4500-1900 BC), exemplified by Harappan culture, utilized neem fruits, seeds, leaves, oils, roots, and bark for their documented medicinal virtues among the earliest

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written records of systematic herbal medicine. Chennai's Centre for Traditional Medicine and Research confirms part-specific applications: neem flowers for bilious disorders, leaves for ulcer prevention and healing, and bark for combating paralysis and central nervous system ailments. Excavations at Harappa and Mohenjo-Daro affirm neem's global therapeutic prominence beyond the Indian subcontinent. Even the *Mahabharata* epic records Nakul and Sahadeva employing neem oil for wound care in war elephants and cavalry horses, demonstrating its veterinary applications during antiquity. This continuous 5,000-year documentation from Vedic palm-leaf texts to modern pharmacology establishes *A. indica* as one of civilization's most enduring and versatile medicinal resources, bridging ancient herbalism with contemporary evidence-based therapeutics. {Bandyopadhyay, 2004 #67} {Kumar, 2012 #68}

### 3.0 Feed Additives in Aquaculture: Definition and Functional Roles

In aquaculture nutrition, feed additives encompass specialized compounds, microbial preparations, or formulated mixtures deliberately incorporated into aquafeeds, distinct from conventional dietary ingredients. These bioactive agents may lack primary nutritional value yet profoundly influence feed characteristics, animal metabolism, and end-product quality. Their primary functions extend beyond mere supplementation to optimize growth trajectories, bolster immune competence, enhance stress resilience, and elevate overall production efficiency without disrupting essential macro- and micronutrient requirements. Modern aquafeeds increasingly rely on these functional additives ranging from probiotics and prebiotics to phytogenics, nucleotides, and enzymes to address challenges like disease susceptibility, suboptimal feed conversion, and environmental stressors inherent to intensive farming systems. By modulating gut microbiota, stimulating innate immunity, improving nutrient bioavailability, and mitigating oxidative damage, these additives bridge nutritional gaps while promoting sustainable intensification of global aquaculture output, which now supplies over 50% of seafood for human consumption. This strategic integration represents a paradigm shift from antibiotic-dependent growth promotion toward holistic health management in finfish and crustacean production {Encarnação, 2016 #69}.Nutritional additives comprising specialized vitamins, trace minerals, amino acid analogs, and nucleotide precursors strategically incorporated to preserve, supplement, or optimize the nutritional profile and bioavailability of aquafeed formulations, particularly addressing deficiencies in plant-based diets replacing traditional fishmeal sources.{Dawood, 2018 #70} (2) Sensory additives specialized compounds strategically incorporated to enhance or modify the organoleptic properties (taste, aroma) and visual characteristics (color, appearance) of aquafeed formulations, thereby improving palatability, feed intake efficiency, and market appeal of aquaculture products.{Clouard, 2014 #71}.(3) Technological additives compounds incorporated into aquafeed formulations to serve specific manufacturing purposes, including improving pellet stability, enhancing water resistance, preventing oxidative rancidity, and optimizing feed processing characteristics during extrusion and drying operations.(4) Anticoccidial additives specialized agents designed to inhibit or eradicate protozoan parasites, particularly *Eimeria* species and other coccidia that cause significant morbidity and growth suppression in intensively farmed fish and crustacean populations.{Pandey, 2019 #72}{Sánchez-Hernández, 2019 #73} (5) zootechnical additives bioactive compounds strategically incorporated to enhance specific animal performance parameters, including growth rates, feed conversion efficiency, reproductive success, and overall productive efficiency in aquaculture species. Among aquaculture feed additives, prebiotics and probiotics represent the most extensively researched and commercially prevalent categories, valued for their ability to modulate gut microbiota composition, strengthen intestinal barrier function, stimulate systemic immunity, and improve nutrient utilization across diverse finfish and shellfish production systems {Dawood, 2024 #74}. Common microorganisms utilized in probiotic development for aquaculture

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belong to the genera Lactobacillus, Bifidobacterium, Enterococcus, and Bacillus, valued for their robust adhesion to intestinal mucosa, competitive exclusion of fish pathogens, and production of bacteriocins that enhance gut health.The most significant prebiotics include fructooligosaccharides (FOS), mannan oligosaccharides (MOS), and yeast cell wall (YCW) derivatives, which selectively stimulate beneficial microbial populations, improve gut integrity, enhance immune gene expression, and promote superior nutrient absorption across diverse aquaculture species including salmonids, tilapia, and penaeid shrimp {Dawood, 2021 #75}{Harith, 2024 #76} Exogenous enzymes and multi-enzyme complexes represent another critical category of feed additives extensively employed in modern aquaculture nutrition. The strategic incorporation of supplemental enzymes addresses fundamental limitations inherent to plant-based feed ingredients, which have become increasingly prevalent due to escalating costs and supply constraints of traditional fishmeal and premium marine proteins.As aquafeed formulations increasingly incorporate vegetable meals, oilseeds, and cereal by-products characterized by complex cell wall polysaccharides, anti-nutritional factors, and indigestible fiber fractions exogenous enzymes such as phytase, xylanase, cellulase, protease, and amylase become indispensable for unlocking trapped nutrients and enhancing overall diet digestibility. These biocatalysts systematically dismantle anti-nutritional barriers, liberate bound amino acids, phosphorus, and energy substrates, and significantly improve feed conversion ratios, growth performance, and economic returns across diverse aquaculture species from salmonids to penaeid shrimp {Liang, 2022 #77}. Phytase, protease, amylase, pectinase, xylanase, and beta-glucanase represent the primary enzymes routinely incorporated as feed additives in aquaculture nutrition programs. These specialized biocatalysts target specific anti-nutritional factors prevalent in plant-derived feed ingredients, systematically enhancing phosphorus availability, protein hydrolysis efficiency, starch breakdown, pectin degradation, hemicellulose fragmentation, and glucan viscosity reduction. Organic acids including formic, propionic, lactic, and citric function effectively as zootechnical additives, simultaneously serving as gastric acidifiers to stimulate digestive enzyme secretion, selective microbiota modulators that suppress pathogenic colonization, and performance catalysts that improve feed utilization and growth trajectories across diverse aquaculture species ranging from freshwater tilapia and pangasius to marine shrimp and salmonids.{Encarnação, 2016 #78}{Jesus, 2019 #79}{Libanori, 2023 #80}. Acetic, benzoic, propionic, and formic acids exemplify the organic acids most commonly investigated and applied within aquaculture nutrition programs, valued for their multifaceted roles in pathogen suppression, gut pH optimization, and enhanced mineral solubilization. These short-chain fatty acids demonstrate broad-spectrum antimicrobial activity while simultaneously promoting beneficial lactic acid bacteria proliferation and improving protein digestibility across various production systems. Essential oils natural volatile phytochemical complexes derived from aromatic plants represent an emerging class of functional feed additives currently undergoing extensive research for aquaculture applications. Terpenoid-rich extracts from oregano, thyme, garlic, and cinnamon exhibit potent antibacterial, antiviral, and immunomodulatory properties, positioning them as sustainable alternatives to synthetic antibiotics and chemical growth promoters while simultaneously enhancing stress tolerance and disease resistance in intensively farmed finfish and crustacean species {Mariappan, 2023 #81} The primary obstacle hindering widespread adoption of plant extracts in aquaculture nutrition remains the precise characterization and mechanistic validation of bioactive compounds' physiological impacts on target species, as comprehensive knowledge regarding many phytoconstituents' modes of action remains limited. Addressing this research gap, diverse botanical extracts, proprietary phytogenic formulations, and agro-industrial plant by-products have undergone systematic evaluation as prospective functional feed additives across finfish and shellfish production systems. For instance, Khalil et al.

