



Review on Neem (*Azadirachta indica* A. Juss.): an Unexplored Medicinal Plant of Unani System of Medicine

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Abstract

Background: One of the oldest methods for preventing and treating a wide range of illnesses is plant-based traditional medicine. People are turning to using traditional ethnomedical plant-based treatments to prevent and treat illnesses as well as to preserve their health because modern medicine is becoming more and more expensive. Because of its pharmacological and therapeutic properties, *Azadirachta indica*, also known as neem, has been utilized as an ethnomedical plant from ancient times. Numerous diseases can be avoided by using various parts of this plant, such as the leaves, fruit, bark, seeds, and flowers. It is possible to isolate and use a variety of structurally intricate and physiologically active components from various neem sections. **Purpose** This review's goal is to draw attention to the significance of the numerous neem sections, each of which has biologically active components that can help prevent and treat a range of illnesses. **Method:** To examine the medicinal potential of neem in various illnesses, Science Direct, Google Scholar, Web of Science, and PubMed were used. **Result.**Neem's anti-cancer, immunostimulant, orodental, skin protection, neuropharmacological, ulcer-treating, anti-pyretic, anti-inflammatory, anti-malarial, anti-bacterial, anti-fungal, anti-viral, anti-parasitic, anti-hyperglycemic, antioxidant, anti-hyperlipidemic, hepatoprotective, renal protection, and hematological parameters maintenance properties have all been shown. **Conclusion.** there is no proof in the literature that neem has any negative consequences. It can be used to cure a variety of health-related illnesses because it is stomach-friendly in all situations, with the exception of those who are allergic.

INTRODUCTION:

Plant-based medicine has been used to cure human illnesses for as long as civilization. The majority of medicines used in traditional health care systems around the world come from plants. These days, both industrialized and developing nations use plant-based medications. Although there are thought to be around 250,000 higher plant species on Earth, only 6% of plants exhibit biological activity, and only 15% of plants have phytochemical characterizations. Global demand for both manufactured and natural products is rising exponentially. (1)

Neem, or *Azadirachta indica*, is utilized extensively in ayurveda, homeopathy, unani, and modern medicine. More than 140 physiologically active substances with complicated structures and a wide range of chemical types can be found in different regions of neem. The bark, roots, fruits, seeds, blossoms, and leaves of the neem tree have all been used historically to prevent and treat a variety of illnesses, including fever, infections,

inflammation, and skin and dental conditions. Neem's medicinal qualities have mostly been associated with its leaves. Because of its many health benefits, such as anticarcinogenic, antimutagenic, antioxidant, antiviral and antibacterial, antifungal, antimalarial, antiulcer, antihyperglycemic, anti-inflammatory, and immunomodulatory properties, neem leaves, both whole and their active constituents, have been used extensively.(2) Therefore, in order to avoid lifestyle-related illnesses and reduce the cost of modern treatment, ethnomedical plants should be incorporated into the daily diet.

Botanical descriptions:

Azadirachta indica A. Juss., often known as neem, is a popular, medium- to large-sized, fast-growing, evergreen tree with a straight trunk and numerous branches that can reach heights of 15 to 20 meters or more under ideal circumstances, and 2.5 meters in diameter. Up to 30 centimeters long, pinnate leaves have 10–12 serrated leaflets that measure 3.5-8 centimeters length by 2.5 centimeters wide on each leaf. The tree is covered with fragrant white flowers that smell like honey. The flowers appear in axillary clusters and typically hang down in panicles up to 25 cm long, throughout the early summer months of March through April. There are olive-sized, semi-sweet fruits that are green in colour and turn golden yellow when ripe, usually appearing throughout the months of June through August. Trees typically start giving fruit around the age of three to five but don't become completely replicable until they are 10 years old; at this age, the tree yields roughly 20.5 kg of fruit year on average. It is a single-seeded drupe with ellipsoid seeds and thick, meaty, oily cotyledons. The bark has small vertical furrows and a dark brown color. Bark is dark brown in colour with shallow vertical furrows. (3,4,5,6)(79,32,171,172)

Geographical distribution: It is indigenous to Pakistan, India, and Burma, and it grows best in tropical and semitropical climates up to an elevation of 1000 meters. (3,4,5,6) It can also be found in America, (7,8,) Nepal, China, Myanmar, Bangladesh, Sri Lanka, Thailand, Malaysia, Mauritius, Fiji, South Africa, East Africa, and America.(10)It has been reported that neem trees have a 200-year lifespan. (10)

Botanical name. *Azadirachta indica* A Juss. (11)

Family. Meliaceae.

