

## AN UPDATE ON THE THERAPEUTIC POTENTIAL OF NEEM AND ITS ACTIVE CONSTITUENTS: A PANACEA FOR ALL DISEASES

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Received on : 09-02-2019

Accepted on : 20-06-2019

### ABSTRACT

Herbal plants play an important role in the global context today. In the last century, approximately 121 pharmaceutical products were discovered based on the information obtained from the plants used in Ayurveda, the Indian traditional system of medicine. Phytoconstituents isolated from natural sources have contributed significantly to the development of novel drugs from medicinal plants. Among all medicinal plants, neem (*Azadirachta indica*) has been widely used in treatment of diseases because it is a rich source of antioxidants. It contains 60 different types of biochemically active components including steroids and terpenoids.

Various parts of neem tree are known to possess antifungal, anticancer, antifertility and other biological activities. The present review provides a bird's eye view of the various medicinal properties and therapeutic applications of this important medicinal plant. It has rightly been called as a 'single solution to a thousand problems'.

**KEYWORDS:** *Azadirachta indica*, Active components, Biological activities, Medicinal uses.

### INTRODUCTION

Neem is a fast-growing evergreen tree used in treatment of multiple diseases for more than 4000 years (1). It is one of the two species in the genus *Azadirachta* and is native to the Indian subcontinent i.e. India, Nepal, Pakistan, Bangladesh, Srilanka and the Maldives. It typically grows in tropical and semitropical regions. The tree also grows in islands located in the southern part of Iran and is indigenous to Southeast Asia and West Africa. Neem has been recently introduced in the Caribbean and several Central American countries including Mexico. The people of India have revered the neem tree for centuries. Two species of *Azadirachta indica* have been reported viz. *Azadirachta indica* A. Juss is native to Indian subcontinent and *Azadirachta excelsa* Kack is confined to Philippines and Indonesia. There is an estimated number of 25 million trees growing all over India of which 5.5% are found in Karnataka, 55.7% in Uttar Pradesh and 17.8% in Tamil Nadu (2). The other states of India where neem tree is found are Andhra Pradesh, Assam, Bihar, Delhi, Gujarat, Haryana, Himachal Pradesh, Kerela, Madhya Pradesh, Maharashtra, Meghalaya, Odisha, Punjab, Rajasthan and West Bengal along with Andaman and Nicobar islands. As per U.S National Academy of Science report of 1992, India stands first in neem seed production and about 4,42,300 tons of seeds are produced annually yielding 88,400 tons of neem oil

and 3,53,800 tons of neemcake (2). Neem usually grows up to a height of 15-20 m and rarely to 35-40 m. New leaves appear in March-April and are bitter in taste (3). Neem was described by De Jussieu in 1830 and its taxonomic classification is as follows:

- Kingdom: Plantae
- Division: Magnoliophyta
- Class: Magnoliopsida
- Subclass: Rosidae
- Order: Sapindales
- Family: Meliaceae
- Genus: *Azadirachta*
- Species: *Azadirachta indica*

Neem is commonly used in Ayurveda because it contains many active components such as azadirone, azadiractin, flavonoids, etc. These active components have potential therapeutic properties (4). In India, with the increase in population size, there has been an ever growing demand for this plant (5). Neem helps in the prevention and treatment of diseases via regulation of a number of biological and physiological pathways (5). The medicinal properties of neem are well-documented (6). Recent studies have focused on antiarthritic, anti-inflammatory, antipyretic, hypoglycemic, antiulcerative, antifungal, antibacterial and antitumor activities of neem (7-10).

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<b>Leaf</b> Leprosy Eye problems Epistaxis	<b>Twig</b> Cough Asthma Piles	<b>Flower</b> Bile suppression Phlegm Elimination of intestinal_worms	<b>Bark</b> Analgesic Antipyretic	<b>Fruit</b> Piles Urinary disorders Diabetes	<b>Seed</b> Leprosy Intestinal worms Cancer
<b>Oil</b> Leprosy Intestinal Worms		<b>NEEM</b> Common Medicinal Uses		<b>Gum</b> Seabies Wounds Ulcers	