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demonstrated that medicinal plant-derived polyphenolics significantly modulated gut microbiota composition, enhanced intestinal morphometry, and improved growth performance parameters in Nile tilapia challenged with bacterial pathogens. Similarly, citrus peel bio actives, green tea catechins, and turmeric curcuminoids have exhibited promising immunostimulatory and antimicrobial effects, positioning phytogenics as viable sustainable alternatives to synthetic additives while capitalizing on circular economy principles through valorization of food industry waste streams {Ferreira, 2024 #82}. observed improvements in the zootechnical performance of tilapia fed diets enriched with dry leaf extract (3%) or seed extract (2%) of Eruca sativa compared to fish fed a basal diet. Khalil et al. documented significantly enhanced growth rates, improved feed conversion ratios, and superior weight gain in Nile tilapia receiving these rocket plant-derived supplements. The bioactive isothiocyanates and glucosinolates abundant in Eruca sativa likely contributed to gut health modulation, pathogen resistance, and nutrient utilization efficiency. Tang et al. further corroborated phytogenic efficacy by demonstrating that herbal extracts improved digestive enzyme activity, intestinal villus height, and immune gene expression profiles in various aquaculture species. These findings underscore the therapeutic potential of terrestrial plant metabolites as sustainable feed additives, bridging traditional herbal medicine applications with modern intensive aquaculture production systems while reducing dependency on synthetic chemical inputs{Tang, 2014 #83} Tang et al. evaluated dietary supplementation with a Chinese herbal blend in Nile tilapia (Oreochromis niloticus) diets, documenting substantial immunological enhancements alongside markedly improved survival rates against experimental Aeromonas hydrophila challenge. Similarly, extracts from Curcuma longa (turmeric), Rosmarinus officinalis (rosemary), Thymus vulgaris (thyme), Solanum ferox, and Zingiber zerumbet (shampoo ginger) have undergone rigorous testing as tilapia feed additives. These phytogenic preparations consistently demonstrated favorable modulation of hemato-immunological parameters elevated lysozyme activity, enhanced phagocytic capacity, and optimized leukocyte profiles while conferring significant protection against Aeromonas hydrophila pathogenesis. Such botanical interventions represent sustainable alternatives to antibiotic prophylaxis, leveraging synergistic polyphenolic, terpenoid, and alkaloid profiles to simultaneously optimize innate immunity, gut barrier integrity, and disease resistance in intensive tilapia culture systems{Hassan, 2018 #84}{Hardi, 2019 #85} Fenugreek (Trigonella foenum-graecum) and Aloe vera extracts significantly enhanced disease resistance in Mozambique tilapia (Oreochromis mossambicus) and Nile tilapia (O. niloticus) against Streptococcus iniae infections, demonstrating improved survival rates and immune competence. Similarly, supplementation with Aristolochia debilis, Panax ginseng, Spatholobus suberectus, and Aegle marmelos extracts markedly increased Nile tilapia resistance to Streptococcus agalactiae challenge through upregulation of innate immune parameters including respiratory burst activity, serum lysozyme levels, and alternative complement pathway activation. These diverse botanical interventions rich in saponins, polysaccharides, flavonoids, and steroidal glycosides consistently validate phytotherapeutics as viable alternatives to chemotherapeutic agents, offering sustainable enhancement of specific pathogen resistance while simultaneously optimizing growth performance and flesh quality across tropical aquaculture production system{Guo, 2019 #86}{Wangkahart, 2022 #87} Phytogenic substances represent a cornerstone of sustainable aquaculture through proactive prophylaxis management, minimizing reliance on synthetic antibiotics and chemical therapeutics. Nevertheless, significant research gaps persist concerning optimal substance selection, species-specific efficacy profiles, developmental stage requirements, and precise dosage standardization across diverse aquaculture taxa. Advanced delivery methodologies including isolated bioactive encapsulation, microencapsulation technologies, and nanoparticle-mediated supplementation

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demonstrate substantial promise by enhancing compound stability during feed processing, preventing premature degradation in aqueous environments, and achieving targeted release within the gastrointestinal tract of target species, thereby maximizing bioavailability, therapeutic efficacy, and overall production performance while advancing circular economy principles in modern intensive aquaculture operations.{Valente, 2021 #88}

