



A Review on Phytochemistry and Pharmacological Activity of *Azadirachta indica* (Neem)

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Abstract

The plant *Azadirachta indica* is mainly cultivated in India belonging to family meliaceae. It is extensively used by human for the treatment of various disease. According to the WHO survey, 80% of the population living in the developing countries depend on this neem tree which is used as medicine for the health care. This medicinal plant is used to treat various diseases in the ayurvedic system of medicine, the homeopathic system of medicine, and the unani system of medicine. The scientific name of this plant neem (*azadirachta indica*) is derived from Persian which means the free tree of India. This review mainly gives the different biological activities like antimicrobial, antioxidant, antidiabetic, hepatoprotective, insecticidal, wound healing, anticancer, antibacterial, antimalarial, in dentistry, CVS, anti-inflammatory, insecticidal, hepatoprotective etc. This review article was put forward with an aim to show the medicinal property of *azadirachta indica*.

Keywords

Azadirachta indica, Chemical constituents, Medicinal activity, Neem

1. INTRODUCTION

The medicinal property of neem (*azadirachta indica*) has been known for most primitive plants. This tree is mostly known as a wonder tree for centuries in India. Today neem is very important for the use as a medicine. Neem extract contains various chemical constituents in which the nimbinine, nimbendiol are the most wanted constituents. The most important advantages of neem is the effect upon the skin. The oils of the tree are used as general antiseptic due to their antibacterial property. (4)

This plant contains various active constituents which are used for traditional medicinal products. (1)

Thousands of years ago the properties of neem (*azadirachta indica*) have been recognized in India. (5) In India where neem tree is found are Andhra Pradesh, Assam, Bihar, Delhi, Gujarat, Haryana, Meghalaya, Orissa, Punjab, Rajasthan, West Bengal. According to the report of United States National Academy of Science, India ranked 1st in neem seed production about 4,42,300 tons of seeds are produced annually yielding 88,400 tons of neem oil and 3,53,800 tons of neem cake. The neem also contains active components such as azadirone, azadirachtin, flavonoids etc. These active components have potential pharmacological action. Neem contains more than 140 biological active components. In

Ayurveda mostly leaves, seeds, fruits and roots have been used. (6)

Various holy books like Bible and Quran also supported the herb role in health care and prevention different types of preparation of azadirachta indica are extremely popular in many countries in disease management. (7)

The review summarizes the medicinal activity of neem in the prevention and treatment in various disease.

2. GEOGRAPHICAL DISTRIBUTION OF AZADIRACHTA INDICA

The tree of Azadirachta indica is found on swalik hills. It is mainly grown in the dry forest of Tamil Nadu, Andhra Pradesh, and Karnataka. The tree Azadirachta Indica (neem) is also found in Irawali valley in a dry region and cultivated west of the Sutlej. (2)

There is two species of Azadirachta – Azadirachta A. Juss which is found in Indian subcontinent and Azadirachta excels which is found in Phillipines and

Indonesia .There are approx. 25 million trees has been grown all over the India of which 5.5% are grown in Karnataka and it is in 3rd place after Karnataka U.P takes 2nd place with 55.7% growth of Azadirachta Indica (neem) and Tamilnadu takes 1st place with 17.8% growth of Azadirachta indica.

The other states of India where neem trees are found Andhra Pradesh, Delhi, Assam, Gujarat, Haryana, Kerala, Himachal Pradesh, Madhya Pradesh, Meghalaya, Maharashtra, Orissa, Punjab, West Bengal, along with Andaman and Nicobar island .All over the world India stands 1st in neem seed production and about 4,42,300 tons of seeds are produced annually .(3)

The tree has been found none less than about 78 countries worldwide. In India it is found that 16.6 million neem trees are grown. Nowadays in study it is being observed that the neem tree has been grown in about 72 countries worldwide other in continents like Africa, Asia, Australia, Central and South America. (9)



2.1. Distribution Map (36)

3. BOTANICAL DESCRIPTION

Azadirachta indica commonly known as neem is a tree and their height are 12-18m with a straight branch. It is mainly found in greater part of India.

