BIOLOGICAL DETAIL AND THERAPEUTIC EFFECT OF AZADIRACHTA INDICA (NEEM TREE) PRODUCTS- A REVIEW

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ABSTRACT

BACKGROUND

The Neem tree (Azadirachta indica) growing in tropical and subtropical regions, is a native tree of India. Neem belongs to Meliaceae family, also known as a Limbo, Nim, Nimba, Medusa and Vempu. It is also called "village pharmacy" of South Asia because of its enormous medicinal properties. Every part of Neem is so useful for the treatment of human disease. Various parts of the tree are well known for their medicinal properties which are prescribed by Ayurvedic, Siddha, and herbal medicine practitioners in India. Currently Azadirachta indica- Neem formulations are effective against a several diseases, ulcers, eczema, sores, burns, ulcers etc. It has been used in ayurvedic medicines for thousands of years because it exhibits therapeutic properties such as anti-viral, anti-fungal, anti-insecticidal, anti-bacterial, anti-allergic, anti-helminthic, anti-inflammatory and anti-dermatic properties. Approximately 135 different structural compounds have been identified from different parts of Neem tree for their beneficial effects.

KEYWORDS

Neem, Meliaceae, Azadirachta indica, Medicinal Properties.

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BACKGROUND

Azadirachta indica is a perennial tree also known as Neem which is being used in Ayurveda for thousands of years.[1] It is cultivated in the countries like Pakistan, Nepal, Indian, and Iran where it has been used for its numerous therapeutic benefits.[2] All the parts of the tree like its bark, flowers, leaves, twigs, fruits, roots, seeds, sap and gum are employed in customary native medication as a source of numerous therapeutic agents.[3] Neem extracts exhibits antiviral, anti-fungal, anti-insecticidal, anti-bacterial, anti-allergic, anti-helminthic, anti-inflammatory properties.[4,5] There are two closely related species of Neem namely A. Indica, A. Juss and M. Azedarac. The former is known as Indian lilac, and the other as Persian lilac.[6]

REVIEW OF LITERATURE

Taxonomic Details

- Domain: Eukaryotae
- Kingdom: Plantae
- Phylum: Spermatophyta
- Subphylum: Angiospermae Class: Dicotyledonae

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Preferred Scientific Name

- Azadirachta indica

Preferred Common Name

- Neem tree

Other Scientific Names

- Antelaea canescens Cels ex Heynh.
- Antelaea javanica Gaertn.
- Azadirachta indica subsp. vartakii
- Azadirachta indica var. minor Valeton
- Azadirachta indica var. siamensis Valeton
- Melia azadirachta L.
- Melia indica Brandis

International Common Names

- **English:** bastard tree; bead tree; cornucopia; Indian cedar; Indian lilac; margosa tree; neem; paradise tree; Persian lilac
- **Spanish:** margosa; mim
- **French:** azadirac de l'Inde; margosier; margousier
- **Arabic:** azad-daraknul-hind
- **Brazil:** neem; nim
- **Ethiopia:** azaddarakhti hindi; nib
- **Haiti:** ninnin
- **India:** baka-yan; balnimb; bevinamana; bevu; bukhain; kadukhajur; kahi-bevu; kirri-bevu; kohumba; limachajhada; limba; limbdo; limbo; neem; nim; nimani; nimbay; nimgachh; nimuri; nindbetain; olle;

taruka; vakam; vembu; vempu; vepa; vepe; veppam; veppu; veppur; yepa

- **Indonesia:** imba; intaran; membha; mempheuh; mimba
- **Iran:** azad-darakhat-hindi
- **Kenya:** mkilifi; mwarubainikamili
- **Laos:** kadao
- **Malawi:** mkina; ndya
- **Malaysia:** baypay; mambu; sadu; veppam
- **Myanmar:** bowtamaka; tamabin; tamaka
- **Nigeria:** dongoyaro
- **Pakistan:** nim
- **Singapore:** kohumba; nimba; veppam
- **Sri Lanka:** kohomba
- **Thailand:** khwinin; sadao; saliam

