

Therapeutic Potential of *Azadirachta indica* (Neem) and Their Active Phytoconstituents against Diseases Prevention

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ABSTRACT

Neem (*Azadirachta indica*) is an important member of the Meliaceae family and its role as health-promoting effect is attributed to it is rich source of phytoconstituents. It has been widely used in Ayurvedic, Chinese and Unani medicines worldwide particularly in Indian Subcontinent in the prevention and treatment of various diseases. Earlier finding confirmed that neem and its phytoconstituents play a key role to scavenge free radical generation and prevention of disease pathogenesis. It is considered as safe medicinal plants and regulates the various biological processes without any adverse effect. In this current review, the role of *Azadirachta indica* is summarized in the prevention and treatment of diseases via the regulation of various physiological and biological pathways.

Keywords: Aflatoxin; spices; Fungal infestation; *Azadirachta Indica*; *Aspergillus flavus*.

INTRODUCTION

From the beginning of society, medicinal plants are the important section and part of human civilization to fight against diseases. The well-known plant in India and its neighboring countries is *Azadirachta indica* which is one of the most versatile medicinal plant for more than 2000 years having a wide spectrum of biological activities. The common name of *Azadirachta indica* is known as Neem. In Sanskrit, the name flowers borne in panicles, bysyncarpous apparently, spikes, cymes and clusters.

Maximum plants are evergreen in this family but approximately are deciduous, either in the dry season or in winter. There are 550 species and 50 genera are present in this family.

A supreme and a blessed gift of natural surroundings is neem. *Azadirachta indica* is a tropical evergreen tree native to India and is also found in other southeast countries (Krishnaiah and Prashantha, 2014). By the United Nations, neem has been approved the “Tree of the 21st century” because it is an inconceivable plant. A circulated report that enable “Neem: A tree for solving global problem is given by the US National Academy of Science in 1992. *Azadirachta indica* is a latin term which is derived from Persian language, indicated as Azad” for “free”, “dirakht” for “tree” and “I” for “Hind” meaning belonging to Indian foundation. Neem is known as “arista” in Sanskrit language, meaning “complete and imperishable” (Gupta *et al.*, 2017).

The tree of neem can grow very fast. From seed planting, it may grow to 20 feet in height in three years. The neem tree will developing that area where rainfall is only 18 inches per year and it blooms in that areas where extreme heat up to 120 degrees is present. The estimated productive life span of neem tree has been 150-200 years. In India, an approximate calculation of quantity of neem trees is about 18millions and it is also initiate all over in Malaysia. The neem tree is widely established in Malaysia, Kedah and Petain. Neem has been presented to the Caribbean in the last year, where it is being used as aforestation in several nations. A major tree species in Haiti is considered as neem (Kumar and Navaratnam, 2013).



Fig:1 *Azadirachta indica* (Neem)

Neem is a large tree growing having semi-swerving to straight stem, 3 m in width and branches are spread to form a extensive crown. Fruiting in neem tree is usually starts after 3-5 years. Neem tree becomes fully productive in about 10 years. Onwards from the tenth year, up to 50 Kg of fruits can be produced by neem annually (Raj, 2015).

The leaves of neem tree are separated into many leaflets, each approximating to a fully-fledged leaf, with small white flowers which are 1.5 to 2cm long, auxiliary in manners, yellow or green fruits in which seeds are present (Yerima *et al.*, 2012).

For normal growth, neem (*Azadirachta indica*) needs 130 mm of adequate rainfall per annum. The bark, leaves and seed have compounds with confirmed antiviral, antiseptic, anti-

ulcer, anti-inflammatory, antifungal and antipyretic uses. The Sanskrit name for neem is Arista meaning 'perfect' imperishable and complete. Neem has considerably offer in solving environmental, agricultural, health and problems (Jagannathan and Vasuki, 2015). The neem tree is resistant to shortage of rainfall and blooms generally in those areas which are sub-arid to sub-humid having the rainfall is between 400-1200 mm per annum. Especially for southern districts and dry coastal, the neem tree is considered as life giving tree (Boadu *et al.*, 2011).

1.2. Classification of Neem plant

Phylum	Vascular plant
Class	Magnoliopsida
Order	Rutales
Suborder	Rutinal
Family	Maliaceae
Subfamily	Melioideae
Tribe	Melieae
Genus	Azadirachta
Species	Indica (More <i>et al.</i> , 2015).

