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Review article

Azadirachta indica A. Juss.: Ethnobotanical knowledge, phytochemical studies, pharmacological aspects future prospects

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Abstract: *Azadirachta indica*, commonly known as Neem, it is a member of the Meliaceae family, a fast-growing evergreen popular tree found commonly in India, Africa and America. All parts of the neem tree, including the seeds, fruits, twigs, leaves, flowers, roots, and bark, have traditionally been used to treat inflammation, infections, fever, skin ailments, and dental diseases. Azadirachtin, nimbolinin, nimbin, nimbidin, nimbidol, salannin, and quercetin are all useful active chemicals extracted from various plant parts. The aim of this review article provides information mainly on various pharmacological activities like Antioxidant Activity, Anti-cancer, Anti-inflammatory, Anti-bacterial, Antiviral Activity, Antifungal Activity, Antihelmethic effects, Antidiabetic action, Wound healing effect, Activity against ulcer, Orodental protection, Contraceptive, Hepatoprotective activity, Immunomodulatory and Growth Promoting, Antinephrotoxicity Effect and Antisnake venom activity of neem plant and medicinal uses. Plant extracts function as both a reducing and capping agent. Neem is a well-known medicinal plant and has been studied for the biosynthesis of nanoparticles. *A. indica* possesses many phytochemicals that can reduce metal ions. The nanoparticles are reported to exhibit good antimicrobial, and antioxidant and cytotoxicity effects against MCF-7 and HeLa cells in vitro.

Keywords: *Azadirachta indica*, Phytochemistry, Pharmacology, Nanoparticles, Ethnobotany, Neem, Meliaceae.

INTRODUCTION

Medicinal plants still play a significant role in healthcare systems for a large portion of the world's population, especially in developing countries where they have been used for a long time. Both industrialized and developing nations are increasingly recognizing the medicinal and financial benefits of these plants. They continue to provide new medicines for humanity. Some of the beneficial properties ascribed to plants have recognized to be flawed and medicinal plant treatment is based on the experimental findings of hundreds to thousands of years (Dar *et al.*, 2017).

Neem belongs to the mahogany family, Meliaceae. It is now known botanically as *Azadirachta indica* A. Juss (Kumar & Navaratnam, 2013). The Persian term for neem has been latinized. *Azadirachta indica*, is derived from the Persian. The word "Azad" denotes the concept of "freedom", "Dirakht" refers to a "tree", and "i-Hind" signifies something that belongs to or is derived from "Indian" origin. Hence it means “the free tree of India”. The neem tree is an extraordinary plant that has been designated by the United Nations as the "Tree of the 21st Century" (Kumar & Navaratnam, 2013). *Azadirachta indica* is a fast-growing tropical evergreen tree found mostly in India, Africa and America (Kumar *et al.*, 2018). It is in India that the tree has been most widely used. It grows from the southern Indian point of Kerala to the Himalayan peaks. It includes regions with tropical and subtropical latitudes that range from humid tropical to semi-dry environments, and extend from sea level up to an elevation of 2,300 feet (Jhariya *et al.*, 2011).

The ethnopharmacological knowledge of medicinal plants is quickly vanishing and this is more obvious in industrialised nations, the degradation of public information on plants is much quicker than in developing ones. In the wake of the fast loss of such knowledge, its documentation as well as a deeper understanding of its botanico-historical foundations has become an urgent responsibility of ethno-allied disciplines (Weldegerima, 2018).

TAXONOMIC CLASSIFICATION (Uzzaman, 2020)

Taxonomic Classification of *Azadirachta indica* A. Juss:

Kingdom	Plantae
Subkingdom	Tracheobionta
Division	Magnoliophyta
Class	Eudicot
Subclass	Rosidae
Order	Sapindales
Family	Meliaceae
Genus	Azadirachta
Species	*A. indica*

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VERNACULAR NAMES (Tripathi & Singh, 2020)

Bengali: Nim, Nimgachh,
Guajarati: Danujhada, Limbado, Limbra, Limdo,
Hindi: Nim, Nimb,
Sanskrit: Arista, Nimba, Nimbah, Picumarda,
English: Indian Lilac, Margosa tree, Neem tree,
Kannada: Bemu, Bevinamara, Bivu, Kaybevu,
Punjabi: Bakam, Drekh, Nim.

DISTRIBUTION

A native to east India and Burma, it grows across the majority of southeast Asia and West Africa, and more lately Caribbean and south and Central America. In India it occurs naturally in Siwalik Hills, dry forests of Andhra Pradesh, Tamil Nadu and Karnataka to a height of roughly 700 m. It is farmed and commonly naturalised in the drier parts of tropical and subtropical India, Pakistan, Sri Lanka, Thailand and Indonesia. It is also cultivated and commonly naturalised in Peninsular Malaysia, Singapore, Philippines, Australia, Saudi Arabia, Tropical Africa, the Caribbean, Central and South America (Tripathi & Singh, 2020).

BOTANICAL DESCRIPTION

It is a tree 40-50 feet or higher, with a straight trunk and long spreading branches generating a large round crown (Fig. 1A). It has rough dark brown bark with extensive longitudinal cracks divided by flat ridges (Fig. 1B). The leaves are compound, imparipinnate, each consisting of 5-15 leaflets. The complex leaves are themselves alternating with one another (Fig. 1C). It has several flowered panicles, primarily in the leaf axils. The selel are ovate and approximately one centimetre long with delicious smelling white oblanciolate petals. It yields yellow drupes that are ellipsoid and glabrous, 12-20 mm long. Fruits are green, becoming yellow on maturing, fragrant with garlic like odour. Fresh leaves and flowers arrive in March-April. Fruits mature during April and August depending upon region (Hashmat *et al.*, 2012).

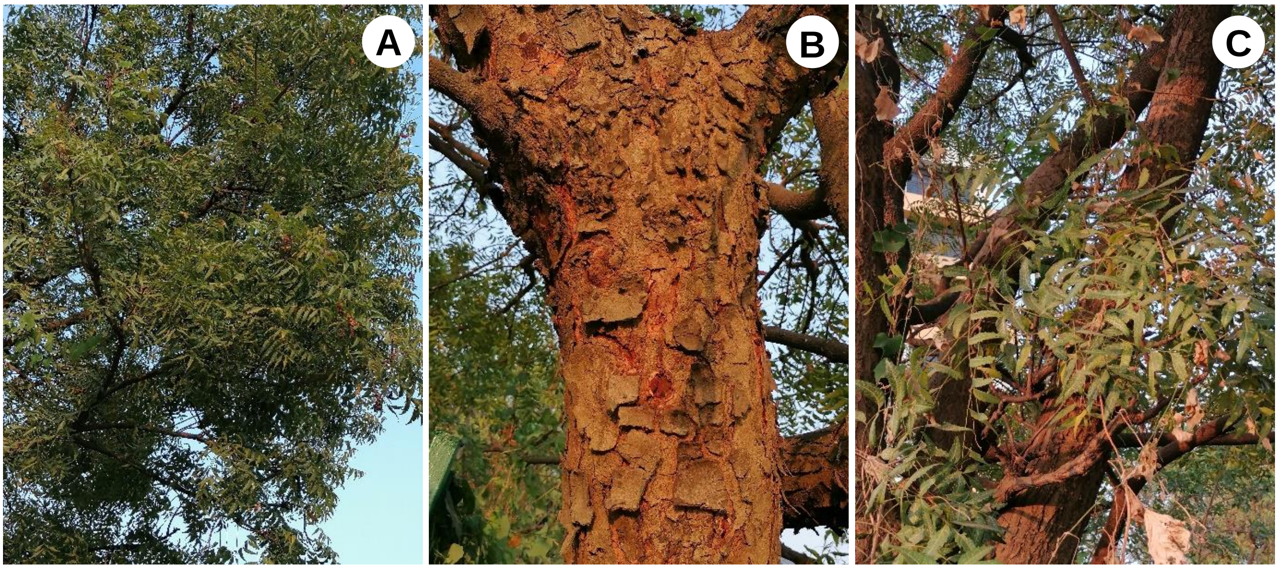

Figure 1. *Azadirachta indica* A. Juss: **A**, Habit; **B**, Bark; **C**, Leaves.