Trade Name

- Neem

Biological Compound Found in Neem

Approximately 135 different structural compounds have been sequestered and identified from different part of Neem tree.[7]

These Compounds have been classified into Two Types:

a. Isoprenoids containing limonoids, protomeliacins, gedunin, azadirone, vilasinin and C- secomeliacins like salanin, nimbin and azadirachtin.[8–10]
b. Non-isoprenoids containing amino acids, polysaccharides, polyphenolics like flavonoids, sulphurous compounds, dihydrochalcone, glycosides, tannins, coumarin and aliphatic compounds.[11–14]

Biological Activity	Function
Anti-fungal	Work against Candida, Microsporum, Trichophyton, Geotrichum, Epidermophyton, Trichosporon etc.[15,16]
Anti-bacterial	It inhibits the activity of bacteria such as Salmonella typhi, Staphylococcus aureus, Streptococcus mutants, M. tuberculosis, Vibrio cholerae, M. pyogenes and Klebsiella pneumoniae.[17,18]
Anti-viral	Treatment of fowl pox, smallpox, chicken pox, Vaccinia virus, warts, moderate inhibition of hepatitis B virus, Chikungunya, herpes virus, and measles virus.[19–21]
Insecticidal	Effective against maggots, horn flies, headlice, blowflies and biting flies.[22]
Promotes oral health	Neem twigs are used as toothbrushes averting periodontal diseases and gum inflammations.[23]
Treatment of ailments	Treatment of arthritis, Chagas disease(kissing bugs that transmit the parasites), malaria, fever, pain, burning sensations, ringworm, respiratory disorders, eczema, intestinal helminthiasis, rheumatism and constipation.[24–26]
Immuno-stimulant	Activates cell-mediated immune pathways to provoke an enhanced response to subsequent mitogenic or antigenic encounter.[27]
Anti-diabetic	Reduces blood sugar level and precludes adrenaline and glucose-induced hyperglycaemia.[28]
Anti-ulcer	Produce highly potent antiulcer activity.[29]
Anti-fertility	Avoids pregnancy and could be used as a way of contraception.[30]
Anti-cancer	Inhibits cell carcinoma in oral mucosa by modulation of glutathione and its metabolizing enzymes.[31]
Anti-oxidant	Eliminates toxins, filter blood, and inhibit damage caused due to free radicals in the body.[32]

Table 1. Biological Activity of Azadirachta Indica's Isolated Compounds

Therapeutic Properties

Internally medicines used of Neem include diseases such as malaria, tuberculosis, rheumatism, arthritis, jaundice and intestinal worms and skin diseases. The extracts are also beneficial for heart diseases, hepatitis, fungal infection, malaria, psoriasis and ulcers. Neem is used externally for ringworm, eczema, psoriasis, lice, fungal infection as well as for painful joints and muscles. The cosmetic use of Neem oil includes acne and pimples as well as improving skin elasticity.[33]

Anti-Bacterial Activity

Ghonmode W. N., Balsaraf O. D et al (2013) evaluated the antibacterial activity of the bark, leaf, seed and fruit extracts of Azadirachta indica (neem) on bacteria which was isolated from adult mouth and results showed that bark and leaf extracts of Neem showed antibacterial activity against test bacteria used. Also, seed and fruit extracts exhibited antibacterial activity only at higher concentrations. Results revealed that Neem bark extract (NBE) significantly blocked HSV-1 entry into cells at concentrations ranging from 50 to 100 μg/mL.[34]

Anti-Viral Activity

Leaf extracts of Neem (Azadirachta indica, A. Juss.) (NCL-11) has shown virucidal activity against coxsackievirus B-4. Interference seen at an early event of its replication cycle.[35]

Anti-Malarial Activity

B. C. Akin-Osanaiya, A. J. Nok, S. Ibrahim et al conducted an experiment in which the anti-malarial activity of extracts using Plasmodium berghei infected albino mice was used and reports led that Neem leaf and stem bark extracts reduced the level of parasitaemia in infected mice by about 51–80% and 56–87%, respectively.[36]

