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Neem (*Azadirachta indica*) in health care: A review

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Abstract
The Neem (*Azadirachta indica*) has a vital role in various problems associated with human health. The chemical constituents present in the neem plant make it a doctor tree due to its wide scope in biological activities associated with it, and has become a global context today. Neem *(Azadirachta indica)* is considered harmless to humans, animals, birds, beneficial insects and earthworms, and has been approved by the US Environmental Protection Agency for use on food crops. Azadirachtin and other active ingredients in the neem seed have insecticidal properties that are effective against a broad spectrum of insects, many mites and nematodes, and even snails and fungi, and do not seem to generate resistance in the pests they affect. Nowadays, neem and its extracts are used in numerous herbal medicines and cosmetics. What's more, even neem contraceptives are available in the market this days. Neem extract which have Nimbinin, nimbandiol as active constituents, alcoholic extract of the leaves was found to possess a significant blood sugar lowering effect, which are very useful against diabetes. Neem is used in Dermatitis Eczema, Acne, Bacterial/Fungal infections and other skin disorders. It has demonstrated its effectiveness as a powerful antibiotic. Neem also has shown antiviral, anti-fungal and anti-bacterial properties. It helps support a strong immune system and is used in cases of inflammatory skin conditions. Neem has been extensively used in Ayurveda, Unani and Homoeopathic medicine and has become a centre of attraction of modern medicine. Hence, the article is aims to utilize the medicinal properties of whole neem plant in various disorders of mankind.

Keywords: *azadirachta indica,* anti-viral, anti-fungal, and diabetic

1. Introduction
In human society from time immemorial medicinal plants have played an important role in prevention and control of diseases. Neem, a native of Indian subcontinent is a highly esteemed tree for the people in the region. In India,it occurs naturally in shivalik hills, dry forests of Andhra Pradesh, Tamil Nadu and Karnataka upto an altitude of 700 m.It is cultivated and frequently naturalized throughout the drier regions of tropical and sub-tropical India. The plant is considered sacred and is used by the Hindus in several ceremonies, rituals and in worship of New Year day (S. Sengupta, 1965) [65]. 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 (Chopra *et al*. 1956) [15]. The Neem tree has been described as *A. indica* as early as 1830 by De Jussieu and its taxonomic position is as follows: Order Rutales Suborder Rutinae Family Meliaceae (mahogany family) Subfamily Melioideae Tribe Melieae Genus *Azadirachta* Species *indica* the genus *Azadirachta* A. Juss which comprises three species of Indo-Malayan origin has been characterized in detail (Pennington *et al*. 1981) [49]. The importance of the Neem tree has been recognized by the US National Academy of Sciences, which published a report in 1992 entitled 'Neem-a tree for solving global problems'. The advancement of Neem research has earlier been documented (Singh *et al*. 1996) [9, 49]. Neem has found to contain a vast array of biologically active compounds, which are chemically diverse and have got an enormous therapeutic potential. Not only this, many reviews have already appeared from time to time on its constituents in general (Siddiqui *et al*. 1988). A huge number of 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 (Mitra *et al*. 1963) [42]. The compounds have been divided into two major classes: isoprenoids and others (Dev kumar *et al*. 1996) [15]. The isoprenoids include diterpenoids and triterpenoids containing protomeliacins, limonoids, azadirone and its derivatives, gedunin and its derivatives, vilasinin type of compounds and Csecomeliacins such as nimbin, salanin and azadirachtin.

The nonisoprenoids include proteins (amino acids) and carbohydrates (polysaccharides), sulphurous compounds, polyphenolics such as flavonoids and their glycosides, dihydrochalcone, coumarin and tannins, aliphatic compounds, etc. The details of the chemistry of various compounds falling under these groups have already been reviewed. Role of few significant compounds whose bioactivity has been studied is presented here. Thus the current review attempts to highlight some of the common uses of compounds derived from Neem which could potentially be developed as therapeutics, reversible contraceptive and insect repellent.

2. Vernacular Names

Bengali: Nim, Nimgachh, Guajarati: Danujhada, Limbado, Limbra, Limdo, Hindi: Nim, Nimb, Sanskrit: Arista, Nimba, Nimbah, Picumarda, English: Indian Lilac, Margosa tree, Neem tree, Kannada: Bemu, Bevinamara, Bivu, Kaybevu, Punjabi: Bakam, Drekh, Nim.