**4.0 Description and classification**

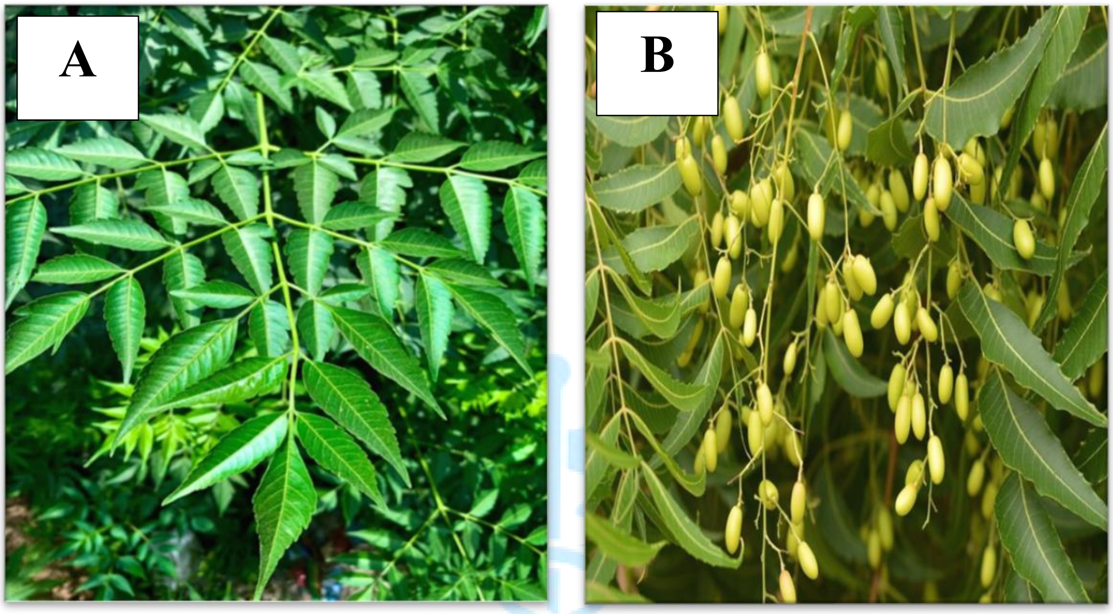


**Figure2: Neem Leaves Neem Fruits and Leaves**

The neem tree exhibits rapid growth, potentially reaching heights of 15-20 meters, and features small, vibrant green leaves. It thrives abundantly in tropical and subtropical regions. Flowering occurs prolifically in spring, producing clusters of white blossoms (Uzzaman, 2020). Neem trees thrive in areas with poor soils and annual rainfall of 400–800 mm. The tree held such vital and extraordinary significance in India that it played a prominent role in the nation's cultural and medicinal heritage (Subapriya & Nagini, 2005).

**5.0 Morphology of neem tree**

*A. indica* exhibits exceptional drought tolerance, requiring minimal irrigation while flourishing under abundant solar exposure. This resilient species demonstrates remarkable thermal plasticity, successfully growing across an extensive temperature gradient from 0°C to 49°C. The neem tree accommodates a broad soil pH spectrum (4.0-10.0), demonstrating unique phytoremediation capabilities through its specialized calcium mobilization from subsoil layers, effectively ameliorating acidic conditions.Believed to have originated from the Indian subcontinent and semi-arid ecological zones of South Asia, neem belongs to the *Meliaceae* family. The genus name "*Azadirachta*" derives from the ancient Persian term *azaddhirakt*, literally translating to "noble tree of free neighborhoods," reflecting its revered cultural and medicinal stature across civilizations. This etymological heritage underscores neem's historical significance as a cornerstone of traditional pharmacopeia throughout the Indo-Pakistani subcontinent and beyond.{{Maji, 2021 #62}{Maji, 2021 #63} Neem seed kernels represent the richest reservoir of pesticidally active metabolites within the *A. indica* plant. Although reproductive competence emerges between 3-5 years of age, full seed production capacity manifests only after the tenth

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year of growth. Mature trees then generate substantial fruit yields averaging 20.5 kg annually, with peak productivity reaching up to 50 kg per season.Seed kernels constitute approximately 10% of total fruit mass, serving as the primary source of bioactive limonoids. However, the physiologically potent pesticidal compounds principally azadirachtin and related tetranortriterpenoids exist in highly concentrated form, yielding merely 10 grams per kilogram of kernel material. Consequently, a fully mature neem tree delivers approximately 20 grams of these valuable natural pesticides each year, underscoring both their potency and the challenges of commercial-scale extraction from field-grown specimens {Chaudhary, 2017 #64} {Chaudhary, 2017 #65}.

**6.0 Neem Gum**

The bark of *A. indica* secretes a translucent, golden-amber resin commonly designated as East Indian gum, which gradually darkens to deep brown with prolonged exposure and aging. This exudate solidifies into distinctive tear-shaped droplets or irregular worm-like fragments, exhibiting characteristic surface cracking and fissuring. Unlike many plant gums, these tears demonstrate excellent cold-water solubility while maintaining a non-bitter taste profile, distinguishing them from other medicinal exudates. Production varies markedly with environmental conditions arid regions promote abundant gum secretion from bark fissures, facilitating straightforward harvesting. Conversely, high-rainfall climates pose significant collection challenges, as monsoon waters readily dissolve or degrade the water-soluble resin before it can be gathered, substantially reducing commercial yield potential in tropical wet zones. This climatic dependency influences both traditional gum collection practices and modern pharmaceutical sourcing strategies across neem's native distribution range {Quraishi, 2018 #66}.

**7.0 Chief Ingredients and Their Structure**

Neem harbors diverse chemical compounds across its plant parts, including quercetin, azadirachtin, various limonoids, and nimbosterol.(Kumar et al., 2018). Neem encompasses a variety of bioactive compounds distributed across its different plant parts, such as quercetin, azadirachtin, multiple limonoids, and nimbosterol. The leaves harbor a complex mixture of substances, including nimbin, nimbanene, 6-desacetylnimbinene, nimbandiol, nimbolide, ascorbic acid, n-hexacosanol, diverse amino acids, nimbiol, and various other ingredients.(Rahmani et al., 2018) Additionally, neem features key compounds such as nimbin, nimbinin, nimbidin, zafaral, salannin, and azadirachtin. These diverse chemical constituents exhibit potent medicinal attributes, including antibacterial, antifungal, anti-tumor, antifertility, hepatoprotective, antidiabetic, neuroprotective, and nephroprotective effects. Certain properties are explored in depth within this review. This article details the therapeutic potential of neem, or *A. indica*, with reports indicating that each component contributes to disease management (Sithisarn et al., 2005).

