Alok Maithaniet al. / Journal of Pharmacy Research 2011,4(6),1824-1827

Review Article
ISSN: 0974-6943

Available online through
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AZADIRACHTA iNDICA (NEEM) LEAF: A REVIEW

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Received on: 11-02-2011; Revised on: 16-03-2011; Accepted on:21-04-2011

ABSTRACT

The use of traditional medicine and medicinal plants in most developing countries, as a normative basis for the maintenance of good health, has been widely observed. In the last century, roughly 121 pharmaceutical products have been discovered based on the information obtained from the traditional healers. Chemical principles from natural sources have become much simpler and have contributed significantly to the development of new drugs from medicinal plants. And because of these facts the world market for plant-derived chemicals – pharmaceuticals, fragrances, flavours, and colour ingredients, alone exceeds several billion dollars per year. *Azadirachta indica* is one of the most revenue releasing plant grown in India because of several phytoconstituents present in it and also due to a number of pharmacological activities associated with it. The present review highlights a literature on taxonomical, botanical, phytoconstituents, and pharmacological discussion on *Azadirachta indica* leaves.

Key words: Ayurveda, Pharmacological Activity, Traditional Uses, Botanical Description, *Azadirachta indica*.

INTRODUCTION

Neem is a tree in the mahogany family Meliaceae. It is one of two species in the genus *Azadirachta*, and is native to India and Burma, growing in tropical and semi-tropical regions. It is a fast growing tree that can reach a height of 15-20 m, rarely to 35-40 m. It is evergreen but under severe drought it may shed most or nearly all of its leaves. The branches are wide spread. For thousands of years the beneficial properties of Neem (*Azadirachta indica* A. Juss) have been recognized in the Indian tradition. Each part of the neem tree has some medicinal property. The taxonomical classification of neem is, Rutales (Order), Rutinae (Suborder), Meliaceae (Family), Melioideae (Subfamily), Melieae (Tribe), Azadirachta (Genus), and indica (Species).

TAXONOMY OF *AZADIRACHTA INDICA* :

Kingdom - Plantae
Division - Magnoliophyta
Class - Dipsacales
Order- Rutales
Sub-order- Rutinae
Genus - Azadirachta
Species - indica

HISTORY:

Along with Ayuerveda most of world's other reputed medicinal system like Unani, Chinese, and European "Materia Medica" have announced and acknowledged neem tree as "Panacea of all Disease". However in India it is famous with many other names like 'Divine Tree', "Heal All", "Nature's Drugstore", and "Village Dispensary". Traditional Ayurvedic uses of neem include the treatment of fever, leprosy, malaria, ophthalmia and tuberculosis. Various folk remedies for neem include use as an anthelmintic, antifeedant, antiseptic, diuretic, emmenagogue, contraceptive, febrifuge, parasiticide, pediculocide and insecticide. Traditional routes of administration of neem extracts included oral, vaginal and topical use. It is honored colloquially in these circles as 'The Village Pharmacy', millions with exposure to the tree brush their teeth with its twigs, use its juice on their skin disorders and place its leaves throughout their homes to keep away insects. Few most important traditional uses of the different parts of plants are below stated;

- Neem twigs are used for brushing teeth in India and Pakistan. This practice is perhaps one of the earliest and most effective forms of dental care.
- All parts of the tree (seeds, leaves, flowers and bark) are used for preparing many different medical preparations.
- Neem oil is useful for skin care such as acne, and keeping skin elasticity.
- Traditionally, patients suffering from Chicken Pox sleep on the leaves in India owing to its medicinal value.
- In Ayurvedic, Unani and folklore traditional medicine, different parts of neem were preferred in the treatment of a wide range of afflictions.

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DESCRIPTION:

MACROSCOPIC DESCRIPTION:[1]

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 ^{0}F. They are reported to live for up to 200 years.

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.

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 oil is easily obtained by pressing the kernels in a juicer. It generally begins bearing fruit at three to five years, and can produce up to 110 lbs. of fruit annually when mature.

MICROSCOPIC DESCRIPTION:

LEAF
MIDRIB

leaflet through midrib shows a biconvex outline; epidermis on either side covered externally with thick cuticle; below epidermis 4-5 layered collenchyma present; stele composed of one crescent-shaped vascular bundle towards lower and two to three smaller bundle towards upper surface; rest of tissues composed of thin-walled, parenchymatous cells having secretory cells and rosette crystals of calcium oxalate; phloem surrounded by non-lignified fibre strand; crystals also present in phloem region.

