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REVIEW

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The Biochemical Wonders of *Azadirachta indica* A. Juss: A Comprehensive Review of its Properties and Potential Benefits

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Azadirachta indica, also known as Neem is an evergreen tree that is native to the Indian subcontinent. It has been traditionally used for various medicinal purposes, including wound healing, fever reduction, and treatment of skin disorders. It has been widely recognized for its various medicinal properties. In this review, A comprehensive overview of the biochemical properties of Neem and its potential benefits are provided. The chemical constituents of Neem including Azadirachtin, Nimbin, and nimbolide, and their biological activities, such as antimicrobial, antioxidant, and anticancer effects are discussed. The potential applications of Neem in medicine, agriculture, and cosmetics are explored. This review highlights the importance of neem as a natural resource with numerous potential benefits for human health and the environment.

Key words: Neem, Biochemical Properties, Antioxidant, Antiviral, Nimbin

Azadirachta indica A. Juss has been used by Indian Population for curing many diseases. Traditionally, it has been in use in the Ayurvedic system of medicines since time immemorial. Also, Phytotherapy is a complementary and promising therapy of medical treatment. Global Health is looking for such an alternative source of medicine. *Azadirachta Indica*, commonly called Neem, is also known as a "Devine Tree" because of its many health benefits. It is originally from India and Myanmar. *Azadirachta indica* (neem) belongs to the Meliaceae family and is commonly found in tropical Africa, Pakistan, Nepal, Bangladesh, and India. It grows fast, reaching a height of 20 to 23 m with a thick trunk diameter of 4 to 5 feet. It produces green drupe fruits that become golden yellow when ripe (Girish and Shankara, 2008). The extract of parts of the Neem tree such as leaves, bark, stem, twigs, and fruit, has been shown to have many biochemical properties like anti-bacterial, anti-inflammatory, diuretic, antioxidant, and even antiviral activity due to the presence of active ingredients.

In the top ten list of plants to be researched for the sustainable development of the earth and living beings, the Neem tree has been included by The International Scientific Community. WHO/UNEP1989 identified Neem tree as one of the most promising trees of the 21st century for its valuable use in agriculture, environment protection, and medicine.

“Nimba” is an ancient sanskrit word which means “Good Health” (Sitasiwi, A. et. al, 2018) and Good Health is internal and physical fitness of human bodyn[3]. Neem is derived from “Nimba”. Nowadays, Neem is used to reference the *Azadirachta indica* (Neem) tree, traditionally thought to bring "good health" to those who take it with them (Arumugam et. al. 2014 and Omóbòwálé, 2016). Every part of the Neem tree is of great medicinal value, its bark, stem, leaves, flower, and fruit, are associated with medical folklore in the treatment of diseases such as diabetes, hypertension, cancer, etc. These potential effects of using the neem tree extract can certainly be attributed to cellular and molecular mechanisms which may include free radical scavenging, detoxification, cell cycle alteration, programmed cell death mitigation and autophagy, anti-inflammatory, anti-angiogenic, anti-metastatic activities and the ability to modulate of various signaling pathways (Arumugam et. al. 2014 and Omóbòwálé, 2016 and Patel et. al. 2016). The phytochemicals of the neem tree are known to have various biological effects (Nagini, 2021).

Methodology:

An extensive review of the literature is done by searching the data electronically with keywords like *Azadirachta Indica,* extraction, Neem Extracts, biochemical activity, antiviral activity, antibacterial activity, antioxidant activity, biochemical molecules, etc. Compilation of data is done to the best in this paper.

Plant Description: The Hierarchy of Neem in the Plant Kingdom is:

Kingdom:	Plantae
Order:	Rutales
Suborder:	Rutinae
Family:	Meliaceae
Subfamily:	Melioideae
Tribe:	Melieae
Genus:	*Azadirachta*
Species:	*indica*

Neem is an evergreen tall tree. It can reach a height of 30-35 feet. The tree is highly branched and has spreading branches forming a rounded crown-like shape. It has usually a straight brown trunk with moderately thick furrowed bark. Its leaves are compound. Its flowers are small, white, and have a honey-like scent. These grow in clusters mostly in the axils of leaves and are a great source of nectar for bees. The new leaves appear in March-April. It is in full bloom in summer when most of the trees shed their leaves. Fruits are small, ellipsoidal drupes. These are green in color when raw becomes yellow on ripening and golden yellow on drying. Flowering in neem occurs in April-May and fruit ripens from June to August (Ross I.A., 2001).

