

A Review on Medicinal Activity and Its Health Impact of *Azadirachta Indica* (Neem)

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ABSTRACT

Azadirachta indica is a fast growing, evergreen tree found commonly in India, Africa and America. Neem is one of the most useful traditional medicinal plant in India. It is a highly esteemed tree with several beneficial properties and applications, especially known for its incredible therapeutic and ethnomedicinal values for mankind. It has been used in different medicinal systems: Ayurveda, unani, homeopathic medicine, therefore considered as cynosure of modern medicine. Neem has been used as the traditional medicine since a long time. The main focus of research on Neem has been on the insecticidal properties but in recent years investigations have expanded to the medicinal utilizations as well. A large number of studies have been published on the medicinal properties of Neem and Neem extracts, covering a wide range of indications and ailments. The present paper reviews the medicinal and therapeutical aspects of Neem. Neem has become valuable plant in the world which shows the solutions for hundreds to thousands problems. Neem has become important in the global context today because it offers answers to the major concerns facing mankind. Neem has been extensively used in Ayurveda, Unani and Homoeopathic medicine and has become a centre of attraction of modern medicine. *Azadirachta indica* (neem) is a rapidly growing evergreen well known tree found generally in various regions of world like America, Africa and India. The aim of this review article provides information mainly on various pharmacological activities like anti-inflammatory, antimalarial, anti- bacterial, anti-allergic, antidermatic, antiulcer, antifungal, insecticidal, larvicidal and other pharmacological activities of neem plant and medicinal uses.

KEYWORDS: *Azadirachta indica*, Pharmacological activities, Medicinal uses

INTRODUCTION

Azadirachta indica, commonly known as neem, nimtree or Indian lilac, is a tree in the mahogany family Meliaceae. It is one of two species in the genus *Azadirachta*, and is native to the Indian subcontinent and most of the countries in Africa. It is typically grown in tropical and semi-tropical regions. Neem trees also grow on islands in southern Iran. Its fruits and seeds are the source of neem oil[1-3]. Medicinal plants are rich source of novel drugs that forms the ingredients in traditional systems of medicine, modern medicines, nutraceuticals, food supplements, folk medicines, pharmaceutical intermediates, bioactive principles and lead compounds in synthetic drugs. WHO pointed out that more than 80% of world's population depends on plants to meet their primary health care needs. However, overexploitation of the selected medicinal plant species lead to the reduction in number of plants in the wild and inclusion of their name in the red data book. Neem (*Azadirachta indica*) commonly called 'Indian Lilac' or 'Margosa', belongs to the family Meliaceae, subfamily Meloideae and tribe Melieae. *Azadirachta indica* has been used medicinally throughout history by many different cultures. Many compounds have been found in the exudates of the, *Azadirachta indica* plant that have been used medically by humans. Neem is a member of the Meliaceae family. *Azadirachta indica* is a fast growing evergreen popular tree found commonly in India, Africa and America. It has been used in Ayurvedic medicine for more than 4000 years due to its medicinal properties[4-7].

Taxonomic Identity: It has similar properties to its close relative, *Melia azederach*. The word *Azadirachta* is derived from the Persian *azadhirakt* (meaning 'noble tree'). The taxonomic positions of neem are as follows:

Kingdom	: Plantae
Clade	: Tracheophytes
Clade	: Angiosperms
Clade	: Eudicots
Clade	: Rosids
Order	: Sapindales
Family	: Meliaceae
Genus	: <i>Azadirachta</i>
Species	: <i>A. indica</i>

Description:

Tree: The neem tree (*Azadirachta indica*) is a fast growing (up to twenty feet in three years) tropical evergreen related to mahogany. It will grow where rainfall is as little as 18 inches per year and thrives in areas that experience extreme heat of up to 120°F. They are reported to live for up to 200 years[8-9].

Leaves: Compound, alternate, rachis 15-25 cm long, 0.1 cm thick; leaflets with oblique base, opposite, exstipulate, lanceolate, acute, serrate, 7-8.5 cm long and 1.0-1.7 cm wide, slightly yellowish-green; odour, indistinct; taste, bitter[10-12].