ETHNOBOTANY

Various elements of neem have been widely employed to treating human illnesses from ancient time. The neem twigs have been used by millions of individuals for brushing teeth (Gupta *et al.*, 2017). Moreover, the neem tree branches are utilized as one of the most efficient kinds of dental care in traditional medicines (Prashant *et al.*, 2007). Flower for the prevention and treatment of bile diseases (Gupta *et al.*, 2017). The dried flower is given orally for diabetes (SriRamaMurthy *et al.*, 2017). Leaf for ulcers (Gupta *et al.*, 2017). The leaves of the neem tree are also used as a natural therapy for acne patients. Therapy of infected eyes may be done by the use of neem leaves. A similar infusion may also be utilised in the treatment of sore throats (Eid *et al.*, 2017). Neem leaves are good for blood circulation and blood purification (Bhowmik *et al.*, 2010). Leaves are placed over the bed of individuals suffering from Chicken and smallpox. Leaf decoctions are consumed by jaundice sufferers. Neem leaf-soaked water is consumed every morning to maintain the body to withstand infections of various types. Similarly, this water is utilised to bathe small children. Neem leaves are frequently burned to keep mosquitoes away; locals sometimes sleep beneath a neem tree for the same reason. Hot water extract of the flower and leaf is used orally as an anti-hysteric treatment and applied topically to heal wound. Leaf juice is provided in gonorrhoea and leucorrhoea. Leaves used as poultice to treat boils, their infusion is used as antiseptic wash to stimulate the healing of wound and ulcers. A paste of leaves is used to heal wounds, ringworms, eczema and ulcers. Bathing with Neem leaves is effective for itching and other skin disorders. Leaf juice is used as nasal drop to cure worm infestation in nose. plants used in treatment of snake bite in Paschim Medinipur district in West Bengal stated that the leaf ash or crushed leaves rubbed into scarification surrounding the snake bite as antidote and leaf juice is administered as decoction. Grains and beans were kept in pots with neem leaves to keep away insects (SriRamaMurthy *et al.*, 2017). Bark for central nervous system, paralysis and psychiatric disorders (Gupta *et al.*, 2017). Neem bark decoctions are consumed by jaundice sufferers. Hot water extract of the bark is administered orally by the adult female as a tonic and emmenagogue. Steam inhalation of bark is beneficial in inflammation of throat. Irulas of Kodiakkarai reserve forest in Tamil Nadu take bark extract of *Azadirachta indica* to cure stomach worms. Epileptic attacks are healed by Santhal and Paharia tribes of Santhal Paragana, Bihar in the following way. Fresh stem bark of *Azadirachta indica* is crushed with leaves and roots of *Cissampelos pareira* and *Aristolochia indica* to form extract, 2–3 drops of this extract is put in nostrils during epileptic seizures. Neem wood was used for cooking and for building the roof of the residence (SriRamaMurthy *et al.*, 2017). The use of aqueous extracts from seeds to cure head lice is widely recognized. Neem oil demonstrated excellent antiseptic properties. It is utilised in the treatment of such skin problems as furuncles and eczema, as well as to cure intestinal worm infections (Eid *et al.*, 2017). Neem oil is also widely included to a range of creams and salves. It is helpful against a wide range of skin problems including eczema, psoriasis, dry skin, wrinkles, rashes and dandruff. Neem oil is highly efficient as a mosquito repellant. Neem oil is an effective and environmentally safe pesticide when it is diluted and sprayed on crops via irrigation systems. It is a healthier alternative to artificial chemical pesticides. Neem oil does not damage the soil and it enhances yields. Neem roots are good for blood circulation and blood purification (Bhowmik *et al.*, 2010). Hot water extract of dried fruit is used for piles and topically for skin problems and ulcers (SriRamaMurthy *et al.*, 2017). Neem cake is flexible and has numerous applications. It may be used as cattle feed, fertiliser and natural pesticide (Bhowmik *et al.*, 2010). *Azadirachta indica* utilised by the Gond and Baiga tribes: A pinch of gum mixed in cold water is used to treat inflamed eyes; it is utilised to cure cracked soles and decoction of the gum is used to treat inflammatory gums. Hot water extract of the whole plant is used as anthelmintic, an insecticide and purgative. Decoction may relieve intermittent fever, general debility convalescent, and lack of appetite after fever. One of the main uses of neem is in malarial fever, both as a preventative and a curative. Used as hair wash for dandruff and for killing lice (SriRamaMurthy *et al.*, 2017).

TRADITIONAL KNOWLEDGE

The neem tree's history extends back to antiquity, with signs indicating it was employed in medicinal treatments approximately 4,500 years ago in India (SriRamaMurthy *et al.*, 2017). The oldest Sanskrit medicinal literature speak to the advantages of different part of Neem. Each of these has been used in the Indian Ayurvedic and Unani medicine systems (Bhowmik *et al.*, 2010). The tree components are effective against many human ailments as traditional medicine for domestic remedy. Each portion of the tree has various therapeutic characteristics which may be utilised to cure numerous different ailments (Abdullah-Al-Emran *et al.*, 2011). All elements of neem trees including leaves, seeds, roots, bark and the flowers of the plant are used to heal diverse illnesses, such as stomach ulcers, jaundice (Sujarwo *et al.*, 2016) and used against a broad range of illnesses such as heat-rash, boils, wounds, leprosy, skin problems, chicken pox, etc (Bhowmik *et al.*, 2010). This plant has been utilised to heal many acute and chronic ailments in different areas of Asia and Africa. The efficacy of this plant in driving away the mosquitos and fever was mentioned far back in 1803 (James & Lond, 1903). The plant is commonly grown in Nigeria as a decorative and therapeutic plant. It is used widely in Nigeria for the traditional treatment of malaria and other related illnesses (Katsayal *et al.*, 2008). Neem has been utilised as a deterrent for smallpox and other infectious illnesses and is recognised to exhibit powerful anti-plasmodial properties. The herb has also been used for urinary tract disorders, gastrointestinal difficulties, hair problems, and blood pressure. It has also been used as a tonic and to eliminate bugs from mattresses, books, grain bins, cabinets, and closets (Sujarwo *et al.*, 2016). In Indonesia, neem leaves are employed as a diuretic and for treating headache, heartburn, and enhancing the appetite (Sujarwo *et al.*, 2016). In addition, the local practitioners report that these medicines typically have less adverse effects (Khattak *et al.*, 1985). Therefore, since several of herbal medications are extensively utilised by traditional practitioners it was believed to be of interest to examine and determine the effectiveness of for their antipyretic properties (Khattak *et al.*, 1985). Apart from that, neem-based products from *Azadirachta indica* are classically used for pest control in agriculture and gardening since long in India (Habluetzel *et al.*, 2009). The health care items based on this traditional system of medicine in the contemporary world include night creams, astringents, hair shampoos, moisturisers, hand lotions, body lotions, cream cleansers and hair conditioners (Gupta *et al.*, 2017). Infusions and teas made from leaves are used to alleviate malaria attacks, intestinal complaints, treat dental, and as insects' repellent, in addition to that it was also used as a diuretic (Sujarwo *et al.*, 2016).