Applications of different parts of the Neem tree:

The neem tree is beneficial in every way. There are

numerous uses for neem tree parts. Therefore, it is called a "divine tree". It has been in use in Ayurveda since 4000 BC for the treatment of various diseases. For thousands of years, Indian farmers have been aware of the insecticidal properties of neem trees. Its branches were hung in granaries to protect stored grain from pest attacks (Brahmachari, Goutam, 2004). Historically, neem has also been used in India for cosmetic and medicinal purposes. Neem oil, for instance, which is derived from the seeds, is used in soap, wax, and lubricants. Neem twigs have also been used as toothbrushes in the past. A drink made of its juice is considered a good tonic to increase appetite and cure fever or to kill intestinal worms. Therapeutically, its leaves and bark have been utilised as crude extracts in folk medicine to treat conditions like leprosy, intestinal helminthiasis, and respiratory illnesses. *Azadirachta indica* is an indigenous medicine as a bitter tonic, antimalarial, antifungal, antibacterial, anti-termite, antipyretic, analgesic, and even has antiviral properties. Some of the uses are listed in Table 1 (Brahmachari, Goutam, 2004).

Table 1: Uses of Neem Tree parts.

Part of the Neem tree	Uses
Neem Leaves	In chickenpox, treatment of malaria, antifungal, keeps termites away, have insecticidal properties
Twigs	Relieves cough, asthma, diabetes, antipyretic and analgesic
Flowers	Bile suppression, elimination of intestinal worms
Fruits	Leprosy, diabetes, healing wounds, an eye problem
Bark	Analgesic, antipyretic, antibacterial, skin infections, leprosy
Neem seed cake	Natural fertilizer, insecticide
Neem oil	Pest control, leprosy, cosmetics, medicines

Chemical Variance of compounds extracted from Neem Tree:

More than 200 compounds have been isolated so far from various parts of the Neem tree. Nimbin was the first compound isolated, followed by nimbidin (G. S. Verma, 1976). The isolated compounds of the Neem Tree have been broadly classified into two classes: Isoprenoids and Non-Isoprenoids. The Isoprenoids are further divided into Diterpenoids and Triterpenoids which include the compounds lie Azadirachtin, Gedunin and its derivatives, salanin, Nimbin, and limonoids. Whereas, Non-isoprenoids include carbohydrates (polysaccharides), sulfur compounds, and polyphenols such as Flavonoids and their derivatives, coumarins. This chemical classification of compounds of the Neem tree has been shown in the form of a flow chart in Fig 1. These compounds have been isolated from various parts of the Neem Tree such as Leaves, Twigs, Flowers, Bark, Seeds, and Roots.

Bioactive Compounds extracted from Neem:

Neem is a great source of bioactive compounds which makes its extract effective for biochemical activity as described in the Ayurvedic system of medicines. More than 200 compounds have been isolated from neem trees since the report on the isolation of Nimbin from neem seed oil (S. Siddiqui, 1942). The compounds isolated from neem trees include terpenoids, flavonoids, polysaccharides, limonoids, tannins, alkaloids, reducing sugar, catechins, sterols gallic acid, and saponins. Flavonoids found in neem inhibit enzymes like protein kinase and phosphodiesterase involved in inflammation. These also inhibit the biosynthesis of prostaglandins and endoperoxides (Batista, 2018). The triterpenes of neem have been found to have a large number of therapeutic uses such as antipyretic, analgesic, anti-inflammatory, antioxidant, antitumor, fungicidal, antibacterial, etc. Nimbin and Nimbidin have shown such therapeutic properties (Naik, 2014). The phytochemical analysis of oil extracts of neem has confirmed the presence of catechins, triterpenes, saponins, and flavonoids. The neem leaf glycoprotein has the potential to restrict tumor growth by modulating immunity as it has shown immune modulatory activity (Banerjee, 2014). Proline, which is a

current treatment for neurological disorders like Alzheimer's and Parkinson's disease, Type 2 Diabetes Mellitus, and Polycythemia, has been found in high concentrations in leaf extracts following biochemical examination (Dash et. al.2017 and Gladkevich , 2007).