Stem Bark: Bark varies much in thickness according to age and parts of tree from where it is taken; external surface rough, fissured and rusty- grey; laminated inner surface yellowish and foliaceous, fracture, fibrous; odour, characteristic; taste, bitter.

Flower, Fruits and Seeds: The tree is often covered in delicate flowers in the early summer. The flowers (white and fragrant) are arranged axillary, normally more-or-less drooping panicles which are up to 25 cm long. It has a semi-sweet, olive-sized fruit. The seed inside is rich in oil with tremendous medicinal and botanical properties. The fruit is a smooth (glabrous), olive-like drupe which varies in shape from elongate oval to nearly roundish, and when ripe is 14–28 mm[13-15]. The fruit skin (exocarp) is thin and the bitter-sweet pulp (mesocarp) is yellowish-white and very fibrous. The mesocarp is 3–5 mm thick. The white, hard inner shell (endocarp) of the fruit encloses one, rarely two, or three, elongated seeds (kernels) having a brown seed coat[16-18].

Active Chemical Constituents

A. indica has complex of various constituents including nimbin, nimbidin, nimbolide, and limonoids and such types of ingredients play role in diseases management through modulation of various genetic pathways and other activities. Quercetin and β -sitosterol were first polyphenolic flavonoids purified from fresh leaves of neem and were known to have antifungal and antibacterial activities. Numerous biological and pharmacological activities have been reported including antibacterial, antifungal and anti-inflammatory. Earlier investigators have confirmed their role as anti-inflammatory, antiarthritic, antipyretic, hypoglycemic, antigastric ulcer, antifungal, antibacterial and antitumour activities and a review summarized the various therapeutic role of neem. *Azadirachta indica* (neem) contains a number of various types of ingredients having therapeutic properties[19-22]. The most important constituent is azadirachtin and others are nimbolin, nimbin, nimbidin, nimbidol, sodium nimbin, gedunin, salannin, and quercetin. Leaves contain ingredients such as nimbin, nimbanene, 6-desacetylnimbinene, nimbandiol, nimbolide, ascorbic acid, n-hexacosanol and amino acid, 7-desacetyl-7-benzoylazadiradione, 7-desacetyl-17-benzoylgedunin, 17-hydroxyazadiradione, and nimbiol. Quercetin and β -sitosterol, polyphenolic flavonoids, were purified from neem fresh leaves and were known to have antibacterial and antifungal properties and seeds hold valuable constituents including gedunin and azadirachtin[23-25].

PHARMACOLOGICAL ACTIVITIES

Anti-inflammatory

Plants or their isolated derivatives are in the practice to treat/act as anti-inflammatory agents. A study result has confirmed that extract of *A. indica* leaves at a dose of 200 mg/kg, p.o., showed significant anti-inflammatory activity in cotton pellet granuloma assay in rats. Earlier finding showed immunomodulator and anti-inflammatory effect of bark and leaf extracts and antipyretic and anti-inflammatory activities of oil seeds. Experimentation was made to evaluate the analgesic activity of neem seed oil on Albino rats and results of the study showed that neem seed oil showed significant analgesic effect in the dose of 1 and 2 mL/kg and oil has dose-dependent analgesic activity. Results of the study concluded that the treated animals with 100 mg kg⁻¹ dose of Carbon Tetrachloride Extract (CTCE) of *A. indica* fruit skin and isolated ingredient azadiradione showed significant antinociceptive and anti-inflammatory activities[26-28].

Antidiabetic and Antihyperlipaemic Activity

The antidiabetic and anti- hyperlipaemic effects of neem seed kernel powder on alloxan diabetic rabbits. In alloxan diabetic rabbits there was a significant ($P < 0.001$) increase in fasting blood glucose and urine sugar and there was a significant decrease ($P < 0.001$) in body weight and total haemoglobin content. There was a significant increase in body weight and haemoglobin level, and a significant decrease in Fasting Blood Glucose (FBG) and urine sugar in diabetic rabbits treated with NP, glibenclamide, insulin and in combination of NP and glibenclamide. To evaluated *in-vivo* diabetic murine model, *A. indica* and *B. spectabilis* chloroform, methanolic and aqueous extracts were investigated for the biochemical parameters important for controlling diabetes. It was found that *A. indica* chloroform extract and *B. spectabilis* aqueous, methanolic extracts showed a good oral glucose tolerance and significantly reduced the intestinal glucosidase activity [29-32].