3. Taxonomical classification of neem

The Neem tree has been described as *A. indica* as early as 1830 by De Jussieu and its taxonomic position is as follows:

Order: Rutales
Suborder: Rutinae
Family: Meliaceae (mahogany family)
Subfamily: Melioideae
Tribe: Melieae
Genus: *Azadirachta*
Species: *indica*
Latin: *Azadirachta indica*

4. Important Formulations

Important Unani formulations containing Azadirachta *indica* are as follows:

- Sharbat Musaffi
- Zimad Mahasa
- Marham Jadeed
- Rawghan Awraq
- Neem Oil
- Gaza Bahar-e Husn

Important Ayurvedic formulations containing Azadirachta *indica* are as follows:

- Neembadi Churna
- Neembadi Toil
- Pancho Tikto ghritogugul
- Brihat Horidra Khanda

(Bangladesh National Unani Formulary 2010, Bangladesh Ayurvedic Formulary 2010.)

5. Biochemical Properties

Table 1

S. No	Compound name	Source	Biological activity	Reference
1.	Nimbin	Seed oil	spermicidal	Sharma VN. and Saksena, 1959 [63]
2.	Nimbidin	Seed oil	Antipyretic Hypoglycaemic Antiarthritic Antifungal Antibacterial Diuretic Anti-inflammatory	David SN, Mediscope, 1969; [16] Pillai *et al*. 1981; [50, 55] Murthy *et al*.1958; [41] Bhide *et al*.1958; [7, 10] Bhargava *et al*. 1970 [8].
3.	Azadirachtin	Seed oil	Antimalarial	Jones *et al*.1994 [31].
4.	Mahmoodin	Seed oil	Antibacterial	
5.	Gedunin	Seed oil	Antimalarial Antifungal	Rao *et al*. 1977; [60] Khalid *et al*. 1989 [33, 35].
6.	Sodium nimbidate		Anti-inflammatory	Koul *et al*. 1990 [32].
7.	Gallicacid, (-) epicatechin and catechin	Bark	Anti-inflammatory Immunomodulatory	Van der Nat *et al*. 1991 [72, 75].
8.	Margolone, Margolonone and isomargolonone	Bark	Antibacterial	Ara *et al*. 1989 [1].
9.	Cyclic trisulphide and cyclic tetrasulphide	Leaf	Antifungal	Pant *et al*. 1986 [51, 56, 57].
10.	Polysachharides		Anti-inflammatory	Schmutterer *et al*. 1995 [62].
11.	Polysachharides G1A,G1B	Bark	Antitumour	Fujiwara *et al*. 1982 [19].
12.	Polysachharides G2A,G3A	Bark	Anti-inflammatory	Fujiwara *et al*. 1984 [20].
13.	NB-2 Peptidoglycan	Bark	Immunomodulatory	Vander Nat *et al*. 1989; [74] Vander Nat *et al*. 1987 [73].
14.	Nimbolide	Seed oil	Antimalarial, Antibacterial	Khalid *et al*. 1989; [33, 35] Rochanakij *et al*. 1985 [59].

6. Botanical Formulations from Neem

The part of the neem plant used for insecticide formulations are the stembark, rootbark, leaves, flowers, fruits, seeds and seed kernels. The formulations can either be in the form of powder (dusts), crude oil extracts, ethanol extracts, aqueous extracts or commercial formulation.

6.1 Powder formulation

The neem plant materials were either sun dried or oven dried and then pulverized into fine powder using pestle and mortar or electric mill and sieved with a fine mesh (0.25 mm diameter sieve) (Jackai and Oyediran, 1991; Jackai *et al*. 1992; Jackai, 1993) [30, 29, 28]. They can also be made into pastes or cakes (Gahukaar, 2006) [22].

Mode of application: For field application, the neem powder, cake or granules can be spread out over the field crops by hand in a manner similar to fertilizer application that is by broadcasting. Alternatively they are applied at planting time along with the basal NPK fertilizer application

and worked into the soil or applied around the growing plants by ring method or side banding (Ahmed *et al*. 1984) [5]. In the case of stored products the desired quantity is measured out with a measuring scale and spread over the products (grains or nuts) and mixed properly before storage (Stoll, 1992; Yusuf *et al*. 1998) [65, 78]. This can be applied to cocoa beans and grains in a situation where they will be stored for a very long time.