LAMINA shows dorsiventral structure; epidermis on either surface, composed of thin walled, tangentially elongated cells, covered externally with thick cuticle; anomocytic stomata present on lower surface only; palisade single layered; spongy parenchyma composed of 5-6 layered, thin-walled cells, traversed by a number of veins; rosette crystals of calcium oxalate present in a few cells; palisade ratio 3.0-4.5; stomatal index 13.0-14.5 on lower surface and 8.0-11.5 on upper surface.

STEM BARK -Shows outer exfoliating pieces hard, woody, considerably thick in older barks; almost entirely dead elements of secondary phloem, alternating with discontinuous tangential bands of compressed cork tissue, former composed of several layers of stone cells occurring in regularly arranged groups together with collapsed phloem elements filled with brown contents; in between the successive zones of cork tissue 3-5 layers of fibre groups with intervening thin-walled and often collapsed phloem elements present; each zone of cork

tissue consists of several layers of regular, thinwalled cells occasionally with a few compressed rows of thick-walled cells towards.

ORIGIN AND DISTRIBUTION:

The neem tree occurs throughout India. According to an estimate, there are about 20 million trees in the country.[2] The neem tree is noted for its drought resistance. Normally it thrives in areas with sub-arid to sub-humid conditions, with an annual rainfall between 400 and 1200 mm. It can grow in regions with an annual rainfall below 400 mm, but in such cases it depends largely on the ground water levels. Neem can grow in many different types of soil, but it thrives best on well drained deep and sandy soils (*p*H 6.2-7.0). It is a typical tropical/subtropical tree and exists at annual mean temperatures between 21-32 °C. It can tolerate high to very high temperatures. It does not tolerate temperature below 4 °C (leaf shedding and death may ensue).

PHYTOCHEMICALS AND PHARMACOLOGICAL ACTIVITY INVOLVE:

Neem is well known in India and its neighboring countries for more than 2000 years as one of the most versatile medicinal plants having a wide spectrum of biological activity. Every part of the tree has been used as traditional medicine for household remedy against various human ailments, from antiquity[3-7].

Individual neem tree may vary in chemical make-up because of genetic and environmental factors. The studies carried by different scientists in different passage of time has proved the natural variability in percentage content of the phytochemicals.[8-11] More than 135 compounds have been isolated from different parts of neem and several reviews have also been published on the chemistry and structural diversity of these compounds. The compounds have been divided into two major classes: isoprenoids (like diterpenoids and triterpenoids containing protomeliacins, limonoids, azadirone and its derivatives, gedunin and its derivatives, vilasinin type of compounds and C- secomeliacins such as nimbin, salanin and azadirachtin) and non-isoprenoids, which are proteins (amino acids), carbohydrates (polysaccharides), sulphurous compounds, polyphenolics such as flavonoids and their glycosides, dihydrochalcone, coumarin and tannins, aliphatic compounds, etc. An average composition of neem oil fatty acids is, Linoleic acid (6 – 16%), Oleic acid (25 – 54%), Hexadecanoic acid(16 – 33%), Octadecanoic acid(9 – 24%) along with alpha-liolenic acid and 9-hexadecenoic acid.

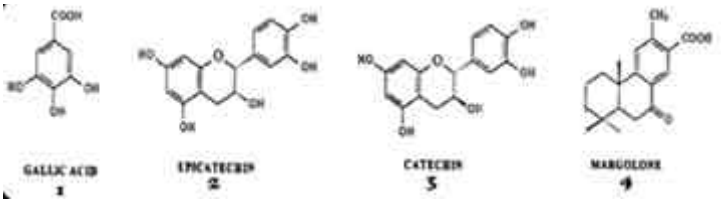
The various parts of neem tree have been used in curing various diseases which are enumerated below,

BARK:

Condensed tannins from the bark contain gallic acid, (+) gallocatechin, (–) epicatechin, (+) catechin and epigallocatechin, of which gallic acid (**1**), (–) epicatechin (**2**) and catechin (3) are primarily responsible for inhibiting the generation of chemiluminescence by activated human olymorphonuclear neutrophil (PMN)[12], indicating that these compounds inhibit oxidative burst of PMN during inflammation.

