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Azadirachta: Biodiversity and its Impact on Health

Dev Dutt Patel, Nisha Bilkhiwal, Ronit Parashar, Shivani Jangeer, Garima Sharma, Priyadarshi Meena; Mahesh Kumar Meena and Ritu Kamal Yadav

Department of Zoology, University of Rajasthan, Jaipur - 302004 (India)
*Corresponding author: monarajkamal@gmail.com

Abstract

Azadirachta is a genus from family Meliaceae; several plants from this genus found throughout the world including neem, Indian lilac, pride of India, chinaberry tree, bead-tree, Cape lilac, syringa berry tree, Persian lilac, and white cedar. It flourishes extensively in desert, tropical, and subtropical regions of the world. The plant parts such as leaf, blossom, seed, bark, and root all contain a variety of medicinal bioactive compounds like Azadirachtin, Catechin, Cyclic Trisulphide, Cyclic Tetrasulfide, Isomargolonone, Gedunin, Gallic acid, Nimbin, Nimbidin, Nimbolide, NB-II peptidoglycan, Mehmoodin, Margolone, Margolonone, Polysaccharides GIA, Polysaccharides GIB, Polysaccharides GIIA, Polysaccharides GIIIA, Polysaccharides, Sodiumnimbidate and Salanin. These phytoconstituents have been shown various biomedical applications like Antioxidant, Anticancer, Anti-inflammatory, Antidiabetic, Antimicrobial, Antimalarial, Anti-nephrotoxicity, Growth-promoting and immunomodulatory effects, hepatoprotective activity and neuroprotective effects. The current review will provide a brief summary of the global biodiversity, importance, and medicinal potentials of genus *Azadiracta*.

Key words : Alkaloids, Antimicrobial, Anti-oxidant, Azadiracta, Azadirachtin, Nimbin, Radioprotector.

Ethnomedicine has historically used chemicals and plant materials to treat a number of diseases. These environmental changes are causing a wide range of ailments in humans that are linked to their way of life. Restoring our ecology, reviving the flora, and renewing mother earth are therefore urgently needed. Humans have a keen sense of place, and they are among the first animals to cherish vegetation. We are becoming less and less able to conserve plants using our own knowledge and wisdom as each century goes by. The flora that surrounds us is incredibly varied and has a myriad of medicinal and therapeutic properties. *Azadirachta*, which belongs to the Meliaceae family, is one of the most well-known genera of medicinal plants among the numerous ones that are immediately accessible. Many other vernacular names have been used to refer to *Azadirachta,* including

nimba, nimbou, and arishtha in Sanskrit, nimb and Neem in Hindi, and Indian lilac in English (Table-1).

Taxonomic Classification[37]

Kingdom : Plantae
Division : Magnoliophyta
Order : Rutales
Suborder : Rutinae
Family : Meliaceae
Subfamily : Melioideae
Tribe : Melieae
Genus : Azadirachta

Fig. 1. *Azadirachta indica*

Table-1. *Azadirachta's* vernacular names in other languages[19]

English	Neem, Indian lilac
French	Azadira d'Inde, margousier, azidarac, azadira
Portuguese	Margosa (Goa)
Spanish	Margosa, Nim
German	Niembaum
Hindi	Neem, Nimb
Burmese	Tamar, Tamarkha
Urdu	Nim, neem
Punjabi	Neem
Tamil	Vembu, Veppan
Sanskrit	Nimba, Nimbou, Arishtha (reliever of sickness)
Sindi	Nimmi
Sri Lanka	Kohomba
Farsi	Azad Darakht-i-Hindi (free tree of India), nib
Malay	Veppa
Singapore	Kohumba, Nimba
Indonesia	Mindi
Nigeria	Dongoyaro
Kiswahili	Mwarubaini (muarobaini)

Plant profile :

The tropical evergreen *Azadirachta indica* A. Juss, commonly known as Neem (Fig. 1), is a native of the Indian subcontinent. Neem has been used for thousands of years in both agriculture and medicine to treat several common human diseases. Nearly all of *A. indica's* various parts, including the bark, flowers, fruits, gum, leaves, roots, seeds and stem have been used as conventional home remedies for human illnesses. Millions of people all over the world also use Neem twigs as chewing sticks for oral hygiene. Researchers in medical sciences and infectious disease have recently begun to pay more attention to the Neem tree as a potential source of therapy for infectious diseases in addition to the uses of *A. indic*a in the domains of oncology, dentistry, dermatology, and endocrinology, among others[44].

Trunk/bark :

The trunk is uncurved. Even in young trees, Neem bark is hard, scratchy, scaly, and fissured. Although older trees can be light or greyish-black, it is often brown.

Branches/twigs :

The spreading branches of this tree can create circular crowns that are up to 20 meters across. It's a great tree for providing shade. Neem usually grows to a height of 15 to 20 meters, although it can occasionally reach 35 to 40 meters.