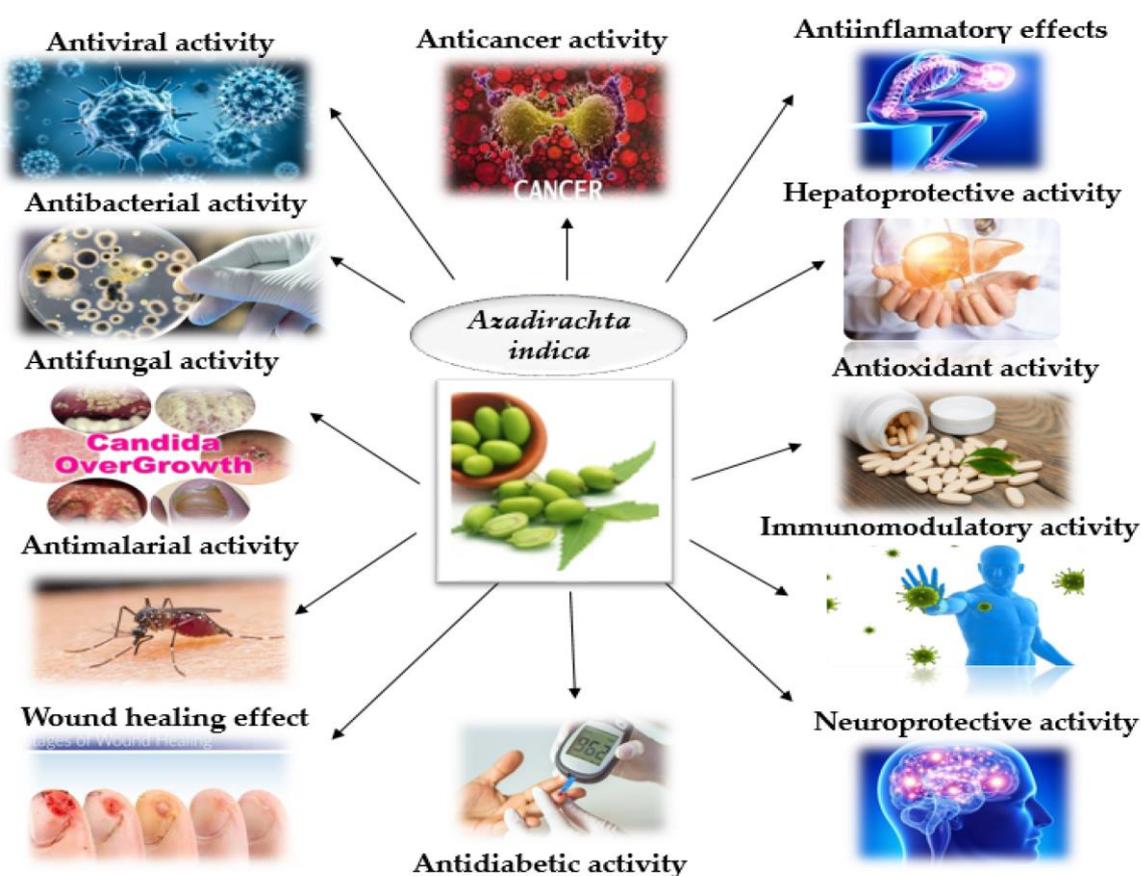


Figure 1. The Medicinal activity of neem and its health impact

Antifertility Activity

Neem has long been documented to have antifertility in males. Oral administration of ethanolic extracts of Neem to adult male mice at 0.5mg, 1.0 mg or 2.0 mg. per kg body weight for 6 weeks interfered with sperm DNA and caused chromosome strand breakage, spindle disturbances and deregulation of genes responsible for sperm morphology. A linear decrease in the percentage of sperm motility was observed with various concentrations (1-50 mg per 1 million sperm) of Neem leaf extract, with motility falling to absolute zero within 20 seconds

of exposure to 3 mg dose. The aqueous leaf extract of Neem when administered to male mice at a dose of 200 mg per kg for 28 days damaged the seminiferous tubules, resulting in the slackening of germinal epithelium, degeneration of germ cells and dearrangement of germ cell types[33-35].

