



Pharmacological and Therapeutical overview of neem (*Azadirachta indica*): A nature's drugstore

*¹ Kana Ram Kumawat, ² Ravi Kumar

¹ Research Scholar, Department of Plant Breeding and Genetics, Swami Keshwanand Rajasthan Agricultural University, Bikaner, Rajasthan, India

² Research Scholar, Department of Plant Breeding and Genetics, Sri Karan Narendra Agriculture University, Jobner, Rajasthan, India

Abstract

Neem (*Azadirachta indica*) is a member of the Meliaceae family and its role as health-promoting effect is attributed because it is rich source of antioxidant. It has been widely used various medicines worldwide especially in Indian Subcontinent in the treatment and prevention of various diseases. It possesses maximum useful non-wood products (leaves, bark, flowers, fruits, seed, gum, oil and neem cake) than any other tree species. These non-wood products are known to have anti-allergenic, anti-bacterial, anti-viral, anti-fungal, anti-inflammatory, anti-diabetic, mosquito-repellent activity, larvicidal, spermicidal and other biological activities. Earlier finding confirmed that neem and its constituents play role in the scavenging of free radical generation and prevention of disease pathogenesis. Each part of the neem tree has some medicinal property. This review gives a bird's eye view mainly on the biological activities of the neem and some of their compounds isolated, pharmacological actions of the neem extracts and products, and plausible medicinal and therapeutical applications.

Keywords: neem, *Azadirachta indica*, pharmacological, therapeutic, medicinal

Introduction

Azadirachta indica is being considered as the most important and useful medicinal and fast growing evergreen popular tree found commonly in India, Africa and America [1]. Its common name is neem which is an omnipotent tree and a sacred gift of nature [2]. Neem is an evergreen tree, cultivated in various parts of India. Each and every part of the tree has been used as traditional medicine for house-hold remedy against various human ailments from antiquity and it is the native source of eco-friendly agrochemical, insecticides, and pesticides [3]. The importance of the neem tree has been recognised by the US National Academy of Sciences, which publish a report in 1992 entitled 'Neem- a tree for solving global problems' [4]. Numerous biological and pharmacological activities have been reported including antibacterial [5], antifungal [6], and anti-inflammatory. This review summarizes the role of neem and its various parts / products from therapeutical point of view.

Botanical description of neem

Neem tree belongs to the family Meliaceae which is found in abundance in tropical and semi tropical regions like India, Bangladesh, Pakistan, and Nepal. It is a tree 40-50 feet or higher, with a straight trunk and long spreading branches forming a broad round crown; it has rough dark brown bark with wide longitudinal fissures separated by flat ridges. The leaves are compound, imparipinnate, with each comprising 5–15 leaflets. The compound leaves are themselves alternating with one another. It bears many flowered panicles, mostly in the leaf axils. Its fruits are green drupes of 12-20 mm long which turn golden yellow on ripening in the months of June-August [7-9].

Taxonomical classification

The Neem tree has been described as *Azadirachta indica* as early as 1830 by De Jussieu and its taxonomic position is as follows (Table 1) [7]:

Table 1: Taxonomical classification of neem (*Azadirachta indica*)

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

Active biological compounds of neem

Azadirachta indica shows therapeutics role in health management due to rich source of various types of ingredients. The most important active constituent is azadirachtin and the others are nimbolinin, nimbin, nimbidin, nimbidol, sodium nimbinat, gedunin, salannin, and quercetin. Leaves contain ingredients such as nimbin, nimbanene, nimbandiol, nimbolide, ascorbic acid, n-hexacosanol and nimbiol¹⁰⁻¹². Quercetin and beta-sitosterol, polyphenolic flavonoids, were purified from neem fresh leaves and were known to have antibacterial and antifungal properties¹³ and seeds hold valuable constituents including gedunin and azadirachtin.

Pharmacological advantages of various neem parts

From the ancient times, different parts of tree have been used for their medicinal properties as described for fruit, bark and

leaf. Extracts of leaf and bark and neem oil have been traditionally used for their therapeutic effect to control intestinal helminthiasis, respiratory disorders, constipation, leprosy and also to promote general health. It is also evident for its use in the treatment of chronic syphilitic sores, indolent

ulcer, and rheumatism. To control different skin infections neem, oil has been found to be useful. Root, bark, fruit flower and leaf have a combined effect in curing burning sensations, phthisis, itching, blood morbidity, skin ulcers, and biliary afflictions (Table 2) ^[14].