**Fig 1: Medicinal Properties Of Different Parts of Neem**

Neem is commonly known by several names in different parts of viz. limbo, nim, nimba, medusa and vempu. It is referred to as the village pharmacy in South Asia on account of its being a panacea for nearly every disease type (11-14). It is also the source of ecofriendly products such as neem oil biodiesel, a non-toxic, biodegradable and renewable fuel (15). Neem as a whole, is a source of more than 140 chemically and structurally complex biological active components. Leaves, seeds, fruits and roots have found ample mention and use in Ayurveda. Some of the important phytocomponents isolated from neem are azadirachtin, meliacin, gedenin, salanin, nimbin,

valassin, kaemferol, quercetin, quercetin-3-galactoside, rutin, isorhamnetin, nimbolide, vilasinin, nimbinene, 6-deacetyl nimbinene, nimbolide, nimocinol,  $\beta$ -sitosterol,  $\beta$ -sitosterol- $\beta$ -D-glucoside, sugiol, nimbiol, nimbin, nimbinin, nimbolin A and B, 6-deacetyl nimbinene, kaemferol-3-glucoside, meliantriol, etc. Neem oil contains tigenic acid (5-methyl-2 butanoic acid). Most of these phytocomponents belong to the chemical class of triterpenoids (limonoids) which are slightly hydrophilic and easily soluble in organic solvents such as alcohols, ketones and esters (15).



(a)



(b)



(c)



(d)

**Fig 2: (a) Leaves (b) Seeds (c) Fruits and (d) Roots of Neem**

Leaves contain ingredients such as nimbin, nimbanene, 6-desacetynim, etc (16). Four new limonoids viz. 7,12-dihydroxyvilasinone, vilasindione, 4-dehydroxynimbandiol and azadiramide B isolated from extracts of *Bacillus subtilis* fermented neem seeds, have been shown to possess cytotoxicity against MDA-MB-231 with an  $IC_{50}$  value of  $15.73 \pm 6.07 \mu M$  (17). In another study, nimbolide has been found to inhibit prostate cancer cell survival and growth by nuclear factor kappa-light-chain-enhancer of activated B cells (NF- $\kappa B$ ) and mitogen activated protein kinase (MAPK) pathways (18). The bark of

neem has been reported to possess antibacterial and antioxidant activity also (19). Alkaline pH has been found to augment the cytotoxic effect of ethanolic extract of neem leaves (20).

## 2. MEDICINAL USES

Neem has been used as a medicine in traditional systems of medicine like Ayurveda, Unani and Siddha (21). Neem has been reported to possess several biological properties as discussed above (22, 23). The medicinal uses of various parts of neem and their active constituents have been summarized in Table 1.

Parts of Neem	Medicinal uses	Chemical constituents	Chemical formula
Leaves	Leprosy, eye problem, epistaxis, intestinal worms, anorexia, biliousness, skin ulcers	glucoside of quercetin	C <sub>21</sub> H <sub>20</sub> O <sub>12</sub>
		glucoside of kaempferol	C <sub>21</sub> H <sub>20</sub> O <sub>11</sub>
		quercetin	C <sub>15</sub> H <sub>10</sub> O <sub>7</sub>
		quercetin-3-galactoside (Hesperidin)	C <sub>21</sub> H <sub>20</sub> O <sub>12</sub>
		rutin	C <sub>27</sub> H <sub>30</sub> O <sub>16</sub>
		isorhamnetin	C <sub>16</sub> H <sub>12</sub> O <sub>7</sub>
		rhamnoside of quercetin	C <sub>21</sub> H <sub>20</sub> O <sub>11</sub>
		quercetin	C <sub>21</sub> H <sub>20</sub> O <sub>11</sub>
		nimbolide	C <sub>27</sub> H <sub>30</sub> O <sub>7</sub>
		vilasinin	C <sub>26</sub> H <sub>36</sub> O <sub>5</sub>
		nimbinene	C <sub>28</sub> H <sub>34</sub> O <sub>7</sub>
		6-deacetyl nimbinene	C <sub>26</sub> H <sub>32</sub> O <sub>6</sub>
		nimbolide	C <sub>27</sub> H <sub>30</sub> O <sub>7</sub>
		nimocinol (6 $\alpha$ -hydroxy-azadirone)	C <sub>28</sub> H <sub>36</sub> O <sub>5</sub>
		$\beta$ -sitosterol	C <sub>29</sub> H <sub>50</sub> O
Trunk		$\beta$ -sitosterol- $\beta$ -D-glucoside	C <sub>35</sub> H <sub>60</sub> O <sub>6</sub>
		neem leaf glycoprotein	-----
		sugiol	C <sub>20</sub> H <sub>28</sub> O <sub>2</sub>
		nimbiol	C <sub>18</sub> H <sub>24</sub> O <sub>2</sub>
		nimbin	C <sub>30</sub> H <sub>36</sub> O <sub>9</sub>
		nimbinin	C <sub>28</sub> H <sub>34</sub> O <sub>6</sub>
Bark	Analgesic, alternative antipyretic	nimbolin a	C <sub>39</sub> H <sub>46</sub> O <sub>8</sub>
		nimbolin b	C <sub>39</sub> H <sub>46</sub> O <sub>10</sub>
		sugiol	C <sub>20</sub> H <sub>28</sub> O <sub>2</sub>
		nimbiol	C <sub>18</sub> H <sub>24</sub> O <sub>2</sub>
		nimbin	C <sub>30</sub> H <sub>36</sub> O <sub>9</sub>
		nimbinin	C <sub>28</sub> H <sub>34</sub> O <sub>6</sub>

