

Pharmacological and Therapeutic Potential of Neem (*Azadirachta indica*)

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ABSTRACT

Azadirachta indica, a member of the Meliaceae family, is commonly known as neem and its role in disease cure has been documented. Different parts of this tree contain numerous types of ingredients such as azadirachtin and quercetin and limonoids such as nimbin, nimbidin, and nimbinin with diverse pharmacological activities. Neem tree parts have also been used as a general folk medicine, and more recently, its constituents have been purified and found to possess greater antioxidant, hepatoprotective, antimicrobial, and anticancerous activities. Moreover, its constituents also show therapeutic implications in the modulation of cell signaling pathways involved in the management of cancer. Moreover, neem and its ingredient might be a potential candidate in prevention and treatment of tumor due to its broader pharmacological activities. This review presents an overview of the health-promoting effects of neem and its ingredients through modulation of biological activities.

Key words: Antioxidant activity, antitumor activity, *Azadirachta indica* (neem), folk medicine, nimbinin, quercetin

INTRODUCTION

Azadirachta indica, a member of the Meliaceae family, is commonly known as neem and has long been recognized for its medicinal properties. It grows in tropical and semi-tropical regions of the world, and the different parts of this tree such as seeds, leaves, flowers, and the bark are widely used for different purposes. Different phytochemicals such as quercetin and azadirachtin and limonoids such as nimbin, nimbinin, and nimbidin have been purified from the different parts of the plant. Moreover, the leaves also contain mixture of compounds such as nimbanene, 6-desacetylnimbinene, nimbandiol, nimbolide, ascorbic acid, n-hexacosanol, nimbiol, various amino acids, and several other types of ingredients.^[1-3] Neem tree extracts have been extensively used in health management since ancient times and have a variety of health-promoting properties.

It has been demonstrated by earlier studies that crude extract of neem leaves possesses significant hypoglycemic as well as hypolipemic activities in addition to hepatoprotective and hypertensive activities.^[4-6] The different parts of the tree and the extracted oils show a role in the management of tumor through the inactivation and activation of various cell signaling pathways. Ethanolic neem leaf extract (NLE) has been observed to enhance the expression of proapoptotic genes including caspase-3 and caspase-8 and suppression of Bcl-2 and mutant p53 expression in the 7,12-dimethylbenz(a)anthracene (DMBA)-induced cancer cells.^[7,8]

A study was designed to evaluate the cellular and molecular mechanisms by which azadirachtin and nimbolide extract induce cytotoxic effects. The result of the study confirmed that these phytochemicals significantly suppressed the viability of cancer cells in a dose-dependent manner through cell cycle arrest induction at G₀/G₁ phase conveyed by p53-dependent p21 accumulation and downregulation of the cell cycle regulatory proteins.^[9]

This review presents a recent overview of the health-promoting effects of neem and its ingredients through modulation of different biological activities.

PLANT DESCRIPTION AND CLASSIFICATION

Neem tree is found in abundance in tropical and semi-tropical regions and is a fast-growing tree that can reach a height of up to 15–20 m with small bright green leaves. Its blossom timing is in spring with numerous white flowers. It is a member of the Meliaceae family and its botanical classification is described [Table 1]. The neem tree and its different parts are shown in Figure 1.

CHIEF INGREDIENTS AND ITS STRUCTURE

Neem constitutes various types of ingredient such as quercetin, azadirachtin, number of limonoids, and nimboesterol in different parts of the plants, respectively. Leaves contain mixture of compounds including nimbin, nimbanene, 6-desacetylnimbinene, nimbandiol, nimbolide, ascorbic acid, n-hexacosanol and different amino acids, and nimbiol and several other types of ingredients.^[1-3] In addition to this, the bark also contains nimbin, nimbinin, and nimbidin. All these constituents have been reported to have a role in disease management. The structure of the major constituents of neem is shown as in Figure 2.