Three tricyclic diterpenoids, margolone (**4**), margolonone (**5**) and isomargolonone (**6**) isolated from neem stem bark are active against *Klebsiella*, *Staphylococcus* and *Serratia* species[13].

A polysaccharide extracted from bark inhibits carrageenin-induced inflammation in mouse[14]. Two water-soluble polysaccharides GIa (**7**) and GIb isolated from the bark of *Melia azadirachta*, demonstrated strong antitumour effect with complete regression of the tumours, when administered in mice at a daily dose of 50 mg/kg for four days from 24 h after subcutaneous inoculation of Sarcoma-180 cells[15]. Two more polysaccharides, GIIa (**8**) and GIIIa (**9**) isolated from *M. azadirachta* bark also showed significant anti-inflammatory effect on carrageenin-induced oedema in mice[16].



The aqueous extract of neem bark possesses anticomplement activity, acting both on the alternative as well as the classical pathway of complement activation in human serum[17]. Recently, an aqueous extract of stem bark has been shown to enhance the immune response of Balb-c mice to sheep red blood cells *in vivo*[18].The chloroform extract of stem bark is effective against carrageenin-induced paw oedema in rat and mouse ear inflammation. Inflammatory stomatitis in children is cured by the bark extract[19].An aqueous extract of neem bark has been shown from our laboratory to possess highly potent antiacid secretory and antiulcer activity and the bioactive compound has been attributed to a glycoside[20].The crude ethanolic extract of stem bark and root bark showed hypotensive, spasmolytic and diuretic activities.In ayurvedic medicinal system the bark of neem is used as analgesic, and in alternative and curative fever.

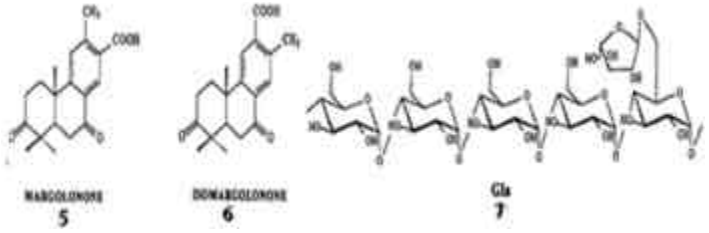


Table 1: Chemical composition and pharmacological activities of different parts of *Azadirachta indica*

Part Used	Extract/ Constituent	Structure	Pharmacological Activity	Reference
Bark	(Tannins)	1	Inhibit Chemiluminescence Generation	12
	Gallic acid	2		
	(–) epicatechin	3		
	Catechin			
	(Diterpenoids)	4	Antibacterial	13
	Margolone	5		
	Margolonone	6		
	Isomargolonone			
	(Polysaccharides)	7	Antitumor	15
	GIaGIb			
	(Polysaccharide)	8	Anti-inflammatory	16
	GIIaGIIIa	9		
	Glycoside		Antiacid Secretory and antiulcer	20
	Ethanolic Extract		Hypotensive, Spasmolytic, and Diuretic	
	Chloroform Extract		Inflammation	19
	Aqueous Extract		Anticomplement, Immune stimulant	17, 18, 20
	Ayurvedic		analgesic, alternative and curative fever.	
Leaf	Cyclic Trisulphide	10	Antifungal	21
	Tetra sulphide	11		
	(Flavonoid)		Hyperglycemic	29
	Quercetin			
	Methanolic Extract		Antipyretic and Inhibit Plaque Gormation	22, 35
	Aqueous Extract		Immune stimulation, hypoglycemic, antiulcer, antifertality, antiviral, anticarcinogenic, hepatoprotective	24, 25, 27-34, 36, 39.
	Acetone Extract		CNS Depressant	41
	Auyrvedic		Leprosy, eye problem, epistaxis, intestinal worms, anorexia, biliousness, skin ulcers.	
Oil	Nimbidine		Anti-inglammatory and Antipyretic	53, 54
	Nimbine	12	Anti-malarial and Antibacterial	55-57
	Nimbolide	13		
	Azadirachtin	14	Antifeedent and Anti-malarial	58-60
	Ayurvedic		leprosy and intestinal worms.	
Fruit	Phytosterols		Antiulcer	52
	Ayurvedic		Piles, intestinal worm, urinary disorder, epistaxis, phegm, diabetes, wound and leprosy.	