**Table 1: Medicinal Uses of Various Parts of Neem and Their Chemical Constituents**

		deacetylnimbin	c28h34o8
		nimbinene	C28H34O7
		6-deacetyl nimbinene	C26H32O6
		nimbolide	C27H30O7
		sugiol	C20H28O2
		nimbiol	C18H24O2
Blossoms		kaemferol	C15H10O6
		quercetin	C15H10O7
		myricetin	C15H10O8
		melicitrin	C20H18O12
		quercetin-3-galactoside(hperin)	C21H20O12
		kaemferol-3-glucoside(astragalin)	C21H20O11
		$\beta$ -sitosterol- $\beta$ -D-glucoside	C35H60O6
Oil	Leprosy, intestinal worms	$\beta$ -sitosterol	C29H50O
		nimbin	C30H36O9
		nimbinin	C28H34O6
		nimbidic acid(salannic acid)	C26H34O7
		salannin	C29H50O
		meliantriol	C29H50O
Fruit	Relieves piles, intestinal worms, urinary disorders, epistaxis, phlegm, eye problem, diabetes, wounds, leprosy	azadirone	C29H50O
		5-hydroxy-methyl furfural	C28H34O6
		nomolin	C28H36O6
		nimolicin	C28H34O5
		17-hydroxy-azadiradione	C28H34O6
		17 $\beta$ -hydroxy-azadiradione	C28H34O6
		17-epi-azadiradione	C28H34O5

**Cont Table 1: Medicinal Uses of Various Parts of Neem and Their Chemical Constituents**

### Therapeutic Properties

Neem has been found to be effective in treatment of malaria, tuberculosis, rheumatism, arthritis, jaundice, parasitic diseases as well as skin diseases. The extracts of various plant parts have also been found to be beneficial in cardiovascular diseases, hepatitis, fungal infection, psoriasis, eczema, lice, fungal infections and ulcers. Neem is also used in cosmetic products for treatment of acne and pimples and improving skin elasticity (24). Given below is a short discussion of the various therapeutic properties found in neem.

#### A. Antibacterial Activity

Activity of the bark, leaf, seed and fruit extracts of neem has been evaluated against bacteria isolated from oral cavity. Results have revealed that bark and

leaf extracts possess activity against all the tested bacteria. Seed and fruit extracts have shown activity at higher concentrations only. Neem bark extract (NBE) has also been found to significantly block HSV-1 entry into cells at concentrations ranging from 50-100  $\mu$ g/mL (25). Neem has also shown potential to be used in wound dressings (26).

#### B. Antiviral Activity

Methanolic extract of neem leaves has shown virucidal activity against coxsackievirus virus B-4 (27). The antiviral activity of neem leaves has been found to be due to the presence of flavonoids, triterpenoids and their glycosides. The minimal inhibitory concentrations (8000 $\mu$ g/mL) of the leaves extract has been found to have no toxicity against Vero (African green monkey kidney) cells (28).



### c. Antimalarial activity

Antimalarial activity of neem leaf and stem bark extracts has been evaluated against *Plasmodium berghei* infected albino mice. The leaf and stem bark extracts have shown efficacy in reducing the level of parasitemia in infected mice to about 51-80% and 56-87%, respectively (29). The effect of methanolic extracts of seed kernels of ripe and unripe fruits of neem have also been studied on early erythrocytic schizogony of *P. berghei* infected inbred mice (30).

### d. Anti-dengue activity

NS2B-NS3 protease (NS2B-NS3 pro) of dengue virus (DENV) is the prime therapeutic target for the development of anti-dengue drugs to combat the DENV infection, which is currently an increasing health problem in many countries (31). An *in silico* study has reported the inhibitory potential of neem and its triterpenoids constituents viz. nimbin, desacetylnimbin, desacetylsalannin, azadirachtin and salannin against DENV NS2B-NS3 pro using molecular docking (32).

### e. Antifungal activity

The *in vitro* antifungal activity of neem leaves and seed kernel have been evaluated against *Monilinia fruticola*, *Penicillium expansum*, *Trichothecium roseum* and *Alternaria* (33, 34). The aqueous, ethanolic and ethyl acetate extracts of neem leaves have also shown significant activity against *Aspergillus flavus*, *A. fumigatus*, *A. niger*, *A. terreus*, *Candida albicans* and *Microsporum gypseum*. Ethyl acetate extract has shown the strongest antifungal activity and its HPLC analysis revealed the presence of nimonol (35). A recent study has shown that addition of neem powder to acrylic resin denture base materials reduces the adhesion of *C. albicans* which prevents denture stomatitis (36).