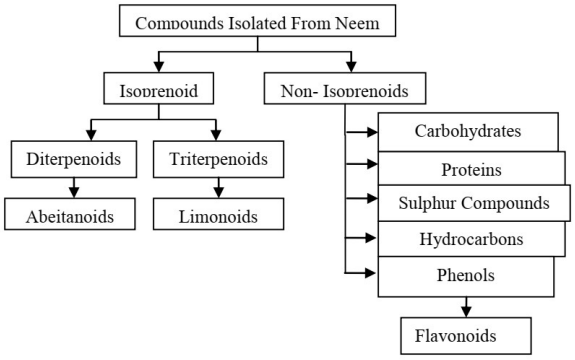

Figure 1. Classification of compounds extracted from Neem Tree

The leaf of the Neem tree has a large number of bioactive compounds and their extraction is solvent dependent. The various studies conducted have shown that the antioxidant activity of leaf extract in different solvents is different. All solvents do not have the same polarity so the compounds extracted are also different. The chloroform extracts have shown the highest antioxidant activity whereas the methanolic extracts have shown the least. Chloroform extracts contain (2E)-3,7,11,15-tetramethyl- 2-hexadecane-1-ol, methyl 14-methylpentadecanoate, lineoleoyl chloride, phytol, methyl isoheptadecanoate, and nonacosane whereas the methanolic extract contains m-toluylaldehyde, methyl-14-methylpentadecanoate, Lineoleoyl chloride, Methyl-isoheptadecanoate. The hexane-derived extract of the Neem tree has the maximum number of biologically active compounds. Some of them are Butyl palmitate, 2,6,10,14-Tetramethylheptadecane, Nonadecane, Isobutyl Stearate, Oxalic acid, Heptacosane, etc (Al-Hashemi & Hossain, 2016) and (Hossain, 2013). The compounds extracted from the flowers of the Neem tree are different from their leaves and have shown anti-mutagenic activity against Trp-P-I, Trp-P-II, and PhIP. Methanolic extract of the Neem tree flowers has shown prenylated flavonoids such as 5,7,4′-trihydroxy-8-prenylflavanone, 5,4′-dihydroxy-7-methoxy-8-prenylflavanone, 5,7,4′-trihydroxy-3′,8-diprenylflavanone. Other compounds extracted from flowers are flowerine, flowerone, O-methylazadironolide and diepoxyazadirol, triterpenoid (trichilenone acetate), flavanones, nimbaflavone, 3′-prenylnaringenin and 4-(2-hydroxyethyl)phenol (Saleem et. al.2018).

Azadirachtin, a main constituent of Neem tree extracts is a complex tetranortriterpenoid limonoid present in seeds and has toxic effects on insects. Neem leaf ethanol extract demonstrated in-vitro antibacterial efficacy against Staphylococcus aureus and MRSA, according to experiments (Akeel, 2017). Some of the bioactive compounds extracted from various parts of the Neem tree are summarized in Table 2.

Medicinal Properties of Neem:

Neem is a great source of traditional treatment for many diseases. The twig of this plant is in use for cleaning teeth for centuries. Many have placed neem leaves in bookshelves, beds, cloth almirahs, grain bins, and cupboards to keep away insects and bugs. In rural India, people often use water decoction of neem leaves for the prevention and treatment of diseases. Various neem formulations are also available in the market nowadays for the treatment of various ailments with promising results. The researchers are also carrying out in vitro and in vivo experiments for searching and confirming the medicinal potential of neem and its derived compounds.

