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PHYTOCHEMICAL CONSTITUENTS AND PHARMACOLOGICAL POTENTIAL OF AZADIRACHTA INDICA (NEEM): A REVIEW

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ABSTRACT

Azadirachta indica A. Juss. (neem) is a tree belonging to the Meliaceae family. It has been traditionally used in South Asian countries for centuries as medicine. It has a number of bioactive compounds, such as limonoids, flavonoids, and phenolic compounds in the leaves, bark, seeds, and flowers and its oil. Laboratory and animal research has reported antimicrobial, anti-inflammatory, antidiabetic, anticancer, antioxidant, and insecticidal activity. There is limited clinical data from humans. Neem is relatively safe at the traditional dose, but neem oil can be poisonous, particularly to infants. The major compounds of neem, pharmacological activities, safety concerns, and research gaps are summarized in this review.

KEYWORDS: Azadirachta indica, neem, limonoids, azadirachtin, nimbolide, pharmacological activity.

1. INTRODUCTION

For thousands of years, plants have been an important source of medicines. Numerous contemporary medications are derived from plant compounds or are based on them [1]. Neem is one of the most popular medicinal trees of the Indian subcontinent. It is known as "Arishta" in Sanskrit, which means "reliever of sickness" [2].

In traditional systems of medicine like Ayurveda, Unani, and Siddha, neem has been used for skin disease, fever, wound healing, dental care, and digestive disorders [2,3]. Neem products are now available in toothpaste, soaps, creams, and agricultural pesticides [4].

Many compounds have been isolated from neem and tested in cells and animals over the past few decades [5,6]. A simple overview of the chemistry and pharmacology of neem is provided in this review. It also identifies areas of lack of evidence and areas of need for further research.



Fig 1: Neem Leaves.



Fig 2: Neem buds and flowers.

2. Botany and Traditional Uses

Neem is a fast-growing evergreen tree that can grow up to 15-20 m in height. It grows well in dry and tropical regions and is native to the Indian subcontinent [2,3]. Currently cultivated in Africa, the Middle East, and the Americas [3]. The leaves are compound and have serrated edges. The flowers are small, white, and sweet-smelling. The fruit is a simple, smooth drupe containing a single seed. Different parts of the tree are used in traditional practice (**Table 1**).

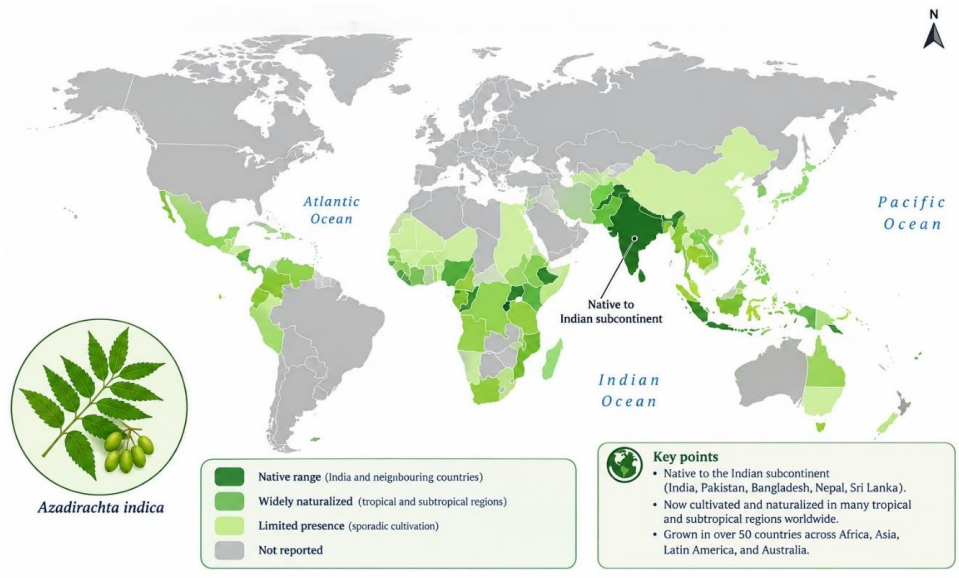


Fig 3: **Global distribution and geographical range of *Azadirachta indica*.**

Table 1. Traditional uses of different parts of neem. [3,5]

Plant part	Common traditional use
Leaves	Wounds, skin disorders, fever, eye problems
Bark	fever, ulcers
Seeds and seed oil	Skin diseases, hair and scalp care, pest control
Flowers	Digestive problems, bile disorders
Twigs	Oral hygiene, Dental care (chewing sticks)

3. Phytochemical Constituents

Over 300 compounds have been reported in neem [6,7]. They are divided into two categories. The isoprenoids are the first group, and these include limonoids and triterpenoids. The other group is the non-isoprenoids, such as flavonoids, phenolic acids, sugars, and proteins.