Anti-Fungal Activity

Neem leaves and seed kernel both were used as an anti-fungal. Neem seed kernel extract reduces significantly ($P < 0.05$) on post-harvest diseases, pathogens of Monilinia fructicola, Penicillium expansum, Trichothecium roseum and Alternaria alternate in-vitro.[22,23] Neem leaves aqueous, ethanolic and ethyl acetate concentration (5, 10, 15 and 20%) from these extracts inhibited human pathogens (Aspergillus flavus, Aspergillus fumigatus, Aspergillus niger,

Aspergillus terreus, Candida albicans and Microsporum gypseum). The 20% ethyl acetate which as strongest above other extract, by the analysis of HPLC and NMR. Ethyl acetate contain nimonol which are the active components.[37]

Anti-Ulcer Activity

Neem is also used in treatment of peptic ulcer. Aqueous neem leaves extract also contain antiulcer activity and very significant effect on Wistar rats at the dose of 600 mg/kg. The anti-ulcer mechanism of aqueous Neem leaf extract to block gastric lesions in rats which has been studied with oxidative damage, apoptosis and acid secretion. It is due to inhibition of H^+K^+ ATPase activity in concentration dependent manner.[38-40]

Hypoglycaemic Activity

The Neem is used as an anti-cancer, anti-fungal and its 70% ethanolic bark, root extract is also used as anti-diabetic. In glucose tolerance test in diabetic rats with Neem extract at the dose of 250 mg/kg demonstrated that glucose levels were significantly less compared to the control group. The dose of 250 mg/kg reduced glucose (18%), cholesterol (15%), triglycerides (32%), urea (13%), creatinine (23%), and lipids (15%).[41-42]

Immuno-Stimulant Activity

Research study report found that 4% Neem leaves infusion at the rate of 50 ml L-1 of fresh drinking water might be effectively used as a potential natural growth promoter and also as an immune stimulant contributing to better body, weight gain, FCR feed conversion ratio, gross return, lower mortality and higher antibody titer against Infectious Bursal Disease (IBD). Neem is one amongst the most useful specific (humoral and cell mediated immunity) and nonspecific immune response (cytotoxic and phagocytic activity of macrophages.[43,44]

Anti-Oxidant Activity

Ghimeray AK, Jin C H et al demonstrated that all the tested leaf and bark extracts/fractions of Neem grown in the foothills (subtropical region) and have significant anti-oxidant properties. Though, in a different study, the bark was found to be more potent compared to leaf in the entire essay with higher phenolic content.[45]

Paul R, P M & Sah N K reported the effect of leaf extract on central nervous system varying degrees of central nervous system (CNS) depressant activity in mice was reported with the leaf extract. Fractions of acetone extract of leaf showed significant CNS depressant activity.[46]

Anti-Cancer Activity

Neem has been an ancient source of herbal medicine against a variety of human health problems. Researchers have been trying to extract active ingredients from this plant. Neem aqueous and ethanolic leaf extract was used as an anticancer drug on different cell lines like breast, lung, cervical.[47] The crude extracts of Neem has been examined in vitro and in-vivo systems to establish their anticancer effects. Neem when is taken in overdose, shows some side effects hence it is, advisable that these products should be used under the supervision and prescription of qualified medical practitioners and physicians.

