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## Neem (*Azadirachta indica*): A Review on Medicinal Kalpavriksha

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### Abstract

Neem, has thrown the light worldwide in recent years, due to its wide range of medicinal properties. The tree has been largely used in Naturopathy, Unani and Homoeopathic medicine and has become a lodestar of current medicine. Further it elaborates a vast array of biologically active compounds that are chemically diverse and structurally complex. More than 150 compounds have been isolated from different parts of neem and these have been divided into two major classes isoprenoids and non-isoprenoids, which are proteins and carbohydrates. Further, it consists of sulphurous compounds, polyphenolic compounds such as flavonoids and their glycosides, dihydrochalcone, coumarin, tannins and aliphatic compounds. All parts of the neem tree viz., leaves, flowers, seeds, fruits, roots and bark have been used traditionally for the treatment of inflammation, infections, fever, skin diseases, dental disorders, etc. Every part of the neem tree viz., roots, seeds, flowers, bark, leaves, fruit pulp and its constituents have been demonstrated to exhibit immune modulatory, anti-inflammatory, anti hyperglycaemic, antiulcer, antimalarial, antifungal, antibacterial, antiviral, antioxidant, antimutagenic, antidiabetic and anticarcinogenic properties.

**Keywords:** *Azadirachata*, chemistry, medicinal properties, neem, pharmacological

### 1. Introduction

*Azadirachta indica* is popularly known as Indian neem or margosa tree. It's been extensively used in ayurveda, unani and homoeopathic medicine since time immemorial. In Sanskrit a "good health" condition is expressed as "Nimba" (Sitasiwi et al., 2018), which on due time derived in to "Neem", further the tree is considered as "*Sarvaroga nivarini*" means cure all ailments. In Ayurveda neem is known as "*Arishtha*" meaning 'reliever of sickness'. The tree is still regarded as "village pharmacy" or "Divine tree" due to presence of medicinal properties in India (Amritalingam, 2001). If the developing countries are considered more than 80% of the population is believed to be dependent on medicinal plants for curing various diseases or disorders (Rupani and Chavez, 2018). Further, the total trade in medicinal plants in India during 2004-05 has been 4,530 crore. India ranks second in the world in terms of the volume and value of medicinal plants export. Neem is one of the indigenous medicinal plants of India which possess medicinal properties in each and every part viz., roots, seeds, flowers, bark, leaves, fruit pulp etc. (Kirtikar and Basu, 1975). Neem is one of the examples of complementary medicine through phytotherapy (Jose et al., 2020). Each of the plant part has been used in the Indian Ayurvedic and Unani systems of medicine and has become a cynosure of modern medicine

In Ayurvedic literature neem is well known for its medicinal

properties viz., Neem bark is cool, bitter, astringent and acrid. In addition to this, it is used to cure tiredness, cough, fever, loss of appetite, worm infestation etc. It also heals wounds and vitiated conditions of kapha, vomiting, skin diseases, excessive thirst and diabetes. Along the bark, chemical compounds present in the leaves are reported to be valuable for eye disorders and insect poisons. It treats Vatik disorder and acts as anti-leprotic. It's fruits are bitter, purgative, anti-hemorrhoids and anthelmintic'. In the view of its immense utilities, this review summarizes the wide range of medicinal uses, pharmacological activities, biological activities of neem tree and its compounds and their chemistry.

### 2. Neem Compounds and Biological Activity

More than 150 compounds have been isolated from different parts of neem. The compounds have been divided into two major classes; isoprenoid (Chatterjee and Pakrashi, 1991) like diterpenoids and triterpenoids containing protomeliacins, limonoids, azadirone and its derivatives, gedunin and its derivatives, vilasinin type of compounds and C-secomeliacins such as nimbin, salanin and azadirachtin) and non-isoprenoids, which are proteins, carbohydrates, sulphurous compounds, polyphenolics such as flavonoids and their glycosides, dihydrochalcone, coumarin and tannins, aliphatic compounds, etc.