Dosage: The application rate of powder formulation ranges from less than 1-20 g/kg of grain/beans, but does not usually exceed 2% of the weight of grains/nuts/beans (Ivbijaro and Agbaje, 1986; Ogunwolu and Idowu, 1994; Yar'adua, 2007) [26, 46, 79]. The neem dust or paste can be used as soil amendments at 100 - 2000 kg/ha for the management of soil borne pest and diseases (Yar'adua, 2007) [79]. However, the concentrations of the commercial dust formulations tested were based on recommendations from the manufacturers.

6.2 Oil formulation

The method utilized mainly for crude extraction of oil from neem seeds is by pounding it lightly in a motar to obtain the kernel after removing the shell or outer coat. The kernel is ground into a paste, which is transferred to a pot and heated. The paste is heated alone briefly before the addition of water. The mixture is allowed to cool after boiling. The oil settles on top of the cooled mixture and is easily scooped off for use (UNIFEM, 1987; Jackai and Oyediran, 1991; Jackai *et al*. 1992; Jackai, 1993) [71, 30, 29, 28]. The extraction is best done in an open area with good ventilation to avoid any hazard from the very strong and sometimes-offensive odour emitted during such boiling. It is better to add small amount of water to the paste while boiling rather than adding large quantity of water at once (Jackai, 1993) [28]. Commercial extraction is usually by mechanical press method, steam and high pressure method, solvent extraction or cold pressed method. The steam and high pressure method is not very reliable as most of the active ingredient and compounds are denatured at high temperature, while the cold press is a very expensive method (GEP, 2008b) [23].

Mode of application: The oil formulation can be applied in the field by the use of conventional knapsack, trombone, ULV or hand sprayers (Passerini and Hill, 1993; Yar'adua, 2007) [52, 79], but this is only feasible for those who can afford the spray equipments. Alternatively the broom sprinkling method is resorted to, which involves the dipping of a long broom or leaf branch into desired concentration of the extract and sprinkling it on the crops (Bottenberg and Singh, 1996) [9]. In this case the desired concentration of the extract is poured into a bucket and a long broom or leaf branch is dipped into it and sprinkled on the trees. The application is usually repeated at 10 days intervals or every fortnight. Oils are more conveniently applied on a volumetric basis and application rates are usually given in ml/kg of grain, with effective rates ranging from 1-10 ml/kg of grain (Lale, 2001; Yar'adua, 2007) [40, 79]. It is usually the practice to add and mix teepol with the extracts before application to improve its sticking properties. The desired concentrations were usually prepared by shaking 1-2 ml of teepol in a small quantity of distilled water and adding the resulting solution to the desired quantity of the oil. The mixture should be thoroughly shaken, added to a measured quantity of distilled water and shaken again to obtain a well-mixed solution (Padi *et al*. 2000; Yar'adua, 2007) [53, 54, 79].

Dosage: The oil extract is usually applied at the rate of 0.25-3% (high volume spray) or about 3 L/ha (low volume spray), while stored products (grains/beans) can be treated at the rate of 2.5-5ml/kg seeds (Yar'adua, 2007) [79].

6.3 Alcoholic or ethanolic extracts

The selected neem plant part was chopped into small pieces and ground in a motar. The resulting paste is mixed with known quantity of absolute ethyl alcohol. The solution is allowed to stand for 72 h, after which the alcohol was evaporated off (recovered) using a rotary evaporator. The paste was then mixed with a measured quantity of distilled water and sieved through a fine nylon mesh to obtain the alcoholic extract solution (Padi *et al*. 2000) [53, 54].

Mode of application: The application methods of this formulation both in the field and storage are same as for the oil formulation above.

Dosage: The concentrations of the crude ethanolic plant extracts tested were same as for the oil formulation above.

6.4 Aqueous formulation

In this case, the pulverised neem plant materials are extracted by using water as the solvent. The aqueous neem solution was obtained by pressing out fresh juice and diluting in water or through maceration (that is steeping in water for prolonged periods). It can also be got by infusion (the immersion of plants in already boiled water for prolonged periods) (Jackai and Oyediran, 1991; Jackai *et al*. 1992; Lale, 1995; Jackai, 1993; N'Guessan *et al*. 2006) [30, 29, 39, 28, 45]. Steeping or immersion of the plant extracts in water for longer period improves the toxicity of the neem aqueous extracts against cocoa mirids (N'Guessan *et al*. 2006) [45].

Mode of application: The application methods of this formulation both in the field and storage are same as for the oil formulation above.

