A REVIEW UPDATE ON PHARMACOLOGICAL ACTIVITIES AND THERAPEUTIC APPLICATIONS OF NEEM (AZADIRACHTA INDICA) PLANT

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ABSTRACT
Nowadays herbal plants play an important role to maintain the health of populations globally. In Indian traditional system of medicine Ayurveda, above 121 medicinal herbs were discovered which are obtained from the plants used in last century. The medicinal phytoconstituents are isolated from natural medicinal plants resources significantly to improve the process of novel drugs development. Among of all medicinal plants, Azadirachta indica which is commonly known as neem which has been widely used in treatment of various diseases because it has a number of medicinal phytoconstituents. Neem has approximately 140 different types of bioactive chemical constituents in different parts of plant and has attracted worldwide prominence in recent years. Neem has been broadly used in Ayurveda, Unani, Homoeopathic medicine as well as modern medicine (Allopathic medicine). In the different parts of neem tree contains various phytoconstituents which possess anti-diabetic activity, anti-oxidant activity, antibacterial activity, anti-viral activity, anti HIV, anti-inflammatory properties, anti-fungal activity, anthelmintic activity, anti-parasitic activity, anticancer activity, antirheumatism, antispasmodic activity, antipyretic activity, antidiarreal, immunomodulation properties, hypolipidemic activity, anti-microbial activity, hepatoprotective properties, gastro protective and antifertility properties. The neem plants are used in various fields like medicinal, pharmaceutical, agricultural as well as commercial field by which the living’s life has become easy to live. This review represents a bird’s eye view of the various medicinal properties, pharmacological activities and therapeutic uses of neem tree.

KEYWORDS: Phytoconstituents, natural sources, Azadirachta indica, bioactive, Ayurveda, Unani, Homoeopathic, Allopathic.

INTRODUCTION
General introduction: Neem is an indigenous plant with a multitudinous uses because it has a number of medicinal properties. There are a number of categories of phytochemicals like alkaloids, flavonoids, triterpenoids, phenolic compounds, carotenoids, steroids, and ketones which are reported in neem tree. Azadirachtin A-G and azadirachtin E are the complex mixture of seven isomeric compounds of Azadirachtin which are the most important biological active constituents of neem. From various parts of the neem plant, secondary metabolites like azadirachtin, meliacin, gedunin, nimbidin, nimbidolides, salanin, nimbin, valassin, and meliacin are also obtained which are responsible for the bitter taste of neem oil. The tiglic acid is also reported in seeds of neem which is responsible for pungent odor. Approximately 30–50% of oil is reported in Neem kernels and the oil contains triterpenes or limonoids. The limonoid contains Azadirachtin, Salannin, Meliantriol, and Nimbin which are insecticidal and pesticidal activity.

Synonyms- Margosa, limbo, nim, nimba, medusa and vempu
Biological source-It consists of all areal parts of Azadirachta indica belonging with family Meliaceae.
Geographical sources- Found in India, Pakistan, Bangladesh, Africa, Thailand and Australia.
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Morphology
- Colour: Green (leaves) brown (Bark)
- Odour: Pungent
- Taste: Bitter
- Height of tree: 15-20 meters.[9]

Taxonomical Classification
- Kingdom: Plantae
- Subkingdom: Tracheobionta
- Division: Magnoliophyta
- Class: Eudicot
- Subclass: Rosidae
- Order: Sapindales
- Family: Meliaceae
- Genus: Azadirachta
- Species: indica[10]

Chemical constituents of neem
Neem fruit, seeds, leaves, stems, and bark contain a number of phytochemicals. Some of these phytoconstituents are summarized below in table-1.

Table no.1: Pharmacological aspects of Azadirachta indica (Neem).