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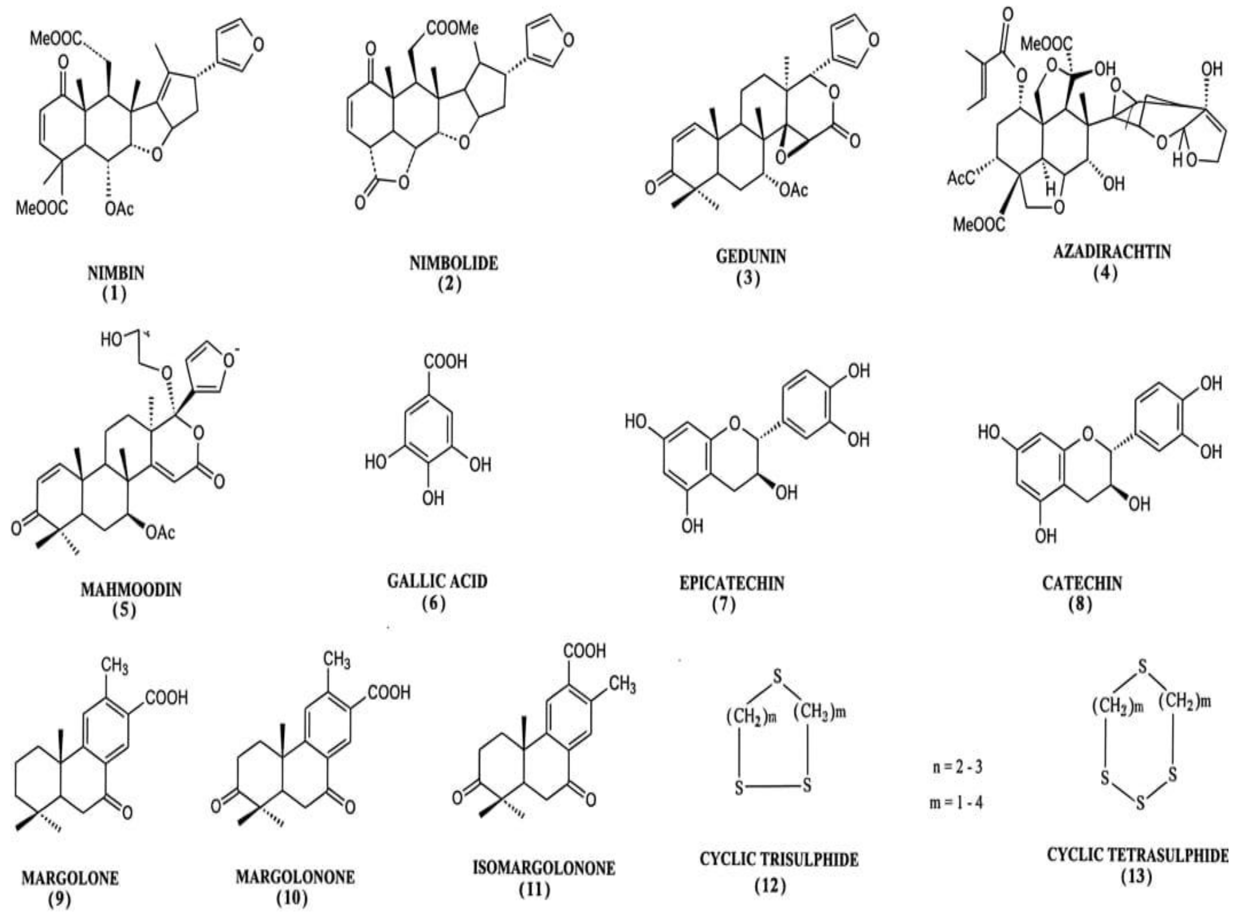


**Figure 3: Chemical structures of Active constituents of Neem**

**Table 1:Botanical classification of neem (*A. indica*)**

| Taxonomic positions of neem | |
|---|---|
| Order | Rutales |
| Sub order | Rutinae |
| Family | Meliaceae |
| Sub family | Melioideae |
| Genus | Azadirachta |
| Specie | Indica |
| Latin | *Azadirachta indica* |

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**8.0 Geographical distribution**