Leaves/needles :

In contrast, the simple pinnate leaves are 20–40 cm long and include 20–30 medium–dark green leaflets that are 3–8 cm long. Petioles of the leaves are brief. The colour of young leaves ranges from reddish to purplish. The leaf edges have teeth.

Flowers :

The white and fragrant Neem blooms appear where the stem and petiole meet. They typically grow in panicles, which are up to 25 cm long clusters of drooping flowers. Between 150 and 250 blooms are seen in these spreading inflorescences. A single blossom is between 5 and 6 mm long and 8 and 11 mm broad. The axillary clusters of the tiny, white, bisexual flowers are produced. They smell like honey and draw a lot of bees.

Fruit :

The fruit is a smooth, drupe-like olive that can be almost spherical or elongate oval in shape. They can range in size from 1.5 to 3 cm by 1 to 1.5 cm when fully ripe. When ripe, the thin fruit skin becomes yellow. The pulp is highly fibrous and yellowish-white with a bitter-sweet flavour. One, rarely two or three, elongated seeds are enclosed in the white, hard inner shell of the fruit. Neem trees typically start producing fruit after 3-5 years, reach peak productivity in 10 years, and then continue to do so for up to 50 kg of fruit per year. It might survive for more than 200 years.

Edible elements :

Each part of the plant—fruit, leaves, flowers, and sap—are edible. The young leaves of plants are cooked and eaten in several regions of Asia. According to '*Plants*

For A Future' (PFAF) leaves can be eaten raw or cooked with other vegetables. Flowers are used as flavouring agents. Fully ripe fruit pulp is consumed fresh, cooked, and in beverages. The refined oil from the seeds can be used in cooking. The most popular Neem product, derived from the fruit's seed kernels, is Neem oil.

Habitat :

Neem prefers disturbed natural vegetation, such as open forests, grasslands, floodplains, riparian zones, and coastal locations. It can grow in both full sun and partial shade. It can withstand drought and favours dry or moist soil. It cannot endure being submerged in water or frigid weather. Neem has become a native plant in several South and Central American nations as well as northern Australia, Southeast Asia, sections of Africa, Fiji, Mauritius, Puerto Rico, and the Caribbean[29].

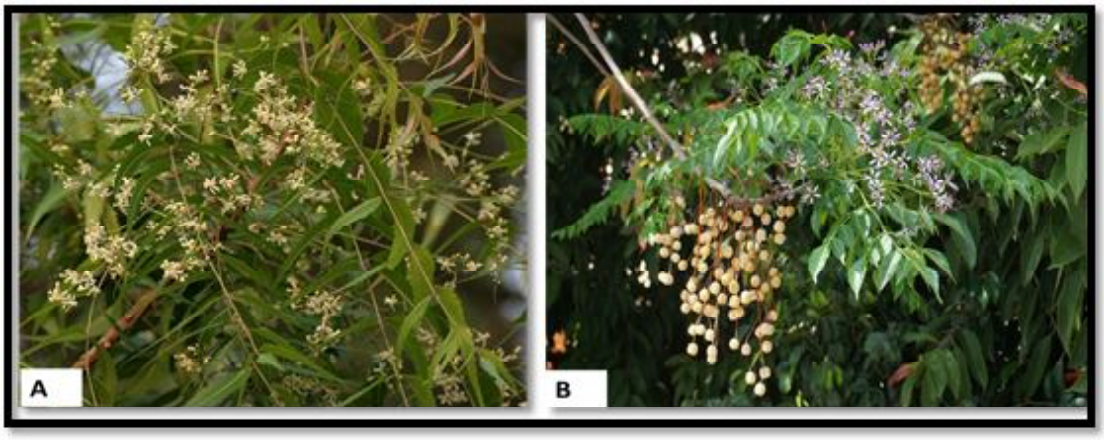
Propagation and growth :

The tree may easily reproduce both sexually and vegetatively. Tissue culture, seeds, seedlings, saplings, or root suckers can all be used to plant it. It is usually cultivated from seeds and either planted directly on the spot or transplanted as seedlings from a nursery. The seeds can be prepared rather easily. The fruit naturally falls from the trees; the pulp can be removed with a rough surface when wet; and the clean, white seeds are retrieved (after being carefully rinsed with water). Because the fruit bats and birds in some nations, including Togo and Senegal, devour the delectable pulp and spit out the seeds beneath the trees, people leave the cleaning to them. According to legend, Neem seeds don't last very long. The general belief is that they will stop growing after two to six months of storage. Recent studies on seeds stored in France, however, revealed that after more than five years, seeds lacking an endocarp still exhibited a good rate of germination (*i.e.,* 42%).

In the lowland tropical regions, the tree is believed to grow "nearly everywhere." However, it often works best in regions with 400–1,200 mm of annual rainfall. It thrives in the hottest environments, where the maximum shade temperature can reach over 50°C, but it cannot tolerate prolonged frigid temperatures. It thrives at altitudes between sea level and perhaps 1,000 m close to the equator. At least in early examples, the taproot can grow twice as tall as the tree.