<table>
<thead>
<tr>
<th>S. no.</th>
<th>Phytoconstituents name</th>
<th>Medicinal value</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Quercetin glycoside</td>
<td>anti-carcinogenic, anti-inflammatory and antiviral activities</td>
<td>[11,13]</td>
</tr>
<tr>
<td>2.</td>
<td>Kaemferol glycoside</td>
<td>Antioxidants, anticancer and anti-inflammatory</td>
<td>[12,13]</td>
</tr>
<tr>
<td>5.</td>
<td>Nimbolides</td>
<td>Anti-carcinogenic, anti-ulcer, anti-Neuroblastoma and antimalarial.</td>
<td>[16,17]</td>
</tr>
<tr>
<td>6.</td>
<td>Isorhamnetin</td>
<td>Antioxidants, antiviral activities</td>
<td>[11,13]</td>
</tr>
<tr>
<td>7.</td>
<td>Nimbine</td>
<td>Anti-carcinogenic</td>
<td>[17,18]</td>
</tr>
<tr>
<td>8.</td>
<td>6-deacetyl nimbinen</td>
<td>Anti-carcinogenic (breast cancer)</td>
<td>[17,18]</td>
</tr>
<tr>
<td>9.</td>
<td>β-sitosterol &amp; β-sitosterol-β-D-glucoside</td>
<td>Anti-inflammatory, immunomodulation, anticancer control cholesterol level</td>
<td>[17,19]</td>
</tr>
<tr>
<td>10.</td>
<td>Nimbinin &amp; deacetylnimbin</td>
<td>Anticancer, antifeedant, insecticidal</td>
<td>[17,20]</td>
</tr>
<tr>
<td>11.</td>
<td>Nimbin</td>
<td>Anti-inflammatory, antifungal, antiseptic,</td>
<td>[21]</td>
</tr>
</tbody>
</table>
Pharmacological aspects of **Azadirachta indica** (Neem) plants

1. **Anti-diabetic activity**- From the research studies, it was evaluated that the blood glucose level is decreased by the using 70% alcoholic extract of bark of neem root at 800 mg/kg dose in controlled and treated rats in comparison with the standard drug glibenclamide at the different dosages (200,400 and 800 mg/kg). The ethanolic extract of bark of neem roots reported the result that at 800 mg/kg dose significantly reduces the blood glucose levels and cholesterol level in treated group of diabetic rats as compare to control group of rats. The results were found out by using an oral glucose tolerance test (OGTT). It was also observed that Azadirachitin display an action to protect the pancreatic β-cells.

2. **Anti-bacterial activity**- It was evaluated that the extracts of bark, leaf, seed and fruit of neem represented the antimicrobial activity against bacteria which was isolated from oral cavity. The extract of leaf and bark of neem in DMSO solvent showed the antibacterial activities against Gram positive and Gram negative bacteria. The alcoholic extract of leaf and bark of Azadirachta indica represented significantly zone of inhibition against *Vibrio cholerae* and *Bacillus subtilis* in agar well diffusion tests. From the various research data it is also observed that neem is also used in wound dressings.

3. **Antifertility activity**- It is investigated that oil of neem seeds displayed a powerful spermicidal activity and also inhibited spermatogenesis. It has also investigated that neem seeds oil also reduce quantity of sperm and it’s motility. Neem also showed anti-implantation and abortifacients activities in female rats. From a research study it has been found that the estrous cycle in Sprague Dawley rats may be disrupted by the administration of alcoholic extract of neem flower which may lead a partial blockage in ovulation. From an investigation it has been also found that spermatozoa of human and Rhesus monkeys may be destroyed within 30 minutes by the using of oil of neem seeds through vaginal route at dose of 1 mL. From another investigation it was also observed that by the using of a single dose of 100 μL of the neem oil through intrauterine may lead a reversible blockage in fertility in female rats and in monkeys.

4. **Antiviral Activity**- A wide spectrum antiviral activity against Coxsackievirus B-4 has been showed by the using of methanolic extract of neem leaves. From another investigational study it was identified that aqueous extracts neem bark contains a potent anti-HSV activity. In a cell culture model the aqueous extracts neem bark prevented the entry of HSV-1 and glycoproteins of virus to the other cells present in culture media. Due to the presence of flavonoids, triterpenoids and their glycosides the neem leaves show inhibitory activity against different types of viruses.

