

# Antimicrobial Properties of Neem (*Azadirachta Indica*): A Comprehensive Review of Phytochemicals and Mechanisms of Action

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## ABSTRACT

*Azadirachta indica*, commonly known as neem, is a well-recognized medicinal plant which is utilized for its antimicrobial, antifungal, and antiviral actions. Neem is mainly used in the Asian continent (India, China, etc.). Neem's potent antibacterial, antifungal, and antiviral properties are due to its diverse array of phytochemicals, which include limonoids (azadirachtin, nimbin, nimbidin), flavonoids (quercetin, kaempferol), tannins, and triterpenoids. These compounds act by several mechanisms, including disrupting microbial cell membranes, inhibiting vital metabolic enzymes, preventing biofilm formation, and inducing oxidative stress in pathogens. Neem extracts have shown promising inhibition against several microbial strains, including *Candida albicans*, *Escherichia coli*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*. The review concludes that neem is a promising candidate for developing safe, effective, and eco-friendly antimicrobial agents. However, further clinical studies, standardization, and regulatory validation are required. Future research should focus on targeted delivery systems, synergistic studies with conventional drugs, and its role in combating antimicrobial resistance (AMR). The main objective of this review is to study the botanical description, phytoconstituents and anti-microbial activity (anti-fungal, anti-viral, etc.) of neem.

**Keywords:** Neem, Anti-microbial, Infections, Phytochemical, *Azadirachta indica*

## INTRODUCTION

Infectious illnesses caused by microbes such as bacteria, fungi, viruses, and parasites have accounted for most of the world's mortality and morbidity. The accelerated development of antimicrobial resistance (AMR) [1] has eroded the effectiveness of conventional antimicrobial therapy over time. The development of multidrug-resistant (MDR) pathogens over time has spawned an urgent need for new treatment techniques, especially those from natural origins with low tendencies for developing resistance. Natural sources, in this case, medicinal plants, have gained increasing attention as possible origins of bioactive compounds showing antimicrobial action [2]. One such crop that has exhibited tremendous potential as an antimicrobial agent is *Azadirachta indica*, commonly referred to as neem. Neem, native to the Indian subcontinent, has been used for centuries in traditional medicine for the treatment of various conditions, including fevers, infections, and

inflammations [3]. Due to its extensive use in rural regions for the treatment of a variety of medical conditions, it is also referred to as the "village pharmacy" [4]. Neem contains a variety of bioactive compounds, including flavonoids, alkaloids, phenolics, and triterpenoids (e.g., azadirachtin), many of which possess potent antimicrobial activity [5,6]. Neem extracts have been reported to possess a broad spectrum of antibacterial, antifungal, antiviral, and antiparasitic activities [7]. These activities are attributed to a variety of mechanisms, including enzyme inhibition, protein and nucleic acid synthesis interference, and disruption of microbial cell membranes [8]. The clinical use of neem-derived antimicrobial therapies remains limited in spite of promising results from in vitro and in vivo studies due to problems with toxicity, bioavailability, and standardization [9]. This review seeks to consolidate what is known about neem's antimicrobial effects, emphasizing its active phytochemicals, modes of

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action, and possible use as a therapeutic substitute for treating infectious diseases.

### Botanical description:

*Azadirachta indica* is a rapidly growing, evergreen tree belonging to the family Meliaceae. Neem is native to the Indian subcontinent but due to its multifaceted medicinal and ecological benefits, it is now cultivated on a large scale in tropical and subtropical regions of the globe. Neem typically grows to a height of 15 to 20 meters and bears a dense canopy of dark green leaves. Its leaves are pinnate

with leaflets that are oblong and possess a very distinctive, strong aroma. It has yellowish fruit containing oily seeds and minute white flowers. Its bark is coarse and grayish-brown, but the most common parts used in medicine are its seeds and leaves [10,11]. Neem is a superior crop for agroforestry systems and pest control in the natural environment since it is insect-resistant and naturally well-suited to dry, arid climates. Due to its richness and widespread application in traditional medicine for various ailments, the tree is often referred to as the "village pharmacy" [12].



