



Neem and its Active Ingredients Therapeutic Use in the Prevention and Treatment of Disease

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ABSTRACT

Due to its numerous medical virtues, *Azadirachta indica*, also known as neem, has gained popularity on a global scale recently. Neem, also known as *Azadirachta indica*, is a tree native to India and Myanmar. Because of its numerous health benefits, many people refer to it as "The village pharmacy" or "Divine tree." Neem produces a wide range of chemically diverse and structurally complex physiologically active chemicals. Neem has become popular in modern medicine due to its extensive use in Ayurveda, Unani, and homoeopathic treatments. From various neem plant components, more than 140 distinct chemicals have been discovered. The traditional use of the neem tree's leaves, flowers, seeds, fruits, roots, and bark for the treatment of inflammation, infections, fever, skin conditions, and dental problems includes all of these parts. Numerous effects have also been investigated, including those that are antibacterial, antifungal, anthelmintic, antiparasitic, anticancer, anti HIV, anti bone resorption, antispasmodic, antipyretic, antidiarrheal, immunomodulatory, hypolipidemic, anti-microbial, hepatoprotective, and gastro protective

Keywords: Anti-Cancerous Properties, Anti-oxidant, *Azadirachta indica*, Chemical Constituents, Neem, Pharmacological activities

1. Introduction:-

Growing interest has been given to medicinal plants in the search for new drugs to treat human diseases including cancer. As opposed to an edible plant that is consumed regularly as food, Park and Pezzuto define a medicinal plant as "a plant that has pharmacological activity to treat sickness." Neem, also known as *Azadirachta indica*, has a reputation on the Indian subcontinent dating back more than 2000 years as one of the most adaptable medicinal plants with a wide range of biological [Park and Pezzuto,2002]

The name *Azadirachta indica*, which translates as "the free tree of India" in Latin, is an alliteration for the neem plant's inherent freedom from pest and disease problems. In Persian, *Azadi* means "free" and *diracht* means "tree." The neem tree is referred to as a "sarvaroga nivarini" (the cure-all for all ailments), as well as a "divine tree," "village pharmacy," and "nature's drugstore." [Subapriya, and Nagini, 2005; Puri, 1999]

Local names for the plant *Azadirachta indica* include "Imba, Nimba, and Mimba". [Sitasiwi, et al., 2018] These names were specifically described in ancient Sanskrit as "Imba, Nimba, and Mimba" which later became Neem. Today, the term "Neem" is referred to as *Azadirachta indica* (Neem) tree, which is believed to provide "excellent health" to individuals who consume it. The Neem tree has been used in traditional medicine for many years and is mostly grown in the southern parts of Asia and Africa. It is an indigenous plant commonly grown in India and its subcontinent. It's important to know that different Neem tree parts, such as the leaves, bark, fruit, flowers, oil, and gum, have been linked to the treatment of many ailments and disorders, including cancer, hypertension, heart disease, and diabetes. [Islas et al., 2020; Elumalai et al., 2012]

2. Taxonomical classification of Neem:-

Kingdom: Plantae

Division: Mangoliophyta

Class: Mangoliopsida

Order : Sapindales

Family : Meliaceae

Genus : *Azadirachta*

Species : *Indica* [Ghosh et al., 2016]

3. Botanical aspects of Neem:-

Neem (*A. indica*) is a substantial tree that can reach heights of 15 to 20 metres. The tree has a 3 m-diameter, semi-straight to straight stem that spreads its branches into the shape of a broad, crown-like structure. Typically, a neem tree begins to bear fruit and become prolific after 3–5 years. The fruit can be oval or spherical, and when ripe, it is between 1.4 and 2.8 cm long and between 1.0 and 1.5 cm in diameter. The morphology of the fruit can be broken down into an outside thin layer of skin (exocarp), a middle pulpy layer (mesocarp), and an interior layer composed of seeds (endocarp) coated with a seed coat.

Neem leaves have a straightforward design with only one leaf blade. A little petiole connects the leaf blade to the stem. The arrangement of neem leaves is the opposite: two neem leaves grow side by side at a single node. Neem leaves are about 7 cm long and 2.5 cm wide, with 10–12 dark green, elliptic leaflets with serrated margins and pinnate venation (i.e., the leaflets are aligned along the mid-vein).