Taxonomical classification:(11)

Order	Rutales
Sub order	Rutinae
Family	Meliaceae
Subfamily	Melioideae
Tribe	Melieae
Genus	<i>Azadirachta</i>
Species	<i>indica</i>

SYNONYMS: (3,7,8)

Language	Synonyms	Language	Synonyms
English	Indian Lilac, Margosa tree, Neem tree	Sanskrit	Arishta, Arkapadapa, Hingu, Cardighna, Vembaka
Unani	Azaad-Darakht-e-Hindi	Bengali	Nim, Nimgachh
Arabic	Neeb	Gujarati	Danujhada, Limbra, Limbadu
Persian	Azad darkht-i hindi, Neeb, Nib	Punjabi	Bakam, Mahanim, Bukhain
Urdu	Neem	Siddha/Tamil	Arulundi, Kinji, Malugam, Kaduppagai, Veppu, Vembu
Hindi	Balnimb, Nimb, Nim	Telgu	Nimbamu, Taruka, Vepa
Ayurvedic	Nimba, Nimbaka, Arishta, Arishtaphala	Marathi	Balantanimba, Limba
French	Agem lilas, Azadirac, Margosier	Oriya	Limbo, Kakopholo, Nimo
Malayalam	Arytikta, Nimbam, Aryaveppu	Burma	Bawtamaka, Kamaka,

Parts used:

All parts of the plant are utilized, but primarily leaves and bark. Other portions include flowers, fruits, seeds, gum, toddy, and root barks. (12)

MICROSCOPIC CHARACTERS OF NEEM:(3,10)**Leafs:**

Midrib: A biconvex outline is revealed by a leaflet through the midrib. The epidermis is externally covered in thick cuticle on both sides, and there is 4–5 layers of collenchyma beneath the epidermis. The stele is composed of one crescent-shaped vascular bundle towards the lower surface and two or three smaller bundles towards the upper surface. The remaining tissues are made up of thin-walled parenchymatous cells with secretory cells and calcium oxalate rosette crystals. The phloem is surrounded by non-lignified fiber strands, and there are crystals in the phloem region.

Lamina: Dorsiventral structures include epidermis on both surfaces, which is made up of thin-walled, tangentially elongated cells covered in thick cuticle; anomic stomata are only present on the lower surface; palisade is a single-layered, spongy parenchyma made up of five to six layers of thin-walled cells, traversed by several veins; rosette crystals of calcium oxalate are present in a few cells; palisade ratio is 3.0-4.5; stomatal index is 13.0-14.5 on the lower surface and 8.0-11.5 on the upper surface.

Stem Bark: It has hard, woody, and relatively thick outer exfoliating pieces that are almost entirely dead secondary phloem elements. These are alternated with continuous tangential bands of compressed cork tissue. The former is made up of multiple layers of stone cells that occur in regularly arranged groups along with collapsed phloem elements that are filled with brown contents. There are three to five layers of fiber groups in between each successive zone of cork tissue, with thin-walled and frequently collapsed phloem elements present. Each zone of cork tissue is made up of multiple layers of regular, thin-walled cells that are occasionally separated by a few compressed rows of thick-walled cells.

Fruit: The transverse section of the epicarp reveals that the cells are parenchymatous, single-layered, squarish to rectangular, and have thick cuticles on their outer tangential walls. The mesocarp area is made up of multiple layers of bigger, primarily polygonal, thin-walled parenchymatous cells. Stone cell endocarps come in a variety of sizes and forms. The seed coat's epidermis has a single layer, thick walls, a square to rectangular shape, and a parenchymatous character. Thick cuticle covers the epidermis's outer tangential wall. Tegmen is a hexagonal structure with eight to ten layers and sclerotic cells inside.

The integument remains as a parenchyma with a single layer. The majority of the embryo consists of the two cotyledons. The cotyledon is made up of parenchymatous and isodiametrically shaped single-layered epidermal cells. Hexagonal to polygonal parenchymatous cells with thin walls make up the cotyledon's ground tissue. Different-sized oil globules are present inside these cells. In this area, aluerone grains have also been observed. (3,13)

Seed: A thin brown testa with isodiametric stone cells covering an integument of loosely packed parenchymatous cells and a cotyledon made up of parenchymatous cells with numerous oil droplets are seen in the fruit seed kernel.(3)

Analysis of fruit/ seed powder: The color of the raw medication powder is a yellowish brown. Pieces of parenchymatous cells, endosperm, embryo epicarp, mesocarp, pitted stone cells with a broad lumen and pronounced wall striations, clusters of lignified fibers, and tracheids are all visible in the crude drug powder. Testicular fragments displaying clearly striped isodiametric stone cells.(3,13)

Macroscopical description: Neem fruit seed kernels have an uneven, conical to ovoid form, measuring 10-15 mm long, 3-5 mm wide, and 3-4 mm thick. They are brown on the outside and ceramist colour on the inside, with a fragrant, garlic-like smell after crushing and a bitter flavour. (3)

