J. Pharm. Res. 2023;22(1):1–7

Print ISSN: 0973-7200
Online ISSN: 2454-8405

Journal of Pharmaceutical Research

Review Article

Neem (*Azadirachta indica*): A Panacea of all Diseases

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ARTICLE INFO

Article history:
Received 23.12.2022
Revised 04.02.2023
Accepted 07.02.2023
Published 08.05.2023

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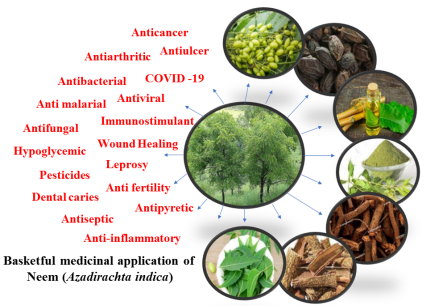
https://doi.org/10.18579/jopcr/v22.1.22.31

ABSTRACT

Neem (*Azadirachta indica*) belongs to the Meliaceae family. Neem is well-known around the world for its medicinal and nutritional properties. Various parts of the plant like fruits, leaves, flowers, twigs, gum, seed, oil, bark, and root are known to have medicinal properties and are scientifically established for the various properties. Since ancient times, plant's parts have been utilized for their medicinal value. The plant contains a high amount of catalase (CAT), peroxidase (POD), polyphenol oxidase (PPO) and ascorbate peroxidase (APX) enzyme, and many other phytoconstituents such as isoprenoid-containing protomeliacins, limonoids, azadirone and Csecomeliacins such as azadirachtin, nimbin, and salanin. The non-isoprenoids include sulphurous compounds, polyphenolics like flavonoids and their glycosides, dihydrochalcone, coumarin and tannins, proteins (amino acids) and carbohydrates (polysaccharides), as well as aliphatic compounds. Due to such type of versatile phytoconstituents, the plants show lots of pharmacological applications. In this review article, we summarized the information regarding the various pharmacological activities of neem plants. All information presented in this review article regarding the beneficial application of Neem (*Azadirachta indica*) has been acquired by imminent various electronic databases including Scopus, Google scholar, Science Direct, Web of Science, and PubMed. The Neem plant, including leaves, bark, latex, seed, and their active constituents, plays a significant part in the management of progressive illness. The neem plant contains active ingredients were accountable for the basketful therapeutic function such as anticancer, anti-inflammatory, antidiabetic, antispasmodic, antifungal, antioxidant, antimicrobial, antimalarial, antifertility, and also helps in proper digestion, hair growth, skin related problems and relief in menstrual pain and many more. The main findings showed that neem has strong medicinal properties and is also useful in cosmetic applications. There is no evidence of adverse effects of neem in literature. Only the people who are allergic to it can have side effects otherwise it is stomach friendly in all conditions due to which it can be applicable for treatment of various health related disorders.

Keywords: Neem (*Azadirachta indica)*, Phytochemical constituents, Therapeutic application