3.1. Bark and Stem

The bark is rough, hard and reddish brown from inside as well as the perimeter of stem is 1.8 -2.4m (2)

According to age and part of tree the bark also varies much in thickness and odour of bark is characteristic and taste is bitter. (5)

3.2. Leaves

The leaves of a neem are 20cm-38cm long with shape like lanceolate ovate. (2)

Leaves are slightly yellowish green, and the taste is bitter. (5)

3.3. Calyx

The calyx of a neem has a five lobe and the size of a sepals are small. (2)

3.4. Ovary

Each cell contains the two collateral ovules. (2)

3.5. Fruit and Seed

The fruit are semi-sweet as well as they are in olive sized. The seed of neem (*Azadirachta indica*) contains rich amount of oil with medicinal and botanical property. (5)

4. MICROSCOPIC DESCRIPTION

4.1. Leaf

Midrib: -

4-5 layer of collenchyma present below the epidermis. Parenchymatous cells consist of rosette crystals of calcium oxalate.

Non lignified fibre strand surrounded the phloem.

4.2. Lamina: -

Lamina generally have dorsiventral structure and shows layer of epidermis on both side of the surface and it is composed of thin wall. Lower surface of neem (*Azadirachta indica*) contains anomocytic stomata.

Stomatal index on lower surface is 13.0- 14.5 and the stomatal index on upper surface is 8.0-11.5 (5)



LEAVES (4)



SEEDS (6)



FRUITS (6)

5. VERNACULAR NAMES

Indian	Holy tree, Indian lilac tree
Hindi	Neem, Nim
Sanskrit	Nimba
Marathi	Balan tanimba
Punjab	Bakam, Bukhain
Balochistan	Nim
Burma	Bawtamaka
Cambodia	Sdoa

French	Agem lilas, Azedaracalic
German	Grossblaettiger, Zedrach
Indo china	Saudau
Persian	Neeb, Nib

Table Showing Vernacular Names (8,2)

5.1. Taxonomy-

Neem (*Azadirachta indica*) belongs to Mahogany family. The taxonomic position of neem is -:

Order	Rutales
Suborder	Rutinae
Family	Meliaceae
Subfamily	Melioidae
Tribe	Melieae
Genus	<i>Azadirachta</i>
Species	<i>Indica</i> (3)

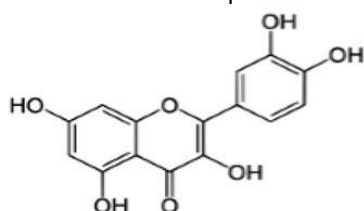
6. CHEMICAL CONSTITUENT OF AZADIRACHTA INDICA

Azadirachta indica consist of more than 135 compounds which is isolated from different parts of the neem.

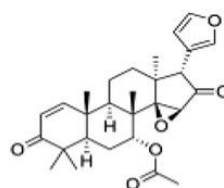
The constituent divided in two major classes like Isoprenoids and non- isoprenoids. The various parts of neem is used for the treatment of diseases like bark, leaves fruits, seeds and oil. The leave part consist of a chemical constituent like quercetin and

the oil of *azadirachta indica* contains nimbin and nimbidine. The bark part contains tannins, gallic acid, diterpenoids are active against klebsiella and staphylococcus species. (5)

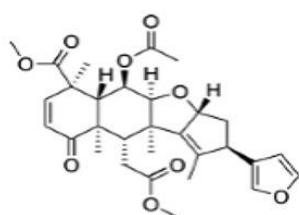
The chief ingredients of the neem are quercetin, azadirachtin, nimboesterol in different parts of plants. Leaves also contains mixture of compounds like nimbanene, 6 – desacetylnimbinene, nimbold and different types of amino acids. (10)



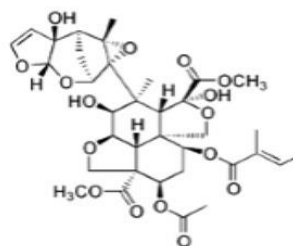
Quercetin



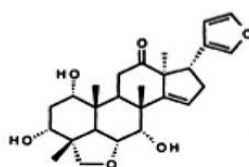
Nimbinin



Nimbin



Azadirachtin



Nimbidin

MAJOR CHEMICAL CONSTITUENTS OF NEEM (10)

7. MEDICINAL ACTIVITY OF AZADIRACHTA INDICA (NEEM)

7.1. Antimicrobial

The study was conducted to determine the antimicrobial activity of leaf extract of neem. The alcoholic extract of neem leaves which shows antimicrobial activity when compared with a standard of gentamycin. The alcoholic extract of neem shows the maximum inhibition on bacillus pumillus, pseudomonas aeruginosa, and staphylococcus aureus. Activity of the neem extract also found useful in inhibiting the growth of carcinogenic bacterium *s. sobrinus*. (Md. Mohashine Bhuiyan et al. 1997). (11)