3.1 Limonoids

Limonoids are triterpenoids that are bitter and oxygen-rich [8]. They are the best-studied compounds of neem and are responsible for much of its biological activity. Important examples include:

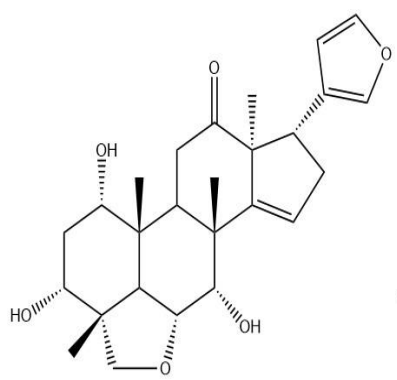
- **Azadirachtin:** the main insect-active compound, found mostly in seeds [9].
- **Nimbin and nimbidin:** studied for anti-inflammatory and antimicrobial effects [8].
- **Nimbolide:** a leaf and flower limonoid studied widely in cancer research [10].
- **Salannin:** an insect antifeedant [9].
- **Gedunin:** studied for antimalarial and anticancer properties [11].

3.2 Flavonoids and phenolics

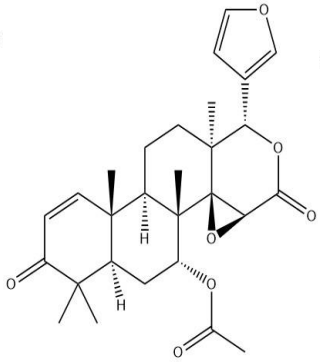
The neem leaves contain flavonoids, including quercetin, kaempferol, and rutin-type. These compounds have antioxidant activity [12]. Leaf extracts also contain phenolic acids like gallic acid and flavanols like catechin [6].

3.3 Other constituents

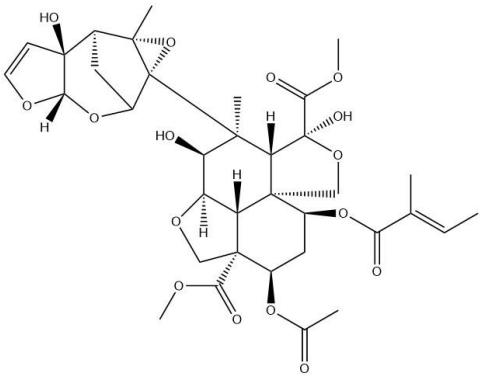
Neem seed oil contains fatty acids such as oleic, stearic, palmitic, and linoleic acids. It also has sulfur compounds, which make it pungent. Sterols like β-sitosterol are also found [6].



Azadirachtin

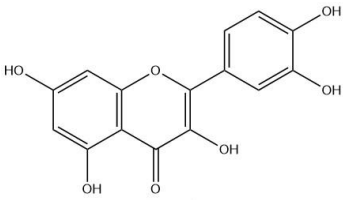


Gedunin

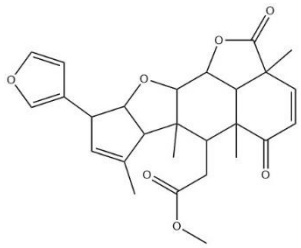


Nimbidin

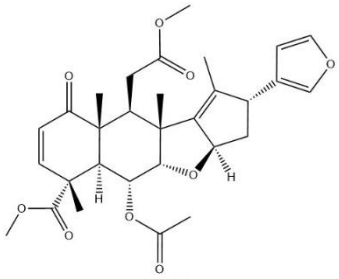
The amount of the individual compounds varies depending on the part of the plant, season, geographical area, and extraction techniques. This makes standardization of neem products a challenge [4,6].