On arid, barren terrain, Neem is recognized for its ability to thrive well. Where soils are barren, stony, and shallow or where there is a hardpan close to the surface, it performs better than most trees. On some acidic soils, the tree can also thrive. Neem leaves that have fallen, which have a pH of 8.2, are thought to be beneficial for balancing acidity in the soil. Neem, on the other hand, cannot tolerate "wet feet" and will perish if the area becomes flooded.

Neem frequently grows quickly. Within approximately 5-7 years, it can be harvested for timber. After an 8-year cycle, the highest reported yields from northern Nigeria (Samara) totalled 169 m^3 of fuelwood per hectare. Between 108 and 137 m^3 per hectare in yields were observed in Ghana during the same period. Rarely do weeds hinder



A. *Azedirachta indica* A. Juss. **B.** *Melia azedarach*

Fig. 2. Species of genus *Azadiracta*

growth. Except for extremely immature plants, Neem can outcompete practically all rivals. In fact, because birds, bats, and baboons transport the seeds, the trees themselves may turn into "weeds" and proliferate widely in suitable site conditions. The spontaneous regrowth under old trees is frequently abundant for the same reason. Despite all of that, Neem is often regarded as a blessing rather than a curse wherever it grows. Almost usually, people enjoy seeing new Neem trees sprout up.

Geographical distribution :

For more than 2000 years, *A. indica* has been used as a versatile medicinal plant with a wide variety of biological activity, including antibacterial properties, throughout India and its neighbouring nations[25]. Neem is a plant with Indian origins that is now widespread in desert, tropical, and subtropical areas of the world. It primarily grows in the southern Terai region of Nepal[25]. All around the southern United States and Hawaii, there are *Melia azedarach* plants, often known as chinaberry trees, China trees, Texas umbrella trees, or white cedar trees (Fig. 2). One kind of *M. azedarach* that grows locally in China is recognized by botanists as a distinct species[32].

Neem is thought to have originated in Assam and Burma (where it is common throughout the central dry zone and the Siwalik hills). Neem is thought to have originated in the arid woods of South and Southeast Asia, including Pakistan, Sri Lanka, Thailand, Malaysia, and Indonesia. Other people assert that Neem is native to the entire Indian subcontinent. India is where the tree is most widely used. It is grown in tropical to subtropical climates, semiarid to wet tropical regions, and at elevations ranging from sea level to around 700 m, from the southernmost tip of Kerala to the Himalayan Mountains.

Africa first encountered Neem early this century. At least 30 countries already have it well established, particularly those that are located close to the southern edge of the

Sahara where it has grown to be a substantial source of fuel and lumber. Although it has been widely naturalized, it has never become an issue. Over the past century or so, the tree has also grown to be established in Fiji, Mauritius, the Caribbean, and a number of Central and South American countries. In certain cases, indentured servants who remembered its advantages from their time spent living in Indian communities may have contributed to its popularization. It has previously been introduced by foresters. Small plants are doing well in southern Florida on the continent of the United States, while research plots have been set up in southern California and Arizona. It is now grown in the more arid subtropical and tropical zones of Southeast Asia, Africa, the Americas, Australia, and the South Pacific Islands[16].

Bioactive compounds present in Genus Azadirachta :

Azadirachta indica has a wide variety of bioactive substances, some of which have medicinal potential. Triterpenes (nimbin, nimbolide, azadirachtin, and gedunin) of *Azadiracta* are the most therapeutically useful[37]. Nimbin has antipyretic, fungicidal, antihistamine, antiseptic effects, anti-inflammatory and antioxidant properties that limit the creation of reactive oxygen species and lessen damage. Flavonoids, which act as prostaglandin biosynthesis inhibitors, endoperoxides, and inflammatory enzymes such protein kinases and phosphodiesterases are also present in neem.

The leaf extracts using up to five different extraction techniques, including hexane, ethyl-acetate, chloroform, butanol, and methanol, and is demonstrated to function as antibacterial and insecticide agents. Azadirachtin, a complex tetranortriterpenoid limonoid found in Neem seeds and a major component, is what causes Neem's harmful effects on insects.

Tetranortriterpenes (resins) from the *Melia azedarach* (commonly known as chinaberry tree), which are enterotoxic and neurotoxic, have been designated as meliatoxins A1, A2, B1, and B2. Toosendanin, the most significant component of the semi-redefined bark of *M. azedarach*, which can be found at quantities as high as 0.5%, has been sold as a natural pesticide, and fruit formulations exhibit insecticidal capabilities, often on par with Neem[4]. Salannin, meliacarpins, and an equivalent of volkensin are just a few of the bioactive limonoids that have been found in the seeds of this tree. Several toosendanin analogues, which are all insect antifeedants, are present in the extract[36].