Neem plants are flower-bearing angiosperms that fall under the magnoliophyte classification. Flowers are all white. The flower inflorescence contains roughly 150–200 flowers that are 5 mm in length and 8 mm in width. Neem trees adapt well to a variety of climatic, geographical, and topographic conditions. The tree needs a lot of sunlight to develop, but it doesn't require much water. As a result, it cannot resist wet environments or locations with inadequate soil drainage. Neem trees may thrive in environments with temperatures as high as 49 °C. Neem trees can grow in practically any soil, including saline, clay, and alkaline soils. [Ghosh et al.,2016 ; Koul et al.,1990]

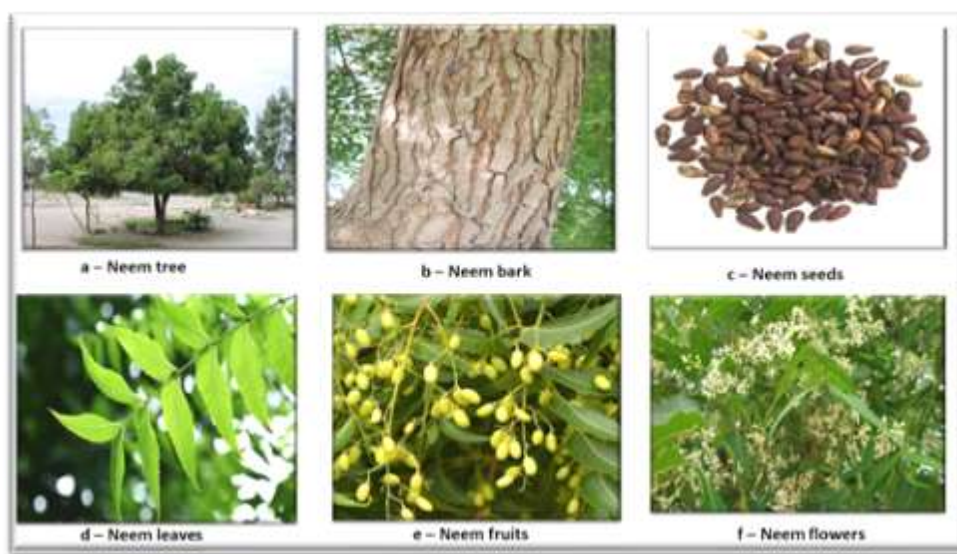


Fig 1:- Neem Tree and its different parts ; a) Neem tree , b)Neem bark , c) Neem seeds , d) Neem leaves , e) Neem fruits , f) Neem Flowers [Ghosh et al.,2016 ; Koul et al.,1990]

4. Chemistry:-

The chemistry of neem tree products has been well investigated. Neem leaves in particular are a "storehouse" of organic substances. Essential oil, which gives neem leaves their distinctive aroma, is present in them in amounts of 0.13 percent. [Puri,1999 ; Atal and Kapur, 1982 ; Parmar and Ketkar, 1993; Subapriya, and Nagini,, 2005]

A total of more over 140 chemically diverse and structurally complex active compounds have been identified from various neem components. Isoprenoids and nonisoprenoids make up the two main families of chemicals. Diterpenoids, triterpenoids, vilasinin-type substances, limonoids and their derivatives, and C-secomeliacins are some of the isoprenoids. A list of the nonisoprenoids includes proteins, polysaccharides, sulphate-containing substances, polyphenolics such flavonoids and their glycosides, dihydrochalcone, coumarin, tannins, and aliphatic substances. [Subapriya and Nagini , 2005; Goutham, 2021; Ravi etal ., 2015 ; Yang and Ametaj , 2021; Sarah et al., 2019 ; Geetha et al.,2020]