1.1. Vernacular names

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

(Hashmat *et al.*, 2012).

1.2 Chemical Composition of Neem

There are more than 300 compounds have been derived from diverse neem parts. The compounds have been broadly classified into two main classes which are isolated from neem: non-isoprenoids and isoprenoids. The compounds included in isoprenoids are diterpenoids and triterpenoids which contain limonoids, azadirone, protomeliacins, and its derivatives, vilasinin type of compounds, gedunin and its derivatives, Csecomeliacins such as salanin, nimbin, and azadirachtin. The compounds included in non-isoprenoids are carbohydrates (polysaccharides), proteins (amino acids), sulphurous compounds, polyphenolics such as glycosides and their flavonoids, dihydrochalcone, tannins, and coumarins, aliphatic compounds, etc. (Biswas *et al.*, 2002), margalonone, margalone, and isomargalonone (Dixit, 2015).

Parts of neem plant

Almost all parts of neem tree discovers its applications in congenital medicine due to its bitter taste. In ancient times, this tree has been in used as domestic pesticides and also for the treatment of a number of human diseases (Deshpande *et al.*, 2014).

1.5.1. Neem Bark

The bark of neem is small, deeply gorge and in form of flakes , moderately dense, scattered tubercles, reddish inside and dark grey outside having colorless adhesive sap (Balami *et al.*, 2013). The twig of neem tree is snap off and chew on it in this way, neem bark is used to clean the teeth which is most common traditional method. The bark is also used to preventing the tooth decay, bleeding gums and foul smell long due to its bitter taste before arrival of tooth paste.

The decoction of neem bark is used as to suppress or relieve dry coughing. Its coal, astringent, bitter property is useful for loss of appetite, cough, fever, intestinal warm, tiredness, helpful for healing wounds, excessive thirst infestation to combat vomiting, and various skin diseases (Dixit, 2015).

The compounds have been isolated from from the aqueous extract of bark of neem are catechin, Gallic acid, margolone, epicatichin, isomargolonone, margolonone, polysaccharides (G1A, G1B G2A G3A) and NB-2 peptidoglucon which possess immunomodulatory anti,- tumor and anti-inflammatory (Pankaj and Lokeshwar, 2011), antioxidant (Ghimeray *et al.*, 2009) and antibacterial activity (Susmitha *et al.*, 2013)). The chloroform extract of stem bark can be effective against mouse ear inflammation and carrageenan-induced paw edema in rat (Tidjani *et al.*, 1989).

1.5.2. Neem Leaves

The leaves of neem are attractive extensive leaves that can grow upto 30 m in height and 2.5 m in girth, diameter of large crown is upto 10 m (20 maximum). The leaves are light green in color, simply pinnate, alternate, 20-40 cm long, crowded near the end of twigs and stipulate. (Jhariya *et al.*, 2013). The leaves of neem are imparipinnate with each comprising 5–15 leaflets and compound. (Alzohairy, 2016). The essential compounds found in the neem leaves are nimbanene, nimbandiol, nimbin, 6- desacetylnimbinene, ascorbic acid, nimbolide, amino acid, n-hexacosanol, 7-desacety-7- benzoylgedunin, 7-desacety- 7benzoylazadiradione, 17-hydroxyazadiradione and nimbiol (Gupta *et al.*, 2017).

A vigorous ingredient isolated from leaves of neem is irocin A which is effective against contributing anxieties of HIV/AIDS and malaria (Anyachie, 2009). Azadirachtin is an active material of neem leaves which possess capability to perform against disease causing viruses, parasites and fungi (Raj, 2015).

Many biological properties such as antimalarial, anti-carcinogenic, anti-inflammatory, antibacterial, antiviral, anti-carcinogenic, anti-fungal, anti-mutagenic, antioxidant, antiulcer, immunomodulatory, anti-hyperglycemic (Subapriya and Nagini, 2005; Paul and Prasad, 2011), analgesic, antimicrobial, antipyretic, cardiovascular, antidiuretic, anthelmintic (El-

Hawary and Badr, 2013), anti-inflammatory attributes, anti-proliferative, (Mosaddek and Rashid, 2008) are exhibited by leaves of neem and its constituents. The treatment of ringworm, acne, eczema and healing of chronic wounds is very effective by using neem leaf. It is stated that neem leaf can purify the blood, neutralize free radicals and remove toxins from the body. It has hypolipidemic effects and hepato-renal protective activity. So, it is used as anti-cancer agent (Deshpande *et al.*, 2014). The first poly-phenolic flavonoids purified from fresh neem leaves were β -sitosterol and Quercetin and were well-known due to their anti-bacterial and anti-fungal activities (Alzohairy, 2016).