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Table 1: Botanical classification of neem (*Azadirachta indica*)^[10]

Taxonomic positions of neem	
Order	Rutales
Suborder	Rutinae
Family	Meliaceae
Subfamily	Melioidae
Genus	Azadirachta
Specie	Indica
Latin	<i>Azadirachta indica</i>

PHARMACOLOGICAL ACTIVITIES

Antioxidant activity

Different parts of neem plants such as leaf, bark, root, seed, and flowers show role in disease management through modulation of various biological activities [Table 2 and Figure 3]. A study was performed to evaluate the antioxidant activity of different extracts obtained from various parts of the neem tree. The results suggest that extracts from leaf, flower, and stem bark hold high antioxidant activity.^[11] In another study, ethanolic extracts of flowers and seed oil were also found to have better free radical-scavenging action.^[12]

In a comparative study, it was also noticed that the bark possessed complex phenolic contents than leaves with higher antioxidant activity.^[13] The methanolic extract of the roots for the estimation of different flavonoids and their free radical-scavenging properties have also been evaluated.^[14] Furthermore, in another study between the methanolic and chloroform extracts of neem leaves, it has been observed that relatively methanolic extracts possess significantly more antioxidant properties.^[15]

Wound-healing effect

As a folk medicine, wound-healing properties of the neem leaves are known since ancient times. In one study, the effects of neem oil in the treatment of chronic, nonhealing wounds were performed, and the results showed that after 8 weeks of treatment, 50% wound healing was observed in almost 44% patients.^[16] In another study, the aqueous extract of neem leaves was used to check the wound-healing activities, and a significant reduction in the longest diameter wounds has been observed.^[17] Based on the studies, the wound-healing properties of the aqueous extracts of neem leaves are supposed to act biochemically through inflammatory response and neovascularization.^[18]

Anti-inflammatory effect

Anti-inflammatory effect of neem plants has been reported by various studies. In an experimental study based on rat models, nimbidin from neem trees was used orally to evaluate its anti-inflammatory response. It was confirmed that the phagocytosis was inhibited, and further, the migration of macrophages to their peritoneal cavities was significantly inhibited in response to inflammatory stimuli.

Moreover, *in vitro* exposure of rat peritoneal macrophages to nimbidin also inhibited phagocytosis and phorbol myristate acetate-stimulated respiratory burst in these cells. Nimbidin inhibited nitric oxide and prostaglandin E2 production in lipopolysaccharide-stimulated macrophages followed as *in vitro* exposure.^[19]

The anti-inflammatory activities of neem fruit skin and its specific ingredient, azadiradione, have also been evaluated. The results have concluded that the animals treated with 100 mg/kg dose of this fruit skin extract and azadiradione exhibited significant anti-inflammatory activities.^[20]

Furthermore, the anti-inflammatory effect of neem seed oil has been examined on rats using carrageenan-induced hind paw edema. The result

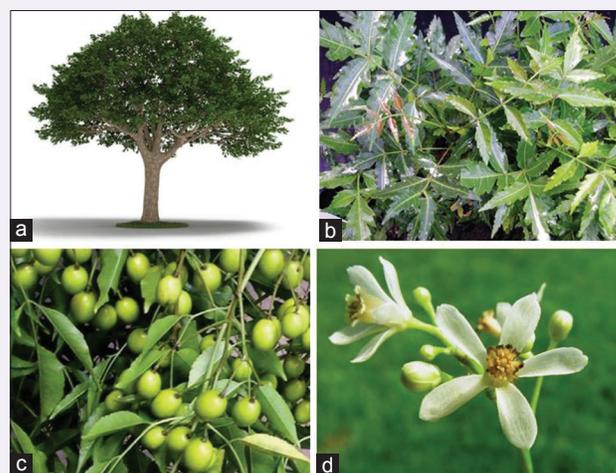


Figure 1: Neem tree and its different parts (Courtesy: Google images). (a) Neem tree, (b) Neem leaves, (c) Neem seeds, (d) Neem flower

