



Review Article

Antibacterial properties of Neem (*Azadirachta indica*): a mini review

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Abstract

Objectives: Neem (*Azadirachta indica*) had been well known for its medicinal values in the ancient Asian country like Bangladesh, India and had probably been the most useful medicinal plant in South Asia. From leaf to root, each and every part of the neem tree has also been used in Bangladesh and neighboring countries for over two thousand years for their medicinal properties. Neem tree drew the attention of natural products chemists by Ayurveda. During the last five decades, considerable progress has been achieved regarding the biological activities and medicinal applications of neem. The current review describes the major biological activities, antibacterial properties of some of the neem compounds isolated, as well as some other environmental, clinical and medicinal applications.

Keywords: *Azadirachta indica*, Ayurveda, biological activity, anti-bacterial.

Introduction

The neem (*Azadirachta indica*) or margosa tree, also called Indian lilac, belongs to the Meliaceae (mahogany) family (Schmutterer 1990). Its origin is mainly in southern and southeastern Asia as it is commonly found in Bangladesh, India, Pakistan and Nepal but currently grows in tropical and subtropical areas of Africa, America, and Australia (Koul et al. 1990). Various parts of this plant such as leaves, barks, fruits, seeds and roots (Figure 1) contain compounds with proven anti-

inflammatory, anti-pyretic, anti-histamine, anti-fungal, antibacterial, anti-ulcer, analgesic, anti-arrhythmic, anti-tubercular, anti-malarial, diuretic, spermicide, anti-arthritis, anti-protazoal, insect repellent, anti-feedant, anti-hormonal properties and anti-cancerous uses (Biswas et al. 2002, Kumar and Navaratnam 2013, Tiwari et al. 2014). That's why neem is also referred to as "Village pharmacy", "Tree of the 21st century" and "A tree for solving global problems" (Paul et al. 2011, Kumar and Navaratnam 2013).

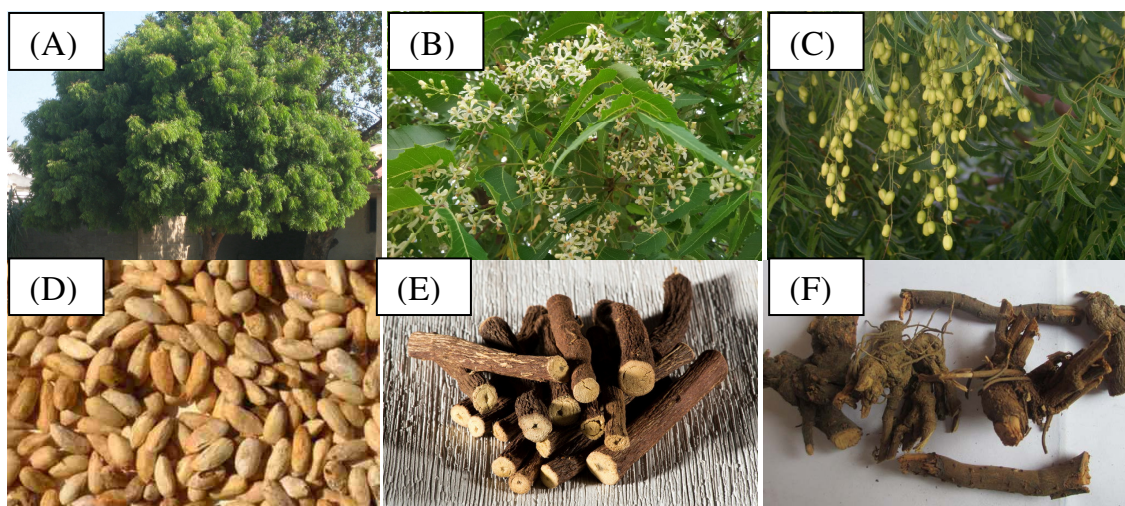


Figure 1. Various photographs of *A. indica* showing (A) a whole tree, (B) flowers, (C) fruits, (D) Seeds, (E) twinges and (F) roots.

Taxonomy of *Azadirachta indica*

De Jussieu (De Jussieu 1830) has described the neem tree as *A. indica* as early as in 1830 and its taxonomic position is as Table 1.

Table 1: Taxonomic position of *Azadirachta indica* (neem).

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

Morphology

Neem is a large evergreen tree that may grow up to 20 meter in height. The leaves are alternate and the leaflets contain 8-19 leaves that may appear in

March-April and they are bitter in taste (Puri 2003).

Although, in early days the neem has been introduced in many countries, mainly for afforestation and fuelwood production in dry areas including use as an avenue or shade tree and as a producer of natural pesticides; but in recent days the scientists are more interested to this multi-beneficial plant, and thus many other important roles have been discovered. In this review the active ingredients and the overall role of neem specially the antibacterial ones are summarized.