### f. Larvicidal activity

A combination of the entomopathogenic fungus *Metarhizium anisopliae* with neem oil has been found to effectively increase the half-life and virulence of the fungus when tested against *Aedes aegypti* larvae, even under simulated field conditions. Neem oil has also been found to display a protective activity towards *M. anisopliae* from the damaging effects of ultraviolet radiation (37, 38).

### g. Antiulcerative activity

Neem has also been used in the treatment of peptic ulcers. Aqueous extract of neem leaves has been found to display a significant antiulcerative activity on Wistar rats at a dose of 600mg/kg (39). The effect of neem has also been evaluated against peptic ulcers in

albino mice (40). The mechanism of antiulcer activity of neem leaves extract has also been determined (41).

### h. Hypoglycemic activity

The ethanolic extract of neem root bark has also been evaluated for antidiabetic activity (42). The neem root bark extract (NRE) showed statistically significant results at 800 mg/kg dose in an oral glucose tolerance test (OGTT). Neem extract at a dose of 250 mg/kg (single dose study) significantly reduced glucose levels (18%) in treated diabetic rats versus the control group as well as reduced cholesterol (15%), triglycerides (32%), urea (13%), creatinine (23%) and lipids (15%). Multiple doses administered over a 15 day period have also been shown to significantly lower the above blood parameters in the treated group (43). Azadirachtin, the active component of neem has also been found to display a protective action against pancreatic  $\beta$ -cells (44).

### i. Immuno-stimulant activity

A study has reported that a 4% infusion of neem leaves in fresh drinking water acts as a natural growth promoter and an immuno-stimulant in chickens contributing to an improved body weight gain, FCR feed conversion ratio, gross return, lower mortality and higher antibody titer against infectious bursal disease (IBD) (45). Aqueous extract of neem has also been found to augment both specific (humoral and cell-mediated immunity) and nonspecific immune responses (46).

### j. Antioxidant activity

Leaf and bark extracts have also been found to possess significant antioxidant property (47).

### k. Anticancer activity

The anticancer activity of aqueous and ethanolic extract of neem leaves has been tested on an number of cell lines viz. breast, lung, cervical (48-50). The crude extracts of neem have been tested *in vitro* and *in vivo* to establish their anticancer effects. Since neem has been reported to show some toxicity and side effects at higher doses, it is advisable that the use of neem as a complementary medicine be done under the supervision of qualified medical practitioners and physicians (51). Neem is routinely used as a combination regimen with cisplatin and other chemotherapeutic agents to improve the efficiency of standard cancer therapies by decreasing chemotherapeutic doses and toxicity of chemotherapy drugs (52). Nimbolide, a phytoconstituent of neem has been found to promote apoptosis via modulation of the phosphoinositide-3-kinase (PI3K) /Protein Kinase B (Akt) /Glycogen synthase kinase 3 (GSK-3 $\beta$ ) signaling pathway in oral cancer (53). Seed oil of neem

has also been found to induce apoptosis in MCF-7 and MDA MB-231 human breast cancer cells (54).

### **l. Antifertility activity**

Neem seed oil has been found to possess a powerful spermicidal as well as spermatogenesis inhibitory property. It has also been found to reduce sperm motility and count. Neem seed oil which is used as a powerful spermicidal and significantly inhibit spermatogenesis. It inhibits sperm motility and count and cessation of fertility. Neem also has anti-implantation and abortifacients properties (55). It has been found that spermatozoa of human and Rhesus monkeys die within 30 min of contact with neem seed oil using an intra vaginal dose of 1 mL (56).

### **m. Pesticide activity**

Neem oil is one of the cheapest pesticides and has been used in crop protection. Neem oil formulations have shown efficacy against *Sitophilus oryzae* and *Tribolium castaneum* adults (57).

### **n. Skin diseases**

Neem has been found to have a significant effect on chronic skin conditions. Neem oil has shown significant efficacy against acne, psoriasis, eczema, ringworm and warts (57).

## **CONCLUSION**

Neem is an important medicinal plant and has a number of therapeutic uses. It contains a plethora of phytoactive constituents with diverse chemical structures. Its multiple therapeutic properties have paved the way for preparation of numerous medicinally and industrially useful formulations with diverse medicinal applications. Neem is used widely in safeguarding human and animal health. Several neem-based commercial preparations are currently available in the market. Several neem derived drugs are in the pipeline for treatment of various acute and chronic diseases. However, further research needs to be conducted on neem as well as its isolated components in order to enhance its commercial and therapeutic use in future.

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