Anti-Fertility

Neem seed oil which is used as a powerful spermicidal and significantly inhibit spermatogenesis. It inhibits sperm motility and count and cessation of fertility. Neem also has anti-implantation and abortifacients properties. It was discovered that spermatozoa of human and Rhesus monkey were immortal and die within 30 min of contact with NSO in an intra-vaginal dose of 1 mL. Vaginal biopsy revealed no side effect, Radioisotope studies indicate non-absorption in the vagina and non-antiovulatory. These findings enabled Neem oil formulation for 'sensual' use in India.[48]

Medicinal Uses

Traditionally, A. indica is used by rural population for its medicinal properties, it has a long history of use dating back to the Vedic period of India (approximately 6000 years BP). In Ayurvedic medicine, the bark and leaves are used for skin diseases, flowers as a tonic and stomachic, and fruits as a purgative and emollient. Various variety of organic compounds have been isolated from different parts of the tree. These organic compounds are widely used as medicines and pesticides. Biologically active, volatile organic sulphur compounds are obtained by crushing fresh seeds. As many as 25 volatile compounds have been found with di-n-propyl-disulfide being the chief constituent. The most active anti-feed ant in the seed is azadirachtin, which is found pure as a microcrystalline solid. Stem and root bark have astringent, tonic, anti-periodic and other medicinal properties. The bark, leaves and fruit are indicated in the treatment of infections and diseases. The bark is bitter, tonic and an astringent and has traditionally been used to treat fever, nausea, vomiting and skin diseases. The root bark is more effective in this case than the stem bark and young fruit.

The leaves are an old and famous remedy for skin diseases. The fresh juice of the leaf is administered along with salt to treat intestinal worms and along with honey for skin diseases and jaundice. As an external application for skin diseases, the leaves are used in variety of forms (poultice, ointment and liniment). A strong decoction of fresh leaves is used as an anti-septic which may be used in place of a weak solution of carbolic acid. A hot infusion of the leaves is used for fomenting swollen glands, bruises and sprains, and appears to be an anodyne. The fruits work as a purgative and an emollient, and are useful in the control of intestinal worms, urinary tract diseases and piles. The dry seeds have almost the same properties as the oil when brushed and mixed with water or other liquids. The seed oil is a very important medicinal product of this species from commercial point of view. It is anti-septic and is found to be effective in treating skin diseases, ulcers, rheumatism and sprains. The oil saponifies readily and is used in the manufacture of a medicinal soap due to of its antiseptic

properties. This soap is very effective for cleaning sores and for general uses similar to those of carbolic soap. The flowers are useful in some cases of atonic dyspepsia and general debility. There are reports that the toddy (fermented sap) of the tree is useful in the care of some chronic diseases.

Neem leaf are considered safe to be taken internally on a regular basis. Neem is one of the very powerful blood purifier and detoxifier in the Ayurvedic system of medicine. Neem leaves relieve the symptoms of viral infections, including common cold, herpes, influenza, and chickenpox. Eating Neem leaves decreases fever associated with viral infection.

Neem oil extract inhibits zearalenone production at 0.1-0.5% concentrations, but the highest inhibition (59.05%) of mycotoxin synthesis occurred at 0.1%.[49]

The aqueous preparation of Neem leaves is found to be effective in activating immune responses against tumor antigens. Studies in experimental stages have shown that the extract, in combination with a breast tumor-associated antigen, was effective in initiating a strong IgG response as compared to the response generated by the breast cancer-associated antigen alone. This show that the extract is capable of enhancing immune responses to tumor vaccines. Also, the released IgG had the ability to mediate antibody-dependent cellular toxicity and also initiated the cytotoxic T cell response. This process was aided by the secretion of IFN-ɣ, which brought a Th1 response while decreasing IL-10, thereby mediating cytotoxicity. In experimental studies, Neem extracts influenced inotropic and chronotropic mechanisms, which in turn induced variable degrees of AV disturbances, arrhythmias, and hypotension. Neem extract is non-toxic and readily available, making it a cost-effective immune enhancer in breast tumor-associated antigen vaccine.[50,51]

CONCLUSIONS

Neem is a most versatile medicinal plant which is a rich source of limonoids that are endowed with potent medicinal properties predominantly antioxidant, anti-inflammatory, and anticancer activities. It is seen that how Neem has led to the preparation of numerous medicinally and industrially useful formulations with potent medicinal applications in the development of novel drugs to treat various acute and chronic diseases. However more research work should be done on its biological constituents for improved commercial and therapeutic use.

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