Biologically active compounds

Azadirachta indica has compound of various constituents that play role in disease management. Although more than 300 natural products have been isolated from different sections of this tree, with new compounds added to

the list every year till now (Sharma et al. 2015), but a few of them have been studied for biological activity (Biswas et al. 2002). Among them some compounds are well-known for their beneficial bioactive actions like anti-inflammatory, antifungal, antibacterial etc. as shown in Table 2.

Table 2. Some bioactive compounds from neem (Biswas et al. 2002).

Neem compound	Source	Biological activity
Nimbidin	Seed oil	Anti-inflammatory, Antiarthritic, Antipyretic, Hypoglycaemic, Antigastric ulcer, Spermicidal, Antifungal, Antibacterial, Diuretic
Nimbin	Seed oil	Spermicidal
Azadirachtin	Seed	Antimalarial
Mahmoodin	Seed oil	Antibacterial
Gallic acid, (–) epicatechin and catechin	Bark	Anti-inflammatory, Immunomodulatory
Polysaccharides GlA, GlB	Bark	Antitumour
Cyclic trisulphide and cyclic tetrasulphide	Leaf	Antifungal

Antibacterial properties

General studies

Werner Fabry et al. (Fabry et al. 1998) in their study tested the extracts of *Azadirachta indica* (stem bark and leaves) against 105 strains of bacteria from seven genera (*Staphylococcus*, *Enterococcus*, *Pseudomonas*, *Escherichia*, *Klebsiella*, *Salmonella*, *Mycobacterium*). The minimum inhibitory concentration reached by 50% (MIC₅₀) and 90% (MIC₉₀) of the strains for the extracts of *A. indica* (stem bark) ranged from 0.25–2 mg/ml and from 0.5 to 2 mg/ml, respectively. Moreover extracts of the edible part (flowers) of *A. indica* also showed antibacterial activity against *Bacillus cereus*, *Staphylococcus aureus*, *Listeria monocytogenes*, *Escherichia coli* and *Salmonella infantis* (Alzoreky and Nakahara

2003). Because of this crucial role of *A. indica* in antibacterial activity, further studies have been carried out and found that methanolic and acetone extracts were more effective against the bacteria compared to that of aqueous extract (Rajasekaran 2008, Singh et al. 2016).

Studies at molecular level demonstrate that *A. indica* contains chemical constituents of alkaloids, terpenoids, tannins and flavonoids (Makkar et al. 2007) responsible to overcome microbial infection specially having antioxidant and antimicrobial biological activities (Scalbert and Williamson 2000, Manach et al. 2004). These chemicals might show the antibacterial activity having the ability to make a complex with the bacterial cell walls. Inhibitory activity towards DNA topoisomerase enzyme II by azadirachtin, a bioactive metabolite of neem (Scalbert 1991) might also involve in the antibacterial potential. Moreover, the Gram-positive bacterial strains were found more sensitive than the Gram-negative ones (Sinaga et al. 2016).

Specific diseases

From a preliminary study it has been found that β -sitosterol, a phytochemical found in *A. indica* has a role in strengthening the immune system (Bumrela and Naik 2011). Hence, many people apply it on skin for treating wounds, burns (www.webmd.com) and for curing skin diseases (Pandey et al. 2014). The phytoconstituents, β -sitosterol along with β carotene in the methanol extract are also a well-known antibacterial agent functioning against a broad spectrum of both Gram negative and Gram positive bacteria, including *S. aureus* (Bumrela and Naik 2011).

A clinical treatment study using formulation of mucoadhesive dental gel containing *Azadirachta indica* leaf extract (25 mg/g) showed microbial evaluation of *Streptococcus mutans* and *Lactobacilli* species which was carried out to determine the total decrease in the salivary bacterial count (Pai et al. 2004). *Enterococcus faecalis* is the most commonly found bacteria in failed root canal. Sodium hypochlorite (NaOCl) and 2% chlorhexidine (CHX) are used as the root canals irrigants (Bazvand et al. 2014), whereas, constant increase in antibiotic resistant strains and side effects of chemical irrigants has led to the

search for alternative herbal medicaments. Thus, Gonmode et al. (Bazvand et al. 2014), Hegde et al. (Hegde and Kesaria 2013), and Damre (Damre 2015) in their studies observed higher inhibition zone of *E. faecalis* culture by neem leaves extract compared to that of NaOCl. Further studies showed that the antibacterial activity of neem could be due to the presence of several active constituents like nimbidin, nimbin, nimbolide, gedunin, azadirachtin, mahmoodin, margolone and cyclotrisulphide (Biswas et al. 2002). Moreover, 10% nonabsorbable neem oil chip has antibacterial effect against *Porphyromonas gingivalis*, a periodontal pathogen (Vennila et al. 2016).