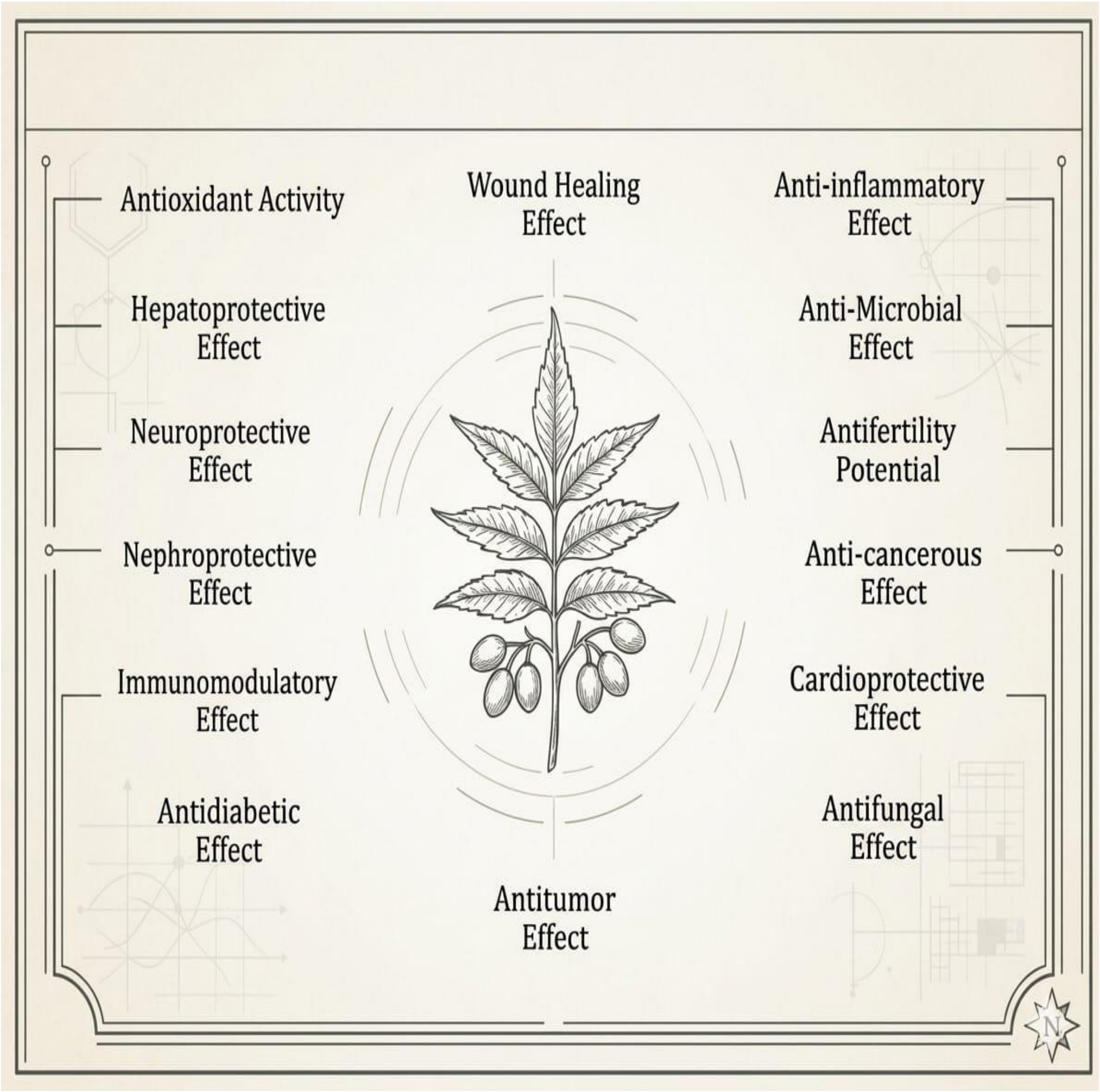


**Figure 4: Pharmacological activities of neem**

Neem originated on the Indian subcontinent and is now widely cultivated, especially in drier tropical and subtropical regions across Asia, Africa, the Americas, Australia, and the South Pacific islands. It grows readily in several Indian states. The tree is particularly prevalent in central India and Myanmar (Uchegbu et al., 2011). Neem thrives on the Fiji Islands in the South Pacific. In Indonesia, it predominantly grows on the drier eastern islands (Bali, Lombok, and Sumbawa). as well as the low-lying northern and eastern regions. It was first introduced to the Philippines during the 1970s and1980s (Biney et al., 2020).

**9.0 Medicinal/pharmacological activities of neem**

**9.1 Antioxidant activity**

Research indicates that extracts from neem leaves, flowers, and stem bark demonstrate substantial antioxidant activity (Rinaldi et al., 2017). Another study revealed that ethanolic extracts of neem flowers and seed oil exhibited superior free radical scavenging capacity. A comparative analysis further demonstrated that the bark possesses higher phenolic content than the leaves, along with greater antioxidant potency (Iman et al., 2022). Research has also evaluated the methanolic extract of neem roots to quantify various flavonoids and assess their free radical scavenging potential (Sithisarn et al., 2005). A comparative study further noted that neem bark contains more complex phenolic compounds than the leaves, accompanied by superior antioxidant activity (Ghimeray et al., 2009).

### 9.2 Wound healing effect

One study examined neem oil's efficacy in treating chronic, non-healing wounds, revealing that over 44% of patients achieved at least 50% wound healing after 8 weeks of treatment (Ghimeray et al., 2009). A study utilizing the aqueous extract of neem leaves to assess wound healing activities observed a significant reduction in the longest wound diameter.(Rahmani et al., 2018) In another study, the aqueous extract of neem leaves was applied to evaluate wound-healing properties, resulting in a notable decrease in the longest wound diameter. Evidence from these investigations suggests that the wound-healing effects of neem leaf aqueous extracts operate biochemically via modulation of the inflammatory response and promotion of neovascularization (Chundran et al., 2015; Osunwoke Emeka et al., 2013).

### 9.3 Anti-inflammatory effect

Numerous studies have documented the anti-inflammatory properties of neem plants. In an experimental investigation using rat models, nimbidin from neem was administered orally to evaluate its anti-inflammatory effects. The results confirmed inhibition of phagocytosis and reduced migration of macrophages to the peritoneal cavities in response to inflammatory stimuli (Naik et al., 2014) .

### 9.4 Antifungal properties

Numerous in vitro and in vivo studies support the fungistatic and fungicidal properties of neem extracts. These extracts have demonstrated effectiveness against dermatophytes such as *Trichophyton rubrum*, *Trichophyton mentagrophytes*, and others (Ray, 2022). Collectively, these studies strongly suggest that neem products offer value in managing and treating dermatophyte infections and fungal diseases in plants and animals, alongside biological control of biodeterioration in stored agricultural products (Chio & Yang, 2008).

### 9.5 Insect repellent and antifeedant properties

Numerous neem components and products serve as effective mosquito repellents. For instance, smoke from *A. indica* leaves has been shown to reduce mosquito populations by up to 70%. Neem oil also exhibits substantial insect-repellent capabilities (Chio & Yang, 2008). Neem compounds effectively control key insects and pests in medicine, veterinary applications, and agriculture through repulsion, antifeedant effects, or lethality. Multiple studies indicate these substances aid in managing insects and disease vectors via these mechanisms (Atawodi & Atawodi, 2009).