Neem, *Azadirachta indica*, plays a therapeutic role in the management of health since it is a rich source of many different kinds of substances. Azadirachtin is the most significant active ingredient, followed by nimbolin, nimbin, nimbidin, nimbidol, sodium nimbinat, gedunin, salannin, and quercetin. Ascorbic acid, n-hexacosanol, amino acids, 6-desacetylnimbinene, nimbandiol, nimbolide, 7-desacetyl-7-benzoylazadiradione, 7-desacetyl-7-benzoylgedunin, 17-hydroxyazadiradione, and nimbiol are among the substances found in leaves. The polyphenolic flavonoids quercetin and β -sitosterol, isolated from freshly picked neem leaves, were known to have antibacterial and antifungal activities. Gedunin and azadirachtin are two important components found in the seeds. [Alzohairy ,2016; Gite et al.,2019]

The major chemical constituents of neem are Terpenes and Limonoids. The main chemical compounds in limonoids include azadirachtin, 3-deacetyl-3-cinnamoyl, azadirachtin, Itigloyl-3-acetyl-II-methoxyazadirachtin, 22, 23-dihydro-23 β -methoxyazadirachtin, nimbanal, 3-tigloylazadirachtol, 3-acetyl-salannoV, nimbidioV, margocin, margocinin, margocilin and others. Isozadirolide, 6 nimboinolide, nimbonone, nibonolone, methyl grevillate and Margosinone are example of terpenoids. Neem improves the liver's capacity to cleanse itself of toxic pollution by increasing the production of glutathione-s-transferase. The most potent bitter substance in neem oil is nimbidin, which is also the primary antibacterial element. These substances are plentiful in neem and are stable. [Upadhayay and Vigyan, 2014; Alzohairy,2016 ; Vigyan, 2014]

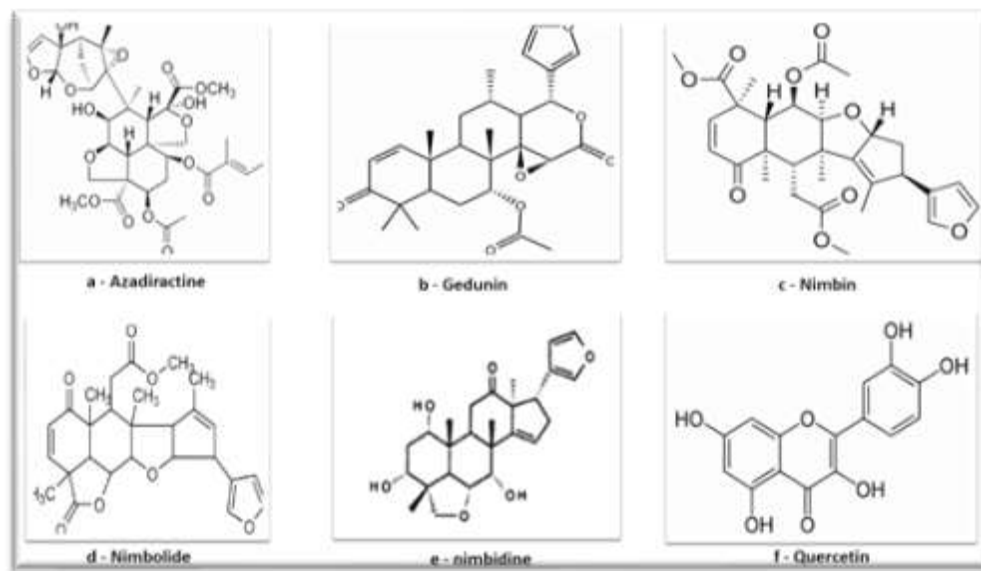


Fig2:- Chemical Structure of Major Constituents of Neem ; a) Azadirachtin , b)Gedunin , c) Nimbin , d) Nimbolide , e) Nimbidine , f) Quercetin [Alzohairy ,2016; Gite et al.,2019]