Figure 1: Neem leaves (*Azadirachta indica*) (Source: google)



Figure 2: Bark of neem tree (source: google)

Neem has been a cornerstone of South Asian traditional medicine for over 5,000 years, particularly in the Siddha, Unani, and Ayurvedic systems. It is known to have multiple therapeutic properties such as detoxification, antioxidant, antidiabetic, antipyretic, anti-inflammatory, and antimicrobial activities [13,14]. Leaves, bark, seeds, and neem oil are used in

numerous formulations ranging from oils, powders, extracts, and decoctions.

**Common names:** Neem, Margosa, Nimtree, Indian Lilac

**Scientific name:** *Azadirachta indica*

**Family:** Meliaceae

**Parts Used:** Seeds, bark, leaves, and fruits

### Biological Source:

The neem is derived biologically from the tree *Azadirachta indica*, also referred to as the neem tree or Indian lilac. Neem trees belong to the family Meliaceae. Preparations and extracts of the seeds, bark, leaves, and fruits of the neem tree are utilized for several medical and other purposes.

### Medicinal Parts of Neem (*Azadirachta indica*):

- 1. Leaves:** Used to treat skin conditions such as acne, eczema, and fungal infections. Also used as an insecticide and to treat fevers and gastrointestinal problems [14].
- 2. Bark:** Known for antidiabetic and anti-inflammatory properties. Often used in decoction

form for malaria, fever, and gastrointestinal issues [15].

- 3. Seeds:** Rich in azadirachtin, with strong insecticidal and antimicrobial properties. Neem seed oil is used topically for skin infections and wounds [16].
- 4. Neem Oil:** Extracted from seeds, used in medicinal and cosmetic formulations. Helpful in treating bacterial/fungal infections, dry scalp, lice, and dandruff [17].

### Principal Phytochemical Classes in Neem:

- 1. Limonoids:** Includes azadirachtin, nimbin, salannin, and nimbidin. Found mostly in seeds; show antifungal, insecticidal, and antimicrobial activities [19].

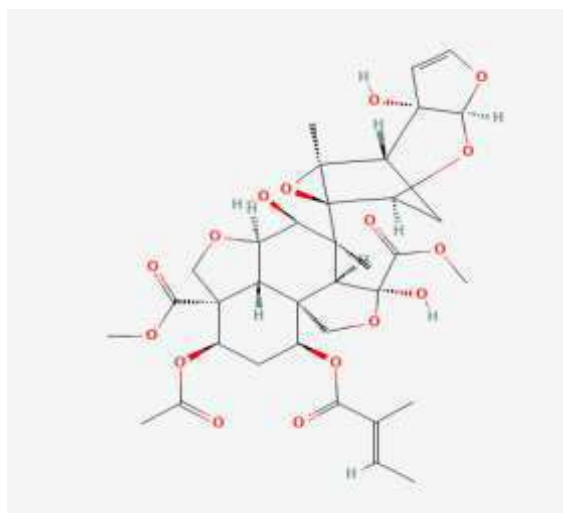


Figure 3: 2-D structure of Azadirachtin

(Source: PubMed CID: 5281303)

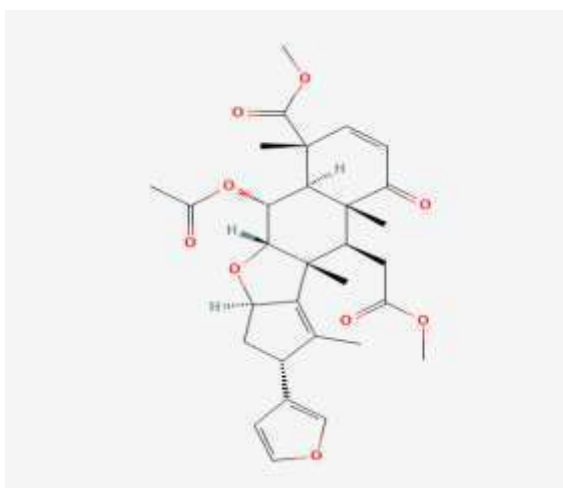
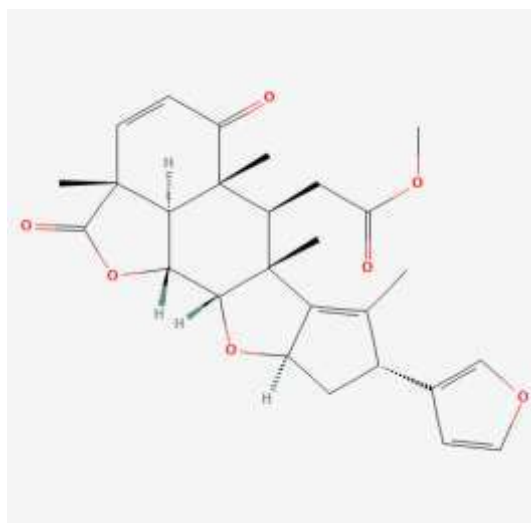