5. **Anti-cancer activity**- Carcinogenesis is a multifactorial and complex process which deals with characterization of multiple steps from precancerous lesions to neoplasia. Carcinogenesis modifies the proliferation process of normal cells into cancerous cells. In an research it was showed that the aqueous and ethanolic fraction of neem leaves showed the anticancer activity against cancerous cells in invitro cell lines cultures of various organs like breast, lung, cervical which were affected from neoplasia. In another researches it was also observed that the neem has prominent anti-cancerous activity due to presence of limonoid-derived compounds which promote modulation of the phosphoinositide-3-kinase (PI3K) and Glycogen synthase kinase 3 (GSK-3β) signaling pathway enhance apoptosis process.

6. **Anti-fungal activity**- From an invitro research studies it was found that the ethanolic extracts of neem leaves at concentration 500 and 1000 μg ml showed significant antifungal activities against pathogenic fungi. Govindachari et al. (1998) also disclose the antifungal activities against *Drechslera oryzae*, Alternation tenius and Fusarium oxysporum fungi by the using of fraction of neem oil in methanol. These antifungal activities were occurred due to presence of polyphenolic flavonoids like Quercetin and β-sitosterol in neem leaves. In another research it was reported that the superficial hydrophobicity of some species of fungi may be increased by using the aqueous extract of neem leaves which may lead the lysis of fungi cells. The methanolic extract of neem seeds was found that it...
may decline the biosynthesis of ergosterol in Aspergillus species fungi.\[43\]

7. Antimalarial activity- In an experiment the antimalarial activity of neem leaves aqueous extract was investigated against the Plasmodium falciparum parasite by using the technique of Trager and Jensen and found that the aqueous extract of neem leaves causes the inhibition of growth of Plasmodium falciparum parasite.\[44\] In plasmodium berghei infected albino mice the antimalarial activity of neem leaf and stem bark extracts was investigated and found that approximately 51-80% parasitic infection was reduced by the using of neem leaf and stem bark extracts.\[45\] In another experimental studies it was investigated that the crude extract of neem showed an inhibitory activity against plasmodium parasites which are responsible for malarial.\[46\] The antimalarial effects of methanolic extracts of ripe and unripe fruits of neem were also showed in an invivo studies in mice who were infected with of Plasmodium erythrocytic schizogy. In this study it was found that the counts of erythrocytic cells were increase by the using of methanolic extract of neem fruits.\[47\]

8. Antioxidant activity- In a study, the extracts of neem was examined on rat models and observed that at different doses between 100–200 mg/kg of neem extract showed a potent antioxidant activity as like vitamin C. The neem extract decreased the level of myeloperoxidase in the serum and also reduced nitric oxide levels which are responsible for oxidative stress.\[48\] The antioxidant activity of Azadirachta indica leaves was investigated at different doses 50, 100, and 200 mg/kg by using heat-induced-mechanical and chemical-induced oxidative stress models in mice and find out that the latency to the thermal stimuli was increased.\[49\] Another experimental study represented that the extract of neem flowers and oil of neem seeds showed antioxidant positive responses against oxidation and approximately 60-66 % cleavage of oxidative DPPH free radicals.\[50\]

9. Ulcer protective activity- In a research study it was investigated that the aqueous extract of neem leaves performed a significant ulcer protective activity against chemical (ethanol) induced peptic ulcer in the Wistar rats at a dose of 600mg/kg body weight. Neem leaves extract recovered the broken mucus membrane.\[51\] In another investigation it was reported that at different doses (250– 600 mg/kg body weight) the extracts in organic solvents showed an effective antiulcerative activity in albino mice.\[52\] In experimental models of rats in which the gastric ulcer was induced by different biochemicals like acetylsalicylate, serotonin and histamine, has been showed an effective ulcer protective activity after oral administration of 40 mg/kg body weight of nimbidin (an active constituent of neem).\[53\]

10. Anti-inflammatory activity- In an investigational study it was reported that azadirachtin (an active constituent of neem) at the doses 50 and 100 mg/kg body weight showed anti-inflammatory activity against acute edema in paw of rats induced by carrageenan. The result was compared with potent anti-inflammatory drug diclofenac sodium.\[54\] The anti-inflammatory activities were also reported in the neem due to presence of an active constituent nimbidin. At dose 40 mg/kg body weight of nimbidin through Intramuscular administration decreased the acute paw edema in rat models.\[55\]