Another study conducted to evaluate the bioactive compound which is used to get new antimicrobial agent. The cultured bacteria used for the study are staphylococcus aureus and enterococcus faecalis in which result shows the leaf extract of a neem shows potent antibacterial activity and bark extract of neem shows good antimicrobial activity on pseudomonas aeruginosa, proteus mirabilis and enterococcus faecalis at all the concentration. The seed extract shows the antifungal activity which is seen at 1000 and 2000 µg/ml against candida albicans but the seed not show any antibacterial activity. (12)

The study conducts to observe the antimicrobial activity of a acetone extract of neem leaf exhibit stronger inhibition against gram negative bacteria (*e. coli* and *p. aeruginosa*). When compared to the chloroform extract for the similar bacteria the C.E shows stronger antimicrobial activity against *B. subtilis*, *B. cereus*, *s. pneumonia* and *s. aureus* which are gram positive bacteria the result proves that to contain many bioactive constituent which have effective antimicrobial activities and also found that it have a good cytotoxicity activities for cancer therapy. (13)

7.2. Antibacterial

The study conducted by Gayathri R menon et al, 2016 to evaluate the antibacterial activity of neem oil by using the bacterial pathogen after the result it is observed that the maximum zone of inhibition was seen with streptococcus mutans which is found to be 27mm in diameter. The zone of inhibition for enterococcus feacalis and lactobacillus acidophilus was observe to be 24mm and 18mm respectively. (14)

Various study conducts on azadirachta indica (neem) in which Uwibabazi francin et al., 2015 are one of them on the antibacterial activity of neem plant against straptophylococcus aureus and Escherichia coli. The aqueous extract and methanol extract of leef shows different result on straptophylococcus aureus strains. The both dried and fresh leaves are

used on the straptophylococcus aureus strain and the comparison are done based on the inhibition zones which is obtained after incubation. The result shows that the neem effect on these bacteria with ethanol extract were more efficient whether for dried and fresh neem bark and leaves. (15)

The aqueous extract of leaves of azadirachta indica shows that the antibacterial activity against the microbial isolates. The detail study is carried out by oluwajobi iyanuloluwa et al, 2019 with the aqueous extract of azadirachta indica, psidium guajava, vernonia amygdalina for evaluate the antibacterial and antifungal activity against the microbial isolates. After the comparision it is observe that the azadirachta indica shows good antibacterial activity than the psidium guajava and vernonia amygdalina. (16)

7.3. Anti-Cancer

Azadirachta indica have been widely used as an anticancer. In the study conducted by the researchers on aqueous neem leaf extract which is used to study on *in vivo* murine system against 3H-B- α -P and the initiation phase of cancer is suppress by using the azadirachita indica extract. In the other study conducted by chaimuangraj et al. on the rats observe that the extract of neem leaf at the dose of (20,100,250mg/kg body weighty) inhibit the ACF (Azoxy methane induced aberrant cryptfoci) and also decrease the proliferating cell nuclear antigen (PCNA). In the recent year it is found that O6-alkylguanines are carcinogenic so, the enzyme which detoxifies O6-alkylguanines are (MGMT) O-6-methylguanine- DNA methyl transferase which try to maintain the integrity of cell. So, in the recent study it is found that aqueous and ethanolic extract of neem enhance the activity of enzyme MGMT. There is also a chemical constituent in neem which possesses the anticancer property ex Azadirachtin A, Nimbolide, and Nimbidin. (17)

In a recent year wide study has been conducted on neem which contains several therapeutic compounds which is used for several disease and suppress the tumor by interfering with the carcinogens in process. The study also conducted by Muhammad et al. to prove the cytotoxicity of the chemical constituent of neem nimbolide in vitro by using different cancer cells and normal cells. The cells are seeded with nimbolide in different concentration for 24 and 48 hours and found that the cytotoxic effect of the neem compound is depend on time and dose which shows a good effect on cancer cell. Other chemical constituent gedunin is a tetranorterpenoid isolated from the seed oil which is demonstrated its anticancer activity and used in breast cancer. (18)

The study conducted to evaluate the antiproliferative activity of ethanolic neem leaf extract (ENLE) on human breast cell and cervical cells (MCF-7) and HeLa cancer cells. The study on ENLE shows that the cytotoxic effect towards MCF -7 And HeLa cells the chemo preventive activity of different concentration of enle on MCF -7 cells , HeLa cells and lymphocytes which is isolated from the healthy nonsmoker adult at similar dose of enle where it is found that MCF-7 and HeLa cells are treated when increased in the concentration of enle (10 to 500 μ g/ml) then the MTT assay was performed on lymphocytes with a similar dose of enle (10-500 μ g/ml) and found there is no effect after the treatment with enle for 24 hour but it shows the effect on cancer cell by which we identify neem as a chemo preventive agent which suppress the carcinogenesis process.(19)