Nimbidin, is responsible for crude bitter principle extracted



from the oil of seed kernels of *A. indica* which possess several biological activities, from this crude principle some tetranortriterpenes, including nimbin, nimbinin, nimbidin, nimbolide and nimbidic acid have been isolated (Siddiqui, 1942; Schumacher et al., 2011; Naik et al., 2014). Further, Biswas et al. (2002) have reviewed the biological activities some of the neem compounds, pharmacological actions of the neem extracts, clinical study and plausible medicinal applications of neem along with their safety evaluation. Further, neem also possess compounds acts as Anti-inflammatory, Antiarthritic, Antipyretic, Hypoglycaemic, Antigastric ulcer, Spermicidal, Antifungal, Antibacterial, Diuretic, Antimalarial, Antitumour, Immunomodulatory etc (Joshi, et al., 2010; Saleem, et al., 2018).

### 3. Chemistry of Neem Compounds

Natural compounds present in neem are triterpenes or limonoids. New limonoids are still being discovered in neem. Azadirachtin, salannin, meliantriol and nimbin are well known (Naik et al., 2014). The bitter constituent, the nimbin contains an acetoxy, a lactone, an ester, a methoxy and an aldehyde group. Nimbidin contains sulphur.

#### 3.1. Bark

The bark exudes a clean bright amber coloured gum which is collected in small tears or fragments. It contains a bitter alkaloid named "margosine". Leaves also bitter principles but in small quantity which are much more soluble in water. This substance is a hydrate of the resin. Seeds contain 10% to 31% of a yellow bitter fixed oil with a strong disagreeable acrid taste. The volatile fatty acids present in the bark consist a mixture of stearic and oleic acids along little amount of lauric acid. Trunk bark yields 0.04% nimbin, 0.001 nimbinin, 0.4% nimbidin, and essential oil 0.02%. Tetracyclic triterpenoids and their derivatives have been isolated from the stem bark along with tricyclic diterpenoids).

#### 3.2. Flowers

Flowers have been found to contain a flavonoid. Nimbicetin is identical to kaempferol. In the dried bark the same bitter components as in the seed oil have been found and in the pericarp of the fruit a bitter principle bakayanin was found.

#### 3.3. Neem oil

Neem oil contains Sulphur 0.427%; a very bitter yellowish substance obtained from the alcoholic extract of the oil, which is supposed to be an alkaloid; resins; glucosides and fatty acids

#### 3.4. Seeds

Meliacins found in the seeds include gedunin, 7-desacetylgedunin, desace-tylnimbin and azedarachtin. The seed oil mainly contains nimbidin, nimbin and nimbinin, which also occur in the stem bark (Ara et al., 1989).

#### 3.5. Toddy

The toddy or sap contains glucose, sucrose, gums and colouring matter.

### 4. Medicinal Uses

#### 4.1. Ayurveda

Neem tree has occupied a prominent place in the traditional Ayurvedic medicine in India from time immemorial. Neem bark, leaf extracts and neem oil have been under use as folk medicine to control various problems viz., leprosy, intestinal helminthiasis, constipation, etc. Further, it plays vital role in treating rheumatism, chronic syphilitic sores and indolent ulcers. Neem oil is well known to control various skin problems. Bark, leaf, root, flower and fruit together cure blood morbidity, biliary afflictions, itching, skin ulcers, burning sensations and pthysis (Saleem et al., 2018).

The root bark and young fruits are used as an alterative, antiperiodic and as a tonic. Green twigs are used as toothbrushes for cleaning teeth and as a prophylactic for mouth and teeth complaints. The bark, gum, leaf and seed are used in snake bite and scorpion sting. The bark is used as a bitter tonic, astringent, antiperiodic, antipyretic and against nausea and vomiting. Gum is demulcent tonic in catarrhal affections. Leaves are used as poultice for boils. Decoction of leaves used as an antiseptic in ulcers and eczema. Dry flowers are stomachic. Seed oil is a stimulant, antiseptic, alterative in rheumatism and skin diseases. Berries are purgative, emollient and anthelmintic. An extract of leaves is used in toothpastes. Neem oil is effective in the treatment of leprosy and skin diseases.

#### 4.2. Homoeopathy

Used against rheumatic pains. Pain in sternum and ribs, in the extremities and aches in hands and toes. Also used against eczema, pemphigus and scabies.

#### 4.3. Unani

Neem finds use as a resolvent and blood purifier. Leaves expel wind, heal ulcers in urinary passages. Used as an emmenagogue and in skin diseases. Fruit is used as an astringent and in leprosy and bronchitis.