Figure 4: 2-D structure of nimbin

(Source: PubMed CID: 108058)

**2. Flavonoids:** Found in leaves — quercetin and kaempferol are potent antioxidants and anti-inflammatory agents [20].

**3. Triterpenoids:** Gedunin and nimbolide are found in seeds and bark. Show anticancer, hepatoprotective, and antimalarial properties [21].



**Figure 5: 2-D Structure of nimbolide**

(Source: PubMed CID: 12313376)

**4. Tannins and Phenolics:** Present in bark and leaves. Responsible for antimicrobial and astringent properties [22].

**5. Steroids and Saponins:** Present in trace amounts; contribute slightly to antimicrobial and immunomodulatory effects [23].

**6. Essential Oils:** Neem seed oil is rich in volatile fatty acids, sulfur compounds, and limonoids contributing to medicinal value [24].

**Table 1: Major phytoconstituents of Neem and their reported activities**

Phytoconstituent's	Plant Part	Type of Compound	Reported Antimicrobial Activity	Mechanism of Action
Azadirachtin	Seeds, Leaves	Limonoid (Triterpenoid)	Antibacterial, Antifungal, Antiviral	Disrupts microbial metabolism and cell replication
Nimbidin	Seed Kernel, Oil	Triterpenoid	Antibacterial, Antifungal	Inhibits bacterial cell wall synthesis, reduces inflammation
Nimbin	Bark, Seed Oil	Triterpenoid	Antibacterial, Antifungal	Disrupts microbial membrane integrity
Nimbolide	Leaves, Flowers	Limonoid	Antibacterial, Antifungal, Antiparasitic	Induces oxidative stress, inhibits microbial DNA/RNA
Gedunin	Seeds	Limonoid	Antimalarial, Antibacterial	Protein denaturation, mitochondrial disruption

#### Neem's Antimicrobial Action Mechanism:

**1. Cell Membrane Integrity Disruption:** Compounds such as nimbidin and nimbin disrupt

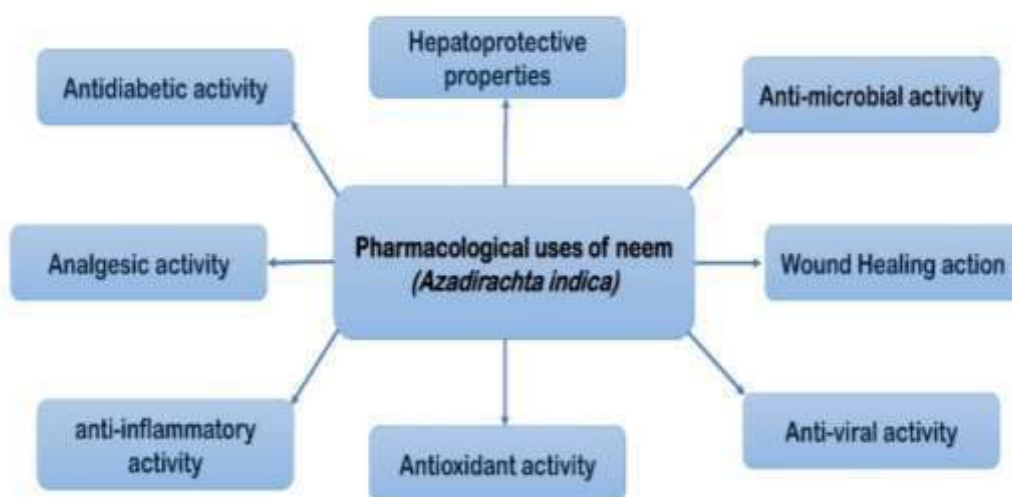
the lipid bilayer of microbial cell membranes. This results in increased membrane permeability, leakage of cellular contents, and ultimately, microbial cell death. These compounds are

particularly effective against Gram-positive bacteria [25].