Mizāj/(temperament): *Hār* (Hot) 1° *Yābis* (Dry) 1° (all parts), Hakeem Ghulam

Imam and Ali Yaar Khan quoted that its temperament is *Murakkab-ul Quwa* and *Ma'il ba Sardī* and according to Vedas it is *Bārid* (Cold) *Yābis* (Dry) but temperament of fruit or seed is *Hār* (Hot) *Raṭab* (Moist).(4,12)

Actions: Neem is known as “reliever of sickness” that’s why it has very effective and many functions which are as follows *Muḥallil* (resolvent), *Musakkin*(analgesic), *Mulayyin*, *Muṣaffī-i Khūn* (blood purifier), *Dāfi'-i Hummā* (antipyretic), *Dāfi'-i Ṣafrā wa Balgam*, *Muqaṭṭi'*, *Mundij* (concoctive), *Dāfi'-i Ta'affun* (antiseptic), *Qātil-i Jarāsīm* (antimicrobial), *Qātil-i Kirm-i Shikam* (anthelmintic/vermifuge), *Munaqqī-i Qurūh*. (90,121) Root bark and young fruit have tonic, antiperiodic, alterative and astringent effects. Bark is bitter, tonic, antiperiodic and astringent and also vermifuge. Bark and

leaves are aphrodisiac, maturant and resolvent. Fruit shows *Muṣaffi-i Khūn* (blood purifier), purgative, emollient and anthelmintic actions. Leaves are discutient, leaf juice is anthelmintic. Oil from nuts and leaves is local stimulant, antiseptic, alterative insecticide and antiseptic. Flowers have *Muṣaffi-i Khūn* (blood purifier), stimulant, tonic and stomachic effects. Gum from the bark is used as stimulant, demulcent and tonic. Toddy is having refrigerant, nutrient and alterative tonic activity. The drug also possesses anti-spirochaetal and emmenagogue properties. Berries have purgative, emollient and anthelmintic functions. Bark, gum, leaves and seeds are also having antidote effects in snake bite and scorpion sting. (12,14,15) Seeds have *Musakkin* (analgesic) and *Mudirr-i Hayḍ* (emmenagogue) actions. (12) **Sap** is considered a *Muṣaffi-i Khūn* (blood purifier), refrigerant, nutrient and alterative tonic. (15)

Iste'māl / (Therapeutic uses):

In Unani system of medicine, all parts of neem are used as a blood purifier in all blood impurities related diseases (*Amrād-i Fasād khūn*). (16)

Leaves: Leaf tea is commonly used to treat fever, anorexia, dermatopathies, and anthelmintics. Apply a poultice of leaves to boils to aid in healing and avoid putrefaction. Because the leaf decoction has antibacterial properties, it is used to treat eczema and ulcers. The juice of fresh neem leaves was extracted and used to a wound infested with worms. Furthermore, worms found in the nose are employed as Qatūr, or nasal droplets. (12,18) Leaves can be used to cleanse wounds, their decoction can be used to bathe in itching and other skin problems, and dry leaves can be used as a dusting powder on wounds. A particularly powerful remedy for earaches is the steam of leaves. (16) For one month, a tablespoon of a mixture including the same amount of leaf, fruit, stem bark, and flower powder was taken twice daily along with a spoonful of ghee and half a spoonful of honey in case of jaundice. Once a week, crushed leaves are applied to the head before washing to stop hair fall. For eight days, crumble young leaves and apply them to the forehead once a day to reduce headaches. (6) In addition, bark and leaves help treat syphilis, lumbago, otalgia (*Waja'-ul Udhun*), leucoderma, piles, and all wounds and inflammations. (15,17)

Stem & root bark: It is mostly effective in helminthiasis, pyrexia, diabetes mellitus and pruritus. (20)

Decoction of neem bark specially used in seasonal fever and killing of intestinal worms. (16) Bark has blood purifier (*Muṣaffi-i Dam*) effect, used in worms' infestation (*Dīdān-i Am'a'*), and root bark used as emmenagogue (*Mudirr-i Hayḍ*) in amenorrhoea. (17)

Young shoots: Crushed green twigs are used as tooth brushes (*Miswāk*) to clean teeth. Gum disease, dental cavities, toothaches, and foul breath can all be cured with this. Neem shields the oral cavity from certain illnesses. (15,16,17)

Sap is considered effective in some chronic and long standing cases of leprosy (*Judhām*) and other skin diseases, syphilis (*Ātishak*), atonic dyspepsia and general debility. (15,16,17)

Flowers: are typically covered by prescriptions for blood purifiers (*Nuskhajāt*) used to purify blood for skin conditions. Neem flower-prepared kajal is also beneficial for itchiness in the eyes. (12) In certain cases of atonic dyspepsia and overall debility, it can be used efficiently. (15)