INTRODUCTION

India is one of the nations that adhere to the Ayurvedic medical system, in which various medicinal plants are employed to treat a variety of illnesses. In particular, *Azadiracta indica* is primarily used in complementary and alternative medicinal system; neem consumes a category of conventional medicine including unani medicine, ayurveda and homeopathy. Neem has a long history of use as a medication for a range of conditions.[1] Along with Ayurveda most of the world's other reputed medicinal systems like Unani, Chinese, and European "Materia Medica" have announced and acknowledged the neem tree as the "Panacea of all Diseases". However, in India, it is famous with many other names like 'Divine Tree', "Heal All", "Nature's Drugstore", "Medicinal hub" and "Village Dispensary".[2] Neem is a tropical classic, profusely branched tree. The neem tree is acknowledged by a variety of names, such as Margosa and neeb (Arabic), Tamar (Burmese), Indian lilac (English), neem (Hindi and Bangla), Bevu (Kannad), Pokoksemambu (Malaysia), Arya-veppu (Malyalam), Dogon yaro (some Nigerian languages), Azadirachta (Persian), Kohomba (Sinhala), nimba (Sanskrit and Marathi), Vaypum (Tamil), and Nimtree, Vepu, Vempu, Vepa (Telugu). In east Africa it is also known as Mwarobaini (Swahili) which means "the tree of the 40" as it is considered a treatment for 40 different diseases.[3] *Azadirachta indica* (*A. Juss*), the scientific name for the neem tree, is an evergreen tropical and subtropical plant with rapid growth that is a member of the Meliaceae family, which also includes mahogany.[4] The neem tree (*Azadirachta indica*) has been perceived as having incredible health-promoting properties for centuries. Because of its many benefits, neem is widely regarded as a "wonder tree".[5] Neem has been applied in Ayurvedic (an Indian holistic medical system) therapy for more than 4,000 years in India, where it is known as "the village pharmacy" due to the variety of ailments it can treat. Neem is frequently used in Ayurveda to balance kapha and pitta. It will generally aggravate Vata due to its cool, light, and dry features. Neem is so frequently administered in combination with other plants to help curb its vataincitin tendency. Because of its unpleasant flavor, neem leaf or bark is regarded as a potent pitta pacifier. As a result, in Ayurveda, it is typically advised during late spring (that is, the month of Chaitra according to the Hindu Calendar which for the most part falls from March to April). Neem is frequently used during festival celebrations in various Indian states. Neem blossoms are well-known in the Indian states of Andhra Pradesh, Karnataka, and Telangana for their use in "Ugadi Pachhadi" (soup-like pickle). During Gudi Padva, the New Year in the Maharashtra province, the old custom of drinking a small amount of neem juice or paste on that, prior day beginning celebrations, is found. The Mariamman temple celebration in Tamil Nadu takes place during the late spring for a very long time between April and June and follows customs that date back 1,000 years. The Neem leaves and blossoms are vital item of the Mariamman celebration. In the coastal Odisha the renowned Jagannath temple deities are carved of Neem heartwood along some other oils and powders.[6] Because of its many uses, authors from several nations have raised to it as a "miracle tree," "multipurpose crop," and "living pharmacy" in addition to its use in afforestation programmes. *Azadirachta indica* is the popular name of Indian neem or margosa tree. In reality, the neem tree is widely used in Ayurveda, Unani, and Homoeopathic medicines in the Asian countries where it originated as a common treatment for a variety of human maladies.[7] Since the neem tree's parts have all been demonstrated to have some medicinal value, they can all be used for commercial purposes.[8] Numerous reviews on the chemistry and structural variety of these compounds have also been published. Countless chemicals have been extracted from various Neem components. Compounds are categorized into two main classes: isoprenoids and others. The isoprenoids include diterpenoids and triterpenoids containing protomeliacins, limonoids, azadirone and its derivatives, gedunin and its derivatives, vilasinin type of compounds, and Csecomeliacins such as Nimbin, salanin and azadirachtin. The nonisoprenoids contain proteins (amino acids) and carbohydrates (polysaccharides), sulfurous compounds, polyphenolics such as flavonoids and their glycosides, dihydrochalcone, coumarin and tannins, aliphatic compounds, etc.[9,10] According to the Hindu culture, it is believed that the goddess of the chicken pox, Sithala lives in the neem tree. Medicinal plants have received growing attention in the drug discovery process for various human disorders.[11] Neem tea is taken to reduce headache and fever. Intestinal issues are treated using its flowers. Neem bark has analgesic properties and can treat high fevers caused by malaria. Neem leaves can treat skin conditions as well. Neem is widely believed in India to be a universal medicine. Neem oil, which is extracted from the plant's seeds, is used in cosmetics, pest control, and other products. and its leaves are used in the treatment of chicken pox. Neem also have anticoccidial effect in broilers and is used as pesticide.[12] There are substances in the seeds, bark, and leaves that have been shown to have antiseptic, antiviral, anticancer, antipyretic, anti-inflammatory, anti-ulcer, anti-arthritic, antibacterial, and antifungal properties.[13,14] In this mini review, we have summarized all part of neem plants with their potent pharmacological activity. Table 1 describes active constituents of various parts of Neem and their medicinal uses. Table 2 outlines the pharmacological study's findings and medical benefits of Neem Leaf and Seed oil Extract. Table 3 presents Pharmacological application of Flower and stick extract of neem and Table 4 presents Pharmacological application of Root bark extract of neem.