Biomedical Applications of Azadirachta Phytoconstituents :

Neem *(Azadirachta indica)* has medicinal implications for the prevention and treatment of illnesses. However, the precise molecular mechanism in pathogenesis prevention is not well understood. All components of the Neem tree, including the leaves, blossoms, seeds, fruits, roots, and bark, have historically been used to treat inflammation, infections, fever, skin conditions, and dental issues[43]. The abundance of antioxidants and other beneficial active chemicals found in *Azadirachta indica*, including azadirachtin, nimbin, nimbidin, nimbidol, nimbolinin, quercetin and salannin are thought to play a therapeutic effect (Fig. 3).

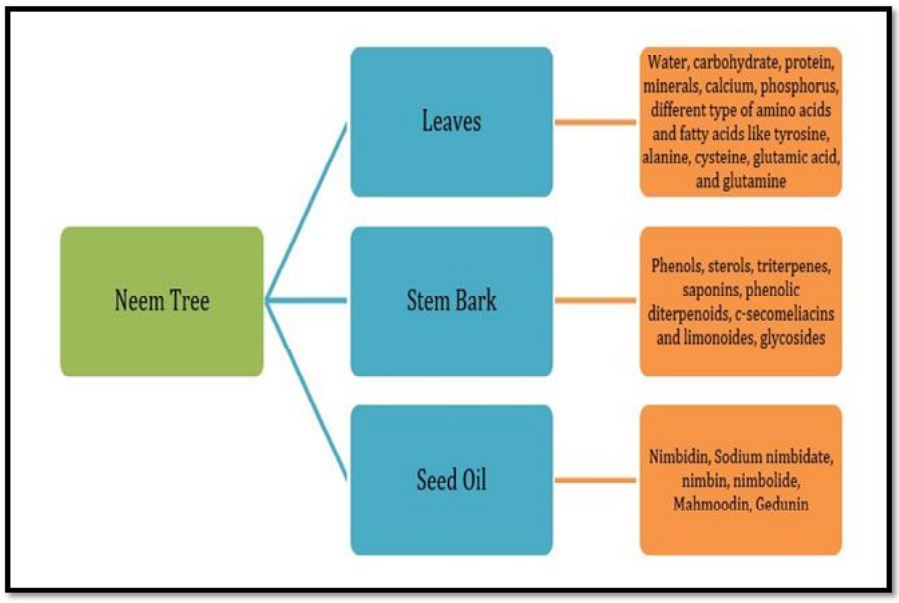


Fig. 3. Schematic description of major bioactive compounds yield from different parts of Neem.

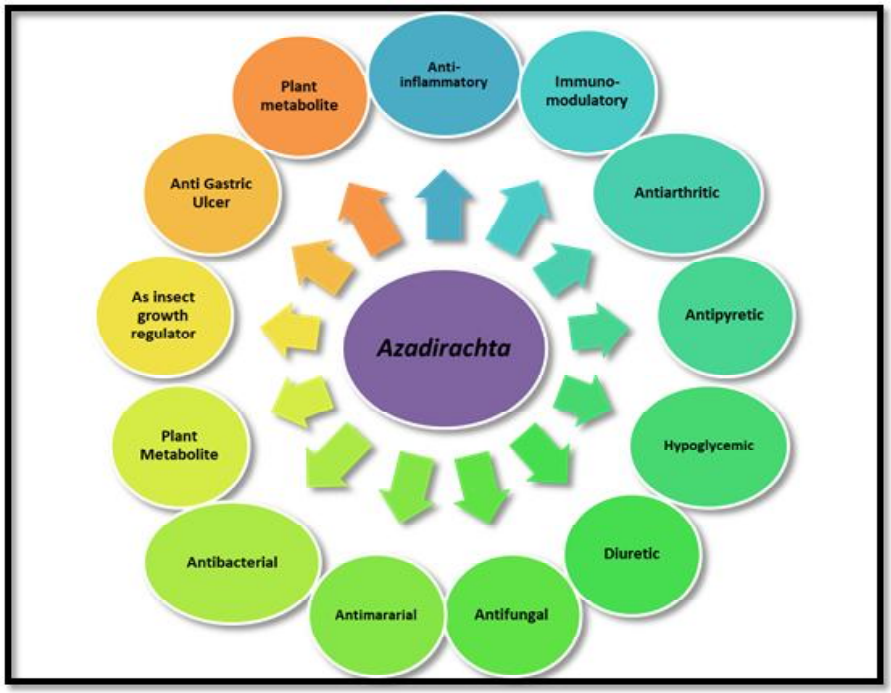
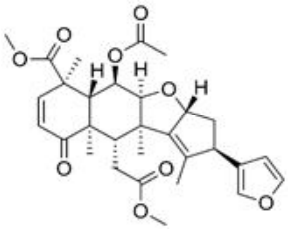
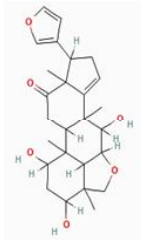
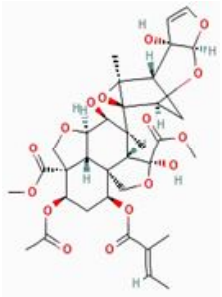
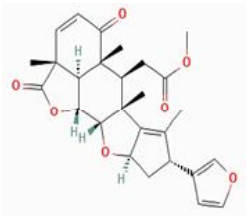
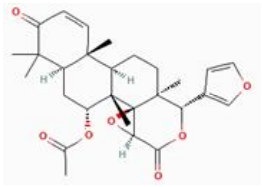
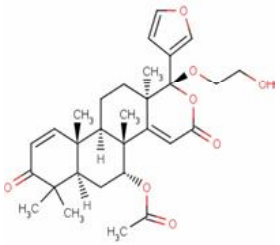
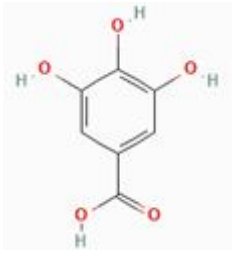
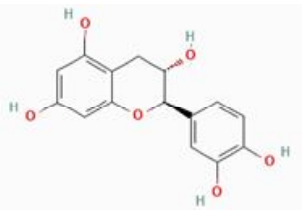
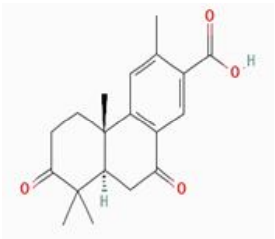
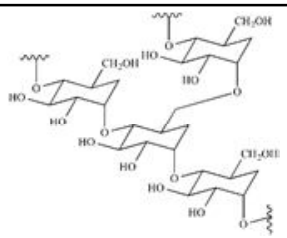
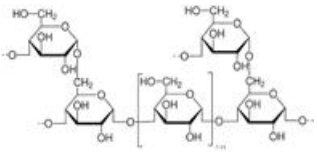
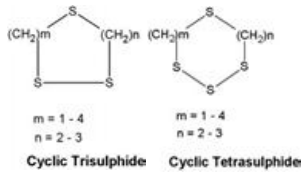
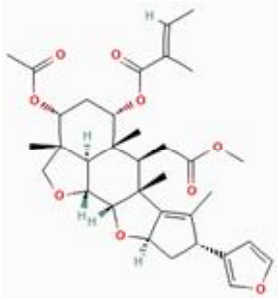