Fruits or Seeds: It is used in skin diseases (*Amrād-i Jild*) as blood purification (*Fasād-i Dam*). (3). Powder of neem seed is very effective in painful menses and dysmenorrhoea due to analgesic (*Musakkin*) and emmenagogue (*Mudirr-i Hayd*) actions. (19) Seeds paste of neem applied on affected part to cure any type of skin diseases twice a day for one week. (6) Seeds' oil of neem used in leprosy, syphilis, tinea, itching and nonhealing ulcers or very bad wounds, if there are worms in the wounds that are also killed by the seeds and it is also very effective in chronic joint pain. Application of the fruit alone or with other medicines on the wounds remove infection and heals the wounds quickly. It is also beneficial in wounds of chronic scrofula (cervical tuberculous lymphadenitis). (16,20)

Eating of ripe fruits have laxative (*Mulayyin*) and blood purifier (*Muṣaffi-i Khūn*), antihelminthic (*Qātil-i Kirm-i Shikam*) effect and used in hemorrhoids that's why it is

included in the formulation of antihemorrhoidal tablets. Moreover, it is also very effective in the killing of head lice, if they are ground into a paste form and applied to the hair follicles. (16) It is majorly used in dermatopathies, diabetes, wounds/ulcers and oedema. (18) Oil is effective in rheumatism and skin diseases due to stimulant, antiseptic and alterative effect. (14) It is very effective in swelling of skin and skin diseases (*Amrād-i Jild*). (13)

Nafa' Khāṣ / **(Main function):** *Muṣaffi-i Dam* (blood purifier) and *Dāfi'-I Sauda, Dāfa'-i Ta'ffun* (antiseptic). (12,20)

Muḍīr / **(Adverse effect):** For persons who has dry temperament. (12)

Muṣliḥ / **(Correctives):** Pure honey, black pepper and oils. (12)

Badal / **(substitute):** One part is substitute of other part. (21)

Doses): Dried leaf 1-3 gm, powder 10-20 gm for decoction, stem bark 2-4 gm powder decoction for external use, leaves juice 10-20 ml, oil 5-10 drops, bark decoction 50-100 ml. (7) When it is used as blood purifier, its green leaf and bark juice or decoction can be taken 6-12 ml, (84) leaves and bark 7-12 gm. (16)

Dosage forms: It can be used as a form of *Ḥubūb* (pills), *Majun*, *Marham* (ointment), *Arq*, *Sufūf* (powder), *Joshānda* (decoction), paste (*Zimaād*), Juice. (7,12) and seed's oil. (16)

Mashūr Murakkabāt / **(Important Unani formulations)**

Ḥabb-i Bawāsīr, *Ḥabb-i Muṣaffi-i Khūn* (22) *Majun Musakkin-i Dard-i Reḥam*, (19) *Majun Bawāsīr*, *Majūn Juzām*, *Arq Murakkab Muṣaffi-i Khūn ba nuskha Kalan*, *Arq Hrābharā*, *Marham Jadwār*, *Marham Sā'ida Chūb* *Neem Wālā*, *Zimād Muhāsa*, *Zimadi Bawāsīr* and *Rogan-i Neem*. (13,21)

Chemical constituents :

Azadirachta indica's chemical composition is extremely complicated due to the wide range of phytochemicals it contains, including terpenoids, flavonoids, coumarins, carbohydrates, proteins, and fatty acids along with their esters and hydrocarbons. (18)

Nimbin, a bitter chemical, was originally isolated from *A. indica* (neem) oil in 1942. From various neem components, more than 140 bioactive chemicals with complicated structures and chemical makeup have been found. (23,24,25). Isoprenoids and others (non-isoprenoids) are the two main groups of these chemicals. (26) The non-isoprenoids include proteins, carbohydrates, polysaccharides, sulfurous compounds,

polyphenolics like flavonoids and their glycosides, dihydrochalcone, coumarin and tannins, aliphatic compounds, and so on. The isoprenoids include diterpenoids, triterpenoids, and steroids containing protomeliacins, limonoids, azadirone, azadiradione, gedunin, vilasinin type of compound, C-secomeliacins like azadirachtin, nimbin, salanin, and its derivatives.(27,28)

Azadirachtin, meliantriol, salanin, triterpenes, β -sitosterol, stigmasterol, cyclic trisulphides and tetrasulphides in leaves, nimbin, nimbidin, azadirachtin, limonoids: meliantriol, nimbidinine and nimbendoil in seeds, nimboesterol, myricitin in seeds oil, and neem seed oil additionally contains Vitamin B and other essential acids. Neem is a significant source of phytoconstituents. The fatty acids oleic acid, palmitic acid, stearic acid, linoleic acid, and other lower fatty acids are contained in the oil.(29,30)