Ayurvedic texts characterize neem bark as having a cooling, bitter, astringent, pungent, and refreshing properties. It helps with fatigue, cough, fever, and worm infestation. It is used to cure wounds and vitiated states of kapha, as well as vomiting, skin disorders, and excessive thirst. It treats the Vatik condition. Its fruits have bitter, purgative, anti-hemorrhoidal, and anthelmintic properties'. Traditionally Neem has been utilised for skin and blood purifying conditions.

Ancient Ayurveda practitioners thought excessive sugar levels in the body produced skin problems; Neem's bitter nature was considered to counteract the sweetness. Indians bathed with Neem leaves soaked in hot water. Since there has never been a record of the topical administration of Neem creating an unfavourable side effect, this is a typical practise to heal skin problems or allergic responses (Bhowmik *et al.*, 2010). Infants are traditionally given a herbal and oil bath, and placed on a soft silk cloth while being fanned with branches from neem trees starting from birth. The child was given low dosages of neem oil when ill, showered with neem tea to cure wounds, rashes, and chicken pox. The neem tree was considered protective to both mothers and children. Delivery chambers were fumigated with its burning bark (SriRamaMurthy *et al.*, 2017).

PHYTOCHEMICAL CONSTITUENTS

Medicinal plants have certain organic compounds which give distinct physiological effect on the human body (Yadav & Agarwala, 2011). There are two kinds of metabolites synthesized in plants viz. Primary metabolites and Secondary metabolites. Primary metabolites are crucial for the plant's normal metabolism such as growth and development. Secondary metabolites generated by plants may have little need for them. These are produced in nearly all parts of the plant such bark, leaves, stem, root, flower, fruits, seeds, etc. The bioactive molecules are known as secondary metabolites (Bansode & Salalkar, 2015). Bioactive substances such as tannins, alkaloids, carbohydrates, terpenoids, steroids, and flavonoids are present (Yadav & Agarwala, 2011).

Neem can be regarded as the "storehouse" of a variety of phytochemicals. More than 300 phytochemicals were isolated from neem tree. The most two major types of phytochemicals which have been identified from diverse portions of neem are isoprenoids, and non-isoprenoids. The most well-known isoprenoids are diterpenoids, vilasinins, triterpenoids, limonoids, and C-secomeliacins, while the non-isoprenoids includes proteins, tannins, carbohydrates (polysaccharides), sulphur compounds, polyphenolics such as flavonoids and their glycosides, dihydrochalcone, coumarin and aliphatic compounds, phenolic acids (Maji & Modak, 2021). Damtew (2022) provided list of active constituents present in different part of *Azadirachta indica* tree (Table 1).

Table 1. Active constituents present in different part of *Azadirachta indica* A. Juss.

Part/Product	Chemicals found
Leaves	Glucoside of quercetin, Glucoside of kaemferol Quercetin, Quercetin-3-galactoside(Hperin), Rutin, Isorhamnetin, Rhamnoside of quercetin, Quercitin, Nimbolide, Vilasinin, Nimbinene, 6-deacetyl nimbinene, Nimbolide Nimocinol(6α-hydroxy-azadirone), β-sitosterol, β-sitosterol-β-D-glucoside, Neem leaf glycoprotein
Trunk	Sugiol, Nimbiol, Nimbin, Nimbinin, Nimbolin a, Nimbolin b
Bark	Sugiol, Nimbiol, Nimbin, Nimbinin, Deacetylnimbin, Nimbinene, 6-deacetyl nimbinene, Nimbolide, Sugiol, Nimbiol
Flowers	Kaemferol, Quercetin, Myricetin, Melicitrin, Quercetin-3-galactoside (hperin), Kaemferol-3- glucoside (astragalin), β-sitosterol-β-D-glucoside, β-sitosterol
Oil	Nimbin, Nimbinin, Nimbidic acid (salannic acid), Salannin, Meliantriol, Azadirone
Fruit	5-hydroxy-methyl furfural, Nomolin, Nimolicin, 17-Hydroxy-azadiradione, 17β-Hydroxy-azadiradione, 17-Epi-azadiradione

PLANT PARTS

Fruits

The fruits contain azadirachtin, an isomer of epoxyazadiradione, azadirachtol, azadirachnol, deacetylazadirachtinol, azadiradione, 17-epi- and 17β-hydroxyazadiradione, azadirone, gedunin, 7-hydroxygedunin, melianone, nimbiol, nimboeinol (7-acetoxy-7-hydroxy-azadiradione), nimocin, 7-deacetoxynimolicinol, nimolinone; nimbochalcin and nimbocetin; 21,23:24,25-diepoxytirucall-7-en-21-ol salannin. Nimolicinol isolated from fresh, ripe fruit (Zeenat *et al.*, 2018).

Kernels

The kernels produce oil of Margosa, which comprises 40.0-48.9% of the kernel and is rich in a variety of compounds, including tocopherol, arachidic, linoleic, margosic, myristic, oleic, palmitic, and stearic acids, as well as azadirone, azadiradione, epoxyazadiradione (nimbinin), gedunin, desacetyl gedunin, meldenin, meliatriol, nimbin, nimbidin, nimbidiol, nimbidic acid, salannin, 3-desacetylsalannin, salannol and its acetate, salannolide, vepinine, vilasinin, 1,3-diacetylvilasinin, 1-tigloyl-3-acetyl-vilasinin, tiglic acid, nimbinene, 6-desacetyl nimbinene, nimbandiol, and 6-O-acetyl nimbandiol, although their specific rotation can vary considerably (Zeenat *et al.*, 2018).

Neem seed oil

Neem seed oil contains Triterpenes and tetranortriterpenes (limonoids and protolimonoids of the gedunin-group): for example nimbolin A and B, nimbin, gedunin; in addition, azadirachtin, 22,23-dihydro-23-β-methoxy-azadirachtin (vepaol) and its C-23 epimer (isovepaol), 7-desacetyl-7-benzoyl derivatives of azadirone, azadiradione, epoxyazadiradione, 2-dihydroepoxyazadiradione, 1β, 2β-diepoxyazairadione, 7-desacetyl-7-benzoyl-gedunin, acetylneotrichilenone, nimbidinin, nimbidin, salanic (nimbidic) acid (seeds). A new tetranortriterpenenimbidinin, which was isolated from the amorphous bitter principle (nimbin) of seeds, has been characterized. Additionally, six new tetranortriterpenoids were isolated from seeds, including 1α-methoxy-1,2-dihydro-epoxyazadiradione, 1β,2β:14β,15β-diepoxyazadiradion, 7-acetylneotrichilenone, and three C-7 benzoates of tetranortriterpenoids (I, II, III) (Zeenat *et al.*, 2018).

Flowers

The flowers contain benzoyl alcohol, β-sitosterol; thioamyl alcohol; arachidic, behenic, linoleic, oleic, palmitic and stearic acids; azadirachtin and margosene; kaemferol and its 3-glucoside, quercetin-3-galactoside and myricetin-3-L-arabinoside (Zeenat *et al.*, 2018).

Leaves

The leaves contain azadirachtin, azadirachtanin, azadirone, azadiradione and epoxyazadiradione, isoazadirolide, nimbin, nimbocinolide, isonimbocinolide, nimbolide, nimbocinolide, isonimocinolide, nimocinone, 2’,3’-dehydrosalannol, kaempferol-3-O-β-glucoside, myricetin and its 3’-L-arabinoside (melictrin), 3-O-α-L-rhamnoside and 3-O-rutinoside, quercetin, its 3-galactiside, 3-O-L-rhamnoside and 3-O-rutinoside, nimbaflavones, scopoletin, amino acids, carbohydrates, nonacosanol, protein and vitamins, β-sitosterol and its β-D-glucoside, β-carotene, n-hexacosanol, nimbandiol, nimbinene and 6-desacetylnimbinene. Leaves include hyperoside, quercitrin, and rutin; meldenindiol is extracted from green leaves; meldenin and isomeldenin are extracted from fallen yellow leaves; and quercetin is isolated as an aglycon from the glycosides of any kind of leaf. In addition, a new tetranortriterpenoid, namely 4α,6α-dihydroxy-A-homoazadirone (IV), has also been isolated. Tannins and a volatile oil are also found in the leaves (Zeenat *et al.*, 2018).