(i) Antibacterial Properties:

The Neem leaf extracts and Neem oil have been shown to have the highest antibacterial activity. Neem oil was shown to be active against Staphylococcus aureus, Salmonella typhi, and Escherichia coli (Jahan et. al. 2007). The Neem leaf extract and its various phytoconstituents such as steroids, tannins, terpenoids, and glycosides have been evaluated and confirmed for their antibacterial activity (Aslam et. al. 2009). Mehmoodin, a limonoid extracted from neem oil is active against various Gram-positive and Gram-negative bacteria (Siddiqui et. al. 1992). Cotton blended with polyester fabric, when treated with neem extract, was reported to have antibacterial activity against Bacillus

subtilis and Proteus vulgaris (Joshi et. al. 2007). The compounds isolated from neem oil are 9-Octadecanoic acid, hexadecanoic acid, tetrahydrofuran-3,4-diyl ester and these are found to be active against Staphylococcus aureus, Escherichia coli, and Salmonella sp. in vitro assays (Zhong et. al. 2010).

(ii) Antidiabetic properties:

Traditionally the neem leaf extracts in the form of either tea or some formulation have been used to treat diabetes. Researchers also have shown the hypoglycaemic effect of ethanolic neem extracts when evaluated in diabetic rats. Ethanolic extracts of *A. indica* leaf normalized the glucose level and reversed dyslipidemia in streptozotocin-induced hyperglycemia (Bisht and Sisodia, 2010). Meliacinolin, a tetranortriterpenoid isolated from chloroform extract of dry neem leaves is a potential anti-diabetic agent as it inhibited the activities of α-glucosidase and α-amylase enzyme in streptozotocin-nicotinamide-induced type 2 diabetes in mice (Perez-Gutierrez and Damian-Guzman, 2012).

(iii) Antiulcer properties:

The neem leaf extract has significant antiulcer activity. Nimbidin, an active constituent of Neem is highly effective in healing ulcers in the duodenum and relieving pain (Garg et. al. 1993). The aqueous extract of Neem bark is highly useful in reducing gastric acid secretion and also possesses anti-ulcer activity. A glycoside present in Neem bark aqueous extract is responsible for its activities. The Neem leaf extracts also have been shown to have anti-ulcer activity as it reduces acid secretion by blocking H^+-K^+-ATPase and preventing oxidative damage (Chattopadhyay et. al. 2004).

(iv) Antifungal Properties:

The Neem leaf and seed extracts have been shown to have antifungal activity. The Neem seed kernel extracts have significantly reduced the growth of pathogens Monilinia fructicola, Penicillium expansum, Trichothecium roseum, and Alternaria alternate (Wang et. al. 2010). Leaf extracts of *A*. *indica* have been shown to reduce seed mycoflora in wheat, leading to better seed germination (Khan and Shah, 1992).

(v) Antimalarial Properties:

The antimalarial properties of Neem have been revealed by researchers. Gedunin, a constituent of Neem has been shown to reduce the growth and development of the malaria-causing parasite *Plasmodium falciparum* (Khalid et. al. 1989). The chloroquine-resistant P. falciparum strain K1 is resistant to the limonoids (meldenin, isomeldenin, nimocinol, and nimbandiol) obtained from the ethanolic extract of the fresh neem tree (Vasanth et. al. 1990). The limonoid azadirachtin has been found to block activity of the rodent malarial parasite, *Plasmodium berghei*, in its vector Anopheles stephensi (Lucantoni et. al. 2010).

(vi) Antioxidant Properties:

Antioxidant properties of Neem have been shown by seed extracts. During germination, when horsegram seeds are treated with Neem extracts, the lipoxygenase enzyme activity decreases along with a decrease in peroxides (Rao et. al.1998). Garlic and neem-leaf extracts together decrease the formation of lipid peroxides and increase the levels of antioxidants and detoxifying enzymes in the stomach (Arivazahagan et. al. 2000). Neem leaves and bark have phenolic content and show antioxidant properties. Researchers have shown the DPPH radical scavenging activity of Neem tree leaves.

(vii) Insecticidal Properties:

Neem tree is well known for its insecticidal properties as it has been used by Indians to repel bugs and insects from stored grains, books, and clothes for a long time. Various tetranortriterpenoids–meliatetraolenone, zafaral, 6a-O-acetyl-7- deacetylnimocinol, meliacinol, 17-β-hydroxyazadiradione, azadironic acid, limocin-A, limocin-B, epoxyazadiradione, mahmoodin, gedunin, nimbin, azadiradione, and 7-deacetylazadirone–isolated from various parts of neem tree have been reported to have insecticidal activities or insect anti-feeding activities. Odoratone, isolated from methanolic extract of neem tree fresh leaves, has a toxic effect on larvae of *the A. stephensi* mosquito. Neem oil is also reported to have larvacidal properties against *A. stephensi, Culex quinquefasciatus*, and *Aedes aegypti* (Dua et. al. 2009). Meliacinin, a dinortriterpenoid isolated from fruit coats, was found to be lethal against mosquitoes (*Anopheles stephensi*) (Siddiqui et. al. 2000).