The polysaccharides G1a, G1b, G2a, and G3a, ditrerpens (sugiol), kaempferol, deacetyl azadirachtinol in fruits, (-) epicatechin, catechin, margolone, margolonone, and isomargolonone in bark are all found. There are additional chemical constituents as well, including meliacine, gedunin, valassin, quercetin-3-galactoside, rutin, isorhamnetin, nimbolide, vilasinin, nimbinene, 6-deacetyl nimbinene, nimocinol, β -sitosterol- β -Dglucoside, nimbolin A and B, 6-deacetyl nimbinene, kaemferol-3-glucoside, mahmoodin, and tigenic acid. The majority of these phytoconstituents are classified as triterpenoids, or limonoids, which are extremely soluble in organic solvents such alcohols, ketones, hydrocarbons, and esters and have a minor hydrophilic nature. (30,31)

The oil extracted from its seeds is used as a liniment for rheumatic illnesses and also functions as a stimulant, alterative, and treatment for skin conditions and rheumatism. It was recently revealed that nimbidin, a substance derived from neem oil, shown strong anti-gastric ulcer efficacy in laboratory animals. Specifically, it was shown to prevent ulcers by lowering stomach output. (32)

EVIDENCE BASED SCIENTIFIC STUDIES:

Anti-inflammatory Activity:

Nimbidin, which was extracted from neem trees, was tested for its anti-inflammatory properties using a rat model of paw oedema caused by carrageenin and kaolin. When compared to phenylbutazone (100 mg/kg), the medication at dose levels of 40 mg/kg and 80 mg/kg had a considerable anti-inflammatory effect. Additionally, nimbidin dramatically reduced the amount of fluid exudation in rats with croton oil-induced granuloma and arthritis in the ankle joint. It was discovered that the medication worked well for both acute and chronic inflammation. Thus, it qualifies as a broad anti-inflammatory drug (32)

because nimbidin inhibits neutrophil and macrophage activities related to inflammation. (33) Nimbidin demonstrated strong anti-inflammatory and antiarthritic properties in an in vitro and in vivo (on rat) investigation by inhibiting several neutrophil and macrophage functions linked to the inflammatory response. It prevents the primary inflammatory cells on the afflicted side from phagocytosing and migrating in response to inflammatory stimuli. (34)

Antimicrobial Study:

The ability of the neem plant to break down cell walls or to hinder the growth of various microorganisms, including bacteria, viruses, parasites, and harmful fungus, is crucial to all components of the plant. The following describes neem's role in inhibiting the growth of microorganisms.

Antibacterial activity: Using ethanol as an organic solvent against four bacterial strains (*Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Salmonella typhi*) and ampicillin as a control, the investigation of neem (*Azadirachta indica*) seed oil extract was conducted using the agar well diffusion method. At 100% extract concentration, the maximum zones of inhibition were seen in *Pseudomonas aeruginosa* (14 mm), *Salmonella typhi* (11 mm), and *Staphylococcus aureus* (10 mm), while *E. coli* (9 mm) had the lowest zones of inhibition. With the exception of *Salmonella typhi*, which showed the least (15 mm) in 100% concentration, ampicillin, the control, likewise demonstrated high zones of inhibition on all test organisms, including *Pseudomonas aeruginosa* (23 mm), *Escherichia coli* (19 mm), and *Staphylococcus aureus* (18 mm). (5) In a different investigation, the novel tetrahydrofuran diester 1 was isolated from a petroleum ether extract of neem oil (*Azadirachta indica*) as an antibacterial component. It was demonstrated that this component was highly efficient against three common bacterial strains: *Salmonella enteritidis*, *E. coli*, and *Staphylococcus aureus*. (189) A fraction of neem oil (*A. indica*), known as NIM-76 (vaginal contraceptive), was investigated for its antibacterial properties against poliovirus, fungi (*C. albicans*), and several bacteria (*E. coli*, *S. typhi*, *S. dysenteroides*, *P. vulgaris*, *P. aeruginosa*, *S. faecalis*, and *S. aureus*). It works better than entire neem oil, particularly against *E. coli* and *Pseudomonas aeruginosa*, which neem oil does not suppress, not even at a dose of 15 mg/ml. Positive control samples included ketoconazole (50 µg/ml) and ciprofloxacin (10 µg/ml) were employed in this investigation as positive controls for bacterial strains and fungal strains (*C. albicans*), respectively. (37,38) The effectiveness of neem seed oil against 14 strains of harmful bacteria was also assessed in a different antibacterial investigation. The suppression of the bacteria's ability to synthesize cell membranes was responsible for the observed bactericidal impact. (35) .