Table 1: Active constituents of neem and their medicinal uses

Parts of Plant	Chemical Constituents	Medicinal uses
Bark	Catechin	Haemostatic [15]
	Nimbin	Anti-oxidant [16]
	Nimbinin	In toothpaste and toothpowder [17]
	Nimbinene	Anti-maralial activity [18]
	Margolonone	Anti-bacterial activity [19]
	NB-II peptidoglycan	Immunomodulatory And anti-complement activity [20]
Blossom	Myricetin	Neuroprotective Activity [21]
	Quercetin	Antibacterial and Antifungal Properties [22]
	Kaemferol-3-Glucoside (Astragalin)	Anti-Inflammatory, Antioxidant, Neuroprotective, Cardioprotective, Anti-Obesity, Anti-Osteoporotic, Anti-Cancer, Anti-Ulcer, And Anti-Diabetic Properties [23]
Trunk bark	*B*-Sitosterol-*B*-D-Glucoside	Induce Apoptosis [24]
	B-Sitosterol	Antibacterial Effect [24]
	Myricetin	Antioxidant [21]
	Sugiol and Nimbiol	Antimicrobial, Anti inflammatory Antimicrobial [4]
	Quercitrin	Antioxidant, Antibacterial [16]
	Rutin	Antioxidant, Antimicrobial [25]
	Isorhamnetin	Anticancer, Antioxidant, Antiviral, Anti-inflammatory [26]
	Rhamnoside of Quercetin	Antibacterial, Antioxidant [27]
	Nimbin	Antibacterial, Antioxidant, Cytotoxic [28]
Oil	Nimbinin	Anti-inflammatory [20]
	Nimbidic acid (salannic acid)	Antifungal [29]
	Salanin	Antifeedant [30]
	Azadirone	Antifungal [31]
	Cyclic Trisulphide And Cyclic Tetrasulphide	Antifungal [32]
	Polysachharides Nimbin	Anti-inflammatory [33]
Leaf	Polyphenol	Eye problem, intestinal worms, anorexia, and skin problem [34]
	Nimbidin	antibacterial, anti-ulcer [35]
	Nimbidol	anti-tubercular, anti-protozoan [35]
	Gedunin	anti-malaria, anti-fungal [35]
	Sodium Nimbinate	diuretic, anti-arthritic [35]

LIMITATION

Neem, despite its wide range of pharmacological activities, does have some limitations. Some of the limitations of neem include:

- **Lack of standardization:** There is a lack of standardization in the production and preparation of Neem products, which can result in variations in quality and potency.
- **Limited clinical research:** Although neem has been used in traditional medicine for centuries, there is limited clinical research on its safety and effectiveness.
- **Potential toxicity:** Neem is generally considered safe, but it can cause gastrointestinal symptoms, liver damage, and blood disorders at high doses or for prolonged periods.
- **Variation in potency:** Different parts of the plant, preparation methods, and age of the plant can affect the potency of neem.
- **Lack of regulation:** Neem products are not regulated, and some may contain harmful additives.
- **Interactions with other drugs:** Be sure to consult your doctor before using neem if you are taking any other medications.

DISCUSSION

Neem (*Azadirachta indica*) is a highly valued medicinal plant in traditional Indian and African medicine. For centuries, it has been used to treat a variety of ailments, such as skin diseases, respiratory problems, and infections. The various pharmacological properties of neem include antimicrobial activity against bacteria, fungi, and viruses,