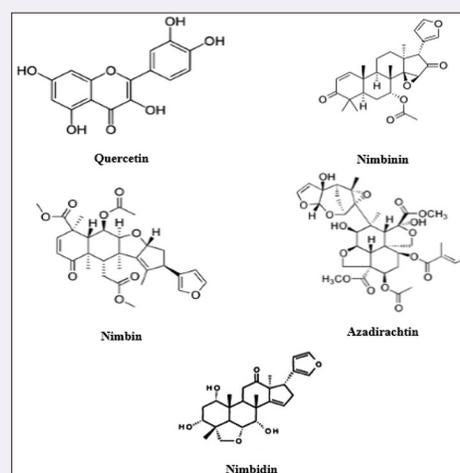


Figure 2: Chemical structure of major constituents of neem (Courtesy: Google images)

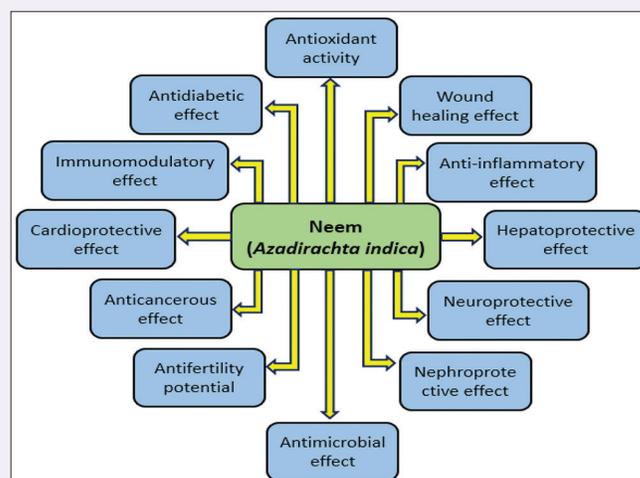


Figure 3: Pharmacological activities of neem and its ingredients

has confirmed that this oil showed increased inhibition of edema with the progressive increase in dose from 0.25–2 ml/kg body weight. Using