Antibacterial Activity

Oil extracted from neem bark, leaves and seeds reveal its potent activity against organisms of gram-negative, gram-positive and mycobacterium tuberculosis. Neem oil extract yields four fractions of hexane in organic solvent methanol, such as methanol miscible for the first fraction (a), methanol immiscible for the second fraction (b), hexane miscible for the third fraction (c) and hexane immiscible for the fourth fraction (d). The first fraction displays a maximum antibacterial effect at 95%. The second and third fractions indicate 85% activity, and the fourth fraction exhibits 65% activity. Methanol, aqueous and petroleum ether extracts of the *A. indica* leaves have been screened for their antimicrobial properties using the cup plate agar well diffusion technique. The evaluation was conducted on six types of bacteria, which were gram-positive bacteria, *Bacillus subtilis* (*B. subtilis*) and *Staphylococcus aureus* (*S. aureus*) and four gram-negative bacteria, *Escherichia coli* (*E. coli*), *Proteus vulgaris* (*P. vulgaris*), *Pseudomonas aeruginosa* (*P. aeruginosa*) and *Salmonella typhi* (*S. typhi*)[36-38].

Antimalarial Activity

The antimalarial activities of the tablet suspension of the bark and leaf of *Azadirachta indica* were evaluated on *Plasmodium yoelli nigeriensis* infected mice. The tablet suspensions exhibited high prophylactic, mode-rate suppressive and a very minimal curative schizonticidal effect. The tablet suspensions from the leaf and bark at a concentration of 800 mg/kg and chloroquine at a concentration of 62.5 mg/kg body weight produced average percentage (%) parasitaemia of 79.6%, 68.2% and 99.5% for leaf, bark and chloroquine, respectively, in chemosuppression. Also in the prophylactic treatment, the tablet suspensions at 800 mg/kg and pyrimethamine at a concentration of 0.35 mg/kg gave an average parasitaemia reduction of 75.3%, 65.6% and 98.3% for the leaf, bark and pyrimethamine, respectively. There was a clear indication of moderate beneficial effect. Extracts of Neem are effective against a variety of protozoal pathogen like *Plasmodium* spp[39-42].

Antifungal Activity

Another study was conducted to determine antifungal activity of various neem leaf concentrates on seed-borne parasites such as *Aspergillus* and *Rhizopus*; the findings showed that the growth of both infectious species was profoundly depressed and regulated by aqueous and alcoholic extracts. Ethyl acetate neem leaf extracts (5, 10, 15 and 20%) inhibited human pathogens (*A. niger*, *Aspergillus flavus*, *A. fumigatus*, *A. terreus*, *C. Albicans* and *M. gypsum*)[43-45]. Antidermatophytic activity against dermatophyte isolates has been demonstrated using the agar dilution method to produce aqueous and ethanolic neem leaf extracts[46-47]. Ethanol extract exhibited more visible activity than aqueous extract . Antifungal properties were also screened using acetone and methanolic extracts of *A. indica* against two distinct fungal strains, such as *A. fumigatus* and *A. niger*. It was stated that methanolic neem extract exhibited extreme antifungal effects compared to acetonic

extracts[48-53].