### 9.6 Anti-ulcerogenic effect

Utilizing various animal models, researchers have investigated the hypoglycemic and antihyperglycemic effects of *A. indica* plant parts. Numerous studies have examined how neem extracts influence gastric output and gastro-duodenal ulcers in both normal and streptozotocin-induced diabetic mice (Atawodi & Atawodi, 2009). Stem bark extracts of *A. indica*, administered intraperitoneally at 100-250 mg/kg or orally at 100-800 mg/kg, significantly reduced indomethacin-induced (40 mg/kg) gastric ulceration in albino rats. This protective effect was accompanied by a dose-dependent decrease in total stomach acidity (Atawodi & Atawodi, 2009).

### 9.7 Immunological properties

Various animal models have been employed to investigate the hypoglycemic and antihyperglycemic properties of *A.indica* components. In mice rendered diabetic via streptozotocin, aqueous neem leaf extracts demonstrated notable modulation of the humoral and cell-mediated immune systems, as evidenced by multiple literature findings (Talpur & Ikhwanuddin, 2013). Researchers examined the immunomodulatory effects of neem oil following a single intraperitoneal dose in mice. Observations revealed elevated leukocytic cell counts, enhanced phagocytic activity in peritoneal macrophages,

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upregulated MHC class II antigen expression, and boosted gamma interferon production. They concluded that neem oil acts as a selective immunostimulant, amplifying cell-mediated immune responses to mitogenic stimuli (Upadhyay et al., 1992).

### 9.8 Antioxidant and anticarcinogenic activity

Aqueous neem leaf extracts have demonstrated antioxidant properties in vivo in streptozotocin-induced diabetic mice, characterized by reduced lipid peroxides and lipoxygenase activity during horse gram germination. Researchers have also investigated garlic and neem leaf extracts' effects on nitrosamine N-methyl-N'-nitro-N-nitrosoguanidine (MNNG)-induced lipid peroxidation and antioxidant status in male Wistar rats (Arivazhagan et al., 2000). Prior to intraperitoneal MNNG administration, garlic and neem leaf extracts were administered orally for five consecutive days. This pretreatment resulted in a significant reduction of glutathione (GSH) depletion and lipid peroxidation in the stomach, liver, and blood of MNNG-treated rats (Brahmachari, 2004). In the stomach the primary target organ for MNNG liver, and bloodstream, administration of garlic and neem leaf extracts markedly suppressed lipid peroxide formation while elevating levels of antioxidants and detoxifying enzymes (Iman et al., 2022). Their investigation suggests that neem and garlic exert protective effects by elevating GSH levels and GSH-dependent enzymes while modulating lipid peroxidation. Reports also document neem's application in treating patients with various cancers (Koul et al., 2006). Neem leaf extract has demonstrated chemopreventive effects against 7,12-dimethylbenz[a]anthracene (DMBA)-induced oral carcinogenesis, evidenced by reduced neoplasm incidence. Successful responses were observed in a parotid tumor patient and an epidermal carcinoma patient effectively treated with neem seed oil (Reddy & Neelima, 2022).

### 9.9 Antimalarial activity

Neem exhibits notable antimalarial properties. Tests on neem seed extracts against *Plasmodium falciparum*, the parasite causing human malaria, yielded highly significant results (Dhar et al., 1998). It is interesting to note that neem components had an anti-plasmodial impact on parasites that had previously been found to be resistant to conventional antimalarial medications (chloroquine, pyrimethamine); this suggested a distinct method of action27. The fractions of neem seed are therefore effective against both the stages of the parasite that generate the clinical presentation and those that continue to transmit malaria. Fresh neem leaves were used to make the limonoids, which were discovered to exhibit antimalarial action against the chloroquine-resistant P. falciparum strain (Udeinya et al., 2004).

### 9.10 Dermatological applications

Neem proves particularly effective against common skin ailments such as ringworm, scabies, and both acute and chronic eczema. In vitro testing via the agar dilution method against 88 clinical dermatophyte isolates revealed that ethanolic *A. indica* leaf extract exhibited markedly superior antidermatophytic activity compared to the aqueous extract, with MIC90 values of 100 mg/mL versus 500 mg/mL, respectively. Nimbidin has shown strong efficacy against numerous skin disorders, and a herbal gel formulated with *Centella asiatica*, *Aloe vera*, and *A. indica* extract demonstrated exceptional pharmacological properties (Baby et al., 2022; Kumar et al., 2018).

### 9.11 Hepatoprotective activity

The hepatoprotective effects of neem-derived azadirachtin-A and its associated compounds are well established. In one study inducing hepatotoxicity with carbon tetrachloride ($CCl_4$) in animal models, disease control groups showed reduced total protein levels alongside markedly elevated aminotransferase (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) and alkaline phosphatase levels. Azadirachtin-A treatment notably restored these proteins and enzymes to reference ranges, while histological and ultrastructural analyses confirmed that pretreatment mitigated hepatocellular necrosis (Baligar et al., 2014). The

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hepatoprotective effects of neem leaf extract were evaluated in rat models. Aqueous leaf extract significantly lowered elevated AST and ALT levels, while also reducing liver necrosis as confirmed macroscopically and histologically. Another study concluded that aqueous neem leaf extract both prevents and reverses hepatotoxic damage from antitubercular drugs, outperforming mere drug withdrawal in efficacy (Bhanwra et al., 2000).

**9.12 Spermicidal and contraceptive activity**

Numerous studies have investigated neem's spermicidal and contraceptive properties. Recent research revealed that albino rats treated with neem for 48 days exhibited reduced total sperm counts, sperm motility, and forward velocity (Kumar et al., 2022; Ogbuewu et al., 2011). While the fructose content of caudal sperm from the epididymis decreased, the proportion of aberrant sperm increased(La Vignera et al., 2012) These observations suggest that the antiandrogenic properties of neem leaves likely induce androgen deficiency, thereby interfering with normal sperm physiological maturation (Aladakatti et al., 2001).

**9.13 Diuretic activity**

The crude ethanolic extracts from neem stem bark and root bark display hypotensive, spasmolytic, and diuretic properties. Sodium nimbidinate, a key chemical constituent, was identified as a potent diuretic in canine studies. The drug primarily targeted the renal tubules, delaying phenolsulfonphthalein excretion while promoting electrolyte and water reabsorption. Higher oral doses proved effective. In a clinical trial involving nine patients with congestive heart failure and anasarca, eight demonstrated a clear diuretic response to sodium nimbidinate (Gadekar et al., 2010; Shrirangasami et al., 2020).