Table 2: Pharmacological applicationof Neem Leaf and Seed oil Extract

Pats of Plant	Pharmacological Application	Finding of study
Neem Leaf Extract	Anticancer	The effect of ethanolic Neem leaf extract on Pi3k/Akt and apoptotic pathways in prostate cancer cell lines (PC-3 and lncap) gives 50% inhibition at a dose of 100 g/ml.[36]
Neem leaves and flowers	Anticancer	To investigate the cytotoxic effects of nimbolide, a limonoid present in leaves and flowers of the neem tree, and find that nimbolide significantly decreased the viability of MCF-7 and MDA-MB-231cells at 24 h with IC_{50} values of 4 μM/ml and 6 μM/ml, respectively.[37]
Neem Leaves Extract	Anticancer	In rat models, the ethanolic fraction of Neem leaf (EFNL) inhibits mammary tumorigenesis induced by chemical carcinogens. Female Sprague Dawley rats were injected with N-methyl-N-nitrosourea (MNU) intraperitoneally.[38]
Neem Leaves Extract	Anticancer	The effects of ethanolic extract of AI and pH have been evaluated on the survival and viability of human breast cancer cell line MDA-MB-231. A combination of low pH (6.2) and AI extract (1600 μg/ml) caused significant mortality (95.7%) in the breast cancer cell line MDA-MB-231. The IC_{50} value for AI extract at pH 7.1 was found to be 200 μg/ml.[39]
Neem leaf	Anticancer	Several concentrations of nimbolide were effective in reducing triple-negative breast cancer growth. The IC_{50} concentration of nimbolide was 7.5 mM and 8.5 mM for MDA-MB-231 and MDA-MB-468, respectively.[40]
Neem Leaves Extract	Anticancer	To determine the IC50 value of supercritical CO_2 extract (SCNE), neem leaf and nimbolide were tested against HT29 and HCT116 cells.[41]
Neem Leaves Extract	Anticancer	It was found that Neem Leaves Extract acted on various levels of the NF-jB pathway and that it induced apoptosis in Jurkat 70 $\pm$ 20, K562 120 $\pm$ 20, PC-3 90 $\pm$ 10, and U937 60 $\pm$ 10.[42]
Neem Leaves Extract	COVID-19	Neem leaves extract and its phytochemicals such as flavonoids and polysaccharides have direct antiviral effects against dengue and Hepatitis C Virus. According to molecular docking studies, nimbolin A, nimocin, and cycloartanols are potential inhibitors of SARS-CoV-2 envelope (E) and membrane (M) glycoproteins.[43]
Neem Leaves Extract	COVID-19	The Neem acetone-water extract is expected to dislodge SARS-cov-2 from the vascular endothelium.[44]
Neem Leaves and bark Extract	Anti-acne	The test extracts were evaluated against acne causing bacteria, namely Staphylococcus aureus (MTCC 96), Staphylococcus epidermidis (MTCC 2639), and Propionibacterium acnes (MTCC *1951), for their in vitro antimicrobial activity, using agar disc-diffusion method.[19]
Neem Leaves Extract	Anti-diabetes	*A. indica* leaf extract (400 mg/Kg body weight) in high-fat-induced rats normalized the altered levels of blood glucose & serum insulin. It plays a significant role in management of Type2 DM.[45]
Aqueous extracts of neem bark and leaf	Immunostimulant activity	Dose of Neem Leaf Preparation was observed to stimulate hematological systems as evidenced by the increase in a total count of RBC, WBC and platelets, and hemoglobin percentage. As histological changes as well as elevation in serum alkaline phosphatase, SGOT, SGPT was not observed in mice treated with three different doses of NLP.[46]
Aqueous extracts of neem leaves	Hypoglycemic activity	Within 2 weeks before alloxan, neem leaf extracts partially prevented the rise in blood glucose levels compared to a diabetic animal.[47]
Leaf extract	Immunomodulatory	At a concentration of 50 ml/l of fresh drinking water, neem infusion successfully improves antibody titer growth.[48]
Leaf extract	Cardiovascular	Neem root bark extract (NRE) significantly reduced blood sugar levels at 800 mg/kg.[49]
Leaf extract	Anti-microbial	It has been found that neem leaf extracts showed zones of inhibition, further confirming that they possess antimicrobial properties, and the extract had significantly greater zones of inhibition than 3% sodium hypochlorite.[50]
Seed oil	Antifertility effect	This study, evaluates the effective concentration of aqueous extract of old and tender *Azadirachta indica* (neem) leaves to immobilize and kill 100% human spermatozoa within 20 s. Sander–Cramer test was used to study the spermicidal activity of neem leaf extract. Under the test conditions, minimum effective spermicidal concentrations for tender and old leaf extracts were 2.91+/- 0.669 mg/million sperm and 2.75 +/- 0.754 mg/million sperm, respectively.[51]
Extracts of neem leaf, neem oil seed kernels	Anti-fungal activity	Several human fungi are susceptible to neem leaf extracts, including Trichophyton, Epidermophyton, Microsporum, Trichosporon, and Geotricum and Candida.[11]
Leaf and seed extract	Antioxidant activity	Based on in vitro antioxidant assays and in vivo inhibitory effects on 7,12-dimethylbenz[a]anthracene (DMBA)-induced hamster buccal pouch (HBP) carcinogenesis, we evaluated *Azadirachta indica* (Neem) leaf fractions for chemoprevention.[52]
Seed extract	Anti-microbial	Seed extracts had a minimum inhibitory concentration of 31 g/mL for all the dermatophytes tested. Furthermore, seed extract at 15 μg/mL concentration was noticed to be sufficient for distorting the growth pattern of the organisms tested.[53]