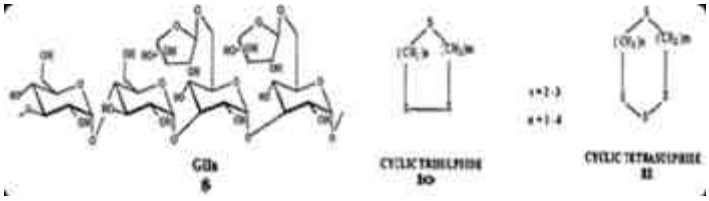
LEAF:

Sulphur-containing compounds such as cyclic trisulphide (**10**) and tetrasulphide (**11**) isolated from the steam distillate of fresh, matured neem leaves have antifungal activity against *Trichophyton mentagrophytes*[21].

A methanol extract of the leaves exerts antipyretic effect in male rabbits[22]. The plant also possesses analgesic activity mediated through opioid receptors in laboratory animals. Anti-inflammatory and antipyretic activities in various extracts have been reviewed[23].

The aqueous extract of leaf also possesses potent immune-stimulant activity as evidenced by both humoral and cell-mediated responses[24,25]. Leaf extract at 100 mg/kg after three weeks of oral administration causes higher IgM and IgG levels along with increased titer of antiovalbumin antibody. Neem oil has been shown to possess immunostimulant activity by selectively activating the cell-mediated immune mechanisms to elicit an enhanced response to subsequent mitogenic or antigenic challenge[26].

Aqueous extract of neem leaves significantly decreases blood sugar level and prevents adrenaline as well as glucose-induced hyperglycaemia[27]. The aqueous leaf extract when orally fed, also produces hypoglycaemia in normal rats and decreased blood glucose levels in experimentally-induced diabetes in rats[28]. Aqueous leaf extract also reduces hyperglycaemia in streptozotocin diabetes and the effect is possibly due to presence of a flavonoid, quercetin[29].

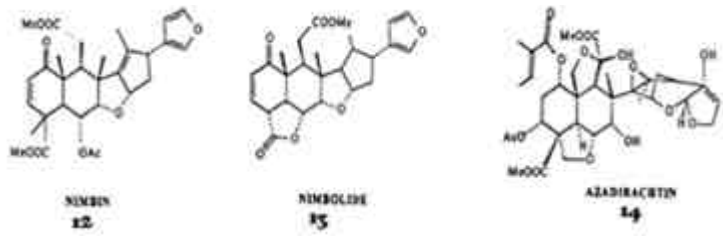


Neem leaf aqueous extract produces antiulcer effect in rats exposed to restraint – cold stress or ethanol orally by preventing mucus depletion and mast cell degranulation[30].

Oral administration of aqueous extract of neem leaf also shows antifertility effect in mice[31]. Purified neem seed extract (Praneem) has also been demonstrated to abrogate pregnancy in both baboons and bonnet monkeys, when administered orally[32].

Aqueous leaf extract offers antiviral activity against Vaccinia virus[33], Chikungemya and measles virus *in vitro*[34]. The antiviral and virucidal effects of the methanolic extract of neem leaves (NCL-11) have recently been demonstrated against group-B Coxsackie viruses[35]. NCL-11 inhibits plaque formation in different antigenic types of Coxsackie virus B at a concentration of 1 mg/ml at 96 h *in vitro*. Further studies indicated that NCL-11 is most effective in Coxsackie virus B-4 as a virusidal agent, in addition to its interference at the early events of its replication.

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[36]. 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*-nitro-*N*-nitrosoguanidine (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[37,38].



The aqueous extract of neem leaf was found to offer protection against paracetamolinduced liver necrosis in rats[39]. The elevated levels of serum aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma glutamyl transpeptidase (GGT) indicative of liver damage, were found to be significantly reduced on administration of the neem leaf aqueous extract.

Varying degrees of central nervous system (CNS) depressant activity in mice was observed with the leaf extract[40]. Fractions of acetone extract of leaf showed significant CNS depressant activity[41]. Leaf extract up to a dose of 200 mg/kg body weight produces significant anxiolytic activity in rats.

Ayurveda reports reveil the use of neem leaf in Leprosy, eye problem, epistaxis, intestinal worms, anorexia, biliousness, and skin ulcers.

