



Pharmacological Benefits of Neem (*Azadirachta indica*) in the light of Unani System of Medicine: A Review article

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ABSTRACT

Neem is very important medicinal plant which is used to treat different diseases in Unani System of Medicine as well as traditional system of medicine like siddha, Chinies and naturopathy since ancient. The use of traditional medicine and medicinal plants in most developing countries, as a normative basis for the maintenance of good health, has been widely observed. In the last century, approximately 130 pharmaceutical products have been discovered based on the information obtained from the traditional scientist and physician. The importance of the Neem tree has been recognized by the US National Academy of Sciences, which publish a report in 1992 entitled 'Neem- a tree for solving global problems'. The scientific name of Neem, *Azadirachta indica*, is derived from the Persian, Azad means "Free" dirakht means "tree" I-Hindi means "of Indian Origin" .Hence it literally means "the free tree of India". The Chemical principles from natural sources have become much simpler and have contributed significantly to the development of new drugs from medicinal plants and because of these facts the domain market for plant derived chemicals, pharmaceuticals, fragrances, flavor's, and color ingredients, alone exceeds several billion dollars per year. The present review highlights a Unani medicine literature as well as scientific on taxonomical, botanical, and pharmacological discussion on Neem.

Keywords: Neem, *Azadirachta indica*, Unani Medicine, Neem, Pharmacological activities of Neem.

1. INTRODUCTION

Neem is an omnipotent tree and a sacred gift of nature. Neem tree is mainly cultivated in the Indian subcontinent. Neem is a member of the mahogany family, Meliaceae. Today it is known by the botanical name *Azadirachta indica* (*A. indica*) A. Juss. Neem has been used extensively by humankind to treat various ailments before the availability of written records which recorded the beginning of history. Since prehistoric times, Neem has been used by humankind.

The latinized name of Neem, *Azadirachta indica*, is derived from the Persian. Azad means “free”; dirakht means “tree”; i-Hind means “of Indian origin”. Hence it literally means “the free tree of India”. The Neem tree is an incredible plant that has been declared the “Tree of the 21st century” by the United Nations. The US National Academy of Science published a report in 1992 entitled “Neem: A tree for solving global problems”



Fig. 1 Neem plant

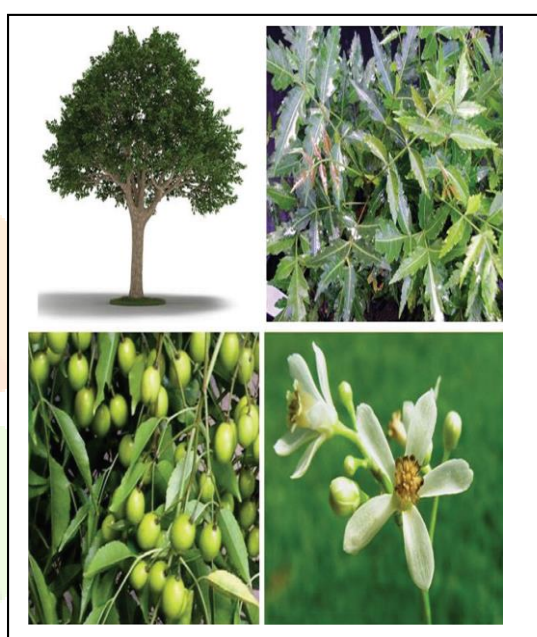


Fig. 2 Neem Fruit, Leaves, flower

Neem is a large found wild and often cultivated in India. The height of the tree is about 12 meters to 15 meters. All the part of the tree is bitter in taste. Its stem is erect and having a girth of 1.75 meters to 2.75 meters with spreading branches. Bark is dark grey and rough. Leaves are green in color, bluntly serrate and alternate. The flowers are white, having a scented odor especially at night. Its fruit is smooth, oblong and small in size and is called, Niboli. Unripe fruit is green in color and bitter in taste while the ripe fruit is yellow colored and somewhat sweetish in taste. Its four varieties viz. Ban, Bakain (Maha Neem), Bhoim Neem and Meetha Neem (Kiryapak) have been mentioned in classical literature

2. Neem in Indus valley civilization:

On the Indian subcontinent, the Neem tree has been used for more than 4500 years. The earliest documentation of Neem mentioned the fruit, seeds, oil, leaves, roots and bark for their advantageous medicinal properties. The first recorded indication that Neem was being used in the medical treatment was about 4500 years ago. This was the high point of the Indian Harappa culture, one of the great

civilizations in the ancient world. There is evidence found from excavations at Harappa and Mohenjo-Daro in Northwestern and Western India, in which several therapeutic compounds including Neem leaves, were gathered in the ruins.