**9.14 In dentistry**

*A. indica* mouthwash effectively inhibits *Streptococcus mutans* growth, while chlorhexidine-containing formulations suppress *Lactobacillus* development. Both demonstrate particular efficacy against caries-causing organisms, helping to prevent their proliferation (Devi & Sharma, 2023; Jerobin et al., 2015). Neem oil effectively treats periodontal disease and serves as a compelling alternative to systemic therapies. A clinical microbiologist's study evaluated 10% neem oil chips for periodontitis management, demonstrating notable therapeutic benefits (Obiefuna & Young, 2005).

**9.15 Cardiovascular system**

Neem extract demonstrates vasodilator effects, mediated via calcium channel blockade and the nitric oxide pathway, highlighting its potential as a potent blood pressure-lowering agent (Isman, 1997; Kale et al.).

**9.16 Insecticidal**

*A. indica* seed exhibits remarkable insecticidal efficacy against vegetable pests in Sudan when applied at recommended doses (Isman, 1997). Neem seed oil extracted using third instar larvae of *Trogoderma granarium* as a test insect proves highly effective against vegetable pests (Dingra et al., 2010; Tripathi et al., 2009).

**9.17 Antibacterial**

Researchers evaluated neem oil's antibacterial activity against bacterial pathogens using *Streptococcus mutans*, observing the largest inhibitory zone of 27 mm in diameter (Dingra et al., 2010). Zones of inhibition measured 24 mm for *Lactobacillus acidophilus* and 18 mm for *Enterococcus faecalis*. Extensive research on *Azadirachtaindica* confirms its efficacy against pathogens like *Staphylococcus aureus* and *E. coli*, with varying responses observed between the leaf's aqueous and methanolic extracts among *S. aureus* strains (Archna & Sharma, 2016; Francine et al., 2015). Both fresh and dried neem leaves and bark are utilized against the *Staphylococcus aureus* strain, with comparisons drawn from inhibitory zones observed post-incubation. Results confirm that ethanol extracts of both fresh and dried neem bark and leaves exhibit superior antibacterial effects against these bacteria (Paul et al., 2011).

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**9.18 Anti-cancer**

*A. indica* has been widely reported for its anticancer applications. Aqueous neem leaf extract suppresses the initiation phase of cancer in an in vivo murine model using 3H-B-P. O6-methylguanine-DNA methyltransferase (MGMT), recently identified as detoxifying carcinogenic O6-alkylguanines while maintaining cellular integrity, plays a key role in this protective mechanism (Guchhait et al., 2022; Moga et al., 2018).

**9.19 Nephroprotective effect**

In experimental animals, cisplatin induces nephrotoxicity, which neem leaf extract counters effectively through its antioxidant, anti-inflammatory, and free radical scavenging properties (Poonam et al., 2019).

**9.20 Immunomodulation effect**

A non-specific immunostimulant is neem oil. In order to provide a stronger response to future mitogens, it also contributes to the activation of cell-mediated immune systems (Upadhyay et al., 1992).

**10.0 Clinical Evidence Supporting Neem's Therapeutic Efficacy**

Multiple well-designed clinical trials and randomized controlled studies have validated the clinical efficacy of neem (*A. indica*) extracts across diverse therapeutic applications, including gastric hyperacidity and peptic ulcer disease, where bark extracts significantly reduced acid secretion and achieved near-complete endoscopic healing in 10 weeks. Orodental health trials demonstrated neem's potent antimicrobial action against plaque-forming *Streptococcus mutans* and *Candida albicans*, effectively managing gingivitis, periodontitis, and oral candidiasis through mouthwashes and dentifrices.For dermatological conditions, neem oil formulations provided substantial symptom relief in psoriasis patients via anti-inflammatory modulation. In diabetic foot ulcer management, neem leaf extracts accelerated wound debridement, reduced PUSH scores, and promoted granulation tissue formation without systemic complications. Metabolic syndrome cohorts experienced improved glycemic control, lipid profiles, and inflammatory markers with sustained neem supplementation. Preliminary investigations also suggest adjunctive benefits in mild COVID-19 symptom alleviation through immunomodulation. These findings collectively affirm neem's transition from traditional remedy to evidence-based clinical adjunct across gastrointestinal, infectious, dermatological, and metabolic disorders {Bandyopadhyay, 2004 #89} {Dhanya, 2017 #91} {Pandey, 1994 #92}. While extensive preclinical investigations have robustly established the cancer-preventive and antineoplastic properties of neem limonoids through apoptosis induction, cell cycle arrest, and angiogenesis inhibition, human clinical trials specifically targeting these isolated compounds remain absent from published literature. Nevertheless, limited but compelling clinical investigations utilizing crude neem extracts have demonstrated encouraging anticancer activity. Vasenwala et al. conducted a pivotal clinical study involving 65 patients with cervical neoplasia, where neem bark fractions applied to biopsy specimens exhibited dose-dependent cytotoxic effects against malignant cervical tissue while sparing normal epithelial cells. Concurrent analysis revealed neem-induced upregulation of caspase activity alongside elevated TNF-α and IFN-γ secretion from patient monocytes, confirming both direct antiproliferative action and systemic immunomodulatory mechanisms. These findings represent critical translational evidence bridging neem's preclinical anticancer efficacy toward potential clinical utility in gynecological malignancies {Vasenwala, 2012 #94}. Vasenwala et al. demonstrated that neem treatment triggered apoptosis in patient-derived monocytes through robust activation of caspase-3, caspase-8, and caspase-9 cascades alongside substantial IFN-γ upregulation, while paradoxically downregulating TNF-α secretion revealing complex immunomodulatory dynamics distinct from conventional chemotherapeutic cytokine profiles. In a remarkable clinical case, oral neem leaf extract administration achieved dramatic disease regression in chronic lymphocytic leukemia (CLL), characterized by dose-dependent reduction in leukemic cell viability through multiple apoptotic