7.4. In Dentistry

Azadirachta indica has been found specifically active against the caries causing organism which have the capability to inhibit their growth mouth wash contain azadirachta indica which inhibits streptococcus mutans and contain chlorhexidine which inhibit the growth of lactobacillus. (24)

Neem oil also used in periodontal disease. It is amazingly effective alternative for systemic therapy for treat periodontal disease patient. A clinical microbiologist vennila. K conduct the study on 10% neem oil chip to evaluate its efficacy in periodontitis the result shows Improvement in p.gingivalis strains that are reduced hence it is found that 10% neem oil chip can be used for treatment of periodontal disease.(25)

7.5. CVS

The neem extract shows the vasodilator effect and the effect is mediated through ca⁺ channel blockade and nitric oxide pathway so study proves that neem extract is as potent vasodilator which cause lower B.P. (26)

7.6. Anti-Malarial

Azadirachta indica have been used as a medicinal plant in the subcontinent among many tribes for the treatment of malaria. The study conducts on leaf extract of azadirachta indica contain chemical constituent against the plasmodium falciparum in vitro and p. vivax in vivo model. The active constituent like tannins, glycosides, alkaloids, flavonoids, terpenoids, saponin, reducing sugar and volatile oil after study it is found that reducing sugar is found in neem in the extraction with solvent such as acetone, ethanol, and methanol. The ethanol extract has consisted of flavonoid, saponin, tannins and reducing sugar. Only glycosides is not found in ethanol extract. Saponin are found in acetone and

ethanol extract. Terpenoids are observe only in the methanol extract. Alkaloid and volatile oil are absent in the acetone, ethanol, and methanol extract this finding confirms that in which the similar constituent is found have shown antiprotozoal activity. The result shows that the leaf extract of neem shows anti-plasmodium activity. (20)

The study has been carried out to determine the chemical constituent and its effect on malaria induce male wistar rats. The quantitative determination was carried out the chemical constituent present in neem are alkaloid (methodology given by Harborne 1973), saponin (methodology reported by Obadoni and ochuko 2002), flavonoids (by the methodology reported by Boham and kocipai 1994), cyanogenic glycosides (determination methodology by Harbone 1973). Azadirachtin which shows anti-plasmodial activity (Jones et al.1994) the gedunin and meldenina isolate from the medicinal plant also shows antimalarial activity (mackinnon et al., 1997). The report of azadirachta indica also shows its effective and show antimalarial against p.falciparum in humans. It also reveals that the causative agent which cause malaria in human do not cause infection in rodents where it is found that p.berghei only cause infection in murine model but not in humans. (Farahna et al. 2010). It was found that the leef extract was safe and nontoxic which shows the anti-malarial property. (21)

7.7. Anti-inflammatory

The study conducted to investigate anti-inflammatory activity in vitro of azadirachta indica and lawsonia inner mis (Henna) individual extract and in the combination of using the same solvent. The ethanolic extract of azadirachta indica shows anti-inflammatory activity with reference to diclofenac sodium. The inhibition of protein denaturation in percentage and percentage of membrane stabilizing ethanolic extract, diclofenac sodium at 50,100 and 200 μ g/ml. It shows 46.62% membrane stabilizing and inhibits 57.3% protein denaturation. The ethanolic extract of Henna at the concentration of 200 μ g/ml shows inhibition of protein denaturation 53.75% and 39.89% protection membrane stabilization if the concentration is above 200 μ g /ml protein denaturation is decrease and membrane stabilization is increase. The ethanolic extract of henna and neem when combine for study of anti-inflammatory activity it shows at the concentration of 200 μ g/ml it shows increase in the anti-inflammatory activity. (29)

7.8. Anti-Diabetic

Neem also used widely as a antidiabetic to evaluate the antidiabetic effect of neem in diabetic albino rats which is induced by alloxan. During the whole

process performed by Dr. Naga shayanag et al, no side effect has been observed. In the present study oily extract of neem is used to evaluate the antidiabetic effect in albino rats. During the oral glucose tolerance test, it is found that neem oil has a better antidiabetic effect the oil shows the low rise in blood glucose level when compared to standard drug (glipalamide). Research conducted by khosla et al, they study azadirachta indica also act by increase release of insulin from β cell. (22)