Fig. 4. Schematic description of major biomedical applications of *Azadiracta* tree.

Table-2. *Azadirachta* genus's main bioactive components and their applications[16]

Bioactive Compounds	Source	Molecular Formula	Chemical Structure	Biological Activity
Nimbin	Seed oil	$C_{30}H_{36}O_9$		Spermicidal
Nimbidinin		$C_{26}H_{34}O_6$		Anti-inflammatory, Anti-arthritic, Antipyretic, Hypo-glycaemic, Anti-gastric ulcer, Spermicidal, Antifungal, Antibacterial, Diuretic
Azadirachtin		$C_{35}H_{44}O_{16}$		Antimalarial
Sodium nimbidate		-	NA	Anti-inflammatory
Nimbolide		$C_{27}H_{30}O_7$		Antibacterial, Antimalarial
Gedunin		$C_{28}H_{34}O_7$		Antifungal, Antimalarial

Mehmoodin	Bark	$C_{30}H_{38}O_8$		Antibacterial
Gallic acid		$C_7H_6O_5$		Anti-inflammatory, Immunomodulatory
Catechin		$C_{15}H_{14}O_6$		Anti-inflammatory, Immunomodulatory
Margolonone (Isomers: Margolone, Isomargol-onone)		$C_{19}H_{22}O_4$		Antibacterial
Polysaccha-rides GIA, GIB		-		Anti-inflammatory
Polysacch-arides GIIA, GIIIA		-		Anti-inflammatory

NB-II peptidoglucan		-	NA	Immuno-modulatory
Cyclic Trisulphide and Cyclic Tetrasulfide	Leaf	-		Antifungal
Polysaccharides		-	NA	Anti-inflammatory
Salannin	Seeds	$C_{34}H_{44}O_9$		As an insect growth regulator, An antifeedant and a plant metabolite.

*NA –Not Available

Numerous studies have proven that Neem extracts have the ability to scavenge free radicals and lessen ROS-mediated cell damage[37]. Additionally, it is employed in the production of soap and as a remedy for several skin conditions. It contains a wealth of bioactive substances in every portion that have been traditionally used to cure a variety of conditions including infectious disorders. Various Neem tree parts have been utilized in traditional Indian medicine for millennia due to their purported antacid, antibacterial, anticancer, antidiabetic, anti-dermatitis, antifungal, anti-inflammatory, antioxidant, antiparasitic, antipyretic, antiviral, contraceptive, dental and other properties.