Heartwood

The heartwood contains tannin, bakalactone, 4, 14-α-dimethyl-5-α-ergosta-8,24(28)-dien-3β-ol, 4α-methyl-5-α-ergosta-8,24(28)-dien-3β-ol, nimatone, nimbinene, 6-desacetyl nimbinene, nimbolins A and B, β-sitosterol and its glucoside, 24- methylene-cycloartenol (Zeenat *et al.*, 2018).

Stem bark

The stem bark contains vanillic acid, catechol, campesterol, stigmasterol, sitosterol, β-amyrin, lupeol, nimbin, nimbidin, nimbinin, sugiol, 6β-hydroxy-4-stigmasten-3-one, 6β-hydroxy-4-campesten-3- one, kulinone, kulactone, kulolactone and methyl kulonate. Gla and Glb, two related arabinofucoglucans, were isolated from the bark. Both arabinofucoglucans are composed of a main chain consisting of repeating glucopyranosyl units linked by (1→4) bonds, and they also have side chains of α-L-arabinofuranosyl units. A process of extracting an anti-inflammatory polysaccharide consisting of glucose, arabinose and fucose in molar ratio of 1:1:1 from bark. The stembark's ethanolic extract contains various compounds including two isomeric diterpenoids, nimbonone and nimbonolone, as well as methylgrevillate. Additionally, three new tricyclic diterpenoids have been identified, namely nimbosodione, nimbisonol, and methylnimbionol, along with phenols such as nimbione ($C_{18}H_{22}O_3$, m.p. 102-103°C), nimbinone ($C_{10}H_9O_2$, m.p. 124-125°C), nimbionone ($C_{18}H_{24}O_4$, m.p. 78-79°C), and nimbionol ($C_{18}H_{24}O_4$, m.p. 127-129°C). Furthermore, the extract contains a c-seco-tetranortriterpenoid called isonimbinolide ($C_{30}H_{36}O_{11}$, m.p. 172-173°C) and two fatty acid derivatives (polyacetates), margosinone and margosinolone. In addition to the previously mentioned compounds, the stem bark also contains pentacyclic nortriterpenoids such as 6-desacetylnimbinen, nimbiol, and nimbinen. Gedunin is also found in the bark's methanolic extract. The bark also contains tannins and a volatile oil (Zeenat *et al.*, 2018).

Neem gum

A glycoprotein with a carbohydrate to protein ratio of 19:81 has been isolated from neem gum. The glycoprotein contains various monosaccharides including mannose, glucosamine, arabinose, galactose, fucose, xylose, and glucose, with a molar ratio of 4:3:3:2:2:1:1 (Zeenat *et al.*, 2018).

Twigs

Margosinolide, isomargosinolide, desacetylnimbinolide, and desacetyl isonimbinolide are all found in the twigs (Zeenat *et al.*, 2018).

Wood and wood oil

Gedunin, 7-deacetoxy-7-oxogedunin, fraxinellone, nimbolin A, cycloeucalenone, melianin A, and melianin B are among the compounds found in the wood. The wood oil contains cycloeucalenol, 24 methylene cycloartenol, β-sitosterol and azadaric acid (Zeenat *et al.*, 2018).

Trunk bark and wood

Nimbiol, sugiol, and nimbosterol are present in the trunk bark, while the trunk wood contains nimbolins A and B (Zeenat *et al.*, 2018).

Root and root bark

The root contains 24-methylene-cycloartenol, 24-methylene-cycloartenone, cycloeucalenol, cycloeucalenone, 4-campesten-3-one, 4-stigmasten-3-one, trans-cinnamic and vanillic acids; root bark contains nimbin and nimbidin. Root bark has been found to contain the diterpenoid nimbidiol ($C_{17}H_{22}O_3$). The rootbark contains the tricyclic diterpenoids margosin, margocinin, margocillin, and nimolinin, as well as a tetranortriterpenoid called nimbilin (Zeenat *et al.*, 2018).

Whole plant

Various parts of the tree contain aesculetin, campesterol, 6-hydroxy-7-methoxy-coumarin, 4α,6α-dihydroxy-A-homoazadirone, isomeldenin, meldenindiol, 17-acetoxymeliacin, 6-O-acetylnimbandiol, desacetylnimbin, nimocinol, isonimolicinolide and nimolinolic acid (Zeenat *et al.*, 2018).

PHARMACOLOGICAL PROPERTIES

Table 2. Pharmacological activities from different part of *Azadirachta indica* A. Juss.

Tree Part	Pharmacological Activities
Leaves	Treatment Of Chicken Pox, Skin Infections, Pest Repellents, Leprosy, Intestinal Infections, Respiratory Disorders, Constipation, (Saleem *et al.*, 2018) Antiemetic, Antifungal, Anticlotting Agent, Anti-Helminthic, Anti-Tuberculosis, Antitumor, Antiseptic, Antiviral, Insecticides, Nematicides, Insect Repellents Activity (Maji & Modak, 2021)
Seeds	Leprosy And GIT Infections (Saleem *et al.*, 2018)
Flowers	GIT Infections (Saleem *et al.*, 2018) Analgesic And Stimulant Property. (Maji & Modak, 2021)
Oil	Pest Repellents, Leprosy, Intestinal Infections, Respiratory Disorders, Constipation (Saleem *et al.*, 2018) Analgesic, Anti-Helminthic, Anticholinergic, Antihistaminic, Antipyretic, Antiviral, Antiprotozoal, Insecticides, Bactericidal, Insect Repellents, Fungicides and as Veterinary Medicines. (Maji & Modak, 2021)
Bark	Malaria, Pest Repellents, Leprosy, Intestinal Infections, Respiratory Disorders, Constipation, Stomachache (Saleem*et al.*, 2018). Antidermatic, Antiallergenic, Antiprotozoal, Antitumor And Antifungal Property (Maji & Modak, 2021).
Twigs	Pyrexia, Increase In Appetite (Saleem *et al.*, 2018) Toothache Reliever (Maji & Modak, 2021)
Sap	Cooling Drink And Stomach Tonic (Saleem *et al.*, 2018)
Gum	Healing Of Wounds, Scabies, Ulcer, Tonic, And Stimulant (Saleem *et al.*, 2018)
Whole tree	Fever, Headache, Rheumatism, Chronic Syphilitic Sores, Ulcer, Skin Disorders, And Blood Purification (Saleem *et al.*, 2018)
Nanoparticles	Antimicrobial, Antioxidant Activity And Cytotoxicity (Patil *et al.*, 2022)

Antioxidant activity

One of the primary reasons in the emergence of many illnesses is the presence of free radicals or reactive oxygen species. However, one of the most important steps in disease prevention is the neutralization of free radical activity. Antioxidants stabilizes or deactivates free radicals, often before they attack biological cell targets. In addition, they have a role in the activation of antioxidative enzymes, which regulate the damage produced by free radicals/reactive oxygen species. Antioxidant properties have been discovered in medicinal plants (Rahmani & Aly, 2015).