- 2. Enzymatic Activity Inhibition:** Neem-derived phytochemicals like azadirachtin and quercetin inhibit critical microbial enzymes such as ATPase and DNA gyrase. This inhibition impairs vital processes like DNA replication and protein synthesis, thereby hindering microbial growth and survival [26].
- 3. Prevention of Biofilm Development:** Ethanolic and aqueous extracts of neem have been shown to prevent the formation of biofilms, which are protective layers that enhance bacterial resistance. This effect has been observed particularly in pathogenic bacteria such as *Staphylococcus aureus* and *Pseudomonas aeruginosa* [27].

- 4. Oxidative Stress Induction:** Flavonoids and polyphenolic compounds present in neem can induce the generation of reactive oxygen species (ROS) within microbial cells. The oxidative stress caused by these ROS damages lipids, proteins, and nucleic acids, leading to microbial cell death [28].

- 5. Interaction with Fungal Cell Wall Components:** Neem phytochemicals interfere with key components of fungal cell membranes, such as ergosterol. This disruption compromises membrane integrity, resulting in cytoplasmic leakage and cell lysis. This mechanism has demonstrated effectiveness against fungi like *Aspergillus* species and *Candida albicans* [29].



**Figure 6: Pharmacological uses of Neem (*Azadirachta indica*)**

### Extraction of Neem Phytochemicals

The method of extraction significantly influences the yield, purity, and biological activity of neem phytoconstituents. The choice of solvent and extraction technique depends on the specific plant part used and the nature of the targeted bioactive compounds. Common Extraction Techniques:

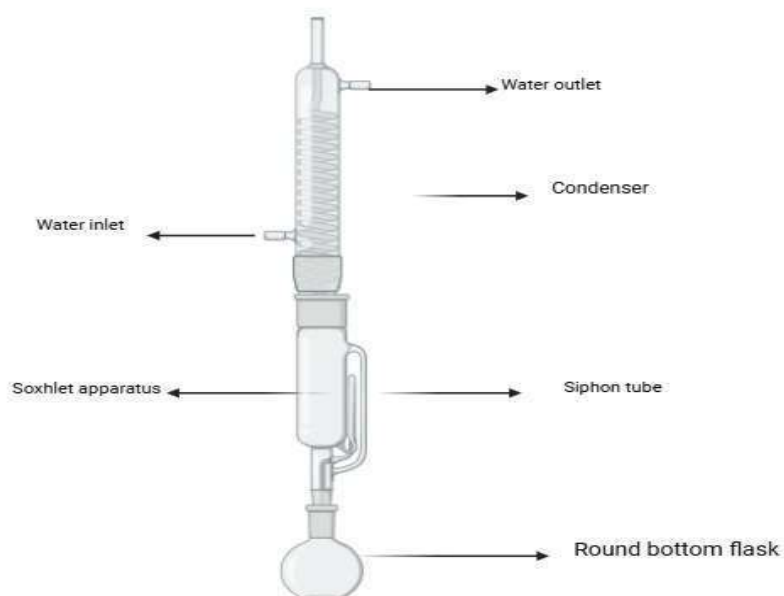
#### 1. Maceration:

Dried and powdered neem leaves, bark, or seeds are soaked in solvents such as ethanol, methanol, or water

at room temperature for 24–72 hours. After maceration, the solution is filtered and concentrated using a rotary evaporator under reduced pressure [30].

#### 2. Soxhlet Extraction:

This method involves continuous extraction of dried neem material using solvents like petroleum ether, chloroform, or ethanol in a Soxhlet apparatus. It is particularly effective for isolating non-polar to moderately polar phytochemicals [31].



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**Figure 7: Soxhlet apparatus (Created in Biorender)**

### 3. Ultrasound-Assisted Extraction (UAE):

High-frequency ultrasonic waves disrupt plant cell walls, enhancing solvent penetration and facilitating the release of bioactive compounds. UAE offers higher extraction efficiency, shorter extraction time, and reduced solvent usage [32].

### 4. Aqueous Extraction:

Commonly used in traditional herbal medicine, this method involves boiling neem bark or leaves in water, followed by cooling and filtration. While simple and safe, it is less effective for extracting non-polar compounds like limonoids.