Antioxidant activity :

Free radicals or reactive oxygen species are one of the main factors that contribute to the development of many diseases. Yet, neutralizing free radical activity is one of the essential steps in disease prevention[3]. Moreover, antioxidants have a role in the activation of antioxidant enzymes that help control the harm caused by free radicals and reactive oxygen species. Antioxidants stabilize and neutralize free radicals, often before they attack targets in biological cells. Plant parts like fruits, seeds, oil, leaves, bark, and roots have a key role in the prevention of disease due to their abundance in antioxidants. Since leaf and bark extracts/fractions of Neem growing in the foothills exhibit significant antioxidant features, the antioxidant activity of *A. indica* leaf and bark extracts has been studied.

The following are the results of a useful study that was conducted to assess the in vitro antioxidant activity in various crude extracts of *Azadirachta indica* leaves and the antioxidant capacity of various crude extracts: methanol extract > hexane extract > ethyl acetate extract > chloroform extract. The new discovery showed that Neem's crude chloroform extracts could be employed as a natural antioxidant.

Higher levels of free radical scavenging activity were found in the leaves, fruits, flowers, and stem bark extracts of the Siamese Neem tree, with 50% scavenging activity at 26.5, 27.9, and 30.6 µ/mL, respectively[16]. Methanolic leaf extract was tested on rats as a pre-treatment for 7 days at 100-200 mg/kg using a model of inflicted intestinal ischemic-reperfusion injury (IIRI), contrasting the extract to untreated and vitamin C (a recognized antioxidant) treated animals. Extracellular regulated kinase (ERK1/2) expression was decreased in IIRI rats, although numerous inflammatory indicators, such as myeloperoxidase in the serum, were decreased in the extract group. Nitric oxide levels remained constant for non-IIRI (control 0.036 mol/l, extract 0.034 mol/l, and vitamin C 0.042 mol/l), while they decreased for IIRI (0.025 mol/l)[31]. Additionally, the extract group elevated GSH levels, which led to the restoration of glucose-6-phosphate dehydrogenase (G6PD)[17].

Anticancer activity :

The plants and their constituents have the ability to prevent the formation of cancerous cells by altering cellular proliferation, apoptosis, the tumour suppressor gene, and a number of other biochemical pathways. Flavonoids and other compounds found in Neem are crucial in the prevention of cancer growth[46]. Neem oil contains a variety of Neem limonoids, which stop 7,12-dimethylbenz (a) anthracene's ability to cause mutations. The development of human choriocarcinoma (BeWo) cells was similarly inhibited by nimbolide treatment, with IC_{50} values of 2.01 and 1.19 M f or 7 and 24 hours, respectively. The limonoids, azadirachtin, and nimbolide suppressed tumour invasion and angiogenesis, which demonstrated their potential as chemopreventive agents. They also prevented the activation of procarcinogens and oxidative DNA damage[35].

Azadirachta indica and its active ingredients are essential in halting the growth and spread of cancer. It is unclear exactly how the molecules in this view function. The component of *A. indica* modulates various cell signalling pathways which inactivate several cancer-related genes like VEGF, NF-B, and PI3K/Akt while activating tumour suppressor genes. Additionally, it stimulates apoptosis, inhibits NF-B signalling, and activates the cyclooxygenase pathway[47]. In hamester model of buccal carcinogenesis, Neem component such azadirachtin, nimbolide, and limonoid concentrate extracts regulate development, apoptosis, and even chemoprotection as well as provided benefits of the NF- pathway's inhibition[17].

Anti-inflammatory :

The component of Neem Limonoid is an inhibitor of the generation of inflammatory mediators. Limonoids are furan lactones that are also recognised as pain analgesics because

they increase the activation of endogenous opioid pathways. The limonoid can reduce edoema and the formation of fibrovascular tissue, with particular inhibition of important inflammatory molecules such tumour necrosis factor alpha (TNF-alpha) and interleukins in damaged rat paws at dosage of 120 mg/kg[41]. Most of the research shows an intriguing correlation between anti-inflammatory effects and anti-cancerous substances.

Epoxy-azadiradione is another intriguing compound that inhibits the release of proinflammatory cytokines including IL-1α, IL-6β, and TNF-α, which gives it anti-inflammatory capabilities and the potential to be cytotoxic in a number of diseases. It controls the tautomeric activity of the macrophage migratory inhibitory factor and the translocation of NF-kβ[2,38].

Triterpenes were also identified in Neem oil as an anti-inflammatory effect. *A. indica* leaf extract demonstrated considerable anti-inflammatory effect in a cotton pellet granuloma assay in rats when administered at a dose of 200 mg/kg, orally[11]. The bark also had immunomodulatory and anti-inflammatory effects, whereas oil seeds had antipyretic and anti-inflammatory properties. Neem seed oil has dose-dependent analgesic activity and significantly reduced pain at doses of 1 and 2 mL/kg[21]. The active component- azadiradione isolated from *A. indica* fruit skin extract in carbon tetrachloride solvent (CTCE) significantly reduced pain and inflammation in the treated rats[17].