Antioxidant properties have been discovered in medicinal plants. Because of their large supply of antioxidants, plants' fruits, seeds, oil, leaves, bark, and roots play an important role in disease prevention. The antioxidant activity of *A. indica* leaf and bark extracts was evaluated, and the study's findings clearly demonstrated that all of the analyzed leaf and bark extracts/fractions of neem cultivated in the foothills had considerable antioxidant capabilities (Ghimeray, 2009). A significant research study was conducted on the extracts of leaves, fruits, flowers, and stem bark of the Siamese neem tree to evaluate their antioxidant activity. The results revealed that the extracts from the leaf, flower, and stem bark exhibit considerable antioxidant potential (Sithisarn *et al.*, 2005).

The antioxidant activity of leaves, fruits, flowers, and stem bark extracts from the Siamese neem tree was evaluated. The study found that leaf aqueous extract and flower and stem bark ethanol extracts had higher free radical scavenging activity with 50% scavenging activity at 26.5, 27.9, and 30.6 microg ml^{-1}, respectively. The total antioxidant activity of the extracts was also determined to be 0.959, 0.988, and 1.064 mM of standard trolox, respectively (Sithisarn *et al.*, 2005).

Anti-cancer activity

Modification of molecular / genetic pathways contributes to cancer genesis and progression. An oncogene, also known as a cancer-causing gene, is a mutated gene that plays an important role in the genesis and progression of malignancies. The effect of leaf extract on the expression of the c-Myc oncogene in 4T1 breast cancer BALB/c mice were studied, and the results showed that the 500 mg kg^{-1} neem leaf extract (C500) group suppressed c-Myc oncogene expression much more than the cancer control group (Othman *et al.*, 2012).

The neem leaf contains various potent antioxidants and anticarcinogens, such as carotenes, ascorbic acid, terpenoids, limonoids, and flavonoids. b-Carotene and vitamin C contained in neem leaf play a significant role in preventing tumour formation through their radical scavenging activities. Limonin 17b-D-glucopyranoside, a limonoid found in neem, has been demonstrated to suppress DMBA induced oral carcinogenesis. Azadirone 1, a limonoid constituent of *A. indica* has been proven to exhibit cytotoxic effect against breast, melanoma and prostate cancer cell lines. Scientist have analysed the cytotoxicity of azadirachtin A in human glioblastoma cell lines. Nimbolide and 28-deoxonimbolide have been found as cytotoxic components of neem leaves. Quercetin and kaemferol, the flavonoids present in neem leaf have been demonstrated to inhibit carcinogenesis during initiation, as well as promotion stages of carcinogenesis by virtue of their radical scavenging activities. Quercetin, a neem bioflavonoid has attracted the maximum focus of study as an anticancer drug. Quercetin has been proven to inhibit the growth of tumour cells in a range of malignant cell lines. The antiproliferative properties of quercetin have been shown in experimental animal models, as well as in humans. Quercetin has also been proven to boost the therapeutic effectiveness of radiation, as well as chemotherapy medicines (Subapriya & Nagini, 2005).

Anti-inflammatory activity

A study found that neem leaf extract has a considerable anti-inflammatory effect, however it is less effective than dexamethasone. Dexamethasone is a well-known and very effective anti-inflammatory steroid (Mosaddek & Rashid, 2008).

According to the findings of one study, nimbidin suppresses the actions of macrophages and neutrophils that are involved in inflammation. Oral injection of nimbidin inhibited chemotaxis as measured by macrophage movement in response to thioglycollate, as well as phagocytosis and respiratory burst in these cells (Kaur *et al.*, 2004).

A lot of researchers made similar observations. The water-soluble component of an alcoholic extract of neem leaves at a dose of 200 mg kg^{-1} orally shown significant anti-inflammatory impact and significantly prevented the biochemical mode of action on inflammation in a cotton pellet granuloma test. This anti-inflammatory action of neem leaf extract might be attributed to lysosomal membrane stability and an anti-proliferative impact (Chattopadhyay, 1998).

Anti-bacterial activity

Another study looked at the antibacterial activity of *Azadirachta indica* bark, leaf, seed, and fruit extracts against bacteria isolated from adult mouths. The results demonstrated that bark and leaf extracts were bactericidal against all of the test bacteria. Furthermore, only at greater doses did seed and fruit extracts exhibit antibacterial action (Yerima *et al.*, 2012).

A study was carried out to evaluate the antibacterial efficacy of herbal alternatives as endodontic irrigant with the standard irrigant sodium hypochlorite, and the results indicated that leaf extracts exhibited zones of inhibition, indicating antimicrobial properties. Leaf extracts also blocked many more zones than 3% sodium hypochlorite (Ghonmode *et al.*, 2013).

Extracts of neem leaves, seeds, and bark have antibacterial activity against a wide range of Gram-negative and Gram-positive pathogens, including *Mycobacterium tuberculosis*, *Vibrio cholerae*, and *Klebsiella pneumoniae* (Mahfuzul Hoque *et al.*, 2007).

Antiviral activity

At doses ranging from 50 to 100 g ml^{-1}, neem bark extract (NBE) strongly inhibited HSV-1 entrance into cells.

Additionally, it was demonstrated that the NBE extract has a direct anti-HSV-1 effect, as evidenced by its inhibitory action when preincubated with the virus rather than the target cells, suggesting that neem bark possesses this capability (Tiwari *et al.*, 2010).

Neem leaf extract has showed virucidal action against coxsackievirus virus B-4 as demonstrated by virus inactivation and yield reduction assays, in addition to interfering at an early event in its reproduction cycle (Badam *et al.*, 1999).

Antifungal activity

Experiments were undertaken to evaluate the efficacy of various neem leaf extracts on the seed-borne fungus *Aspergillus* and *Rhizopus*, and the results demonstrated that both fungal species' development was significantly inhibited and controlled by both alcoholic and water extracts. Furthermore, alcoholic neem leaf extract inhibited the development of both fungal species better than aqueous extract. Another study found that neem cake aqueous extracts have antibacterial action against three sporulating fungi, including *Curvularia lunata*, *Helminthosporium pennisetti* and *Colletotrichum gloeosporioides* f. sp. *Mangiferae* (Kumari *et al.*, 2013). The results of the investigation showed that methanol and ethanol extracts of *Azadirachta indica* inhibited the growth of *Aspergillus flavus*, *Alternaria solani*, and *Cladosporium* sp. (Shrivastava & Swarnkar, 2014).

The antifungal activity of *Azadirachta indica* L. was investigated in a study against *Alternaria solani* Sorauer, and with a MIC of 0.19 mg, the ethyl acetate fraction was shown to be the most effective in inhibiting fungal growth, and it was also more effective than the fungicide (metalaxyl + mancozeb), which has a MIC of 0.78 mg (Jabeen *et al.*, 2013).

Antihelmethic effects

Diseases caused by parasitic helminths continue to be a severe production limitation in livestock, particularly in small ruminants in the tropics and subtropics. The main impact of parasite infections in the developing countries is in direct and prospective productivity losses. The majority of the losses caused by nematode parasite infections are subclinical, and economic analyses demonstrate that the financial consequences of internal parasitism are significant. *A. indica* leaves were fed to animals without being processed, not even locally (Tibebu *et al.*, 2017).

Antidiabetic action

Various animal models were used to assess the hypoglycemic and anti-hyperglycemic effects of *A. indica* plant parts. Aqueous leaf extracts of *A. indica* had an anti-hyperglycemic effect in normal and streptozotocin-induced diabetic animals but had little or no impact on peripheral glucose use or hepatic glycogen metabolism (Chattopadhyay, 1996).