1.5.3. Neem Fruit

The neem fruit is olive-like fleshy indehiscent fruit with a single seed and smooth which differs in form lengthened to oval to approximately roundish, bitter sweet pulp (mesocarp) is yellow-white in color and very tough having width between 0.3 - 0.5 cm, thin exocarp, hard inner shell endocarp white in color hardly two or three drawn out seed (kernels) having a brown seed coat that comprise between 25-45% neem oil. Fruiting starts from after 3-5 years of planting. After ten years, it can produce up to 50 kg of fruits annually (Balami and Aliyu, 2014). There are green drupes of fruit which on ripening turn to golden yellow in the months of June- August (Alzohairy, 2016).

1.5.4. Neem seeds

More than 100 active compounds are present in neem seeds which collectively called liminoids or triterpenoids together with azadirachtin that would be one of the most significant bio-pesticides (Tindo and Amusant, 2012). In 1968, Azadirachtin was first isolated by Butterworth and Morgan (1968). Azadirachtin, a tetranortriterpenoid, is an important biologically active constituent of neem seed kernel. It is used for pest control (Gupta and Tripathi, 1998). There is a combination of seven isomeric compounds characterized as Azadirachtin A-G and Azadirachtin E is extra effective (Dash and Dixit, 2017). The interference in mitosis can also be done by Azadirachtin, in similar way as colchicine has uninterrupted histo-pathological effects on muscles, fatty tissues and gut epithelial cells of insects which result in limited movement and reduced flying activity. Nimbodin and nimbin primarily present in antiviral activity while salannin and meliantriol as well as act to prevent the feeding of insects (Campos *et al.*, 2016).

After extraction of the neem oil from neem seeds (neem seed cake), the remaining waste can be used as a bio-fertilizer, which provide the essential macronutrients for the growth of plant (Ramachandran *et al.*, 2007).

1.5.5. Neem oil

The neem seed kernels are processed to obtain neem oil. A much amount about 50% oil can be present in kernels. Neem oil acts as skin care ingredient, fertilizer, insect repellent and pesticides. In cosmetics such as nail polish, purified neem oil is used. In south-Asia, a huge amount of neem oil is available and it is non-edible. Traditionally, the neem oil has been

used as for lightening purpose such as fuel in lamps in rural areas. The neem oil is also used on industrial scale for preparation of cosmetics, pharmaceuticals, soaps and other non-edible products (Balami and Aliyu, 2014).

A variety of biologically active compounds has been found in neem which are diverse chemically and contain a lot of therapeutic activities. The isolation of three products namely nimbinin, nimbidin and nimbin was report to first from neem oil (Bansal *et al.*, 2010). Four important fatty acids are present in neem oil from which two are saturated such as stearic and palmitic acid. A monounsaturated acid is known as oleic acid and a polyunsaturated fatty acid is linoleic acid (Kaushik, 2002). A crude bitter ingredient called “Nimbidin” is extracted from the oil of seed kernels of *Azadirachta indica*. Other important tetranortriterpenes have been isolated by following the same principle namely nimbinin, nimbidic acid, nimbin and nimbolide. The anti-inflammatory activity is shown by sodium nimbidate and nimbidin against carrageen in is significant dose dependent which promotes acute paw oedema in rats and arthritis is induced by formalin (Bhargava *et al.*, 1970; Pillai and Santhakumari, 1981). Moreover, it has antifungal, antibacterial and medicinal properties (Luo *et al.*, 1999).

Oil shows many physicochemical characteristics in its use such as production of biofuel and soaps. It contain for major compounds, linoleic acid oleic acid, palmitic acid and stearic acid. Composition of glyceride shows triglycerides constitute 97.69%. Majority of oil triglycerides can be SOL and POL. Unsaponifiable fraction shows β -sitosterol is by far the major sterol.