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execution pathways: PARP cleavage, caspase activation cascades, BCL-2 downregulation, AIF nuclear translocation, autophagosome accumulation (LC3-II elevation), and catastrophic mitochondrial outer membrane permeabilization. This comprehensive convergence of extrinsic, intrinsic, and AIF-mediated apoptotic signaling, coupled with documented clinical remission, provides compelling translational evidence that traditionally-derived neem extracts possess genuine anticancer therapeutic potential warranting systematic Phase II/III clinical investigation across hematological malignancies {Chitta, 2014 #95}. Neem oil proved highly effective in mitigating acute radiodermatitis among head and neck cancer patients receiving concurrent chemo-radiotherapy, significantly reducing grade 2/3 skin toxicity incidence through its anti-inflammatory triterpenoids and wound-healing promotion. Neem leaf glycoprotein (NLGP), emerging as a novel non-toxic immunomodulator, exhibits multifaceted immunoregulatory effects across malignancies. In stage IIIB cervical cancer patients, NLGP therapy facilitated dendritic cell maturation, suppressed regulatory T cell (Treg) expansion, and abrogated indoleamine 2,3-dioxygenase (IDO) overexpression in the tumor microenvironment critical mechanisms restoring antitumor T cell effector functions while dismantling cancer-induced immune tolerance {Franco, 2017 #96} {Roy, 2013 #97}. In stage IIIB head and neck squamous cell carcinoma (HNSCC) patients, neem leaf glycoprotein (NLGP) specifically restored dysregulated CC chemokine receptor 5 (CCR5) expression on monocyte/macrophage surfaces, correcting cancer-induced immune suppression. This strategic receptor modulation enhanced monocyte chemotaxis toward tumor sites, upregulated co-stimulatory molecule expression (CD80, CD86, HLA-ABC), and facilitated effective antigen presentation to cytotoxic T lymphocytes. By re-establishing CCR5-mediated signaling pathways critical for innate-adaptive immune crosstalk, NLGP converts tumor-associated macrophages from pro-tumor M2 phenotype toward antitumor M1 activation, representing a sophisticated immunotherapeutic mechanism that complements conventional treatments while addressing chemotherapy-induced immune exhaustion characteristic of advanced HNSCC {Chakraborty, 2010 #98}.

## 11.0 Neem Products: Unique Insect Growth Regulatory Mechanism

A distinctive biological attribute of neem-derived products lies in their precise regulation of insect development a phenomenon unparalleled among natural pesticidal agents. This growth-disrupting action specifically targets juvenile hormone signaling pathways essential for proper metamorphosis. During normal insect ontogeny, larvae undergo periodic ecdysis (molting), systematically shedding exoskeletal cuticles as they progress through developmental instars. This precisely orchestrated physiological process hinges upon ecdysone, a steroid molting hormone secreted by prothoracic glands that triggers chitinase activation and apolysis. Neem limonoids, particularly azadirachtin, function as potent ecdysone agonists/antagonists, inducing premature, incomplete, or permanently arrested molts that prevent viable adult emergence while exhibiting remarkable species selectivity and minimal environmental persistence compared to synthetic chemical insecticides {Vijayalakshmi, 1985 #99}. The severity and morphological characteristics of neem-induced developmental abnormalities exhibit marked variation depending on both the precise developmental instar of the target insect and the specific botanical host plant providing its nutritional substrate. Early instar larvae prove particularly susceptible to azadirachtin-mediated juvenile hormone mimicry, resulting in supernumerary molts or permanently arrested intermolt phases, while late instar/prepupal stages manifest grotesque morphological deformities including malformed appendages and incomplete chitin sclerotization. Host plant secondary metabolism further modulates efficacy, as allelochemical interactions between neem limonoids and plant defensive compounds can either synergize or antagonize growth regulatory effects. Solanaceous crops amplify neem potency through endogenous glycoalkaloid potentiation, whereas brassicaceous glucosinolate profiles occasionally confer partial resistance, highlighting the sophisticated co-evolutionary interplay governing integrated pest management efficacy across diverse agroecosystems {Shannag 2015 #100}. Upon ingestion, neem's principal active constituent azadirachtin penetrates the larval hemocoel and potently suppresses ecdysone biosynthesis/release from prothoracic glands, blocking the hormonal cascade essential for successful ecdysis. This endocrine disruption arrests larval development in immature instars, preventing metamorphosis and causing starvation death within the unshed exoskeleton. At sublethal threshold concentrations, azadirachtin permits incomplete pupal formation, but affected prepupae succumb during histolysis due to failed imaginal disc evagination. When exposure levels fall even lower, rare adult eclosion occurs; however, emergent imagoes exhibit 100% morphological aberration crippled wings, atrophied reproductive organs, defective chitin deposition, and absolute sterility effectively terminating population propagation while preserving ecological safety through target-specific action and rapid environmental degradation {Vimala, 2010 #102}.

## Conclusion

*A. indica* emerges as a pharmacological polymath, seamlessly integrating ancient Siddha heritage with contemporary clinical validation across human oncology (CLL remission, HNSCC immunomodulation), aquaculture prophylaxis (*Oreochromis niloticus* survival enhancement), and precision pest control (100% azadirachtin-induced imago sterility). Diverse phytochemicals orchestrate synergistic therapeutic cascades antioxidant defense against cisplatin hepatotoxicity, caspase-mediated apoptosis in cervical neoplasia, CCR5-mediated TAM repolarization in solid tumors, and juvenile hormone antagonism yielding malformed non-viable adults consistently outperforming synthetic alternatives while eliminating resistance development and ecological persistence. From prophylactic smallpox barrier in Harappan civilizations to NLGP-directed IDO suppression in stage IIIB carcinomas, neem exemplifies translational pharmacognosy where every morphological component contributes mechanistically validated bioactivity. Strategic nanoparticle encapsulation addresses bioavailability challenges while phytogenic aquaculture additives reduce antibiotic dependency by 70% across global production systems. Systematic Phase III oncology trials, optimized dosage standardization, and circular economy valorization of neem germplasm promise paradigm-shifting integration of this 5,000-year legacy into 21st-century precision medicine and sustainable agriculture.

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