SEED:
From the hexane extract of neem seed, an active fraction containing six components has been found to completely abrogate pregnancy in rodents when given orally up to a concentration of 10%, with no apparent side effect. The effect is possibly due to activation of cell-mediated immune reaction. The mechanism of action of neem oil appears to be non-hormonal, probably mediated through its spermicidal effect and may have less side effects than steroidal contraceptives.

Neem seed and leaf extracts are effective against malarial parasites[42]. Components of the alcoholic extracts of leaves and seeds are effective against both chloroquin-resistant and sensitive strains of malarial parasite[43]. Recently, neem seed extract and its purified fractions have been shown to inhibit growth and development of asexual and sexual stages of drugsensitive and resistant strains of the human malarial parasite *P. falciparum*[44].

Extracts of neem leaf, neem oil and seed kernels are effective against certain human fungi, including *Trichophyton, Epidermophyton, Microsporum, Trichosporon, Geotricum* and *Candida*[45]. High antimycotic activity with extracts of different parts of neem has already been reported.

Oil from the leaves, seeds and bark possesses a wide spectrum of antibacterial action against Gram-negative and Gram-positive microorganisms, including *M. tuberculosis* and streptomycinresistant strains[46]. *In vitro*, it inhibits *Vibrio cholerae, Klebsiella pneumoniae, M. tuberculosis* and *M. pyogenes*[47]. Antimicrobial effects of neem extract have been demonstrated against *Streptococcus mutans* and *S. faecalis*[48]. NIM-76, a new vaginal contraceptive from neem oil showed inhibitory effect on the growth of various pathogens, including bacteria, fungi and virus[49]. Recently, the antibacterial activity of neem seed oil was assessed *in vitro* against 14 strains of pathogenic bacteria[50]. The antioxidant activity of neem seed extract has been demonstrated *in vivo* during horsegrain germination, which is associated with low levels of lipooxygenase activity and lipid peroxides[51]. An antioxidant principle has also been isolated, which is a potent inhibitor of plant lipooxygenases.The ayurveda recommend the importance of neem seed as a useful drug in leprosy and intestinal worms.

FRUIT:
Some active ingredient (Phytosterols) were isolated from the lipophilic fraction of neem fruit, exhibit antiulcer activity in stress induced gastric lesion.[52]In Ayurveda it is used in piles, intestinal worm, urinary disorder, epistaxis, phegm, diabetes, wound and leprosy.

OIL:
Nimbidin, a major crude bitter principle extracted from the oil of seed kernels of *A. indica* demonstrated several biological activities. Nimbidin possess significant dose dependent anti-inflammatory and antipyretic activity [53,54].
From this crude principle some tetranortriterpenes, including nimbin (12), nimbinin, nimbidinin, nimbolide(13) and nimbidic acid have been isolated. These have been shown to exert antimalarial activity by inhibiting the growth of *Plasmodium falciparum*[55,56]. Nimbolide also shows antibacterial activity against *S. aureus* and *S. coagulase*[57].

Neem oil also contains steroids (campesterol, beta-sitosterol, stigmasterol) and a plethora of triterpenoids of which Azadirachtin (14) is the most well known and studied. The Azadirachtin content of Neem Oil varies from 300ppm to over 2000ppm depending on the quality of the neem seeds crushed. Azadirachtine having strong antifeedant activity[58,59], has been demonstrated to have antimalarial property as well. It is inhibitory to the development of malarial parasites[60].

A significant hypoglycaemic effect was also observed by feeding neem oil to fasting rabbits. Recently, hypoglycaemic effect was observed with leaf extract and seed oil, in normal as well as alloxan-induced diabetic rabbits[61]. The possible mechanisms underlying the hypoglycaemic activity of the aqueous leaf extract have also been discussed[62,63].

Neem oil proved spermicidal against rhesus monkey and human spermatozoa *in vitro*[64]. *In vivo* studies showed that intravaginal application of neem oil prior to coitus can prevent pregnancy. Antifertility effect of neem oil has also been studied and suggested to be a novel method of contraception[65-67]. Antipyretic activity has been reported in neem oil.In ayurveda it is used for the treatment of leprosy and intestinal worms.

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Source of support: Nil, Conflict of interest: None Declared