**Table 2: Solvent used in extraction of phytochemical from neem**

Solvent	Target Compounds
Water	Flavonoids, tannins
Ethanol/Methanol	Alkaloids, terpenoids, flavonoids
Hexane	Fixed oils, non-polar terpenoids
Chloroform	Limonoids, steroids

### Formulation of Neem-Based Antimicrobial Products

Neem extracts are prepared in different dosage forms for therapeutic and cosmetic applications. Formulation depends upon the use, route of administration, and stability of active constituents.

#### Common formulations:

**1. Topical Gels/Creams:** Neem leaf or oil extracts are added to gels or ointments with carbopol or emulsifying bases. These are used extensively for the treatment of acne, fungal infections, and wounds [33].

**2. Mouthwashes and Toothpastes:** Neem bark and leaf aqueous or alcoholic extracts are added to dental products due to their antibacterial property against oral pathogens [34].

**3. Soap and Shampoo:** Neem oil and leaf extract are incorporated in formulations to control skin infections, dandruff, and lice.

**4. Capsules and Tablets:** Standardized neem leaf extract is encapsulated or compressed for internal use, particularly in metabolic and infectious disorders.

**5. Nano-formulations:** Recent developments involve encapsulation of neem extracts within nanoparticles or liposomes in order to increase bioavailability and target delivery [35].

### Toxicity, Safety, and Limitations

**Toxicity** Although neem is widely regarded as safe in traditional medicine, certain constituents of neem, especially in concentrated or improperly processed forms, can exhibit toxic effects

**Liver toxicity:** High doses of neem oil have been linked to liver damage in animal studies as well as isolated human cases, particularly in children [36].

**Nerve toxicity:** Consuming large amounts of neem oil has led to symptoms such as vomiting, drowsiness, and encephalopathy, particularly in infants — a condition referred to as neem oil poisoning [37].

**Reproductive toxicity:** Some neem extracts have shown antifertility effects in animal studies, affecting sperm production and ovulation [38].

**Allergic reactions:** Topical use can cause contact dermatitis or hypersensitivity reactions in some individuals.

### Safety Profile

Neem extracts and formulations are generally recognized as safe when used in appropriate therapeutic amounts. Standardized formulations, particularly for oral care applications, topical uses, or consumption as dietary supplements, have demonstrated good safety profiles in both preclinical and clinical investigations: Acute toxicity assessments indicated that neem leaf extracts possess high LD50 values, indicating low acute toxicity [39]. Topical products (such as neem cream and gel) have been shown to be non-irritating and non-sensitizing in human patch tests.

**Regulatory status:** Neem products are approved for use in traditional medicine and agriculture in many countries, including being classified under GRAS (Generally Recognized As Safe) for specific applications in the US.

### LIMITATIONS

**Lack of standardization:** Variances in extraction methods and phytochemical composition across different regions limit the reproducibility of results. **Stability concerns:** Neem compounds like azadirachtin are sensitive to light, heat, and changes in pH, which affects their shelf life and effectiveness.

**Limited clinical evidence:** Most antimicrobial findings are based on in vitro studies; thus additional human trials are needed to validate efficacy.

**Low bioavailability:** Numerous neem phytochemicals have poor solubility and limited absorption into systemic circulation, undermining their therapeutic potential unless they are formulated into advanced delivery systems like nanoparticles.

### CONCLUSION:

Due to its numerous phytochemicals, including azadirachtin, nimbin, and quercetin, neem (*Azadirachta indica*) has strong antimicrobial properties and is an important therapeutic plant. The review has discussed its traditional uses, bioactive compounds, mechanisms of antimicrobial action, and its application in modern formulations such as gels, oils, and nano-carriers. The efficacy of neem against a wide range of bacterial and fungal pathogens is supported by the results of several studies.

### Future Scope:

Despite being well-documented, the standardization of neem extracts and clinical trials is required to convert these observations into regulated pharmaceuticals. Future research needs to focus on:

1. Identifying the synergistic effects of neem phytochemicals and conventional antibiotics
2. Creating stable, targeted nano-formulations for systemic and skin infections
3. Evaluating the effectiveness of neem in managing antimicrobial resistance (AMR)
4. Molecular tools are used to investigate mechanisms and gene-level interactions.
5. Conducting extensive, randomized clinical trials to validate efficacy and safety

In an era of growing resistance, neem has the potential to be integrated into mainstream medicinal and pharmaceutical applications as a natural substitute or complement to synthetic antimicrobials.



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