Table 2: Pharmacological activity and uses of various parts of neem

Part / product	Medicinal value / use
Bark	Analgesic, alternative and curative of fever Flower Bile suppression, elimination of intestinal worms and phlegm
Seed pulp	Intestinal worms and leprosy
Fruits	Relieves piles, intestinal worms, epistaxis, urinary disorder, eye problem, phlegm, diabetes, wounds and leprosy
Flowers	Bile suppression, elimination of intestinal worms and phlegm
Leaves	Eye problem, leprosy, intestinal worms, epistaxis, anorexia, skin ulcers, biliousness
Oil	Intestinal worms and leprosy
Gum	Effective against skin diseases like ring - Worms, scabies, wounds and ulcers
Twig	Relieves cough, piles, phantom tumor, asthma, spermatorrhea, intestinal worms, diabetes, obstinate urinary disorder
Root, bark, leaf, flower and fruit together	Blood morbidity, itching, biliary afflictions, burning sensation, skin ulcer and leprosy

Medicinal and therapeutic implications of neem

Active constituents of neem play significant role in the diseases cure via activation of anti-oxidative enzyme, rupture the cell wall of bacteria or other micro-organisms and play role as chemo-preventive through the regulation of cellular pathways. Pharmacological and therapeutical activities of neem are discussed in detail.

Anti-oxidant activity

Free radical or reactive oxygen species are one of the main culprits in the genesis of various diseases. However, neutralization of free radical activity is one of the important steps in the diseases prevention. Antioxidants stabilize or deactivate free radicals, often before they attack targets in biological cells and also play role in the activation of anti-oxidative enzyme that plays role in the control of damage caused by free radicals / reactive oxygen species¹⁵. Medicinal plants have been reported to have antioxidant activity¹⁶. An important study was performed based on leaves, fruits, flowers, and stem bark extracts from the Siamese neem tree to assess the antioxidant activity and results suggest that extracts from leaf, flower, and stem bark have strong antioxidant potential^[17].

Anti-cancer activity

The alteration of molecular / genetic pathways plays role in the development and progression of cancer. An oncogene or cancer causing gene is a mutated gene that plays significant role in the development and progression of tumours. Experiment was performed to investigate effect of leaf extract on c-Myc oncogene expression in 4T1 breast cancer BALB/c mice and results revealed that 500mg/kg neem leaf extract (C₅₀₀) group showed significant suppression of c-Myc oncogene expression as compared to the cancer control group^[18].

Anti-inflammatory activity

Results of a study revealed that neem leaf extract showed significant anti-inflammatory effect but it is less efficacious than that of dexamethasone^[19] and study results suggest that nimbidin suppresses the functions of macrophages and

neutrophils relevant to inflammation^[20]. An another study result has confirmed that extract of neem leaves at a dose of 200 mg/kg showed significant anti-inflammatory activity in cotton pellet granuloma assay in rats^[21].

Anti-bacterial activity

An experiment was made to evaluate the antibacterial activity of the bark, leaf, seed, and fruit extracts of *Azadirachta indica* on bacteria isolated from adult mouth and results revealed that bark and leaf extracts showed antibacterial activity against all the test bacteria used^[22]. Results of an another study showed that leaf extracts and grape seed extracts showed zones of inhibition suggesting that they had antimicrobial properties^[23].

Anti-viral activity

Leaf extract of neem (NCL-11) 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^[24]. Results of an experiment showed that neem bark extract significantly blocked HSV-1 entry into cells at concentrations ranging from 50 to 100µg/mL^[25].

Anti-fungal activity

A study showed the antimicrobial role of aqueous extracts of neem cake in the inhibition of spore germination against three sporulating fungi such as *C. lunata*, *H. penniseti*, and *C. gloeosporioides* f. sp. *Mangiferae*²⁶ and results of the study revealed that methanol and ethanol extract of *Azadirachta indica* showed growth inhibition against *Aspergillus flavus*, *Alternaria solani*, and *Cladosporium*^[27].