In 1922, British archaeologists began to excavate the sites of Harappa and Mohenjo-Daro. They uncovered the remains of long-forgotten cities. British archaeologists discovered the 5 000 year-old Indus Valley civilization. They were amazed to discover two cities - Mohenjo-Daro and Harappa. These cities were so advanced that they could practically compete with cities today in areas of architecture, engineering and construction. The streets were designed in a grid system that was well planned and organized. There was an underground sewer system with stone manhole covers for access. A sophisticated water supply and drainage system with waterproof brickwork ran throughout the city. The houses were spacious in the upper class sections containing modern amenities like lavatory facilities. They also found skulls upon which cranial surgery had been performed, and clay pots, which contained medicinal herbs. One of the most prominent medicinal herbs they found was *A. indica*, which is also known as Neem. It shows the first evidence of an advanced medical system that includes both surgery and phyto pharmacology in one of the world's most ancient and developed civilizations.

2. Distribution of Neem.

At the beginning of this century, the Neem tree was still highly esteemed by Indian emigrants who took it along to the places where they settled. Thus, the Neem tree was introduced in places such as Australia, East and sub-Saharan Africa, South East Asia, and South America. Today, the Neem is well established in at least 30 countries worldwide, in Asia, Africa and Central and South America. Some small scale plantations are also reportedly successful in Europe and United States of America. Neem trees are fast growers, and in three years may grow to 20 feet in height from seed planting. It will grow where rainfall is only 18 inches per year and it thrives in areas of extreme heat up to 120 degrees. It is estimated that a Neem tree has a productive life span of 150 - 200 years. It is estimated that there are around 18 million Neem trees in India. Neem tree is found all over in Malaysia. In 1995, the researcher of Chinese Academy of Forestry introduced the Neem in India to the hot river valley areas in Yunnan and the Neem grows well there. The research group has introduced the Neem from South Asia, Southeast Asia and Africa to China since 1997. In 1998, the demonstration of industrial Neem planting was started out in China. Because of the advantages on climate and terrain, the Neem planting was popularized and promoted in Yunnan rapidly. Yunnan has had the largest area of Neem plantation. Chinese Academy of Forestry plays an important role in cultivating technology of Neem. In the last two decades, research on Neem has been intensified and many of the agricultural and medical properties of Neem were rediscovered. Today, Neem plays a major role in the rural industry of India, and projects for the commercial use of Neem have been successfully introduced in the places like Kenya. Earlier this century, people somehow managed to introduce this Indian tree to West Africa, where it has since grown well. They probably expected Neem to be useful only as a source of shade and medicinal especially for malaria. Africa considers Neem as a green gold. In

Senegal, Neem tree is known as the “Independence Tree”. The world's largest Neem plantations are 10 sq km in the plains of Arafat, Saudi Arabia. A Saudi philanthropist planted 50 000 Neem trees to shade and comforts the two million pilgrims. In the last decade, Neem has been introduced into the Caribbean, where it is being used to help reforest several nations. Neem is already a major tree species in Haiti.



Fig. 3 Health Benefits of Neem



Fig. 4 Benefits of Neem plant

4. FAAL (Pharmacological Actions)

Various Pharmacological action described in Unani Classical literature are as follows,

Nafe jaroooh wa qurooh (Useful in burns and wounds) , Nafe falij and laqwa (Useful in paralysis and hemiplegia) , Nafe istisqa (Useful in Dropsy), Nafe wajaul mufasil (Anti rheumatic) , Nafe darde gosh (Useful in ear ache), Rade (Repellent) Dafe humma (Antipyretic), Dafe yarqaan (Useful in Jaundice, Dafe tafffun (Antiseptic), Hazim (Digestive), Habise ishaal (Antidiarrheal) , Kasire riyah (Anti flatulent) , Munzij (Concoctive) ,Musakkine alam (Analgesic) Nafe amrazz jild (Skin Diseases) Mundamile Qurooh (Cicatrizant) Musakkine atash (Thirst quenching) , Muqavvi snan wa lissa (Teeth and gum tonic) , Muqavvi basar (Eye tonic) Musakkine suaal (Antitussive) Mudire Haiz (Emmanagogue) , Musakkine Suda (Headache Reliever) , Mane nazool (Anti hydrotic), Nafe zibetus (Anti Diabetic) , Nafe zeequnafas (Useful in asthma)