The Neem Products. (A) Twigs, (B) Leaves, (C) Fruits, (D) Seeds (with endocarp), (E) Seeds (without endocarp).

Traditional uses of Neem

In Ayurvedic and Unani out-of-date medicine, in the treatment of a varied range of illnesses, different parts of neem were preferred. In India and Pakistan, the neem twigs are used for brushing or scrub the teeth. This practice may be one of the most effective and earliest

forms of dental care. For the preparation of different medicines, all parts of neem tree (leaves, seeds, bark and flower) are used.

Conventionally in India, patientgrief Chicken pox sleep on the leaves owing to its medicinal value (Maithani *et al.*, 2011).

This is a traditional treatment of Malaria used by Nigerians and other conditions is formed by the consumption of unspecified quantities without due regards to its toxicological effects. Aqueous extracts of seeds is used for head lies. Neem oil is good antiseptic for the treatment of skin as furuncles, eczema and intestinal worm infections (Eid *et al.*, 2017).

The pesticide activity has shown by neem and it is acknowledged for it. Against insects, one of the principal mode of action of neem is metamorphosis disruption and the bitter taste of neem keep the insects away from host plants and make it classic repellent and anti-feedent (Senthil Kumar *et al.*, 2018).

A significant blood sugar lowering effects possessed by the alcoholic extract of neem leaves that are very beneficial against diabetes. Many fever-reducing and pain-relieving compounds are produced by neem that can assist in healing of cuts, earaches, burns, headache, sprains as well as fever. Neem extracts are as well used for the cure of malaria (Hla *et al.*, 2011).

1.7. Medicinal uses of Neem

Because of healing versatility of neem, it is known as “the village pharmacy” and due to its medicinal properties, the tree has been used in Ayurvedic medicine (*Krishnaiaha and Prashantha*, 2014). The important medicinal use of neem consist of rheumatism, malaria, intestinal worms, jaundice, tuberculosis, skin and as well as arthritis. A unique property has been shown by neem tree is known as calcium mining which means have the capability to neutralize acidic soils. The neem extracts are also helpful for hepatitis, psoriasis, fungal infection, heart diseases, malaria, and ulcers. A significant anti-diabetic potential has been demonstrated by the extract of Neem leaves. The immune system is enhanced by neem and it is also considered as the possible substance for the treatment of cancer patients and AIDS. Blood sugar level is reduced by the help of neem, possibly will be reduce the 30%-50% use of insulin also used as operative compound for diabetic patients.

The neem extracts are also advantageous for hepatitis, heart diseases, psoriasis, fungal infection, malaria and ulcers. Externally, neem is used for eczema, fungal infection, ringworm, psoriasis, lice as well as for muscles and painful joints. The neem oil also used as fighting of pimples, acne as well as refining skin elasticity (Manisha and Sachin, 2014). Neem has been considered as a potential source of many therapeutic agents (El-Hawary and El-Tantawy, (2013).

1.8. Biological Activities of Neem

1.8.1. Antiulcer

The extract of neem bark reduced the hyper-secretion of gastric acid in human, gastro-duodenal and gastro-esophageal ulcers. The duodenal ulcers were almost fully cured after 10 weeks; one case of gastric ulcer and esophageal ulcer were fully cured after 6 weeks (Bandyopadhyay *et al.*, 2004).

1.8.2. Antioxidant Activity

Antioxidants are the substances that inhibits oxidation or inhibits reactions promoted by oxygen or peroxides. They reduce the formation of free radicals and help to shield the body from damage of cell. The chemical species that acquired an unpaired electron are called free radicals that can be considered as very reactive fragments of molecules. Free radicals are generated as a result of toxic metals. They are the source to oxidative destruction of DNA, protein and other vital molecules and also cause the cardiovascular (heart related diseases), cancer and oxidative stress (Hla *et al.*, 2011).

Curcumin and neem are substantive antioxidant materials comparable to other herbal and traditional medicinal agents. Invitro test using MCF-7 cells indicated that ALA, curcumin and neem leaf extract produce a concentration-dependent inhibition of cancer cell growth. Combination treatments using ALA and curcumin or ALA and neem extract, resulted in a significant loss in efficacy of each agent. The findings are consistent with past literature suggesting that lipid peroxidation and oxidative stress may be negative risk factors for breast cancer and that antioxidants may on some occasions impair rather than support other therapies (Cheung and Nigam, 2016). It have been reported that the active neem leaf fractions showed the protective and antioxidant effects against hydrogen peroxide which induce oxidative damage to pBR322 DNA and red blood cells, Manikandan *et al.*, (2009).