In a different investigation, the antibacterial activity of neem bark, leaf, seed, and fruit extracts was investigated using the agar well diffusion method against adult mouth-isolated strains of *Pseudomonas aeruginosa*, *Corynebacterium diphtheriae*, and *Bacillus* spp. All of the test bacterial strains that were used were inhibited by the bark and leaf extracts, and the zone of inhibition grew as the extract concentrations increased. Furthermore, antibacterial activity was only observed at greater concentrations in fruit and seed extracts. (36)

Antifungal activity:

In this study, extracts from *Azadirachta indica* seed kernels were tested for their antifungal properties against 15 *Candida* species using ten different solvent systems (hexane, methanol, chloroform, water, petroleum ether, 5% dimethylsulfoxide, dichloromethane, acetone, methanol: chloroform: water (12:5:3) and absolute alcohol). Fluconazole was used as the standard control. The seed kernel hexane and ethanol extracts showed excellent results, blocking over 13 of the 15 strains of *Candida*; however, all species of *Candida* were resistant to the chloroform generated via the sequential extraction method and the methanol:chloroform:water (12:5:3) extracts. Nonetheless, a direct chloroform extract was able to block 9 out of 15 strains, while additional

extracts demonstrated adequate inhibition. Additionally, the antifungal control fluconazole result showed that: 8 were sensitive, 2 were resistant, and five were doses that were susceptible. (39)

The antifungal efficacy of *Azadirachta indica* leaf and fruit methanol extracts against the fungus *Alternaria solani* was assessed in a different investigation.

When applied to *Alternaria solani*, the leaf extract significantly inhibited fungal growth more than the fruit extract did. (40) Aqueous, ethanolic, and ethyl acetate extracts of neem leaves have demonstrated a significant effect in this in vitro study against a variety of human pathogens, including *Candida albicans*, *Aspergillus fumigatus*, *Aspergillus niger*, *Aspergillus terreus*, and *Microsporum gypseum*, at concentrations of 5, 10, 15, and 20%. Out of the three extracts, the ethyl acetate extract at a 20% concentration was shown to exhibit the highest inhibition of fungal strain growth. Additionally, its HPLC examination revealed the presence of anemonol. (41) According to a recent study, neem powder added to acrylic resin denture base materials shown antifungal effectiveness by decreasing *Candida albicans*' adherence to denture stomatitis. (42)

Antimalarial activity: Methanolic extracts of the seed kernels of both ripe and unripe neem fruits have been tested for their in vivo antimalarial activity against early erythrocytic schizogony of the rodent malaria parasite *Plasmodium berghei* in two different inbred mice, BALB/c and C57BL/6. On day four after infection and after four days of treatment, parasitaemia was ruled out in both BALB/c and C57BL/6 mice. When C57BL/6 and BALB/c mice were treated with an extract of neem fruit at a dose of 150 mg/kg, their parasitaemia was 5.4% and 7.4%, respectively. When mice were treated with an extract of ripe fruit at a dose of 150 mg/kg, their parasitaemia was 5.1% and 7.4%, respectively. When comparing the C57BL/6 mice treated with neem formulations to the solvent (H₂O containing 10% DMSO, 5% Tween 80) given controls, parasitaemia was reduced by around 30% on day 4. As an effective control, artesunate at a dose of 5 mg/kg decreased parasitaemia in C57BL/6 mice by 45% and in BALB/c mice by 60% as compared to the corresponding untreated (i.e., solvent-administered) controls. (43)

Using artemether, quinine, and chloroquine at doses of 10 mg/kg as standard medications, the impact of methanolic extracts of neem leaf and stem bark against *Plasmodium berghei*-infected albino mice was also assessed. The levels of parasitaemia in infected mice were effectively reduced by the leaf and stem bark extracts by roughly 51–80% and 56–87%, respectively, while the standard medications showed 85.49%, 73.39, and 29.85%, respectively, for artemether, quinine, and chloroquine. (44)

Antiviral Activity:

The in vitro antiviral efficacy of four fractions of neem seed kernel alcoholic extract against Duck Plague Virus (DPV) was assessed in an experimental investigation. At concentrations less than 31.25 µg/ml, fraction 4 did not exhibit any cytotoxic effects on Duck Embryo Fibroblasts (DEF) cells. (45) The Newcastle disease virus (NDV) was tested for antiviral activity using neem bark phosphate-buffered saline (PBS) extract using the spot assay and micro-hemagglutination test. Neem bark extract was found to exhibit cytotoxic action in addition to considerable antiviral activity at higher doses (1:2 dilution) in an in vitro research. Non-significant antiviral activity was detected at lower concentrations (1:8 dilution). (46)

Wound healing effect:

The clinical trial assessed the effectiveness of neem oil in treating chronic non-healing lesions. According to the study's findings, 43.80% of the 60 patients had 50% wound healing after 8 weeks of therapy. (47)

In a different in vivo investigation, twenty male wistar rats (control and test groups comprised ten animals each) were used to examine the wound-healing properties of an aqueous neem leaf extract. The control rats received a dressing of regular saline. A 2 cm by 2 cm diameter wound was created on the right dorso-lateral aspect of the thoracic wall.