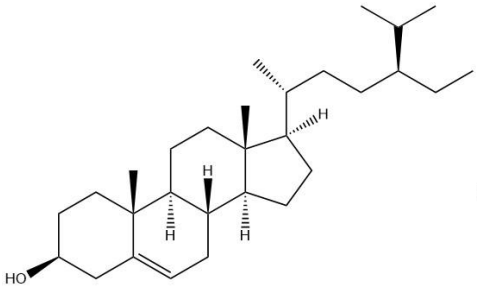
Nimbin



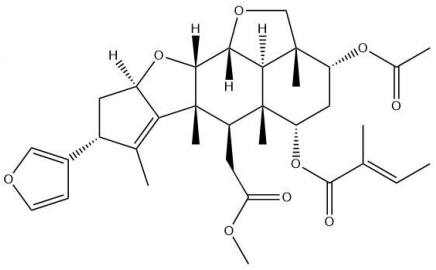
Nimbolide



Quercetin



Salannin



β-Sitosterol

Table 2. Major phytochemicals of neem and their reported activities. [6,8]

Compound	Class	Main plant part	Reported activity
Azadirachtin	Limonoid	Seed	Insect antifeedant, growth regulator
Nimbin	Limonoid	Seed, leaf	Anti-inflammatory, antimicrobial
Nimbidin	Limonoid mixture	Seed oil	Anti-inflammatory, antiulcer
Nimbolide	Limonoid	Leaf, flower	Anticancer, anti-inflammatory
Salannin	Limonoid	Seed	Insect antifeedant
Gedunin	Limonoid	Seed, bark	Antimalarial, anticancer
Quercetin	Flavonoid	Leaf	Antioxidant, anti-inflammatory
β-Sitosterol	Sterol	Leaf, seed	Anti-inflammatory

4. Pharmacological Potential

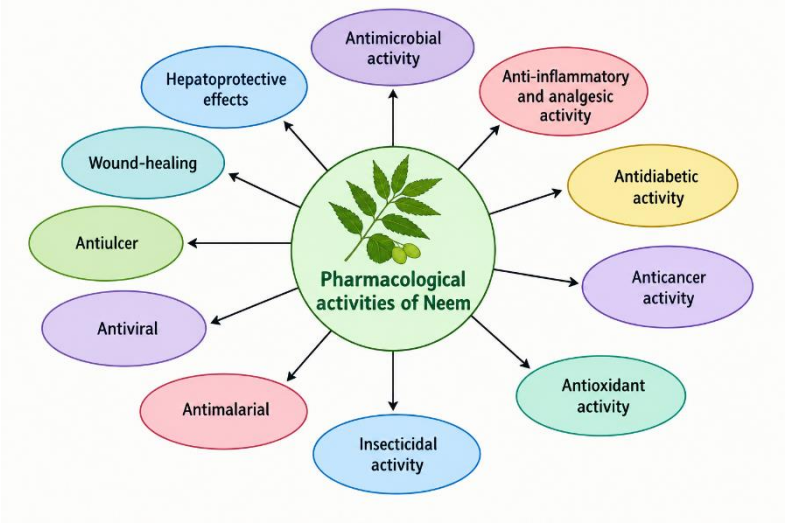


Fig 4: **Diverse pharmacological activities of *Azadirachta indica*.**

4.1 Antimicrobial activity

In laboratory tests, neem extracts exhibited activity against various bacteria and fungi. In an *in-vitro* study, leaf extracts were able to inhibit the growth of *Staphylococcus aureus*, even methicillin-resistant strains [13]. Nimonol compound was also found to exhibit antifungal activity against human pathogenic fungi, along with extracts from the plant's leaves [14]. These results are promising. But they're the results of test tube studies. The doses used are often high, and the results may not apply to patients.

The leaves and twigs of neem are also used as an oral care agent. Their antibacterial activity against mouth bacteria is described in reviews [13,15], but few good clinical trials are available.

4.2 Anti-inflammatory and analgesic activity

In animal models, a number of compounds of neem demonstrated anti-inflammatory activity, such as nimbidin, nimbin, and nimbolide [10,16]. These compounds have been shown to have anti-inflammatory properties by downregulating the inflammatory signal NF-κB, which regulates many inflammatory genes [17]. Neem preparations have also been found to possess anti-inflammatory and anti-pyretic properties in animal studies [5].

4.3 Antidiabetic activity

Animal studies suggest that neem leaf extract can lower blood glucose levels [18]. The proposed mechanisms are improved insulin action and reduced glucose uptake from the gut [7]. Some small human studies exist, but they are limited in size and quality. Due to this, it would not be advisable to use neem as a substitute for conventional treatment for diabetes.