Anti-diabetic activity

Results of an important study suggested that leaves extracts of *Azadirachta indica* and *Andrographis paniculata* have significant anti diabetic activity and could be a potential source for treatment of diabetes mellitus^[28]. Another experiment was conducted to examine the pharmacological hypoglycaemic action of neem in diabetic rats and results showed that in a glucose tolerance test with neem extract 250

mg/kg demonstrated glucose levels were significantly less as compared to the control group and neem significantly reduce glucose levels at 15th day in diabetic rats [29]. Results of a study undertaken to evaluate the 70% alcoholic neem root bark extract (NRE) in diabetes showed that neem root bark extract showed statistically significant results in 800 mg/kg dose [30].

Larvicidal activity

In a study, aqueous extracts of four plants were tested for larvicidal properties. Laboratory reared larvae were exposed to 1, 2, 3, 4 and 5 ppm concentrations of the extracts of *Azadirachta indica* A Juss., *Gymnema sylvestre*, *Nerium indicum* Mill. and *Datura metel* L., respectively, in Zoology research laboratory of DAV Degree College, Kanpur, India. Result showed that the *Azadirachta indica* elicited 70-99% mortality, followed by *G. sylvestre* (44-89%), *N. indicum* (41-74%) and *D. metel* (19-54%) mortality to larvae. The extracts of *A. indica* and *G. sylvestre* were found to be significantly effective in controlling *Culex* larvae [31].

Anti-ulcer activity

Neem bark extract reduced human gastric acid hypersecretion, and gastro-esophageal and gastroduodenal ulcers. After 10 weeks, the duodenal ulcers were nearly fully healed; after 6 weeks one case of esophageal ulcer and gastric ulcer were fully healed [32-33].

Anti-dental activity

Nimbidin gargal and dentifrices have been found effective in bleeding gums and pyorrhoea. Silvose T and Silvo TRS which are patented extracts of the bark neem. It is active ingredient in tooth paste and other oral hygiene preparation. Neem extract when added to a tooth paste in preventing and healing the inflammation of gums [34].

Anti-skin disorders activity: *Azadirachta indica* can treat many skin disorders, including scabies and lice; in a paste combination with *Curcuma longa* (turmeric), neem was used to treat scabies in 814 people and 97% of them were cured within 3 to 15 days of application, and no adverse reactions were observed [33].

Anti-malarial activity

The anti-malarial activities of the tablet suspension of the bark and leaf of neem were evaluated on *Plasmodium yoelli nigeriensis* infected mice. The tablet suspensions exhibited high prophylactic, moderate suppressive and a very minimal curative schizonticidal effect [35]. An another experiment was conducted to evaluate the anti malarial activity of extracts using *Plasmodium berghei* infected albino mice and results revealed that neem leaf and stem bark extracts reduced the level of parasitemia in infected mice by about 51–80% and 56–87%, respectively [36], and other studies showed that azadirachtin and other limonoids available in neem extracts are active on malaria vectors [37].

Wound healing activity

A study was made to evaluate the wound healing activity of the extracts of leaves of *A. indica* and *T. cordifolia* using

excision and incision wound models in Sprague Dawley rats and results revealed that extract of both plants significantly promoted the wound healing activity in both excision and incision wound models [38]. Results of another study showed that leave extracts of *Azadirachta indica* promote wound healing activity through increased inflammatory response and neovascularisation [15].

Hepatoprotective activity

A study was carried out to evaluate the protective effect of active constituent of neem such as nimbolide against carbon tetrachloride (CCl₄) induced liver toxicity in rats and results suggest that nimbolide possesses hepatoprotective effect against CCl₄ induced liver damage with efficiency similar to that of silymarin standard [15, 39] and another study finding revealed that leaf extract was found to have protection against paracetamol-induced liver necrosis in rats [15, 40].

Neuroprotective activity

An experiment was conducted to investigate the neuroprotective effects of neem leaves against cisplatin induced neurotoxicity and results showed that morphological findings of neem before and after cisplatin injection implied a well-preserved brain tissue. On other side, no changes in biochemical parameters were observed with neem treated groups [15, 41].