5. Pharmacological activity of Neem:-

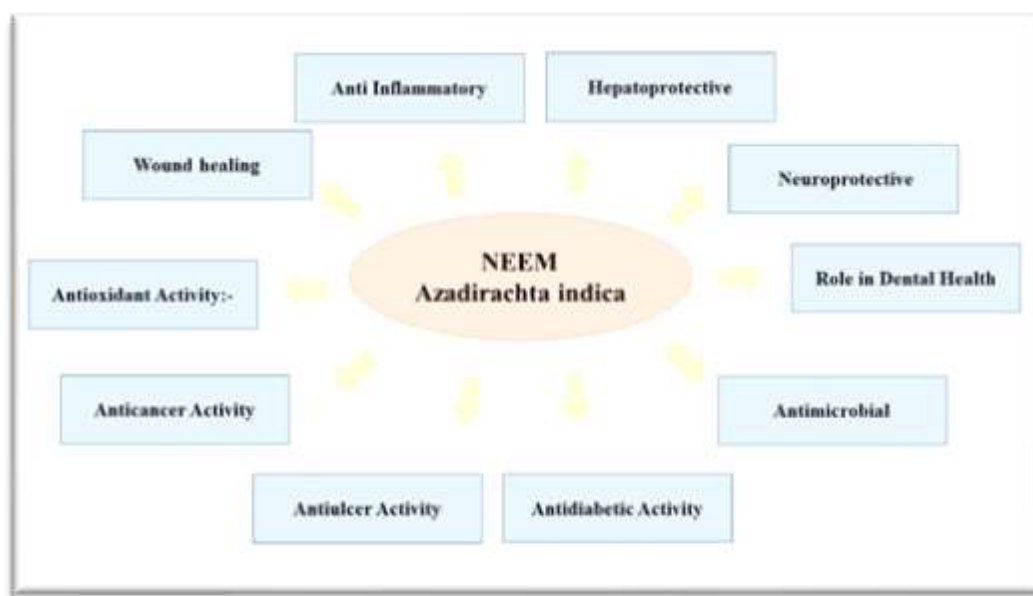


Fig 3:- Pharmacological Activity of Neem and its ingredients

Sr.No.	Part of Neem Tree	Biological Activity
1.	Leaf	Anticancer
		Antibacterial
		Antimalarial
		Antifertility

		Antipyretic
		Anti-inflammatory
		Analgesic
		Antiulcerogenic
		Antihypertensive
		Antihyperglycemic
		Neuropharmacological
		Antidermatophytic
		Oro dental protection
		Hepatoprotective
		Immunostimulant
		Antioxidant
		Antigenotoxic
		Antifungal
2.	Bark	Anticancer
		Antibacterial
		Antimalarial
		Anti-inflammatory
		Antiulcer effect
		Hepatoprotective
		Immunostimulant
3.	Flower	Anticancer
		Antioxidant
4.	Seed	Anticancer
		Antioxidant
		Antifertility
		Antimalarial

Table 1:- Pharmacological Activities of Different Parts of Neem[Subapriya and Nagini, 2005]

5.1:-Antioxidant Activity:-

One of the primary players in the development of many diseases is the free radical or reactive oxygen species. A crucial step in the prevention of diseases, though, is the neutralisation of free radical activity.[Nunes et al, 2012] Antioxidants also have a function in the activation of antioxidant enzymes that play a part in the regulation of damage produced by free radicals and reactive oxygen species. Antioxidants stabilize/deactivate free radicals, frequently before they assault targets in biological cells.[Rahmani and Aly, 2015] Antioxidant activity in medicinal plants has been noted. Plants have a significant role in disease prevention since they are a rich source of antioxidants in their fruits, seeds, oil, leaves, bark, and roots.

An important study was conducted to assess the in vitro antioxidant activity in various crude extracts of the leaves of *Azadirachta indica* (neem), and the antioxidant capacity of various crude extracts was as follows:

chloroform > butanol > ethyl acetate extract > hexane extract > methanol extract . According to the current findings, neem crude extracts in chloroform could be employed as a natural antioxidant.[Alzohairy,2016 ; Vigyan, 2014; Nunes et al, 2012; Rahmani and Aly, 2015 ; Ghimeray et al.,2009; Sithisarn et al., 2005]

5.2:-Wound healing:-

Since ancient times, neem leaves have been used as a folk medicine for their ability to cure wounds. Excision and incision wound models were used in a study to assess the wound healing activity of extracts from the leaves of *A. indica* and *T. cordifolia* in Sprague Dawley rats. The results showed that extracts from both plants significantly promoted the wound healing activity in both excision and incision wound models. Additionally, it was discovered that both plant-treated groups' healing tissue tensile strength was much higher than that of the control group in incision wounds. Other findings indicated that *Azadirachta indica* leaf extracts stimulate wound healing activities by enhancing the inflammatory response and neovascularization.[Alzohairy,2016 ;Ofusori, et al.,2010 ; Barua et al., 2010; Osunwoke et al .,2013]