The study's findings showed that on day six, the experimental group's mean percentage of wound contraction was $72.34 \pm 2.49\%$, compared to 62.39 ± 7.94 for the control group. and on day nine, the experimental animals' mean percentage of wound contraction was 92.20 ± 6.66 , compared to 85.19 ± 7.84 for the control group. The day of full wound closure, the *Azadirachta indica* leaf extract in the experimental group was found to be substantially greater ($p < 0.05$) than in the control group. (48)

In a different study, the ethanolic extract of neem leaves was used to test the wound healing activities. After 15 days of treatment, there was a significant decrease in the largest diameter wounds, and there was no significant difference in the longest diameter of wounds between the control drug, povidone iodine, and the test drug, neem leaves extract. (49)

Antioxidant activity:

Neem plant sections that modulate different biological functions, including as the root, bark, leaf, flower, and seed, play a role in managing diseases. The 1,1-diphenyl-2-picrylhydrazyl (DPPH) scavenging assay was used to assess the antioxidant activity of several sections of the Siamese neem tree (*Azadirachta indica* A. Juss var. *siamensis* Valetton, Meliaceae) in aqueous and ethanolic extracts.

The findings show that extracts from the Siamese neem tree's leaves, flowers, and stem bark have a significant antioxidant capacity. (50)

In a different investigation, the antioxidant potential of neem flower and seed oil extracts in aqueous, ethanolic, and methanolic forms was investigated. The study findings indicated that the maximum free radical scavenging activity, $64.17 \pm 0.02\%$ and $66.34 \pm 0.06\%$, respectively, were detected in the ethanolic extract of flowers and seed oil at 200 $\mu\text{g/ml}$. This effect may be caused by the largest level of total phenol content. (51)

It was found in another study that the methanolic and chloroform extracts of neem leaves had substantially greater antioxidant qualities than the chloroform extract. (52) According to this comparison study, the antioxidant activity of the bark is higher (93.11%) than that of the leaves (82.45%), and it is even higher than that of the conventional medication (vitamin C, 92%). The greater phenolic levels in the bark extracts (66.63 to 629.04 $\mu\text{g/mg}$) and leaf extracts (23.85 to 237.00 $\mu\text{g/mg}$) may be the cause. (53)

Nephroprotective effect: Neem leaf extract (methanolic) was found to be considerably beneficial at 500 mg/kg against oxidative stress and nephrotoxicity caused by Cisplatin (CP) in rats participating in a nephroprotective investigation. (54)

Antidiabetic effect:

Neem leaf extract was tested for its anti-diabetic properties in alloxan-induced diabetic mice in an experimental investigation. A single intraperitoneal dose of alloxan (240 mg/kg body weight) was used to cause diabetes in mice, and the mice were subsequently treated with continuous oral dosing of 500 mg of neem leaf extract/kg of body weight forty-two days. Following 42 days of therapy, the outcome showed a marked reduction in the elevated levels of total plasma cholesterol, including triglycerides and LDL, and blood sugar (TG). In addition to these, revealed a notable rise in erythrocytes and a fall in total leukocyte count and the greatest increase in body weight were discovered. This justification suggests that neem leaf crude extract could be a useful alternative medication for people with diabetes. (55)

The effects of neem (*Azadirachta indica*) seed oil on hypoglycemia and hypolipidemia were investigated in diabetic wistar albino rats produced with alloxan (150 mg/kg in 3 doses administered subcutaneously). The rats' plasma glucose and lipid profile levels were monitored 48 hours after the alloxan injection. For 21 days, the test group was given an oral dose of 5 ml/kg of neem seed oil, and no therapy is provided for diabetes management. The findings indicated that control group had a serum cholesterol of 170 ± 6.1 , a plasma glucose level of 280.4 ± 14.2 , and a serum HDL 18.91 ± 3.18 and triglycerides 93.3 ± 6 (mg/dl) in the test group plasma serum triglycerides 75.8 ± 3.6 , serum cholesterol 149 ± 7.0 , and serum glucose level 126.32 ± 6.20 and serum HDL levels were 32.61 ± 0.32 (mg/dl). It has been demonstrated by these data that neem seed oil is highly beneficial in treating hyperglycemia and hyperlipidemia. (56)

In a different trial, rabbits were given 500 mg/kg of neem kernel powder and 0.5 mg/kg of glibenclamide alone or in combination with 250 mg/kg of neem kernel powder and 0.25 mg/kg of glibenclamide as an antidiabetic drug. The findings demonstrated that these two drugs, either alone or in combination, considerably lower serum glucose, fat, and enzyme activity concentrations. (57)

Furthermore, the administration of 200 and 400 mg/kg of neem root bark extract was successful in lowering blood glucose levels, whereas 800 mg/kg of the extract demonstrated a noteworthy decrease in blood sugar levels. It lowered blood glucose levels by 54% as compared Glibenclamide (0.5mg/kg), the control drug. (58)