5. AFAAL OF NEEM GUM

The bark exudes, a clear, bright, amber colored gum, known as the East Indian gum which blackens with age. It forms into small tears or vermiform pieces, and the surface is cracked or fissured. The tears are soluble in cold water and are non- bitter. The tears in the drier areas produce the gum very freely. In wet climate, the gum is liable to be washed away or spoiled before collection.

Neem gum is mentioned as Muqavvi (Tonic), Muharrik (Stimulant), Muzliq (Demulcent) and Mana-e-Nazla (Anti catarrhal).

6. CHEMISTRY OF NEEM GUM

Analysis of gum gave moisture 13.8%, and ash 3.0%. Purification of gum with alcohol gave a non-reducing gum having $[\alpha]_D^{21.5} -70.6^0$. On hydrolysis it yielded L-Arabinose, L-fructose, D-galactose and D-glucouronic acid. The aldouronic acid component of the gum, obtained by graded hydrolysis, was found to be 4-O- (D-glucopyranosyl uronic acid) -D-galactopranose. The presence of D-glucosamine is also reported in the gum. Almost every part of the tree has long been used in folklore and traditional systems of medicine for the treatment of a variety of human ailments, particularly against diseases of bacterial and fungal origin. Nimbidin is anti- arthritic and anti-inflammatory in its action and possesses significant antiulcer potential whereas various other fraction have antipyretic and anti-inflammatory and antitumor properties. The extracts and various factors derived from Neem also possess diverse biological effects on insects such as repellency, phagodeterrence, reduced growth, abnormal development and reduced oviposition. An antineoplastic drug has also been obtained from the bark of bark plant.