4.4 Anticancer activity

Research to combat the cancer is rapidly expanding on neem [7,10]. Neem extracts and nimbolide and gedunin have been reported to inhibit the growth of cancer cells in vitro and in animal models [10]. It is reported that the mechanisms are:

1. Causing programmed cell death (apoptosis) in cancer cells.
2. Stopping the cell cycle.
3. Reducing cancer cell movement and spread.
4. Blocking signaling pathways that support tumor growth.

These findings are promising. However, no neem-based anticancer drug has been approved. Human trials are lacking.

4.5 Antioxidant activity

Flavonoids and phenolic compounds in neem leaves can neutralize free radicals in laboratory tests [12]. Oxidative stress is linked to diabetes, cancer, and heart disease [6]. This may partly explain the wide range of neem's effects. However, antioxidant activity in a test tube does not always mean a health benefit in the body.

4.6 Other activities

Reviews also report antimalarial, antiviral, antiulcer, wound-healing, and liver-protective effects of neem in laboratory or animal studies [5,6]. Most of these reports need confirmation in well-designed studies.

4.7 Insecticidal activity

Azadirachtin is the most important natural insect-control compound from neem. It reduces feeding and disrupts insect growth and molting [9]. Neem-based pesticides are considered a safer alternative to many synthetic pesticides [19]. They break down in the environment and generally pose a lower risk to mammals and most non-target organisms, although fish, aquatic invertebrates, and some beneficial insects can be sensitive.

Table 3. Summary of pharmacological evidence for neem. [6,13]

Activity	Main compounds involved	Level of evidence
Antibacterial / antifungal	Nimbin, nimonol, flavonoids	In vitro
Anti-inflammatory	Nimbidin, nimbolide	In vitro and animal
Antidiabetic	Leaf extract constituents	Animal; few small human studies
Anticancer	Nimbolide, gedunin	In vitro and animal
Antioxidant	Flavonoids, phenolics	In vitro
Insecticidal	Azadirachtin, salannin	Field and laboratory studies

5. Safety and Toxicity

Neem preparations of leaves and bark have been in use for centuries and are known to be relatively safe at traditional dosage levels [5,19]. The toxicity test of neem-based pesticides showed low toxicity to mammals when applied as directed [19]. A toxicity study on acute toxicity of neem seed oil in animals was also conducted to determine the safety limits of neem oil.

Neem oil is, however, toxic. Cases of poisoning in infants and young children have been reported with the administration of neem (margosa) oil [20,21,22]. Symptoms were vomiting, drowsiness, seizures, and liver and brain damage similar to Reye's [20]. For this reason, neem oil is not recommended for children.

Other points to keep in mind:

- Long-term and high-dose studies in humans are limited [6,13].
- Neem has been reported to affect fertility in animal studies [23], so pregnant women and those planning pregnancy should avoid it.
- Quality varies between products [7]. Contamination and wrong dosing are possible.

6. CHALLENGES AND FUTURE DIRECTIONS

Despite the large number of studies, several problems remain:

1. **Few clinical trials.** Most evidence comes from cell and animal studies [6,13].
2. **Lack of standardization.** The content of active compounds varies with plant part, region, and extraction method [4,7].
3. **Poor understanding of absorption and bioavailability.** Many limonoids dissolve poorly in water, which may limit their effect in the body [6].
4. **Unclear mechanisms.** Many studies test crude extracts rather than pure compounds [5].

Further studies should be directed towards the isolation and standardization of active compounds, the study of their pharmacokinetics, and the conduct of proper clinical trials in humans. To increase the solubility and targeting of neem compounds, modern delivery systems like nanoparticles could be utilized [24]. Molecular docking and ADMET prediction are computational tools that can be used to screen the neem compounds before undergoing expensive experiments [25].

7. CONCLUSION

Neem is an excellent source of bioactive compounds like limonoids, including azadirachtin, nimbolide, gedunin, flavonoids, and phenolics. Its traditional uses have been substantiated by

laboratory and animal studies as an antimicrobial, anti-inflammatory, antidiabetic, antioxidant, and anticancer agent and as a natural insecticide [5,6]. But there is still little human evidence. Neem oil is also potentially toxic, particularly in children [20,22]. There is a need for more standardized, good-quality clinical research in order for neem compounds to become approved medicines.

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