1.8.3. Antibacterial Activity

The extract of neem leaf had no effect on the growth of *F. nucleatum* and on the co-aggregation of the two bacteria and also had shown prominent dose-dependent antibacterial activity against *P. gingivalis*. The leaf extract of neem adhere to oral surfaces due to the presence of polyphenols that have ability to afford long-term synergic antioxidant activities as well as anti-bacterial activity when in composite with red blood cells, lysozyme and bacteria. Thus it might be particularly operative in periodontal diseases (Heyman *et al.*, 2017). The antibacterial activity of leaf, fruit, seed and bark extracts of *Azadirachta indica* (neem) isolated from adult mouth was carried out on bacteria by using agar well diffusion method. The antibacterial activity against all the test used bacteria is shown by the extracts of leaf and bark of neem. With increase in concentrations of the extracts, the zone of inhibition also increased. The antibacterial activity only at higher concentrations is shown by the extracts of fruit and seed. Therefore, the results confirm the usage of neem in sustaining oral hygiene traditionally (Yerima *et al.*, 2012).

1.8.4. Antimalarial Activity

It has been earlier reported that the extracts of Neem leaves (*Azadirachta indica*) from Nigeria show anti-malarial activities (Ekanem, 1971). The development of contemporary drugs from less toxic plant products which is supported by current global scenario with verified medicinal properties. Various medicinal properties has been reported by each part of neem

plant (*Azadirachta indica*) and has been in use in many regions for centuries. In recent times, IRAB is known as a fractionated extract of neem-leaf was reported against HIV/AIDS anti-malarial activity and cancer has been developed into a drug and currently marketed in Nigeria as IRACAP (Anyachie, 2009).

To evaluate the antimalarial activity of extracts by means of *Plasmodium berghei* infected albino mice, another experiment was made and results exposed that the extracts of neem stem bark and leaf lesser the level of parasitemia by about 51–80% and 56–87%, in infected mice and this is shown by the other studies that other liminoids and Azadirachtin available in extracts of neem are vigorous on malaria vectors (Alzohairy, 2016).

1.8.5. Anti-diabetic Activity

To examine the pharmacological hypoglycemic activity of *Azadirachta indica* in diabetic rats, an experiment was performed. The results of neem extract 250 mg/kg with glucose tolerance test revealed that there is less glucose level in comparison to control group. Glucose level is significantly reduced by *Azadirachta indica* at 15th day in diabetic rat (Patil *et al.*, 2013).

1.8.6. Antisnake venom activity

It is reported by Ashis *et al.* (2008) that isolation of a snake venom phospholipase A2 (PLA2) inhibitor (AIPLAI) from leaves of *A. indica* (neem) and in vitro condition, technical aspects of working of PLA2 inhibition by AIPLAI was also studied.

1.8.7. Anti-carries

The extract of Neem has been found to be specifically active against the caries causing organisms with the capability of not only inhibiting their growth but also reversing incipient caries. The following clinical and in-vitro studies give the glimpses of its beneficial anticariogenic effect (Gupta *et al.*, 2017).

1.8.8. Anti-tubercular activity

The growth of mycobacterium anxieties is inhibited by 12.5 mg/ml concentration of neem oil. Neem oil and Nimbidol in higher concentration exhibited partial inhibitory influence whereas Nimbidin prolong the survival period of mice affected with T.B (Manisha and Sachin, 2014).

CONCLUSION

Popularity of natural products in diseases prevention and cure is increasing worldwide due to their lesser side effects. Neem and its ingredients have therapeutics potential and have been traditionally used worldwide particularly in Indian Subcontinent since ancient time. Clinical based studies showed that neem plays pivotal role in prevention of numerous diseases. The role of active ingredients as chemopreventive effect has been noticed in various tumour via modulation of numerous cell signaling pathways. The detailed study should be made based on animal to know the exact mechanism of action in the diseases management.

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Muhammad Jahangir Latif, *et al.*, J. Chem. & Cheml. Sci. Vol.10(3), 98-110 (2020)

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