Table 2: Biological activities of Neem and its constituents

Plants parts	Activities	Findings of the study	Reference
Leaf, flower, and stem bark	Antioxidant	Extracts from leaf, flower, and stem bark possess higher antioxidant activity	[11]
Flowers and seed	Free radical scavenging	Ethanol extracts of flowers and seed oil were found to possess greater free radical-scavenging activity	[12]
Leaves	Wound healing	Aqueous extract of leaves showed significant reduction in the longest diameter wounds	[17]
Leaves	Wound healing	Wound-healing properties of the aqueous extracts of neem leaves are supposed to act biochemically through inflammatory response and neovascularization	[18]
Fruit skin and its specific ingredient, azadiradione	Anti-inflammatory	Animals treated with 100 mg/kg dose of fruit skin extract and azadiradione exhibited significant anti-inflammatory activities	[20]
Seed oil	Anti-inflammatory	Oil showed increased inhibition of edema with the progressive increase in dose from 0.25-2 ml/kg body weight	[21]
Leaf	Hepatoprotective	Leaf extract significantly reduced elevated levels of AST, ALT, and gamma-GT. In addition to this, paracetamol-induced liver necrosis was also found to be reduced as observed macroscopically and histologically	[23]
Leaf	Hepatoprotective	Leaf extract prevents and reverses the hepatotoxic damage caused by antitubercular drugs	[24]
Leaf	Neuroprotective	Leaf extract has also been checked to study its neuroprotective effects and it has shown quite efficient reversible effects of cisplatin	[26]
Leaf	Nephrotoxicity	Leaf extract has shown significant protective effects against cisplatin-induced nephrotoxicity as this extract exhibits antioxidant, anti-inflammatory, and other free radical-scavenging activities	[27]
Leaf	Immunomodulatory	Neem infusion has been found to successfully improve the antibody titer growth performance when used at the level of 50 ml/l of fresh drinking water	[29]
Flower	Antifertility	Extract caused a statistically significant reduction in the number of ova sheds in the morning of estrus	[30]
Oil	Antifertility	Intra-vas administration of oil resulted in a block of spermatogenesis without affecting testosterone production	[31]
Stick	Reduction in plaque and gingival	Significantly reduce the plaque and gingival scores as compared to baseline	[32]
	Treatment of dental caries	Extracts of neem have a strong antimicrobial activity and suggest that it can be useful in the treatment of dental caries	[33]
Root bark	Antidiabetic	Neem root bark extract (NRE) was given in the dose of 800 mg/kg showed significant reduction in blood sugar level. Moreover, it reduced blood sugar level by 54% after 4 hours as comparison to control. But in comparison to glibenclamide it was not showing significant result	[35]
Leaf	Cardioprotective	Neem extract shows equipotent cardioprotective activities as compared to Vitamin E	[37]
Leaf	Antimicrobial	Neem leaf extracts have been found to show zones of inhibition and further confirming that they contain antimicrobial properties and the extract showed significantly greater zones of inhibition than 3% sodium hypochlorite	[39]
Seed	Antimicrobial	Minimum inhibitory concentration of seed extracts was 31 µg/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	[40]
Bark	Antimicrobial	Bark extract confirmed that neem bark extract significantly blocked HSV-1 entry into cells	[42]
Leaf	Antitumor	Leaf extract considerably reduced the incidence of DMBA-induced hamster buccal pouch carcinomas and tumor burden	[50]
Leaf	Antitumor	Treatment with leaf extract inhibited MNU-induced mammary tumor progression and treatment was also highly effective in reducing mammary tumor burden and in suppressing mammary tumor progression even after the cessation of treatment	[53]
Leaf	Antitumor	Leaf extract gives 50% inhibition at a dose of 100 µg/ml in both PC-3 and LNCaP cells	[54]

AST=Aspartate aminotransferase, ALT=Alanine aminotransferase, DMBA=7,12-dimethylbenz(a)anthracene

the dose of 2 ml/kg body weight, this oil showed maximum inhibition of edema at the 4th h of carrageenan injection.^[21]

Hepatoprotective effect

The hepatoprotective role of neem-derived azadirachtin-A and its other ingredients is well known. In one study, carbon tetrachloride (CCl₄) was used to induce hepatotoxicity in animal models and it was observed that the disease control groups exhibited decreased total protein level and significantly increased aminotransferase (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) and alkaline phosphatase levels. Treatment with azadirachtin-A significantly improved the reference range of these proteins and enzymes.

In addition, the histological and ultra-structural studies confirmed that pretreatment with azadirachtin-A reduced hepatocellular necrosis.^[22] Hepatoprotective effect of leaf extract was examined based

on rats. Aqueous leaf extract significantly reduced elevated levels of AST and ALT. In addition to this, liver necrosis was also found to be reduced as observed macroscopically and histologically.^[23] Another finding concluded that aqueous leaf extract of neem prevents and reverses the hepatotoxic damage caused by antitubercular drugs, and this reversal is better to that effected by withdrawal of antitubercular drugs.^[24]

Neuroprotective effect

The neuroprotective effects of standardized extract of neem in animal models have also been observed. The results of the peripheral neuropathy (induced by partial sciatic nerve ligation) animal models revealed a significant decrease in allodynia, hyperalgesia, motor coordination, and motor nerve conduction velocity while chronic treatment with this extract significantly attenuated such behavioral changes.