5.3:-Anti Inflammatory:-

Numerous research have revealed that neem plants have anti-inflammatory properties. Nimbidin from neem trees was utilised orally in an experimental investigation using rat models to assess its anti-inflammatory activity. The inhibition of phagocytosis and the migration of macrophages to their peritoneal cavities in response to inflammatory stimuli were both proven to occur.

Additionally, nimbidin prevented phagocytosis and phorbol myristate acetate-stimulated respiratory burst in rat peritoneal macrophages when they were exposed to the drug in vitro. As a result of in vitro exposure to lipopolysaccharide-stimulated macrophages, nimbidin reduced the generation of nitric oxide and prostaglandin E2.[Kaur et al., 2004]

Azadiradione, a particular component of neem fruit peel, has also been studied for its anti-inflammatory properties. The findings showed that the rats given azadiradione and 100 mg/kg of this fruit skin extract showed strong anti-inflammatory effects. [Ilango, et al.,2013]

Neem seed oil's ability to reduce inflammation has also been tested on rats with carrageenan-induced hind paw oedema. The outcome Research on the anti-inflammatory activities of azadiradione, a specific component of neem fruit peel, has also been done. The results demonstrated that the rats administered 100 mg/kg of this fruit skin extract and azadiradione had potent anti-inflammatory effects. At the fourth day after carrageenan injection, this oil at a dose of 2 ml/kg body weight demonstrated the greatest edema inhibition. [Rahmani and Aly, 2015; Kaur et al., 2004; Ilango, et al.,2013 ; Naik et al.,2014]

5.4:- Hepatoprotective

Neem-derived azadirachtin A and its other components' hepatoprotective properties are well established. In one study, carbon tetrachloride (CCl₄) was used to produce hepatotoxicity in animal models. It was shown that the disease control groups displayed decreased total protein levels and dramatically raised aminotransferase (AST and ALT) and alkaline phosphatase levels. The reference range of these proteins and enzymes was dramatically expanded after treatment with azadirachtin A. Additionally, the results of the histological and ultra-structural tests supported the notion that azadirachtin A pre-treatment decreased hepatocellular necrosis. [Bhanwra et al., 2000]

Rats were used to test the leaf extract's hepatoprotective effects. High levels of AST and ALT were dramatically lowered by aqueous leaf extract. Additionally, as seen macroscopically and histologically, liver necrosis was also reported to be reduced. Another study found that neem leaf extract protects and reverses the hepatotoxic damage brought on by antitubercular medications, and that this reversal is superior to that brought on by stopping the use of antitubercular medications. [Rahmani and Aly, 2015; Bhanwra et al., 2000 ; Kale et al.,2003]

5.5:- Anticancer Activity:-

The multifaceted disease of cancer is a significant global health issue. Changes in molecular and genetic processes contribute to the emergence and spread of cancer. The allopathic treatment plan works well on one side but has negative effects on healthy cells as well. According to earlier research, plants and their constituents can prevent the formation of cancerous cells by altering cellular proliferation, apoptosis, the tumour suppressor gene, and a number of other biochemical pathways. [Alzohairy,2016 ; Rahmani et al.,2014]

Flavonoids and other compounds found in neem are crucial in the control of the growth of cancer. Numerous epidemiological studies have suggested a link between increased flavonoid intake and a lower risk of cancer. [Alzohairy,2016 ; Le Marchand, 2002]

Neem oil contains a variety of neem limonoids that mitigate 7,12dimethylbenz(a)anthracene's mutagenesis effects. Study results showed that treatment with nimbolide resulted in dose- and time-dependent reduction of proliferation of human choriocarcinoma (BeWo) cells with IC₅₀ values of 2.01 and 1.19 M for 7 and 24 h, respectively. Nimboide is a cytotoxic compound found in leaves and flowers. [Alzohairy,2016 ; Harish et al.,2010; H Kumar et al., 2009; Othman et al., 2012; Selvakumar et al.,2022 ; Sundarasivarao and NJ , 1977 ; Devakumar and Sukhdar,1996]