Dosage: The concentrations of the crude aqueous plant extracts tested were same as that of oil formulation above. (Asogwa *et al*. 2003)

6.5 Commercial formulation

The bioactive components in neem tree are normally extracted in organic solvents particularly methanol, ethanol, acetone, hexane, petroleum ether, diethyl ether, chloroform or methyl chloride (Ofuya *et al*. 1992; Egwunyenga *et al*. 1998; Anonymous, 2006). The resulting extracts are further purified by solvent partitioning in hexane to remove fatty esters. Extraction of pesticidal components in neem kernels is done after first extracting the oil components using hexane (Gahukaar, 2006) [22]. However, extraction of the azadirachtin and other terpenoidal and non-terpenoidal compounds is best done in 95% ethanol, using chromatographic techniques, which include open column chromatography, flash chromato-graphy, thin layer or vacuum liquid chromatography on silca gel and liquid chromatography (Schmutterer, 2002). The extraction can be done in standard laboratories or in a small-scale industry. Some examples of commercial formulations of neem based

insecticides (NBIs) products are: Neemol, Super Neemol, Neem Azal and Potenised Neem Systemic Oil (Padi *et al*. 2000) [53, 54]. In some countries, especially India, NBIs are available in the open market (eg Repelin, Wellgro, Nimbosol, and Neemark (Saxena, 1989; Schmutterer, 1990; Gahukaar, 2006) [22]. *A. indica* (neem tree) has also been commercialized in the USA where it is registered as "Margosan O" and "Azatin E.C." (Larson, 1989).

Mode of application: The application methods of this formulation both in the field and storage are same as for the oil formulation above.

Dosage: The concentrations of the commercial neem oil formulations tested were based on recommendations from the manufacturers.

7. Commercial Products

List of some Products launched in the market, containing Azadirachta indica; Table 2.

Table 2: Some Products launched in the market, containing *Azadirachta indica*.

Name of the Product	Company
Syrup Safi, Capsule Safi	Hamdard Laboratories (Waqf) Bangladesh.
Neem diabetic capsule, Skin care soap, Beauty Face Pack, Neem Tea, Tooth Paste Neem Leaf Capsule, Pure Neem oil	Neem Organic Ltd.
Syrup Sarsin	Manson Pharmaceuticals (Unani)
Syrup Chirol	The Ibn Sina Pharmaceutical Industry Ltd.

8. Therapeutic uses of neem compounds

Each part of the Neem tree has some medicinal property and is thus commercially exploitable. Several pharmacological activities and medicinal applications of various parts of Neem are well known. Although a large number of compounds have been isolated from various parts, a few have been studied for biological activity as shown in Table 1. Nimbidin, a major crude bitter principle extracted from the oil of seed kernels of *A. indica* demonstrated several biological activities. From this crude principle some tetranortriterpenes, including nimbin, nimbinin, nimbidinin, nimbolide and nimbidic acid have been isolated (C. Devkumar, S.K. Mukherjee, 1983). Nimbidin and sodium nimbidate possess significant dosedependent anti-inflammatory activity against carrageenin induced acute paw oedema in rats and formalin-induced arthritis (Govindachari, 1992). Antipyretic activity has also been reported and confirmed in nimbidin (David, 1969). Oral administration of nimbidin demonstrated significant hypoglycaemic effect in fasting rabbits (Pillai *et al*. 1981). A significant antiulcer effect was observed with nimbidin in preventing acetylsalicylic acid, indomethacin, stress or serotonin-induced gastric lesions as well as histamine or cysteamine-induced duodenal ulcers (Murthy *et al*. 1958) [41]. Nimbidin can also suppress basal as well as histamine and carbachol-stimulated gastric acid output and may act as an antihistamine by blocking H2 receptors, thereby helping as an antiulcer agent (Bhide *et al*. 1958) [7, 10]. The spermicidal activity of nimbidin and nimbin was reported in rats and human as early as 1959 (Jones *et al*. 1994) [31]. Nimbidin also demonstrated antifungal activity by inhibiting the growth of *Tinea* rubrum (Rao *et al*. 1977) [60]. *In vitro*, it can completely inhibit the growth of *Mycobacterium tuberculosis* and was also found to be bactericidal. Diuretic activity was also reported for sodium nimbidinate in dogs (Khalid *et al*. 1989) [33, 35]. Nimbolide has been shown to exert antimalarial activity by inhibiting the growth of *Plasmodium falciparum* (Van der Nat *et al*. 1991) [72, 75]. Nimbolide also shows antibacterial activity against *S. aureus* and *S. coagulase* (Pant *et al*. 1986) [51, 56, 57].