A. indica has a blood-lowering impact leaf extract was found to be statistically higher than *Catharanthus roseus*, *Gymnema sylvestre*, and *Ocimum sanctum* due to significant blockage of the inhibitory effect of serotonin on insulin secretion mediated by glucose or peripheral utilisation of glucose and glycogenolic effect due to epinephrine action blockage. Scientists speculated that because *A. indica* extract demonstrated antiperoxidative, hypoglycemic, and cortisol-lowering properties, it might potentially control corticosteroid-induced diabetes mellitus (Kar *et al.*, 2003).

Furthermore, the oral consumption of *A. indica* at doses of 100 and 200 mg kg^{-1} bw for a duration of 45 days, as part of a polyherbal preparation referred to as "hyponidd," resulted in a reduction of diabetes complications such as glycosylated haemoglobin, plasma thiobarbituric acid reactive substances, and hydroperoxides, while also increasing levels of endogenous antioxidants, specifically plasma reduced glutathione and vitamin C, in streptozotocin-induced diabetic animals (Babu & Prince, 2004).

Furthermore, in normal and alloxan-induced diabetic animal models, Khosla *et al.* (2000) demonstrated that 2 weeks prior to alloxan treatment, pretreatment of rabbits with *A. indica* leaf extract or seed oil administration partially prevented the rise in blood glucose levels when compared to control diabetic animals. After 4 weeks of dosing, it likewise produced substantial hypoglycemia effects equivalent to glibenclamide.

Wound healing effect

Neem oil has active compounds that aid in the healing process. Because it immediately aids the skin's ability to preserve its natural state while healing. It also contains a high concentration of essential fatty acids, which serve to keep the skin moist and soft during the process. In addition to skin restructuring, antibacterial action of neem leaf extracts and seed oil keeps the lesion free of microorganisms, reducing healing time. Neem also plays a significant part in wound healing by inhibiting inflammation, which lengthens the healing process. Finally, it promotes the production of granulation tissue, elastin, and collagen (Osunwoke Emeka *et al.*, 2013).

Anti-ulcer activity

Human stomach acid hypersecretion, as well as gastro-esophageal and gastroduodenal ulcers, were reported to be reduced by neem bark extract. After 10 weeks, the duodenal ulcers were practically totally healed, whereas one esophageal ulcer and one stomach ulcer were fully cured after 6 weeks (Srivastava *et al.*, 2020).

Orodental protection

A neem-extract dental gel considerably reduced plaque and bacteria (*Streptococcus mutans* and *Lactobacillus* species) when compared to a commercially available mouthwash containing the germicide chlorhexidine gluconate (0.2% w/v). According to early research, neem suppressed *Streptococcus mutans* (the bacteria that causes tooth decay) and corrected incipient carious lesions (i.e., primary dental caries) (Srivastava *et al.*, 2020).

Gingivitis and periodontitis have been treated using neem leaves. Neem has also been demonstrated to be more effective in the treatment of oral infections and in the inhibition of plaque formation in periodontal diseases (Subapriya & Nagini, 2005).

Contraceptive

The addition of aqueous sodium nimbidinate salt to rat and human semen resulted in varying percentages of sperm mortality. Neem oil has been shown to have spermicidal activity against rhesus monkey human spermatozoa in vitro, and when used intra vaginally, it prevents pregnancy in rats with a concentration of 20 microliter and in rhesus monkey and women with a concentration of about 10 milliliters, and an oral dose as low as 25 microliter prevents implantation in rats and has no side effects when used repeatedly. Similarly, Neem extract (Nim-76) has been proven to be more efficient than raw neem oil as a spermicidal with no change in hormonal parameters values (Nishan & Subramanian, 2014)**.**

Aqueous extract of old and fragile leaves kills 100% of human spermatozoa in 20 seconds without changing their shape (head, midpiece and tail) (Biswas *et al.*, 2002). As a result, 100% sperm death might be attributed to a blockage of some metabolic process, such as energy usage, which would require additional research (Khillare & Shrivastav, 2003).

A single intravenous dose of neem oil has a long-term contraceptive effect in male rats, according to the researchers. The antifertility effect was examined for 8 months and was shown to be a viable alternative to vasectomy. There were no inflammatory or obstructive alterations in the epididymis or vas deferens. Blood testosterone levels were unchanged. Praneem, a purified neem seed extract, has been shown in rats, baboons, and monkeys to trigger pregnancy termination through bleeding and a drop in progesterone levels. It has also been found to prevent pregnancy in primates (Khillare & Shrivastav, 2003).

Hepatoprotective activity

In rats, an aqueous extract of neem leaf was demonstrated to protect against paracetamol-induced liver necrosis. After ingestion of the neem leaf aqueous extract, serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma glutamyl transpeptidase (GGT) levels were significantly reduced (Biswas *et al.*, 2002).

Immunomodulatory and growth promoting

During an experiment aimed at examining the impact of neem leaf infusion on broiler chicks, it was observed that the inclusion of neem infusion in their fresh drinking water at a concentration of 50 ml liter^{-1} had positive effects on their growth promotion, as well as immunomodulatory responses. Specifically, the results revealed that neem infusion significantly enhanced the antibody titre, growth performance, and overall gross return (Durrani *et al.*, 2008).

Another study looked at the effects of giving powdered dry *A. indica* on humoral and cell-mediated immune responses in broilers, and the results showed that giving *A. indica* (2 g kg^{-1}) significantly enhanced antibody titres against the NCDV antigen (Sadekar *et al.*, 1998).

Antinephrotoxicity effect

The effects of *Azadirachta indica* (MLEN) methanolic leaves extract on cisplatin- (CP-) produced nephrotoxicity and oxidative stress in rats were studied, and the results demonstrated that the extract successfully rescues the kidney from CP-mediated oxidative damage.

Furthermore, PCR findings for caspase-3, caspase-9, and Bax genes were shown to be downregulated in MLEN-treated groups (Abdel Moneim *et al.*, 2014).

Antisnake venom activity

Mukherjee *et al.* (2008) isolated and studied the mechanism of PLA2 inhibition by a snake venom phospholipase A2 (PLA2) inhibitor (AIPLAI) from the leaves of *A. indica*.

NANOPARTICLES

Plant-mediated green synthesis of nanoparticles is a widely established biomimetic approach for producing biocompatible and biodegradable nanoparticles on a large scale. This method is simple, fast, and reproducible, and it was created utilizing bioresources. Plants used in this technology are generally naturally and abundantly accessible in the normal flora, making the green synthesis of nanoparticles a cost-effective procedure. The green biosynthesis of nanoparticles is important because it is free of physical and chemical contamination (Sohail *et al.*, 2020).

Azadirachta indica, is well-known for its several uses, particularly its therapeutic properties. Terpenoids and flavanones, which function as reducing and capping agents and aid in the stabilisation of nanoparticles, are among the phytochemicals found in Neem (Zambri *et al.*, 2019) (Table 3).

Table 3. Nanoparticles of *Azadirachta indica* A. Juss. and their activities.

Nanoparticles	Activity
ZnO nanoparticles	Antibacterial activity (Sohail *et al.*, 2020)
Ag nanoparticles	Antimicrobial activity (Girish, 2018, Antioxidant Activity And Cytotoxicity (Kumari *et al.*, 2022)
S-CaO nanoparticles	Antibacterial activity (Patil *et al.*, 2022)
Co_3O_4 nanoparticles	Breakdown of toxic textile dye waste, Antibacterial activity (Patil *et al.*, 2022)
Cr_5O_{12} shell nanoparticles	Antibacterial activity, Anti-fungal activity (Patil *et al.*, 2022)
MoO_3 nanoparticles	Antibacterial activity, Anti-fungal activity (Patil *et al.*, 2022)

ZnO nanoparticles

The disc diffusion method was used to test the antibacterial potential of the green ZnO-NPs (size 20 nm) fabricated here against bacterial species including Gram-positive bacteria (*Streptococcus pyogenes*, *Bacillus subtilis*, and *Staphylococcus aureus*) and a Gram-negative bacterium (*Escherichia coli*). ZnO-NPs outperformed methicillin in terms of antibacterial activity against these bacterial species. (Sohail *et al.*, 2020).