(viii) Antiviral properties:

Neem (*Azadirachta indica*) has been shown to have antiviral potential against a number of viruses, including avian influenza, group B coxsackievirus, duck plague, poliovirus type 1, bovine herpes virus type 1, dengue virus type 2, Newcastle disease virus, and Newcastle disease virus. Neem seed oil inhibited transmission of potato virus Y to sweet pepper by the green peach aphid, *Myzus persicae* (Sulzer) when applied on foliage, suggesting that the oil interferes with virus transmission (Lowery et. al. 1997). A methanolic extract of neem tree leaves showed antiviral activity against the Coxsackie B group of viruses (Badman et. al. 1999). Fever, cough, asthma, and diarrhoea are among the main clinical signs of COVID-19 and are all commonly treated with neem in Ayurvedic therapy. Neem is reported to enhance both humoral and cell-mediated immune response during viral infection (Roy and Bhattacharyya 2020).

Table 2: Bioactive compounds extracted from Neem

S.N.	Name of the compound	Type of compound	Source of compound	Pharmacological action	The probable mechanism of action
1.	Nimbidin	Triterpene	Seed oil	antipyretic, fungicidal, antihistamine, antiseptic properties, anti-inflammatory (Naik et. al. 2014) and antioxidant effects,	Suppresses the function of macrophages and neutrophils (Kaur et. al. 2004)
2.	Nimbolide	Tetranortriterpenoid	Seed oil	Antibacterial, antimalarial, anticancerous (Nagini, 2021)	Antiproliferative effect (Nagini, 2021)
3.	Gedunin	Triterpenoid	N Seed oil	Antiallergic, anticancer, antimalarial,	Heat shock protein inhibitors (Braga et. al.2020)
4.	Mahmoodin	Triterpenoid	Seed oil	Antibacterial	
5.	Nimbin	Triterpenoid	Seed oil	Spermicidal	
6.	Gallic acid, catechin	Flavanol, polyphenol	Bark	Immunomodulatory, anti-inflammatory (Batista et. al. 2018)	Inhibits prostaglandin biosynthesis (Batista et. al. 2018)
7.	Margolone, isomargolonone, margolonone	Diterpenoid	Bark	Antibacterial	
8.	Polysaccharides GIa, Gib	Polysaccharide	Bark	Antitumor	
9.	NB-II peptidoglycan		Bark	Immunomodulatory	
10.	Quercetin	Flavanoid	Leaf	Hypoglycaemic (Bule et. al. 2019)	Lowers serum glucose level (Bule et. al. 2019)
11.	Cyclic tetrasulfide		Leaf	Antifungal	
12.	22,23-dihydronimocinol and des-furano-6a-hydroxazadiradione	Triterpenoid	Leaf	Insecticidal	
13.	Flavanone compound	Flavanoid	Gum	Antifungal	
14.	Salanin	Triterpenoid	Fruit pulp	Spermicidal	
15.	Azadirachtin	Triterpenoid	Seed	Locust antifeedant, antimalarial (Gaaboub and Hayes, 1984)	inhibiting molting in larvae of the insect (Gaaboub and Hayes, 1984)

CONCLUSION

Neem i. e. *Azadirachta indica* is a rich source of bioactive compounds with a wide range of potential therapeutic and practical benefits. Its bioactive compounds have been found to have antioxidant, anti-inflammatory, anticancer, antimicrobial, and antiulcer effects among others. Neem has also been explored for its applications in agriculture. Further detailed research is needed to fully understand the potential benefits of neem and its constituent bioactive compounds and to explore their clinical applications.

CONFLICTS OF INTEREST

The authors declare that they have no potential conflicts of interest.

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