11. Immunomodulatory activity- In an experimental study the immuno stimulation activities of both specific (humoral and cell-mediated immunity) and nonspecific immune responses were showed by the using of aqueous extract of neem leaves and barks.\[56\] It was also investigated that the oil of neem seeds has also represented the immuno modulating activities by enhancing the cell-mediated immune modes.\[57\]

12. Pesticidal activity- In an invivo experimental study it was found that the extract of neem leaves in petroleum ether showed insecticidal activity and causes death by damaging the pivotal organs of the digestive system of the insects. In this study, it was showed that the petroleum ether extract of neem leaves caused stomach toxicity in various types of insects. The oil of dried neem seeds also showed toxic effect against larva of insects and controlled the populations of insects.\[58\]

13. Anti-venom activity- In various invivo and invitro investigations it was observed that the alcoholic as well as aqueous extracts of neem leaves containing protomeliacins, limonoids, Azadirone, gedunin and its derivatives, vilasinins, nimbin, salanin and azadiractin which provided protection against the lethal dose of tested venoms in the albino rat models by causing anticoagulant as well as neuro protective actions. In an invitro the anti- edema activity was also observed in the 5 rat models in which edema was caused by the administration of 0.05 ml venom sample of snake in the foot pads of rats.\[59\]

Requirements of neem in various fields

1. Medicinal requirements- The whole parts of neem (Azadirachta indica) tree including roots, stems, bark, leaves, flowers, fruits as well as ripped fruit seeds are widely required as medicines by various traditional medicine system including Ayurvedic medicine system, Unani medicine system, Homeopathic medicine system, Siddha medicine system as well as Allopathic medicine system as medicines like anti-carcinogenic, anti-inflammatory and antiviral, antibacterial, antifungal etc for prevention and treatment of various disease.\[11-24\]

2. Pharmaceutical requirements- In the pharmaceutical industries as well as pharmaceutical laboratories there are wide requirements of whole parts of neem plant to obtain the medicinal valuable chemical constituents like azadirachtin, meliacin, gedunin, salanin, nimbin, valassin, Kaemferol,
Quercetin, β-sitosterol etc through various extraction, isolation and purification process for the preparation of formulations.\textsuperscript{[11-24]}

3. **Agricultural requirements**- The neem leaves, seeds, fruits, as well as oil of neem seeds are widely required in the agriculture because neem acts as pesticides (insecticides and larvicides) and as fertilizers and helps in the cultivation of crops without causing any toxic effect to the crops during cultivation.\textsuperscript{[23, 58 & 60]}

4. **Commercial requirements**- Ethno veterinary requirements for animal health, Eco-friendly agrochemicals requirements for environmental health, Animal feeds requirements for animals food resource, fuel requirements economical requirements to the human.\textsuperscript{[23, 58 & 60]}

**CONCLUSION**

Neem is an important plant that has different medicinal value as well as number of therapeutic uses. Neem contains various varieties of bio active structural phyto constituents. In whole parts of neem plant, above 140 different types of bioactive chemical constituents are reported. Neem has been broadly used in Ayurveda, Unani, Homoeopathic medicine as well as modern medicine (Allopathic medicine). Neem plants are the rich sources of secondary metabolites which are also rich sources of drugs. From the various literature survey it is showed that neem plant has potential effects and shows anti-diabetic, anti-oxidant, antibacterial, anti-viral, anti HIV, anti-inflammatory, anti-fungal, anthelmintic, anti-parasitic, anticancer, antitumor, antiresorptive, antispasmodic, antipyretic, antidiarrheal, immunomodulation, hypolipidemic, anti-microbial, hepatoprotective, gastro protective and antifertility properties, radio protective activities. Multiple therapeutic properties of neem play an important role in the preparation of numerous medicinal and pharmaceutical formulations as well as also play an important role in maintenance of humans, animals and environmental health.

**REFERENCES**