Anticarcinogenic Activity

Neem leaf aqueous extract effectively suppresses oral squamous cell carcinoma induced by 7, 12-dimethylbenz [a]anthracene (DMBA), as revealed by reduced incidence of neoplasm[54-57]. Neem may exert its chemopreventive effect in the oral mucosa by modulation of glutathione and its metabolizing enzymes. That neem leaf extract exerts its protective effect in N-methyl- N ϵ -nitro-N-nitroso- guanidine (MNNG) (a carcinogenic material)- induced oxidative stress has also been demonstrated by the reduced formation of lipid peroxides and enhanced level of antioxidants and detoxifying enzymes in the stomach, a primary target organ for MNNG as well as in the liver and in circulation[58-60].

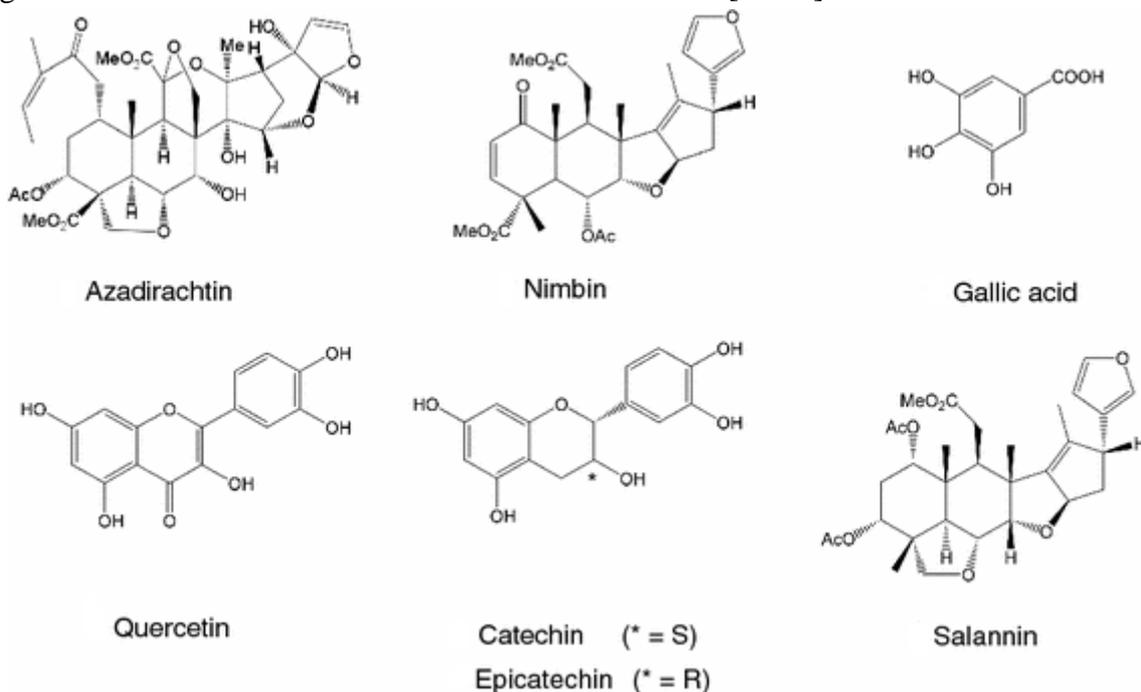


Figure 2. Active Chemical Constituents of *Azadirachta indica*

Antimalarial Activity

Ball shaped wood scrapings which is soaked in 5% neem oil (*Azadirachta indica*) which is diluted in acetone and in 45 days the breeding of *Anopheles stephensi* and *Aedes aegypti* were controlled, when it is placed in water storage over head tanks[61-64]. Nimbolide isolated from neem extracts shows the antimalarial activity by preventing the growth of *Plasmodium falciparum*. Gedunin isolated from neem seed oil has been reported to show antimalarial activities. Both aqueous and alcohol extracts of bark and leaves of neem are effective antimalarial agents, particularly on chloroquine resistant strains[65-69].

Antiulcer Activity

The antiulcer effect was obtained with nimbidin in preventing acetyl salicylic acid, indomethacin, serotonin-induced gastric lesions or stress as well as cysteamine induced duodenal ulcers or histamine[70-74]. Leaf extract of *A. indica* (Neem) shows antiulcer effect was reported the inhibition of mucus depletion and most cell defragmentation as possible

mechanism. Bandyopadhyay *et al.*, isolates the phenolic glycoside as an active constituent, whose characterization and mechanism are under investigation[75-77]. Therefore, *Azadirachta indica* offers another option for an effective antiulcer drug and which is safe.