Effect of Neem on Oncogene- A mutant gene known as an oncogene is important in the initiation and development of tumours. The 500 mg/kg neem leaf extract (C500) group demonstrated a significant decrease of c-Myc oncogene expression as compared to the cancer control group in an experiment to determine the influence of leaf extract on c-Myc oncogene expression in 4T1 breast cancer BALB/c mice. [Alzohairy,2016 ; Othman, et al., 2012]

Through apoptosis, leaf extract treatment of MCF-7, HeLa, and normal cells differentially inhibits the development of cancer cells in a dose- and time-dependent way. In addition, when leaf extract and cisplatin were combined at lower doses than either medication alone, the cells' proliferation was synergistically inhibited. [Alzohairy,2016 ; Sharma et al., 2014]

It has been proven through research that nimbolide's ability to induce apoptosis caused it to have an anticancer impact. The goal of the experiment was to determine how NLE affected the development of chemical carcinogen-induced breast carcinogenesis. N-methyl-N-nitrosourea-induced mammary tumour advancement was prevented by extract administration, which was also very effective in reducing mammary tumour burden and stifling mammary tumour progression even after treatment stopped. [Elumalai et al.,2012 ; Arumugam et al., 2014]

The results of the study showed that leaf extract decreased the expression of Bcl-2 and increased the expression of Bim, caspase-8, and caspase-3 in the buccal pouch, indicating that it has apoptosis-inducing effects in the target organ. Leaf extract also caused a dose-dependent decrease in the viability of chronic lymphocytic leukaemia (CLL) cells, with significant apoptosis being seen at 0.06% (w/v) by 24 Neem's primary ingredients and isolated compounds exhibit a variety of activities that have an impact on numerous targets. They also contribute to the activation of apoptotic cell death in cancer. [Subapriya, et al., 2005 ; Chitta et al., 2014; Schumacher et al., 2011 ; Priyadarsini et al., 2010]

6. Pre-Clinical And Clinical Study Based on Neem :-

Studies based on clinical trials have shown that herbal remedies or items derived from natural ingredients are essential for the prevention and treatment of disease. Only a few research on active substances, including nimbidin, were conducted to evaluate their effectiveness in the management of health. An important investigation into the role of neem bark extract as an antisecretory and antiulcer effect in human beings was conducted using human subjects. Gastric acid output was significantly reduced (77%) after 10 days of taking the extract in lyophilized form at a dose of 30 mg twice daily.

When administered at a dose of 30 mg twice daily for six weeks, the bark extract totally healed one case of oesophageal ulcer and one case of stomach ulcer. The duodenal ulcers were virtually completely healed. [Bandyopadhyay et al., 2004]

In 50 cases of uncomplicated psoriasis receiving conventional coal tar therapy, a double-blind clinical drug trial was conducted to evaluate the efficacy of a drug containing an aqueous extract of neem leaves. The results showed that patients receiving the drug in addition to coal tar demonstrated a quicker and better response than the placebo group. [Pandey et al., 1994]

Neem extract dental gel was tested clinically for six weeks with chlorhexidine gluconate mouthwash serving as a positive control. The study's findings revealed that the dental gel with neem extract considerably reduced the plaque index and bacterial count when compared to the control group. [Pai et al., 2004]

A study found that nimbidin greatly accelerated the healing of chronic stomach ulcers caused by acetic acid in albino rats and dogs. [Pillai and Santhakumari 1984]

7. Conclusion:-

The use of allopathic medications in treatment is widespread, but while they may be rapid, they can have negative health implications. The knowledge of medicines made from natural ingredients is growing, though, and there are many additional advantages to using them. Through the modification of many cellular pathways, neem and its constituents represent a vital role in the treatment and prevention of disease in this viewpoint. This review article illustrates how neem and its active ingredient might improve overall health through their anti-oxidant, anti-inflammatory, wound healing, hepatoprotective and anti-cancerous properties. For the correct mechanism of action in health management, more research on its many constituent types is needed.

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