Antibacterial activity along with antisecretory and antihemorrhagic activity was found against the multi-drug-resistant *Vibrio cholerae* (serotypes O1, O139 and non-O1, non-O139), a causative agent of watery diarrhea such as cholera, from the methanol extract of neem leaf (Thakurta et al. 2007).

Recently, endophytic actinomycetes from *Azadirachta indica* have been paying attention to explore the novel bioactive natural compounds that can be used to design new drugs replacing those against which pathogenic strains have rapidly acquired resistance (Verma et al. 2009). In recent years, more than seven newly defined antibiotic compounds were revealed from endophytic *Streptomyces* (Castillo et al. 2002, Pullen et al. 2002, Ezra et al. 2004). Some of them (e.g., Coronamycin) had remarkable activity against malarial parasites (Pullen et al. 2002, Ezra et al. 2004). This observation recommends that endophytic actinomycetes offer promise for the discovery of unique natural products with pharmaceutical prospective.

Other environmental, clinical and medicinal applications

The whole neem plant is full of domestic, industrial and pharmaceutical values as shown in **Table 3**.

Mainly owing to its various effects on insects, azadirachtin (AZ, a steroid-like tetranortriterpenoid (limonoid)) is considered the most important active ingredient in neem seed kernels (NSK) (Schmutterer 1990). It can act as a green corrosion (deterioration of materials by chemical processes) inhibitor against various metals,

especially for mild steel, aluminum and tin (Sharma et al. 2015).

Table 3. Medicinal uses of different parts of neem (*A. indica*) tree (Paul et al. 2011).

Parts of Neem	Treatable ailments
Bark	Alternative and curative of fever, Analgesic
Twig	Intestinal worms, spermatorrhoea, obstinate urinary disorder, diabetes, cough, asthma, piles, phantom tumor
Leaf	Intestinal worms, anorexia, biliousness, skin ulcers, cancer, leprosy, eye problem, epistaxis
Flower	Bile suppression, elimination of intestinal worms, phlegm
Fruit	Intestinal worms, urinary disorder, epistaxis, piles, phlegm, eye problem, diabetes, wounds, leprosy
Seed	Intestinal worms, leprosy, cancer
Oil	Intestinal worms, leprosy
Gum	Ulcers, skin diseases, scabies, wounds

From various research articles it can be presumed that *A. indica* has chemopreventive and chemotherapeutic potential against various cancer models. For instance, (i) crude aqueous extracts of *A. indica* leaves and seeds inhibited the growth of Ehrlich ascites carcinoma cells or acting against the breast cancer cells (Amer et al. 2010), (ii) against gastrointestinal tract and associated cancers, a neem leaf glycoprotein (NLGP) was found effective (Goswami et al. 2010), and also working against (iii) OVCAR-5 ovary cancer cells (Sastri et al. 2006), (iv) ethanolic and aqueous extracts of neem leaf effective in case of hematological cancer reducing the viability of E6-1 leukemic cells (Roma et al. 2015), (v) ethyl acetate fraction of crude leaf extract showed modest antiproliferative effects against A-549 lung cancer cells (Jafari et al. 2013) and other compounds against prostate cancer, skin cancer, connective tissue cancers, paracetamol hepatotoxicity (Chattopadhyay 2003) and so on. The details of these effective compounds and possible mechanism of actions are reviewed earlier (Patel et al. 2016). IRAB, a fractionated neem-leaf extract was reported having activities against Malaria, HIV/AIDS and cancer has been developed into a drug and currently marketed in Nigeria as IRACAP® (Anyahie 2009).

Several studies also showed that the neem seed can be used as a protein source in animal feed (Adjorlolo et al. 2016). Other than most non-leguminous tree leaves, neem leaves have higher crude protein concentration which coupled with a low level of fiber, making it suitable as a protein supplement for ruminants on poor quality diets. And, recent studies also showed that combined use of the natural antioxidant neem with other plant (e.g. curcumin) having antioxidant property may reduce the inhibitory effect of α -Linolenic acid towards MCF-7 breast cancer cells (Cheung et al. 2016).

Practical problems and safety evaluation

Despite of versatile qualities of neem, it is required to be used with care as indiscriminate use of its extracts may cause unpleasant side effects. It may also be a reason for damage to liver and kidney that may result in jaundice and in low or no urine production, respectively. Moreover, it might also destroy red blood corpuscles (Haque et al. 2006). Furthermore, neurotoxicity might be caused in case of excessive use of neem (Paul et al. 2011). Another important concern about its use is its ability to interfere with the normal reproductive systems fostering infertility (Sinha et al. 1984, Lal et al. 1986, Khosla et al. 2000, Khillare and Shrivastav 2003).

Conclusion

It can be concluded that various components of *A. indicaseems* to act as promising agents against several diseases. Further studies should be conducted on its clinical as well as industrial, environmental and pharmaceutical applications.

Conflict of Interests

None to declare.

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