Wound Healing Activity

The wound healing properties in small animal model, the excision and incision wound models were used and water, ethanol-water (1:1, v/v) and ethanol extracts were applied topically (15% w/w in ointment base)[78-82]. In the excision wound model, wound contraction, hydroxyproline content, DNA content, protein content, and nitric oxide levels were estimated after 14 days of topical treatment along with histopathological examinations. In the incision wound model, wound breaking strength was determined after 10 days of topical application of different extracts of AI. The animals treated with water extract of AI exhibited significant increment in rate of wound contraction (93.39%, $P < 0.01$), hydroxyproline content (13.31 ± 6.65 mg/g of dry tissue, $P < 0.001$), DNA content (20.99 ± 0.68 μ g/100 mg of tissue, $P < 0.01$), protein content (100.53 ± 7.88 mg/g of wet tissue, $P < 0.01$) and nitric oxide level (3.05 ± 0.03 mMol/g of tissue, $P < 0.001$) as well as in wound breaking strength (289.40 ± 29.45 g, $P < 0.01$) when compared with vehicle control group which was also supported by histopathological studies. The water extract of stem bark of AI possesses significant wound healing property, validating its traditional use[83-87].

Insect Repellent

Azadirachtin is a powerful insect antifeedant that disrupts metamorphosis in moth larvae at extremely low concentrations[88-90]. A number of studies have shown that Neem compounds are more effective insect repellent than the widely used synthetic chemical known as N,N,-diethyl -m-toluamide, a suspected carcinogen. Neem oil affects the efficacy of commercially available insecticides. Neem seed extracts are effective against both asexual and sexual stages of chloroquinresistant as well as sensitive strains of malarial parasites *P.falciparum*. Seed extract have inhibited growth and development of the human malarial parasitic agent[91-94].

Herbal Cosmetics

"The curer of all ailments" Neem's role as a wonder drug is stressed as far back as 4500 years ago. Some of its health restoring benefits. Effective in skin infection, rashes and pimples, immunity booster, anti obesity, blood purifier for beautiful and healthy skin, piles, hair disorder and oral disorders[95-97].

Antiviral Activity

Results showed that neem bark (NBE) extract significantly blocked HSV-1 entry into cells at concentrations ranging from 50 to 100 μ g/mL. Furthermore, blocking activity of NBE was noticed when the extract was preincubated with the virus but not with the target cells suggesting a direct anti-HSV-1 property of the neem bark. Leaves extract of neem (*Azadirachta indica* A. Juss.) (NCL-11) has shown virucidal activity against coxsackievirus virus B-4 as suggested via virus inactivation and yield reduction assay besides interfering at an early event of its replication cycle[98].

CONCLUSION

Popularity of natural products or their derivatives role in diseases cure and prevention is increasing worldwide due to less side effect properties. Neem and its ingredients have therapeutics implication and have been traditionally used worldwide especially in Indian Subcontinent since ancient time. By reviewing the importance of neem tree in national, regional and international perspective there is an urgent need to study its diversity and develop effect measures to store it for present and future use. At the same time it is also necessary to undertake ethnobotanical studies to link its various therapeutic uses with folklore remedies used by tribes in various areas of its occurrence. For the last few years, there has been an increase tendency and attention in neem research. Quite a significant amount of research has already been carried out during the past few decades in exploring the chemistry of different parts of neem. Several therapeutically and industrially useful preparations and compounds have also been marketed, which generates enough encouragement among the scientists in exploring more information about this medicinal plant. Neem provides various pharmacological activities like anti-inflammatory, antimalarial, antibacterial, anti-allergic, anti-dermatic, anti-ulcer, anti-fungal, insecticidal, larvicidal and other pharmacological activities of neem plant and medicinal uses.

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