Hepatoprotective activity :

The components of medicinal herbs are crucial for hepatoprotection without causing any adverse side effects. Neem's azadirachtin-A has hepatoprotective properties in rats with carbon tetrachloride (CCl_4) - induced liver damage. At higher doses, the pre-treatment with azadirachtin-A reduced hepatocellular necrosis in a dose-dependent manner. Similar to this, nimbolide showed hepatoprotective effects in rats when exposed to carbon tetrachloride (CCl_4), which causes liver damage[6]. The leaf extract also defended against rat liver damage brought on by paracetamol[8] and liver toxicity brought on by antitubercular drugs. The histological changes and changes in the serum levels of bilirubin, protein, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase were both considerably lowered by the aqueous leaf extract when compared to the control.

Hepatoprotective effect of methanolic and aqueous extracts of *Azadirachta indica* leaves showed that the plant had a strong chance of acting as a hepatoprotective agent[6,8]. Neem extract also protects against ethanol-induced gastric mucosal lesions in rats[30].

Antidiabetic activity :

Since ancient times, the Indian medical system has routinely employed *A. indica* to treat diabetes. Numerous accounts point to *A. indica's* risk for hypoglycemia[15,24,40]. The 800 mg/kg dose of 70% alcoholic Neem root and bark extract demonstrated a significant outcome on diabetes[34]. Dose of 250 mg/kg of *A. Indica* extract demonstrated pharmacological hypoglycaemic action, significantly lower glucose level at the 15th day in diabetic rats[12].

Chloroform extract of *A. indica* and aqueous, methanolic extracts of *B. spectabilis* plants significantly decreased intestinal glucosidase activity using an in vivo diabetic murine model, hence demonstrating good oral glucose tolerance. Similarly, *Andrographis paniculata* and *A. indica* leaf extracts have strong antidiabetic action[3].

Antimicrobial effect :

Neem and the components that make it up hinder the growth of many pathogens, including viruses, bacteria, and harmful fungus. The role of Neem in limiting the growth of microorganisms is described in each of its components below:

Antibacterial activity :

The antibacterial effectiveness of *Azadirachta indica* (Neem) bark, leaf, seed, and fruit extracts on bacteria isolated from the adult mouth was also tested. The results demonstrated that all of the test microorganisms used were sensitive to bark and leaf extracts. Moreover, the antimicrobial effects of seed and fruit extracts were only seen at higher concentrations[45].

Antifungal activity :

Both alcoholic and aqueous Neem leaf extract was strongly suppressed and controlled both seed-borne fungus species -*Aspergillus* and *Rhizopus* growth[26]. Additionally, Neem leaf alcoholic extract was superior to Neem leaf aqueous extract in terms of slowing the growth of both fungal species. Neem cake aqueous extract also shows inhibition of spore germination against three sporulating fungi, including *Currularia lunata, Helmintho-sporium pennisetti,* and *Colletotrichum gloeosporioides* f. sp. *Mangiferae*[22]. Also, the results of the study showed that *Azadirachta indica* methanol and ethanol extracts exhibited growth inhibition against *Aspergillus flavus, Alternaria solani, and Cladosporium*[39]. With a MIC of 0.19 mg, the ethyl acetate fraction of *Azadirachta indica* L. outperformed the fungicide (metalaxyl + mancozeb), which has a MIC (Minimum Inhibitory Concentration) of 0.78 mg, in terms of inhibiting *Alternaria solani sorauer* fungal development[18].

Antiviral activity :

The results demonstrated that Neem bark extract (NBE), at doses between 50 and 100 g/mL, effectively blocked HSV-1 entrance into cells[45]. Neem bark appears to have a direct anti-HSV-1 property because inhibitory effects of NBE were also seen when the extract was pre-incubated with the virus but not with the target cells. As demonstrated by virus inactivation and yield reduction assays, Neem (*Azadirachta indica* A. Juss.) leaf extract (NCL-11) demonstrates virucidal effect against coxsackievirus virus B-4 and suppresses an early stage of its reproduction cycle[5].

Antimalarial activity :

An examination employing albino mice infected with *Plasmodium berghei* revealed that Neem leaf and stem bark extracts reduced the level of parasitaemia in infected mice by roughly 51-81% and 56-87%, respectively[1]. The activity against both the sexual and asexual forms of the malaria parasite, *Plasmodium falciparum*, was assessed using a crude acetone/water (50/50)

extract of leaves. Asexual parasite counts were fewer than half as many in a separate 72-hour culture of mature gametocytes and parasites treated with IRAB (0.5 microg/mL), compared to control cultures, which exhibited parasitaemia levels of 8.0% and 8.5%, respectively falciparum. Azidirachtin and other limonoids found in Neem extracts were also active against malaria vectors, according to additional investigations[3,28,42].

Anti-nephrotoxicity effects :

The effects of *Azadirachta indica* methanolic extract of neem leaves (MENL) on cisplatin (CP)-induced nephrotoxicity and oxidative stress were investigated in rats. The extract was beneficial in preventing kidney damage from CP-mediated oxidative stress. Caspase-3, Caspase-9, and Bax genes revealed down-regulation in MLEN-treated groups as per PCR data[27].