Chloroform extract of azadirachta indica and aqueous methanol extract of *B. spectabilis* is used for the treatment for 21 days. It is found that it reduces the fasting glucose to the normal level which suggest its antihyperglycemic property. The parameter in diabetes is body weight which increase when treated with azadirachta indica chloroform extract and *B.spectabilis* aqueous extract but in the study we found treated mice increase in their body weight while the mice with diabetes lose their body weight. (23)

7.9. Hepatoprotective

The study conducts on the effect of azadirachta indica leaves powder against ccl4. The rat liver damage after administered intraperitoneally ccl4 (group 2-5) dose of 0.5gm/kg neem leaf powder administered orally to each rat of group 4. Dose of 0.007 gm/kg of silymarin orally to each rat of group 5. In study investigation after treatment of neem leaf powder the damage occur by ccl4 is recovered. Some sign of recovery also shows by hepatocytes so leaf powder of azadirachta indica is an effective hepatoprotective agent at the dose of 0.50 gm kg. (32)

The activity of aqueous extract of neem leaf also shows hepatoprotective activity against the antitubercular drug which induced hepatotoxicity in albino rats. The alteration caused by antitubercular drugs prevent by the administration of azadirachta indica aqueous leaf extract. The serum level of bilirubin, protein, alanine aminotransferase, aspartate aminotransferase and alkaline phosphatase are prevented after administered so it can be concluded that azadirachta indica aqueous leaf extract shows the hepatoprotective activity. (33)

7.10. Insecticidal

The seed of azadirachta indica shows significant result as insecticide in Sudan where optimal dose is used for vegetable pest. The seed of neem are used for the extraction of oil which store at normal room condition and used against the third inster larvae of trogoderma granarium which is used as test insect and result was shown that it is effective against vegetable insect. (30)

The azadirachta indica neem leaves are used to prepare the insecticide now insecticide is applied on the skin when it compares to total no of bites received before application and total no of bite received after application. After half an hour it is observe that no bites were recorded after application of insecticide and after 2 hours it is recorded that few bites which gives the efficacy of insecticide. 84.5% -85% where research shows that neem leaves are used as an insecticide for mosquito eradication which is less toxic. (31)

7.11. Wound Healing

The study of plant azadirachta indica is conducted to evaluate wound healing activity on excision wound model. The ethanolic extract of stem bark of neem is used, and it is compared with standard drug povidone iodine ointment (0.01% w/w). This test is performed on adult rat of both strains (Albino and Wistar). As comparison to the standard drug povidone iodine the ethanolic extract of azadirachta indica stem bark shows faster wound closure and wound contraction. (27).

The neem extract has high wound healing property in the excision wound model. Wound healing percentage is increased ($P < 0.05$) from day 0 till day 12 which was 99% and 100% in the case of neem ointment and gel. In the study conducted by Nakao et al. 2009 shows that after application of neem ointment and neem gel to the wound of the diabetic rat (group 2, 3) it increases the rate of wound contraction ($P < 0.05$) when compared to diabetic contraction (group c). By day 12 diabetic animal wound are treated with neem gel and ointment which close the wound 92.83% and 92% respectively while standard formulation of tetracycline which also closed wound by 94% in which is found that the topical formulation of tetracycline have increased percentage of wound healing in diabetic rats. (28)

7.12. Antioxidant

The study conducted on azadirachta indica flower and the seed oil to evaluate the antioxidant property on the basis of scavenging activity of 2,2 diphenyl 2-picrylhydrazyl (DPPH) free radical has been determine according to method given by (Brand – Williams et al.1995) in the study of ethanolic fraction of neem flower it consist of scavenging activity with high percentage $64.17 \pm 0.02\%$ in comparision to methanol and water extract which is $52.30 \pm 0.05\%$ and $41.03 \pm 0.06\%$ and the invitro antioxidant study of neem flower and oil shows more ability to scavage DPPH (34)

Azadirachta indica is one of the most used medicinal plant which consist of a various bioactive compound this study was conducted on neem leaf extract to determine the antioxidant activity and their

efficiency. The higher concentration of plant inhibits the DPPH free radical which is measured in the term of percentage 71.23% followed by decrease inhibition activity in lower concentration. (35)

8. CONCLUSION

The importance of a neem plant is that it is used widely as a medicinal herb. It consists of very bioactive chemical constituent which shows various medicinal activity. It is extremely popular worldwide for the prevention and in cure of a disease and have less side effect property. The role of active ingredient is as hepatoprotective, antidiabetic, antimalarial, anticancer, and as wound healing has been noticed. On the azadirachta indica the significant amount of research has been carried out on the different parts of the plant.

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