Moreover, the neem extract significantly reduced the enhanced effects of oxidative and nitrosative stress, inflammatory mediators, and mRNA expression of Bax and iNOS, studied in animal models.^[25]

Cisplatin has been used as an experimental neurotoxic agent in animal models, which increases the levels of lipid peroxidation and nitric oxide and decreases the glutathione level. Among other trial medicinal plants, NLE has also been checked to study its neuroprotective effects and it has shown quite efficient reversible effects of cisplatin.^[26]

Nephroprotective effect

Cisplatin is also used in experimental animals to induce nephrotoxicity. Methanolic leaf extract of neem has shown significant protective effects against cisplatin-induced nephrotoxicity as this extract exhibits antioxidant, anti-inflammatory, and other free radical-scavenging activities.^[27]

Immunomodulatory effect

Neem oil is also used as a nonspecific immunostimulant as it plays a role in the activation of cell-mediated immune mechanisms to elicit an enhanced response to subsequent mitogens.^[28] Besides this, neem infusion has been found to successfully improve the antibody titer growth performance when used at the level of 50 ml/l of fresh drinking water.^[29]

Antifertility potential

A study was performed on rat models to determine the effects of alcoholic extract of neem flowers to observe its effects on estrous cycle, ovulation, fertility, and the fetal morphology. The results of this study clearly confirmed that estrous cycle of 80% of the rats was altered with a marked prolongation of the diestrus phase. This extract caused a statistically significant reduction in the number of ova sheds in the morning of estrus.^[30] Besides, this, intra-vas administration of neem oil resulted in a block of spermatogenesis without affecting testosterone production.^[31]

Role in dental health

Neem extract based on different types of organic solvents shows antimicrobial activity. A comparative analysis was performed between neem stick and a commercial toothbrush along with toothpaste to analyze the plaque removal and gingival health. The results clearly confirmed that there was no significant difference between these two ways of cleaning teeth and both considerably decrease the plaque and gingival scores as compared to baseline.^[32]

The antimicrobial properties of specific neem extract against bacterial strains were evaluated. Findings have confirmed that petroleum ether and chloroform extract show strong antimicrobial activity against *Streptococcus mutans*. Moreover, the results further demonstrate that the chloroform extracts have a strong antimicrobial activity.^[33]

Antidiabetic effect

The neem tree extract has also been evaluated for its antidiabetic activities. Earlier finding confirmed that diabetic rats treated with neem extract (250 mg/kg b. w.) exhibited glucose levels significantly less as compared to the control group.^[34] Neem root bark extract showed reduction in blood sugar level at dose of 200 and 400 mg/kg b. w. Higher dose of this extract (800 mg/kg b. w.) showed significant reduction in blood sugar level and it reduced blood sugar level by 54% as comparison to control.^[35]

Furthermore, the effects of neem kernel powder and glibenclamide either separately or in combination were used as an antidiabetic agent on laboratory animals. The results revealed that these two agents either

separately or in combination significantly decrease the concentration of serum glucose, lipids, and activities of serum enzymes.^[36]

Cardioprotective effect

As a folk medicine, the neem tree extract is well known for its cardioprotective properties as well. In this regard, *A. indica* extract at a dose of 250–1000 mg/kg significantly restores most of the hemodynamic, biochemical, and histopathological parameters. The study further concluded that neem extract shows equipotent cardioprotective activities as compared to Vitamin E.^[37]

Antimicrobial activity

Neem extracts are rich in antimicrobial compounds as some studies have clearly shown that neem extracts can be potentially useful to control some foodborne pathogens and other spoilage organisms.^[38] NLEs have been found to show zones of inhibition further confirming that they contain antimicrobial properties, and the extract showed significantly greater zones of inhibition than 3% sodium hypochlorite.^[39]

Another study was performed to evaluate the minimum inhibitory concentration (MIC) and minimum fungicidal concentration for the extracts of the leaves and seeds against various dermatophytes. The result revealed that MIC of seed extracts was 31 µg/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.^[40]