Neuroprotective effects :

An examination into the cisplatin (CP)-induced neurotoxicity and the neuroprotective effects of *Azadirachta indica* leaves was revealed in well-preserved brain tissue from morphological observations of Neem before and after CP injection[27].

Growth-promoting and immunomodulatory effects :

Neem leaf glycoprotein (NLGP), a strong immune-modulator and antiangiogenic, has been shown to control effector NK cells, NKT cells, and CD8+ T cells to influence both local and systemic immunity in melanoma and carcinoma-bearing mice models. NLGP also downregulates CD31, VEGF, and VEGFR2 receptors and normalizes vascular tone[7]. In a study to assess the growth-promoting and immunomodulatory effects on broiler chicks, Neem infusion successfully enhanced antibody titre, growth performance, and gross return at a level of 50 mL/Litre of fresh drinking water[14].

Anti-radiation effect :

Genotoxicity, which appears as DNA damage and may have inheritable effects, is brought on by radiation. In the medical field, radiation's harmful effects must be avoided. Contemporary research has focused on radiation protection medications and countermeasures. It has been studied and demonstrated that plants that have developed in radiation-rich areas have the ability to shield other living organisms from radiation. Crude extracts, fractionated extracts, isolated phytocompounds, and plant polysaccharides from a range of plants have all been used in radioprotection studies[13].

The radiosensitizing abilities of Neem oil and its ability to prevent potentially fatal damage repair led researchers to the conclusion that Neem oil will probably be highly helpful as an adjuvant to the treatment of cancer. As Neem oil inhibits both sub-lethal damage repair (SLDR) and potentially lethal damage repair (PLDR), it will be extremely helpful in human cancer chemotherapy and radiotherapy[20]. *Azadirachta indica* caused radioexposed neuroblastoma xenografts to become more sensitive to radiation by activating pro-apoptotic signalling[23]. Another study utilizing an ethanolic extract of Neem leaves to

examine the relative activation of NF-kβ after fractional radiation therapy found that Neem leaf extracts significantly decreased both constitutive and radiotherapy-induced NF-kβ. Neem leaf similarly reduced the expression of genes activated by fractionated radiotherapy[2].

Toxicity studies on Azadirachta :

Neem extracts were the least poisonous to aquatic creatures, however, Neem insecticides or their compounds showed moderate to high toxicity. Since these extracts have only been studied in animals for acute toxicity when administered intramuscularly or intraperitoneally, more study on chronic effects is necessary. It is crucial to assess the safety of *A. indica's* extracts and/or isolated chemicals due to its possible pharmacological effects, particularly when utilizing mammalian models. The toxicological profile of medicinal plants can be quickly examined using acute and subacute toxicity screens, which provide researchers with knowledge about the compounds' potential for harm or safety. The study examined the substantial amount of data on the toxicity of Neem to mammals. Neem extracts and related compounds are harmful in terms of sub-acute and sub-chronic toxicity, although it depends on the dose.

No matter the manner of delivery, bigger doses were discovered to be riskier. The majority of the study described changes to both the male and female reproductive systems, while some of it did not detect any effects on reproduction or teratogenicity. Neem extracts have negligible to no acute toxicity in mammals. Subacute and sub-chronic toxicity in these animals can be entirely eliminated by administering lower doses. Due to these safety features and their well-known pharmacological properties, the Neem tree and its compounds/ extracts have a large commercial potential and can be regarded as serious contenders for new natural pharmaceutical therapy[9,10].

Future recommendation :

It is critical that researchers strive for safe, inexpensive, and dependable solutions to a variety of lifestyle issues[33]. One of the most advantageous medicinal plants with disease-preventive characteristics is Neem (*Azadirachta indica*). The leaf, blossom, seed, bark, and root of the Neem tree all contain a variety of bioactive compounds that can be isolated and used in herbal medicines. Many research on the subject have shown that these bioactive Neem components have distinct regulatory effects on a variety of biological processes, including angiogenesis, apoptosis, inflammation, and immunomodulation. Many studies have been conducted on limonoids, such as nimbolide and azadirachtin, which are among the bioactive compounds. There is no or very little acute toxicity in Neem extracts. Subacute and sub-chronic toxicity in these animals can be fully prevented by using lower doses.

Considering all the aforementioned benefits, Neem tree and its compounds/ extracts have a high commercial value and are potential candidates for novel natural therapeutic treatments because of their high levels of safety and well-established pharmacological effects. Neem can be used as a treatment for a number of illnesses since *A. indica* has been shown to regulate various biological processes. For toxicity assessments and future research, it is important to identify

potential medical applications, do additional research on other Neem bioactive components, and examine the pharmacokinetic features of Neem compounds, or their absorption, distribution, metabolism, and excretion. It is worthwhile to mention that our group is continuously working on selection of radioprotectors originating from herbal/ microbial origin. Further studies are carrying on developing some strategies for radioprotection and killing cancer cells using nanoparticles of *Azadiracta indica* which is not evaluated yet.

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