#### 4.4. Immunostimulant activity

Various studies have revealed that the aqueous extract of leaf and bark possesses anticomplement and immunostimulant activity. Neem oil has been shown to possess activity by selectively activating the cell-mediated immune mechanisms to elicit an enhanced response to subsequent mitogenic or antigenic challenge (Sen et al., 1992; Biswas et al., 2002).

#### 4.5. Hypoglycaemic activity

Neem leaf extracts showed promising results in decreasing blood sugar level and prevents adrenaline as well as glucose-induced hyperglycaemia. Recently, hypoglycaemic effect was observed with leaf extract and seed oil in normal as well as alloxan-induced diabetic rabbits (Ray et al., 1996).

#### 4.6. Antiulcer effect

Neem leaf and bark aqueous extracts produce highly potent antacid secretory and antiulcer activity. 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



(Pillai and Santhakumari, 1981).

#### 4.7. Antifertility effect

Neem seed and leaf extract possess the chemical constituents which can act as anti-fertility sources. Studies on this concept have revealed that intra-vaginal application of neem oil, can prevent pregnancy, thereby stating it as a novel method of contraception. NIM- 76, a refined product from neem oil, was studied in 10 human volunteers, where intra-vaginal application before sexual intercourse could prevent pregnancy with no adverse effect on vagina, cervix and uterus, further, the study revealed that intrauterine treatment is safe. Aqueous extracts of seeds and leaves contain sodium nimbinate (triterpene) which showed antifertility activity (Pillai et al., 1978; Sinha, 1984; Upadhyay et al., 1994).

#### 4.8. Antimalarial activity

Neem seed and leaf extracts are effective against both chloroquin-resistant and sensitive strain malarial parasites. One of the neem's components, "gedunin" (a limonoid), is as effective as quinine against malaria. Malaria is one of the pandemic diseases causing millions of deaths every year in India and several other countries. China has adopted neem in a big way to reap the antimalarial effects of neem. The anti-malarial formulation "Quinahausa" prepared in China will be available in India as well. Neem oil treated mosquito nets and mosquito-repellent cheap tablets are also becoming popular, due of growing problems of resistance to conventional treatments, it is becoming more and more difficult to control malaria. Clinical trials have been conducted to check the efficacy of neem extracts to control hyperlipidemia in a group of malarial patients severely infected with *P. falciparum*. The lipid level, especially cholesterol, was found to be lower during therapy when compared to non-malaria patients (Rochanakij et al., 1985; Mukherjee et al., 1999).

#### 4.9. Antifungal activity

From time immemorial it is believed that Neem is effective against certain fungi that infect the human body. Some important fungi against which neem preparations have been found to be effective are: athlete's foot fungus that infects hair, skin and nails; a ringworm that invades both skin and nails of the feet, fungus develops in intestinal tract, bronchi, lungs, and mucous membranes and a fungus that is part of the normal mucous flora that can get out of control leading to lesions in mouth (thrush), vagina, etc. Extracts of neem leaf, neem oil seed kernels are effective against certain fungi including *Trichophyton*, *Epidermophyton*, *Microspor*, *Trichosporon*, *Geotricum* and *Candida* (Kalid et al., 1989)

#### 4.10. Antibacterial activity

Neem derives compounds especially Azadirachtin is well known for its role as antibacterial agent. It is a complex tetranortriterpenoid limonoid present in the seeds as well as leaves which is highly responsible for toxic effect on microbes. (Quelemes et al., 2015; Gupta, et al., 2019). Extracts of the leaves, seed and bark possesses a wide spectrum of antibacterial action against Gram-negative and Gram-positive

microorganisms, including *M. tuberculosis* and streptomycin resistant strains. *In vitro*, it inhibits *Vibrio cholerae*, *Klebsiella pneumoniae*, *M. tuberculosis* and *M. pyogenes* (Khan and Wassilew, 1987). Antimicrobial effects of neem extract have been demonstrated against *Streptococcus mutans* and *S. faecalis* (Chopra et al., 1952). Apart from azadirachtin, other components such as nimbidin, nimbin, nimbolide, gedunin, mahmoodin, margolone, and cyclic trisulfide contribute to the anti-bacterial activity of neem (Al Akeel et al., 2017; Heyman et al., 2017). Further, neem extracts are a ray of hope to cure deadly diseases viz., Chagas disease in Latin America which was uncontrolled by any other means of medicines. This disease is caused by a parasite which is carried by an insect called kissing bug. Research has shown that feeding neem to the bugs not only frees them of parasites, but azadirachtin prevents the young insects from molting and the adults from reproducing.