Anti-HIV/AIDS activity

A study was performed in HIV/AIDS patients, a 12 week oral administration of acetone water neem leaf extract (IRAB) had a significant influence in vivo on CD4 cells (which reduces HIV) without any adverse effects in the patients. The mean levels of CD4 cells increased by 159% in 50 patients, which is a major increase; the number of HIV/AIDS pathologies decreased from the 120 baseline to 5; and significant increases were experienced in body weight (12%), haemoglobin concentration (24%), and lymphocyte differential count (24%) [32]. IRAB is recommended as part of an HIV/AIDS drug treatment program [42].

Mosquito repellent activity

Azadirachtin is a powerful insect antifeedant that disrupts metamorphosis in moth larvae at extremely low concentrations [43]. Neem seed oil extracted from *Azadirachta indica* and formulated in Vanishing cream base was evaluated for repellent action against. Many mosquito-borne diseases, such as malaria, dengue fever, dengue hemorrhagic fever and filariasis are some of the serious problems all over the tropical regions [2, 43].

Contraceptive activity

Several small studies showed that neem oil appears to be a safe and very effective contraceptive, pre and post coital. The way it was applied in the studies it was 100% effective in preventing pregnancies. During *in vitro* experiments neem oil also totally immobilized sperm cells within 20 to 30 seconds of being in contact with neem oil [44].

Anti-allergic activity

Neem can help inhibit allergic reactions when used externally

or consumed internally. Neem is an anti-inflammatory and helps as an antihistamine which may be helpful in skin rashes and bronchial allergy. Application of a neem oil or lotion can help alleviate itching and inflammation of rashes. A neem tea; liquid extract; or supercritical extract capsules may be taken internally for allergies to pollen, molds, cedar and other allergens [45].

Hair care activity

From hair growth to dandruff, neem oil is the nature's cure for scalp and hair problems. Regular application of the neem oil will promote thicker, stronger, and more luxurious hair growth. Neem oil contains several fatty acids such as linoleic, oleic, stearic acids that nourish and condition the scalp and hair [46].

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. The above collected information regarding the use of *Azadirachta indica* in world is matched with available literature. Thorough screening of literature available on *Azadirachta indica* depicted the fact that it is a popular remedy among the various ethnic groups, Unani, Ayurvedic and traditional practitioners for treatment of ailments. Researchers are exploring the therapeutic potential of this plant as it has more therapeutic properties which are not known. An extensive research should be undertaken on neem and its products for their better economic and therapeutic utilisation.