Cardioprotective effect:

Rats with isoprenaline-induced myocardial infarction were administered aqueous neem leaf extract at doses of 250, 500, and 1000 mg/kg orally in a cardioprotective experimental investigation based on hemodynamic, biochemical, and histological findings. Vitamin E, a proven cardioprotective antioxidant, at an oral dose of 100 mg/kg utilized as a comparison. The findings of the study showed that neem leaf substantial normalization of the majority of the hemodynamic, biochemical, and parameters of histopathology. The conclusion is that equipotent is produced by neem extract. Cardiovascular protecting properties in contrast to vitamin E. (59)

Immunomodulatory effect: The primary advantages of neem for the body are its immunomodulatory qualities. By injecting harmful substances into the assailants, "Killer T" cells, which have the capacity to eradicate bacteria, viruses, and cancer cells, strengthen both the cell-mediated and lymphocytic immune systems. (33) An investigation using an aqueous neem leaf extract at an oral dose of 100 mg/kg revealed strong immune stimulant effect after three weeks, as demonstrated by humoral and cell-mediated reactions. (60)

Aqueous extract of neem flowers has also been revealed that the flowers increase both specific (humoral and cell mediated immunity) and nonspecific immune responses (cytotoxic and phagocytic activity of macrophages). (61) Also, in an *in vivo* study, the results show that neem oil has a non-specific immunostimulant effect and that it selectively activates the cell-mediated immune (CMI) mechanisms to elicit an enhanced response to subsequent mitogenic or antigenic challenge. (62)

Hepatoprotective effect:

An investigation into the hepatoprotective properties of azadirachtin-A in rats with hepatotoxicity induced by carbon tetrachloride (CCl₄) was conducted. The findings showed that pre-treatment with azadirachtin-A dose-dependently decreased hepatocellular necrosis, as demonstrated by histology and ultrastructure studies. Furthermore, the study's findings show that azadirachtin-A pretreatment at higher dose levels somewhat returns the rat liver to normal. (63)

Another study used silymarin as a positive control and investigated the hepatoprotective effects of neem (*Azadirachta indica*) seed oil on Wistar rats treated with carbon tetrachloride (CCl₄) in a dose-dependent manner. Regarding nearly all measures, the results indicate that there is no significant difference ($P > 0.05$) when compared with the control. (64) Additionally, a study was designed to determine the hepatoprotective effect of an alcoholic neem leaf extract at doses of 250 and 500 mg/kg daily for 30 days on rats that had acute liver failure caused by rifampin (RFI). The study's findings demonstrated that, through an antioxidant and anti-inflammatory mechanism, the neem leaf extract considerably normalized serum biomarkers and improved histopathological alterations as compared to the control group. (65)

Role in dental health:

A clinical trial was conducted to compare the effectiveness of mouthwash containing neem with chlorhexidine in terms of its antigingivitis impact. According to the study's findings, mouthwash containing neem is just as efficient as a placebo in lowering plaque indices and gingival bleeding in both groups over the course of 21 days. As a result, it can be applied as an adjuvant therapy to gingivitis caused by plaque. (66)

To examine plaque clearance and gingival health, a clinical trial comparing a neem stick and a commercial toothbrush with toothpaste was conducted. The outcomes unequivocally demonstrated that there was no significant distinction between these two teeth-cleaning techniques and both approaches somewhat reduce the gingival and plaque scores relative to the starting point. (67)

Anticancer activity:

Aqueous and ethanolic neem leaf extracts have been tested for their anticancer properties on a variety of cell lines, including cervical, lung, and breast. (68,69,70) The individual and combined effects of ethanolic neem leaf extract were investigated in an experimental investigation. and pH have been examined at various times on the human breast cancer cell line MDA-MB 231. dosages (400, 600, 800, and 1600 µg/ml) at different pH

levels in 1% DMSO between 6.2 and 7.4. The study's findings demonstrated a significant impact (about 95.7%). cytotoxicity) in a combination trial using neem extract at a dosage level and a low pH (6.2). on MDA-MB 231 cells, 1600 µg/ml. (70)

CONCLUSION:

The presence of numerous physiologically active components that are beneficial against cancer, aberrant lipid levels, high sugar levels, liver damage, kidney toxicity, and many other conditions makes *Azadirachta indica*, also known as neem, one of the most significant traditional medicinal plants that have been used for generations.

For these reasons, the people should benefit from the usage of this significant medicinal plant in the contemporary medical system. To isolate, purify, and characterize the numerous physiologically active components found in various plant sections, more investigation is needed. These ingredients should be utilized to prepare a number of functional and nutraceutical foods for human consumption as well as to prevent and treat various health-related conditions.

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