#### 4.11. Antiviral activity

Aqueous leaf extract offers antiviral activity against Vaccinia virus, Chikungunya and measles virus (Rao et al., 1969; Baswa et al., 2001). Nimbin and nimbidin have been found to have antiviral activity. They affect potato virus X, vaccinia virus, and fowl pox virus.

#### 4.12. Anticancer activity

Neem leaf aqueous extract effectively suppresses oral squamous cell carcinoma induced by 7, 12-dimethylbenz[a]anthracene (DMBA), as revealed by reduced incidence of neoplasm (Gogati and Marathe, 1989). Pramanik et al. (2016) has conducted a study in chemoprotective neem compounds viz., azadirachtin, nimbolide and limonoid enrich extracts on models of buccal carcinogenesis in hamsters. Overall studies were tested positive to reduce the expression and cell proliferation antigens. Further, researchers have shown prominent anti-cancerous activities from limonoid-derived compounds from neem. Amongst these, both 1-O-deacetylchinchinolide B and 15-O-deacetylnimbolindin-B are proved to be beneficial to hinder cell growth in human cervical adenocarcinoma (Zhu et al., 2017; Chen et al., 2018). A very recent study discovered that alkaloid-derived limonoid, azadiramide-A, is primarily found in Neem leaf ethanolic extracts, showed to stop cell growth and induce apoptosis in both the estrogen independent MDAMB-231 and estrogen dependent MCF-7 cell lines of breast cancer in human beings (Elumalai et al., 2012; Zhu et al., 2017).

#### 4.13. Antioxidant activity

The antioxidant activity of neem seed extract has been demonstrated *in vivo* during horse- grain germination which is associated with low levels of lipooxygenase activity and lipid peroxides (Balasenthil et al., 1999). An antioxidant principle has also been isolated, which is a potent inhibitor of plant lipooxygenases. Anti-oxidants derived from neem is simple and cost effective way to supplement with natural extracts like those derived from Neem, in forms such as teas and oils, seem to be a simple and cost-effective way to introduce antioxidants (Alzohairy, 2016).



#### 4.14. Anti-diabetic effect

Diabetes is one of the major chronic degenerative disorders now the world is facing (Joshi et al., 2010; Shori, 2012; Hieronymus and Griffin, 2015). According to the health survey conservatively by 2030 there is expectancy for diabetes to be the 11<sup>th</sup> leading cause of death (Mathers and Loncar, 2006). Keeping in view of the severity of disease searching the ways for lower cost treatments must be need of hour. Among the various methods and pharmaco therapies being developed, the use of Neem extracts has steadily grown in interest (Joshi et al., 2010; Al Akeel et al., 2017). Several studies carried out in induced-diabetic rat models have revealed rescue of the G6PD when treated with Neem extracts (Basir and Shailey, 2012; Upreti et al., 2013).

#### 4.15. Effect on central nervous system

Varying degrees of central nervous system (CNS) depressant activity in mice was observed with the leaf extract (Rao et al., 1998). Fractions of acetone extract of leaf showed significant CNS depressant activity (Singh et al., 1987). Leaf extract up to a dose of 200 mg/kg body weight produces significant anxiolytic activity in rats (Singh et al., 1980). The crude ethanolic extracts of stem bark and root bark showed hypotensive, spasmolytic and diuretic activities (Bhakuni et al., 1971).

#### 4.16. Other activity

The gum from bark is a stimulant and demulcent tonic. It possesses anti-leprosy, antispasmodic, and immunomodulatory properties. Neem is widely used for treating fevers. It has anti-pyretic (fever-reducing) property. Apart from these benefits, neem products also have analgesic (pain-relieving) and anti-inflammatory effects, i.e. for most common ailments neem can provide organic, cheap, easily available and local medicines, thereby neem can bring sustainable livelihood to many people especially in rural and tribal regions.

### 5. Conclusion

Neem is one the best nontoxic biological sources for development of modern drugs. Therefore, wide variety of neem extracts extend their benefits beyond traditional medical folklore, hence through the use of scientific and technological advance now we can use neem extracts as current medical adjuvants, on humans, animals and plants by understanding their potential. Considering the immense importance of this “Kalpavriksha” it can be explored for economic and therapeutic utilization for a sustainable development.

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