The effects of the neem limonoids such as azadirachtin, salannin, deacetylgedunin, gedunin, 17-hydroxyazadiradione, and deacetylnimbin on *Anopheles stephensi* were evaluated. Azadirachtin, salannin, and deacetylgedunin showed high bioactivity at all doses, whereas the rest of the neem limonoids were less active. In addition, azadirachtin was the most potent in all experiments and produced almost 100% larval mortality at 1 ppm concentration.^[41] Antiviral activity of neem bark extract confirmed that bark extract extensively blocked HSV-1 entry into cells at 50–100 µg/ml concentration.^[42] Antifungal activity of extracts of seed on *Candida* spp. has also been evaluated, and the finding of the study has concluded that neem seed extract appears to be hopeful anticandidal agents.^[43]

Anticancerous activity

Natural products or products of plants show a pivotal role in the inhibition of tumor growth through modulation of cell signaling pathways.^[44-47] The superior medicinal properties of neem tree were further validated as it was found to possess anticancerous properties. A study was designed to examine the cellular and molecular mechanisms of azadirachtin and nimbolide for cytotoxic effects in the human cervical cancer (HeLa) cell line. The finding revealed that azadirachtin and nimbolide extensively suppressed the viability of HeLa cells in a dose-dependent manner by inducing cell cycle arrest at G0/G1 phase accompanied by p53-dependent p21 accumulation and downregulation of the cell cycle regulatory proteins.^[9]

In addition to this, dose of 500 mg/kg of ethanolic NLE was found to induce apoptosis in 4T1 breast cancer cells in a mouse model.^[48] Other previous study has reported that administration of ethanolic NLE considerably reduced the incidence of DMBA-induced hamster buccal pouch carcinomas and tumor burden. Moreover, this extract downregulated Bcl-2 expression and upregulated Bim, caspase-8, and caspase-3 expression in the buccal pouch.^[8] NLE also plays role in the induction of dose-dependent reduction in chronic lymphocytic leukemia cell viability with significantly observed apoptosis, and the extract causes loss of mitochondrial outer membrane permeability and nuclear translocation of apoptosis-inducing factor.^[49]

With the evidence of data, it is demonstrated that nimbolide showed anticancer effect through its apoptosis-inducing property.^[50] The experiment was performed to evaluate the role of NLE in the inhibition of progression of chemical carcinogen-induced mammary tumorigenesis. Treatment with extract inhibited N-methyl-N-nitrosourea-induced mammary tumor progression and treatments was also extremely efficient in dropping mammary tumor burden and in suppressing mammary tumor progression even after the stop of treatment.^[51]

Another study was performed to examine the effect of leaf extract on PI3K/Akt and apoptotic pathway in prostate cancer cell lines. Result of the study demonstrated that extract gives 50% inhibition at a dose of 100 µg/ml in both PC-3 and LNCaP cells and extract decreased the protein expression of PI3K as well as p-Akt and the mRNA expression of Akt-1 and Akt-2 in both the cells.^[52]

The treatment of MCF-7, HeLa, and normal cells with leaf extract differentially suppresses the growth of cancer cells in a dose- and time-dependent manner through apoptosis. Moreover, lower dose combinations of leaf extract with cisplatin resulted in synergistic growth inhibition of the cells compared to the individual drugs.^[53]

Earlier studies suggest that neem leaf preparation signifies a high potential for antitumor activity *in vivo* through radical-scavenging effect by encountering free radicals.^[54] The limonoids of neem have proven its role in the target of oncogenic signaling kinases and transcription factors mainly and JAK/STAT signaling pathways. Moreover, limonoids target several pathways that are abnormal in cancer and are ideal candidates for cancer chemoprevention and therapy.^[55]

CONCLUSION

The approach of treatment based on allopathic drugs is common, but such types of treatment may be quick but cause adverse side effects on health. However, the knowledge of medicines based on natural products is increasing considerably and their usage has far more benefits. In this vista, neem and its constituents represent a key pivotal role in treatment and disease prevention through modulation of various cellular pathways [Figure 3]. This review article demonstrates some general health-promoting effect of neem and its active compound through antioxidant, anti-inflammatory, antimicrobial, and anticancerous activities. Further studies on its different types of ingredient are required to know the proper mechanism of action in health management.

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Conflicts of interest

There are no conflicts of interest.

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