Ag nanoparticles

The findings indicated antibacterial action, indicating that cotton cloths infused with biologically produced AgNPs might be used for wound dressing (Girish, 2018).

Newly produced AgNPs inhibited the growth of gentamycin and ampicillin-resistant *Klebsiella pneumoniae*, gentamicin and piperacillin-resistant *Salmonella typhi*, fluconazole-resistant *Candida albicans*, and various drug-resistant *Escherichia coli* (Girish, 2018).

Neem-mediated biosynthesized NPs with sizes of 70-80 nm inhibited urinary tract infection (UTI) pathogens such as *S. aureus*, *Proteus* sp., *Pseudomonas* sp., and *Escherichia coli* significantly (Girish, 2018).

Green synthesized AgNPs were from 1 mM $AgNO_3$ solution using aqueous leaf extract of neem and demonstrated antibacterial action against *Salmonella typhi* and *Klebsiella pneumoniae* (Girish, 2018).

After 30 minutes of contact, this silver nanoparticle-coated polyurethane foams (PU) was capable of eliminating the whole load of bacteria (*Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*) from water samples with starting loads of $1x10^5$ and $1x10^6$ CFU ml^{-1}. The water treated with the control sample (pure PU) grew significantly on the plates. Even after 30 minutes of treatment, the AgNPs had stable binding with PU and did not mix with water (Girish, 2018).

Antimicrobial activity of AgNPs produced from neem leaves against Gram-positive (*Staphylococcus aureus*) and Gram-negative (*Escherichia coli*) bacteria was investigated. AgNPs had strong antibacterial effectiveness, with zones of inhibition seen against *S. aureus* and *E. coli* of roughly 10 mm and 12 mm for 50 μg ml^{-1}, respectively, and 13 mm and 15 mm for 100 μg ml^{-1} (Girish, 2018).

AgNPs made from aqueous neem leaf extract and aqueous solution (1 mM) of $AgNO_3$ were efficient against Gram-positive (*Bacillus subtilis*) and Gram-negative (*Escherichia coli*) bacteria (Girish, 2018).

The inhibitory zones observed suggested that the produced NPs had the highest antibacterial activity when compared to the plant extract or AgNO3 solution applied separately. The antibacterial activity of AgNPs against disease-causing bacteria *Bacillus subtilis*, *Klebsiella planticola*, *Klebsiella Pneumoniae*, *Staphylococcus* sp., and *Escherichia coli* was tested using neem leaf extract (Girish, 2018).

At 90 μl concentration, produced AgNPs had considerable antibacterial action against all tested bacteria, outperforming ampicillin. Gram-positive (*Micrococcus* sp., *Bacillus* sp., and *Staphylococcus* sp.) and Gram-negative (*Klebsiella* sp. and *Escherichia coli*) bacteria were inhibited by AgNPs produced from 1 mM $AgNO_3$ solution and aqueous leaf extract of neem. AgNPs were synthesized by combining an aqueous extract of neem leaves with silver salt. At 12 mg ml^{-1} of AgNPs, the maximum zone of clearing was 6 mm (Girish, 2018).

In a research, silver nanoparticles (Ag-NPs) were synthesised from *Azadirachta indica* aqueous extract and examined for in vitro antioxidant activity and cytotoxicity against MCF-7 and HeLa cells. *Azadirachta indica* aqueous extract was able to bio-reduce $AgNO_3$ to AgNPs (Kumari *et al.*, 2022).

The aqueous extract of neem leaves efficiently reduces several forms of cell carcinomas. Furthermore, researchers have shown that limonoid-derived neem chemicals have potent anticancer properties. According to a recent study, ethanolic extracts of neem leaves inhibited cell growth and induced apoptosis in both the estrogen-independent MDAMB-231 and estrogen-dependent MCF-7 human breast cancer cell lines (Kumari *et al.*, 2022).

In MCF-7 and HeLa cell lines, the MTT assay was utilised to investigate the anticancer activity of different dosages of biosynthesized Ag-NPs and aqueous leaf extract. In both MCF-7 and HeLa cell lines, biosynthesized Ag-NPs and aqueous leaf extract displayed dose-dependently greater cytotoxic activity (Kumari *et al.*, 2022).

The IC50 values were determined for biosynthesized Ag-NPS, aqueous leaf extract, and the standard cisplatin for MCF-7 and HeLa cell lines. The average IC50 values for MCF-7 cell lines were 0.90 ± 0.07 mg ml^{-1}, 1.85 ± 0.01 mg ml^{-1}, and 0.56 ± 0.08 mg ml^{-1}, respectively, while for HeLa cell line they were 0.85 ± 0.01 mg ml^{-1}, 1.76 ± 0.08 mg ml^{-1}, and 0.45 ± 0.10 mg ml^{-1}, respectively. The biosynthesized Ag-NPs displayed a higher proportion of cytotoxicity as compared to the aqueous leaf extract. These data reveal that Ag-NPs significantly inhibited the growth of both MCF-7 and HeLa cell lines (Kumari *et al.*, 2022).

The current study revealed that incubation both cancer cell lines, MCF-7 and HeLa, with biosynthesized Ag-NPs reduced their viability and raised the number of dead cells considerably with a higher concentration of biosynthesized Ag-NPs. Even at extremely low concentrations, Ag-NPs revealed 20% dead cells (Kumari *et al.*, 2022).

The current green synthesis procedure might be improved to create monodispersed Ag-NPs, emphasising their potential therapeutic application in cancer and other disorders due to their non-toxicity, low cost, and environmental safety (Kumari *et al.*, 2022).

S-CaO nanoparticles

The antibacterial efficacy of sucrose capped and uncapped CaO NPs against *Bacillus* bacteria was investigated. It was discovered that sucrose-capped CaO-NPs have greater zones of inhibition than uncapped CaO-NPs (Patil *et al.*, 2022).

Co_3O_4 nanoparticles

Co_3O_4-NPs were discovered to be responsible for the breakdown of toxic textile dye waste, which is responsible for protein contact dermatitis. These Co_3O_4-NPs have the potential to be employed in the catalytic reduction of 4-nitrophenol and 4-nitroaniline to phenylene amino compounds (Patil *et al.*, 2022).

Finally, using the disc plate method, researchers tested their antibacterial activity against *Staphylococcus aureus*, *Bacillus subtilis*, *Pseudomonas aeruginos*, and *Escherichia coli* (The zone of inhibition was found to be comparable to that exhibited by chloramphenicol) (Patil *et al.*, 2022).

Cr_5O_{12} shell nanoparticles

Researchers also used a well diffusion experiment to investigate the anti-microbial activity of Cr_5O_{12} shell nanoparticles and discovered that bacterial strains *Staphylococcus aureus* and *Enterobacter* are more susceptible to being destroyed by Cr_5O_{12} shell nanoparticles than fungus strain *C. albicans*. Cell wall damage might be the mechanism of its antimicrobial action (Patil *et al.*, 2022).

MoO_3 nanoparticles

Researchers investigated the antibacterial efficacy of MoO_3 NPs against bacterial strains *Staphylococcus aureus*, *Escherichia coli* and fungal strains *Aspergillus flavus*, *Candida albicans* using the agar plate technique. They discovered that MoO_3 NPs have larger zones of inhibition as compared to ketoconazole (Patil *et al.*, 2022).