Table 3: Pharmacological applicationof Flower and stick extract of neem

Pats of Plant	Pharmacological Application	Finding of study
Flower extract	Antifertility	The extract caused a statistically significant reduction in the number of ova sheds in the morning of estrus.[54]
Stick extract	Dental caries	Neem extracts have strong antimicrobial properties, suggesting that they can be used to treat dental caries.[55]

Table 4: Pharmacological application of Root bark extract of neem

Pats of Plant	Pharmacological Application	Finding of study
Root bark extract	Anti-diabetic	At 800 mg/kg, neem root bark extract (NRE) significantly reduced blood sugar levels. Moreover, it reduced blood sugar levels by 54% after 4 hours as a comparison to the control. But in comparison to glibenclamide it was not showing a significant result.[56]
Aqueous extracts of neem leaf and bark	Antiulcer effect	An aqueous extract of Neem bark was orally administered to patients with acid-related problems and gastroduodenal ulcers. For 10 days, the lyophilized powder of the extract caused a significant (p b 0.002) decrease (77%) in gastric acid secretion when administered twice daily. The volume of gastric secretion and its pepsin activity was also inhibited by 63% and 50%, respectively. By taking 30-60 mg twice daily for 10 weeks, the bark extract almost completely healed duodenal ulcers monitored by barium meal X-ray or endoscopy.[57]

making it effective for treating infections. Neem has anti-inflammatory effects, and it beneficial for treating skin conditions like acne, psoriasis, and eczema. It also has pain-relieving properties, making it useful for reducing discomfort. Neem contains antioxidants that protect cells from damage caused by free radicals, making it useful for preventing or treating oxidative stress-related diseases. Neem extracts have antifungal properties, which may be effective for treating fungal infections such as ringworm and athlete's foot. Its insecticidal properties make it a valuable tool in agriculture for controlling pests. Neem is valued for its diverse pharmacological activities, making it useful for treating a range of diseases and disorders. However, more research is needed to fully understand its mechanisms of action and potential side effects

CONCLUSION

The findings of this study indicate that neem has potential for a wide range of medicinal values, including treating infections, skin problems, pain, and diseases caused by oxidative stress. Its insecticidal properties make it a valuable asset in agriculture for controlling pests. While this study provides valuable new information on the pharmacological activity of neem, it is important to note that there are some limitations that should be taken into account. The ongoing global search for non-toxic, safe, and effective plant-based remedies makes it crucial to continue exploring the potential of neem as a source of modern medicine. Neem's diverse parts and extracts are safe, affordable, and environmentally friendly as pesticide, insecticide, parasiticide, and agrochemical. In recent years, there has been a growing interest in neem research, and its commercial potential is becoming increasingly recognized. This "Divine tree" or "Living Pharmacy" deserves special attention from the global community due to its unique properties and applications in various areas of needs.

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