8. Pharmacological effect of various Neem plant parts.

Abortive effect: Seed and leaf extract

Analgesic effect: Leaves

Anti-dermatophytic effect: Leaves

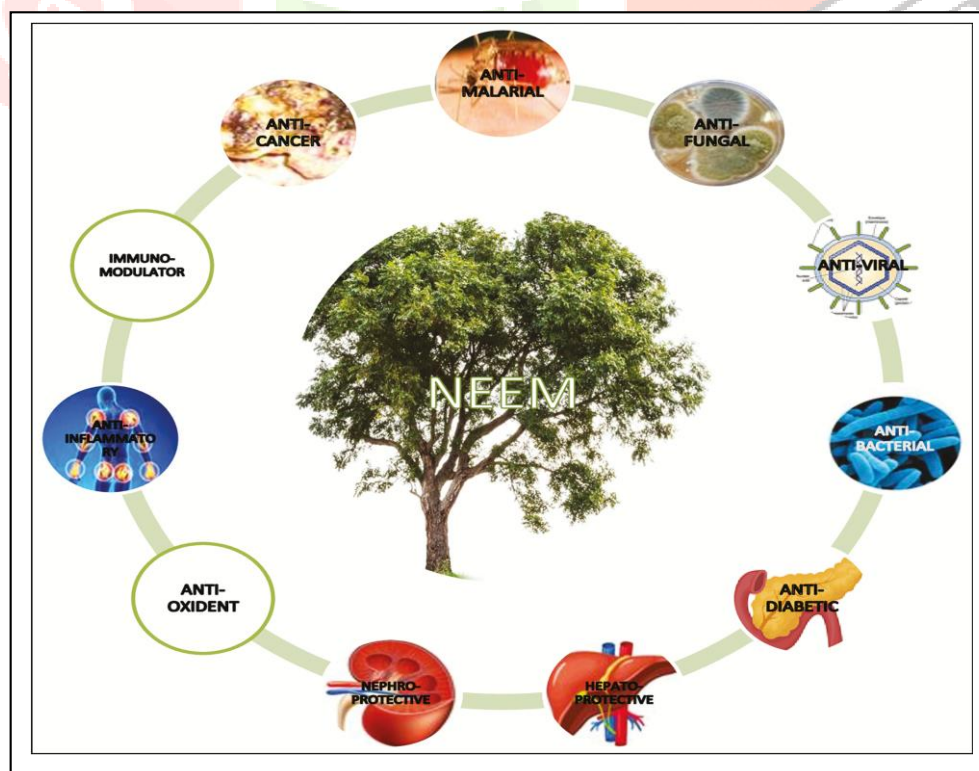


Fig. 5 various pharmacological activities of Neem plant

Antifertility effect: Neem oil

Anti-inflammatory effect: Leaves

Gastric antiulcer effect: Leaves

Hypotensive effect: Leaves

Immuno modulatory effect: Stem bark

Larvicidal effect: Isolated hydrocarbon fraction from dried leaves

Metabolic effect: Seed

Neuropsychopharmacological effect: Leaves

Toxic effect: Neem oil

9. MIQDARE KHORAK (Dose)

The doses described for Neem's different parts by various Unani physicians are as follows:

- A. 3-6 gm (leaves decoction)
- B. 2-4 Tola (Arq of root)
- C. 8-10 gm (Arq of bark)
- D. 9-6 gm. (Leaves Decoction)
- E. 1 Misqal (Fruit)
- F. 2-4 Tola (Whole plant Arq)

MUZIR (Adverse Effect):Neem has adverse effect on the dry Mizaj (temperament) people.

MUSLEH (Corrective): Shahad (Honey), Filfil Siyah (Piper nigrum) and Roghaniyat are the drugs recommended as corrective (Musleh) for Possible side effects caused by Neem

10. Various Pharmacological Activities of Neem.

A. Antioxidant activity of Neem.

Different parts of Neem plants such as leaf, bark, root, seed, and flowers show role in disease management through modulation of various biological activities. 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. In another study, ethanolic extracts of flowers and seed oil were also found to have better free radical-scavenging action. In a comparative study, it was also noticed that the bark possessed complex phenolic contents than leaves with higher antioxidant activity. The methanolic extract of the roots for the estimation of different flavonoids and their free radical-scavenging properties have also been evaluated. 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.

B. Hypoglycemic activity of Neem.

The seed oil possesses active constituents capable of lowering blood glucose in both norm and hyperglycemic animals. The aqueous extract of the leaves produced some hypoglycemia in normal and diabetic rats. Effect of water soluble alcoholic extract of *A. Indica* leaves on isolated tissue preparation were studied with a view to find out the possible mechanism of its reported anti-hyperglycemic effect. Neem oil produced a significant blood glucose lowering activity in normal as well as alloxan induced diabetic rats after 3h and 6h. The decrease in blood glucose level was more pronounced in hyperglycemic rats.

The Neem tree extract has also been evaluated for its anti-diabetic 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. 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. 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.

C.



Fig. 6 Neem plant used in skin infection

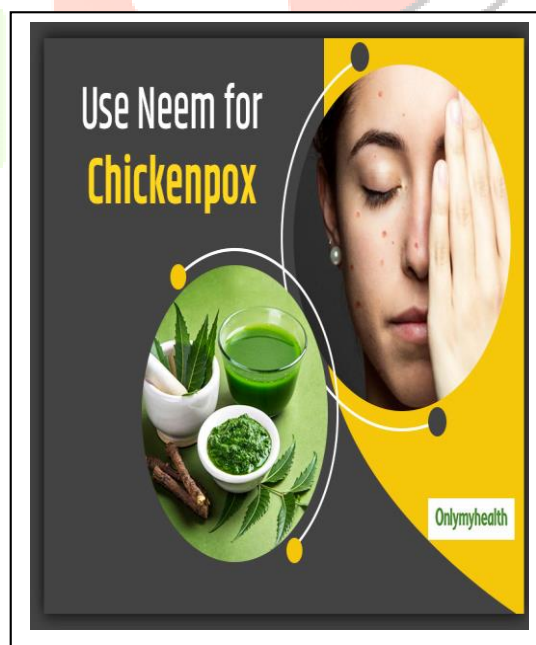


Fig. 7 Neem plant for chickenpox

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. 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. 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.