References

- Pingale Shirish S. Hepatoprotection study of leaves powder of *Azadirachta indica* A. Juss. International Journal of Pharmaceutical Sciences Review and Research 2010; 3(2):37-42.
- Aneesa N and Gayathri, Beneficial effects of neem oil-an updated review. J Pharm. Sci. & Res. 2016; 8(8):756-758.
- Brahmachari G. Neem – an omnipotent plant: a retrospection. Chembiochem. 2004; 5(3):408-421.
- Biswas K, Chattopadhyay I, Banerjee RK, Bandyopadhyay U. Biological activities and medicinal properties of neem (*Azadirachta Indica*). Curr Sci. 2002; 82(11):1336-1345.
- Singh N, Sastry MS. Anti microbial activity of neem oil. Indian Journal of Pharmacology. 1997; 13:102-106.
- Kher A, Chaurasia SC. Antifungal activity of essential oils of three medical plants. Indian Drugs. 1997; 15:41-42.
- Giris SBS. Neem, a green treasure. Electronic Journal of Biology. 2008; 4:102-111.
- Parotta JA. Healing plants of Peninsular India. New York, CABI Publishing, 2001, 495-496.
- Ross IA. Medicinal plants of the world: chemical constituents, traditional and modern medicinal uses. Totowa, New Jersey. 2001; 2:81-85.
- Ali A. Textbook of Pharmacognosy, Publication and Information Directorate, New Delhi, India, 1993.
- Hossain MA, Shah MD, Sakari M. Gas chromatography–mass spectrometry analysis of various organic extracts of *Merremia borneensis* from Sabah. Asian Pacific Journal of Tropical Medicine. 2011; 4(8):637-641.
- Kokate C, Purohit AP, Gokhale SB. Pharmacognosy, Nirali Prakashan, Maharashtra, India, 2010.
- Govindachari TR, Suresh G, Gopalakrishnan G, Banumathy B, Masilamani S. Identification of antifungal compounds from the seed oil of *Azadirachta indica*. Phytoparasitica. 1998; 26(2):109-116.
- Kim JH, Choresca CHJ, Shin SP, Han JE, Jun JW, Park SC. Occurrence and antibiotic resistance of *Vibrio vulnificus* in seafood and environmental waters in Korea. J Food Saf. 2011; 31(4):518-524.
- Alzohairy MA. Therapeutics role of *Azadirachta indica* (neem) and their active constituents in diseases prevention and treatment. Evidence-Based Complementary and Alternative Medicine, 2016, 1-11. Online available <http://dx.doi.org/10.1155/2016/7382506>
- Rahmani H, Aly SM. *Nigella sativa* and its active constituents thymoquinone shows pivotal role in the diseases prevention and treatment, Asian Journal of Pharmaceutical and Clinical Research. 2015; 8(1):48-53.
- Sithisarn P, Supabphol R, Gritsanapan W. Antioxidant activity of siamese neem tree. Journal of Ethnopharmacology. 2005; 99(1):109-112.
- Othman F, Motalleb G, Peng SLT, Rahmat A, Basri R, Pei Pei C. Effect of neem leaf extract (*Azadirachta indica*) on c-Myc oncogene expression in 4T1 breast cancer cells of BALB/c mice. Cell Journal. 2012; 14(1):53-60.
- Mosaddek ASM, Rashid MMU. A comparative study of the anti-inflammatory effect of aqueous extract of neem leaf and dexamethasone. Bangladesh Journal of Pharmacology. 2008; 3(1):44-47.
- Kaur G, Alam MS, Athar M. Nimbidin suppresses functions of macrophages and neutrophils: relevance to its anti-inflammatory mechanisms. Phytotherapy Research. 2004; 18(5):419-424.
- Chattopadhyay RR. Possible biochemical mode of anti inflammatory action of *Azadirachta indica* A. Juss in rats. Indian Journal of Experimental Biology. 1998; 36(4):418-420.
- Yerima MB, Jodi SM, Oyinbo K, Maishanu HM, Farouq AA, Junaidu AU. Effect of neem extracts (*Azadirachta indica*) on bacteria isolated from adult mouth. Journal of Basic and Applied Sciences. 2012; 20:64-67.
- Ghonmode WN, Balsaraf OD, Tambe VH, Saujanya KP, Patil AK, Kakde DD. Comparison of the antibacterial efficiency of neem leaf extracts, grape seed extracts and 3% sodium hypochlorite against *E. faecalis*-an in vitro study. Journal of International Oral Health. 2013; 5(6):61-66.
- Badam L, Joshi SP, Bedekar SS. *In vitro* antiviral activity of neem (*Azadirachta indica* A. Juss) leaf extract against group B coxsackieviruses. Journal of Communicable Diseases. 1999; 31(2):79-90.