8.1 Antifertility Activity of Neem

Neem has long been documented to have antifertility in males (Kasturi *et al*. 1995). Oral administration of ethanolic extracts of Neem to adult male lice 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 (Awasthy *et al*. 2001). 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 (Mishra *et al*. 2005). Neem leaf powder when given to Rats for 48 days reduced motility and density of sperm and caused structural changes of Leydig cells and seminiferous tubules (Khan *et al*. 2013).

8.2 Antibacterial Activity of Neem

The susceptibility of the microorganisms to the extracts of Neem leaves was compared with certain specific antibiotics. The methanol extract of *Azadirachta indica* exhibited pronounced activity against *Bacillus subtilis* (28 mm) (Shravan *et al*. 2011). Neem oil preparations have been found effective against a wide spectrum of bacteria viz., *B. cerus*, *B. pumilus*, *S. aureus*, *M. tuberculosis*, *E. coli*, *P. vulgaris*, *S. typhi*, *K. pneumonae*, *S. dysenterae*, *Enterococcus faecalis*, *Streptococcus mutans*, *Streptococcus salivarius*, *Streptococcus mitis*, *Streptococcus sanguis* and even *Streptomycin* resistant strains(Rosaline *et al*. 2013). *Azadirachta indica* leaves possessed good anti-bacterial activity, confirming the great potential of bioactive compounds and is useful for rationalizing the use of this plant in primary health care.Neem oil also has definite antiplaque activity (Elavarasu *et al*. 2012). Neem leaf extract can inhibit the formation of biofilm in *Pseudomonas aeruginosa* (Harjai *et al*. 2013).

8.3 Antimalarial Activity of Neem 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 (Isah *et al*. 2003) [25]. Extracts of Neem are effective against a variety of protozoal pathogen like *Plasmodium spp.* An active ingredient irodin A isolated from Neem leaves is toxic to causative strains of malaria (WHO *et al*. 2008) [77]. *In vitro* experiments have demonstrated cent-percent mortality within 72 h even in a ratio of 1:20,000.

8.4 Anti-Ulcer Activity of Neem

Inhibition of acid secretion was confirmed by inhibition of H+ K+ ATPase activity, while blockade of oxidative damage of gastric mucosa was evident from blocking of lipid peroxidation and scavenging of endogenous hydroxyl radical (OH). Furthermore, they compared the bark extract with known antiulcer drugs ranitidine and omeprazole in the PL and the stress ulcer models and found that the extract was almost equipotent to the standard drugs. The bark extract exhibited more anti-oxidant activity than a variety of known anti-oxidants. There has also been reported an antiulcer effect of Neem leaf extract and the prevention of mucus depletion and mast cell degranulation as possible mechanism (Pant *et al*. 1986) [51, 56, 57]. Neem extracts give significant protection from discomfort and speed the healing of gastric and duodenal lesions (Maity *et al*. 2009) [44].

8.5 Insect Repellent

Azadirachtin is a powerful insect antifeedant that disrupts metamorphosis in moth larvae at extremely low concentrations (Van *et al*. 2004) [76]. 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 (Stark *et al*. 1995) [70]. Neem seed extracts are effective against both asexual and sexual stages of chloroquin-resistant as well as sensitive strains of malarial parasites *P. falciparum*. Seed extract have inhibited growth and development of the human malarial parasitic agent. Neem extract was found to have some neuronal protective effect in malaria positive cases (Farahna *et al*. 2010) [21] and thus mitigate the inflammation of central nervous system. (Bedri *et al*. 2013) [11] Azadirachtin present in Neem can be used as a potential agent for controlling *Argulus*, a common ectoparasite of ornamental fish.

8.6 AIDS

The National Institutes of Health reports Neem extracts killed the AIDS virus and patents have been awarded for these extracts as an AIDS treatment (Anyaehie, UB. 2009) [4].

8.7 Periodontal disease

German researchers have proven Neem extracts prevent tooth decay and periodontal disease (Chava *et al*. 2012) [12] leading to good oral health. Neem leaf extract has a antimicrobial effect on *Enterococcus faecalis* and *Candida albicans*. Therefore, it can be a potential endodontic irrigant.

9. Conclusion

Considering the significance of Neem tree in the field of ethnomedicinal science, work must be carried out to exploit the therapeutic utility of this plant to combat diseases. Attention must be given on the development of modern drugs after thorough investigations on the bioactivity, mechanism of action, pharmacotherapeutics, toxicity and similar aspects of chemical constituents of Neem extract. There is still a lot of scope in this field for better utilization of this wonder plant.

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