D. 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. 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.

E. Hepato protective activity of Neem.

The hepato protective 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. Hepato protective 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. Another finding concluded that aqueous leaf extract of Neem prevents and reverses the

hepatotoxic damage caused by anti-tubercular drugs, and this reversal is better to that effected by withdrawal of anti-tubercular drugs.



Fig. 8 Neem Oil

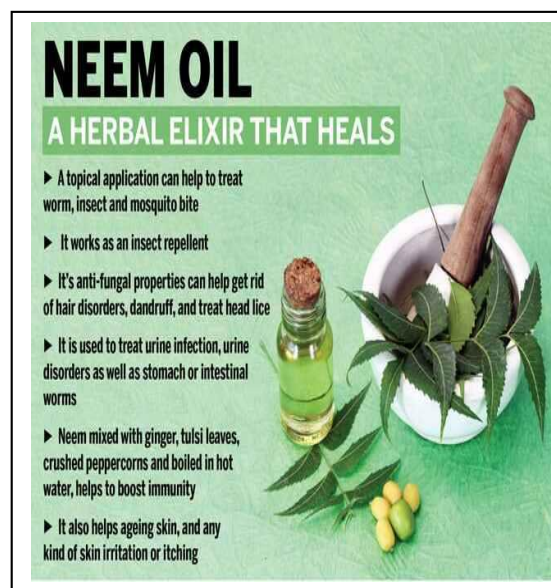


Fig. 9 Benefits of Neem oil

F. Neuro-protective activity of Neem.

The neuro-protective 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. 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 medicinal plants, NLE has also been checked to study its neuro protective effects and it has shown quite efficient reversible effects of cisplatin.

G. Nephro protective activity of Neem.

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. Immunomodulatory effect Neem oil is also used as a nonspecific immune-stimulant as it plays a role in the activation of cell-mediated immune mechanisms to elicit an enhanced response to subsequent mitogens. 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.

H. Antifertility activity of Neem.

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. This, intra-vas administration of Neem oil resulted in a block of spermatogenesis without affecting testosterone production.

I. 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. 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.



Fig. 10 Neem and Honey



Fig. 11 Neem plant Honey

J. Cardio protective activity of Neem.

As a folk medicine, the Neem tree extract is well known for its cardio-protective 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 histo-pathological parameters. The study further concluded that Neem extract shows equipotent cardio protective activities as compared to Vitamin E.

K. Antimicrobial activity of Neem.

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. 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. 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. The effects of the Neem limonoids such as azadirachtin, salannin, deacetylgedunin, gedunin, 17-hydroxyazadiradione, and de acetylnimbin 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. Antiviral activity of Neem bark extract confirmed that bark extract extensively blocked HSV-1 entry into cells at 50–100 µg/ml concentration. 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 anti-candidal agents.

L. Anti-cancer activity of Neem.

Natural products or products of plants show a pivotal role in the inhibition of tumor growth through modulation of cell signaling pathways. The superior medicinal properties of Neem tree were further validated as it was found to possess anti cancerous 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. 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. 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. 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. With the evidence of data, it is demonstrated that nimbolide showed anticancer effect through its apoptosis-inducing property. 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. 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.

CONCLUSION

The parts (Green Leaves, Ripe fruits and its coat, Neem seed, Root, Bark, Uncrushed twigs, Stem bark, Root bark, Fresh whole fruit and Dry leaves) of *Azadirachta indica* (Neem) have been in use since times immemorial to treat the wide range of disease. It has been subjected to somewhat extensive phytochemical, experimental and clinical investigations. Experimental studies have demonstrated its anti-fungal, anti-aging, antibacterial, Anti-diabetic, Abortive effect, antihypertensive, anti-inflammatory, antioxidant, antispasmodic, antitussive, reflux esophagitis, Anti-dermatophytic effect, Cardiac stimulant, hypnotic, Larvicidal and respiratory system. It has no toxic effect on vital organs. The scientific studies have proved most of the claims of traditional medicines. However, further, detailed clinical research appears valuable to explore the full therapeutic potential of this plant in order to establish it as a standard drug. Looking upon wide prospects and potential of Neem for various purposes, it is worthwhile to cultivate the plant at large scale. This will help in financial upliftment of poor and landless farmers.

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