25. Yerima MB, Jodi SM, Oyinbo K, Maishanu HM, Farouq A A and Junaidu A U. Effect of neem extracts (*Azadirachta indica*) on bacteria isolated from adult mouth. *Journal of Basic and Applied Sciences*. 2012; 20:64-67.
26. Anjali K, Ritesh K, Sudarshan M, Jaipal SC, Kumar S. Antifungal efficacy of aqueous extracts of neem cake, karanj cake and vermicompost against some phytopathogenic fungi. *The Bioscan*. 2013; 8:671-674.
27. Shrivastava DK, Swarnkar K. Antifungal activity of leaf extract of neem (*Azadirachta indica* Linn). *International Journal of Current Microbiology and Applied Sciences*. 2014; 3(5):305-308.
28. Akter R, Mahabub-Uz-Zaman M, Rahman MS. Comparative studies on anti diabetic effect with phytochemical screening of *Azadirachta indicia* and *Andrographis paniculata*. *IOSR Journal of Pharmacy and Biological Sciences*. 2013; 5(2):122-128.
29. Dholi SK, Raparla R, Mankala SK, Nagappan K. *In vivo* anti diabetic valuation of Neem leaf extract in alloxan induced rats. *Journal of Applied Pharmaceutical Science*. 2011; 1(4):100-105.
30. Patil PR, Patil SP, Mane A, Verma S. Antidiabetic activity of alcoholic extract of Neem (*Azadirachta indica*) root bark. *National Journal of Physiology, Pharmacy and Pharmacology*. 2013; 3(2):142-146.
31. Aditi G, Bhandari BS, Rai N. Antimicrobial activity of medicinal plants *Azadirachta indica* A. Juss, *Allium cepa* L. and *Aloe vera* L. *Int. J Pharm Tech Res*. 2011; 3(2):1059-1065.
32. Hashmat I, Azad H, Ahmed A. Neem (*Azadirachta indica* A. Juss) - a nature's drugstore: an overview. *I. Res. J. Biological Sci*. 2012; 1(6):76-79.
33. Deswal H, Singh Y, Grover HS, Bhardwaj A, Verma S. Neem: a boon in medical and dental therapies: a review. *Innovare Journal of Agri. Sci*. 2016; 4(2):1-3.
34. Sonalkar Manisha Y, Nitave Sachin A, Kagalkar Amrita A. Review on neem plant. *World Journal of Pharmacy and Pharmaceutical Sciences*. 2014; 3(4):590-598.
35. Isa AB, Ibrahim YK, Iwalewa EO. Evaluation of the antimalarial properties and standardization of tablets of *Azadirachta indica* (Meliaceae) in mice. *Phytother Res*. 2003; 17(7):807-810.
36. Akin-Osanaiya BC, Nok AJ, Ibrahimetal S. Antimalarial effect of Neem leaf and neem stem bark extracts on plasmodium berghei infected in the pathology and treatment of malaria. *International Journal of Research in Biochemistry and Biophysics*. 2013; 3(1):7-14.
37. Nathan SS, Kalaivani K, Murugan K. Effects of neem limonoids on the malaria vector *Anopheles stephensi* Liston (diptera: culicidae). *Acta Tropica*. 2005; 96(1):47-55.
38. Barua CC, Talukdar A, Barua AG, Chakraborty A, Sarma RK, Bora RS. Evaluation of the wound healing activity of methanolic extract of *Azadirachta indica* (neem) and *Tinospora cordifolia* (guduchi) in rats. *Pharmacologyonline*. 2010; 1:70-77.
39. Baligar NS, Aladakatti RH, Ahmed M, Hiremath MB. Evaluation of acute toxicity of neem active constituent, nimbolide and its hepatoprotective activity against acute dose of carbon tetrachloride treated albino rats. *International Journal of Pharmaceutical Sciences and Research*. 2014; 5(8):3455-3466.
40. Bhanwra S. Effect of *Azadirachta indica* (neem) leaf aqueous extract on paracetamol induced liver damage in rats. *Indian Journal of Physiology and Pharmacology*. 2000; 44(1):64-68.
41. Abdel Moneim AE. *Azadirachta indica* attenuates cisplatin-induced neurotoxicity in rats. *Indian Journal of Pharmacology*. 2014; 46(3):316-321.
42. Mbah AU, Udeinya IJ, Shu EN, Chijioke CP, Nubila T, Udeinya F. Fractionated neem leaf extract is safe and increases CD4+ cell levels in HIV/AIDS patients. *Am. J. Ther*. 2007; 14(4):369-374.
43. Ben-Erick V, Michael W. *Medicinal plants of the world*, Times Editions, Singapore, 2004, 64.
44. Pregnancy: Neem Oil As Contraceptive - Neem For Birth Control. <http://www.discoverneem.com/neem-oil-birth-control.html>. Online accessed on 25-10-2017.
45. <http://neemking.org/shop-by-symptom/allergies>. Online accessed on 26-10-2017.
46. <http://www.hairbuddha.net/benefits-of-neem-oil-for-hair>. Online accessed on 26-10-17.