TOXICOLOGY

Scientists examined a variety of toxicological research conducted between 1970 and 1987. They conclude that leaf and/or bark extracts, as well as isolated limonoids, have very low acute toxicity, especially when given orally. However, there have been anecdotal cases of renal failure in Ghanaians who consumed *A. indica* leaf tea over a lengthy period of time. Despite the highly extensive traditional use of leaf tea in India and elsewhere, and despite the lack of reported incidences of renal failure or other adverse effects in scientific literature, more research into chronic toxicity should precede any long-term administration programmes There have been instances of acute toxicity in rats and rabbits at low dosages of crude seed oil. This might be due to aflatoxin, a very poisonous byproduct of the fungus *Aspergillus flavus* that frequently contaminates wet neem seed: subsequent toxicological testing in rats using oil produced from clean aflatoxin-free neem kernels revealed no deleterious effects even at 5,000 mg kg^{-1}. Local gatherers should be encouraged not to collect fallen neem seed from under trees and to dry seed soon after gathering to minimise aflatoxin contamination. Another possibility for the reported toxicity is contamination with poisonous seed of *Melia azedarach*, which is frequently misidentified with *A. indica*. As a topical agent for skin issues, neem is not mutagenic and is non-irritant. The 'Praneem' contraceptive formulation has been shown to be safe when used for 7 days in a row (Bodeker *et al.*, 2001).

POTENTIAL COMMERCIAL APPLICATIONS

Researchers from all around the world are studying the Neem tree and its qualities to develop new anti-infection medications. Different parts of the Neem tree are frequently used in the production of cleansers, skin creams/salves, shampoos, toothpastes, beauty aids, and toiletries. Its principal applications in agriculture include being a bug spray in food storage, soil transformation, manure proficiency booster, and potent foliar insecticide. Ranchers now have a potent anti-bug remedy in the form of neem oil. Neem fresh leaves are also used on a small scale for the capacity of nutrition grain at home effectively, although this is done on a limited scale. Using neem cake in soil results in larger and more advantageous plants with minimal or no problems related to pests or diseases. Neem cake is more extravagant in plant-accessible supplements than fertilizers; it kills harming nematodes, advanced vast populace of night crawlers, helped keep nitrogen in the dirt accessible for plants and give critical assurance from bugs (Giri *et al.*, 2019). Neem has been examined in heart disease, cancer, and diabetic models. This effort, along with others not included in this review, has resulted in the creation of patentable technology for clinical and commercial applications (Islas *et al.*, 2020). Neem subsidiaries may fill in as reasonable and generally accessible contraceptives (Giri *et al.*, 2019). It is crucial to note that, unlike standard pill formulations, the use of oil does not interfere with hormone cycle control because it is administered externally. Azadirachtin inhibits the respiratory chain by uncoupling mitochondrial oxidative phosphorylation. Other components of neem that contribute to its antibacterial action include nimbidin, nimbin, nimbolide, gedunin, mahmoodin, margolone, and cyclic trisulfide. Neem in diabetes, and the development of an unique herbal combination in which Neem acts as a beta cell stimulant, boosting the generation of native insulin. These applications are based on various intriguing features found in neem extracts and aim to improve overall quality of life (Islas *et al.*, 2020).

CONCLUSION

In recent years, ethnobotanical and traditional applications of natural chemicals, particularly those of plant origin, have attracted a lot of interest since they have been thoroughly evaluated for efficacy and are usually thought to be safe for human consumption. It is the most traditional strategy in the quest for novel compounds for the treatment of various ailments. The article highlights the traditional, pharmacological and commercial importance of *Azadirachta indica*. Neem tree belonging to family Meliaceae is native to India. Neem is versatile medicinal plant; variety of phytochemicals have been isolated from various extracts of different parts of the plant. It is used for variety of application. Flowers, fruits, oil, leaves, roots, bark, twigs and seed have been used for medicinal and dietary applications. Antioxidant Activity, Anti-cancer, Anti-inflammatory, Anti-bacterial, Antiviral Activity, Antifungal Activity, Antihelmethic effects, Antidiabetic action, Wound healing effect, Activity against ulcer, Orodental protection, Contraceptive, Hepatoprotective activity, Immunomodulatory and Growth Promoting, Antinephrotoxicity Effect and Antisnake venom activity are few of the reported activities. On a commercial level there is very limited exploration. It has several applications in both people and animals as a therapy for a variety of illnesses caused by microorganisms and other factors. The majority of the produced nanoparticles have shown to be useful in a variety of scientific fields. It may be inferred that various metal nanoparticles can be made utilizing *A. indica* leaf extracts and assessed for various applications. But recent studies have reported its use in variety of commercial applications. Further investigation of the reported properties would lead to increase the use of neem on the commercial level.

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REFERENCES

Abdel Moneim A.E., Othman M.S. & Aref A.M. (2014). *Azadirachta indica* attenuates cisplatin-induced nephrotoxicity and oxidative stress. *BioMed Research International*, 2014: 1-11.

Abdullah-Al-Emran, Shahed S., Ahmed F., Saha S., Das S. & Bachar S.C. (2011). Evaluation of brine shrimp lethality and antimicrobial activity of *Azadirachta indica* leaf extract on some drug resistance bacteria in Bangladesh. *Pharmacognosy Journal*, 3(20): 66-71.

Babu P.S. & Prince P.S. (2004). Antihyperglycaemic and antioxidant effect of hyponidd, an Ayurvedic herbomineral formulation in streptozotocin-induced diabetic rats. *Journal of Pharmacy and Pharmacology*, 56(11): 1435-1442.

Badam L., Joshi S. & Bedekar S. (1999). 'In vitro' antiviral activity of neem. *The Journal of Communicable Diseases*, 31(2): 79-90.

Bansode T. & Salalkar B. (2015). Phytochemical analysis of some selected Indian medicinal plants. *International Journal of Pharmacy and Biological Sciences*, 6(1): 550-556.

Bhowmik D., Chiranjib Y.J., Tripathi K. & Sampath Kumar K. (2010). Herbal remedies of *Azadirachta indica* and its medicinal application. *Journal of Chemical and Pharmaceutical Research*, 2(1): 62-72.

Biswas K., Chattopadhyay I., Banerjee R. & Bandyopadhyay U. (2002). Biological activities and medicinal properties of neem (*Azadirachta indica*). *Current Science*, 82(11): 1336-1345.

Bodeker G., Burford G., Chamberlain J. & Bhat K. (2001). The underexploited medicinal potential of *Azadirachta indica* A. Juss. (Meliaceae) and *Acacia nilotica* (L.) Willd. ex Del. (Leguminosae) in sub-Saharan Africa: A case for a review of priorities. *International Forestry Review*, 3(4): 285-298.

Chattopadhyay R. (1996). Possible mechanism of antihyperglycemic effect of *Azadirachta indica* leaf extract. Part IV. *General Pharmacology*, 27(3): 431-434.

Chattopadhyay R. (1998). Possible biochemical mode of anti-inflammatory action of Azadirachta indica A. Juss. in rats. *Indian Journal of Experimental Biology*, 36(4): 418-420.

Damtew M. (2022). A review on chemical composition, medicinal value and other applications of *Azadirachta indica*. *Agricultural and Biological Research*, 38(2): 268-272.

Dar R.A., Shahnawaz M. & Qazi P.H. (2017). General overview of medicinal plants: A review. *Journal of Phytopharmacology*, 6(6): 349-351.

Durrani F., Chand N., Jan M., Sultan A., Durrani Z. & Akhtar S. (2008). Immunomodulatory and growth promoting effects of neem leaves infusion in broiler chicks. *Sarhad Journal of Agriculture (Pakistan)*, 24(4): 655-659.

Eid A., Jaradat N. & Elmarzugi N. (2017). A Review of chemical constituents and traditional usage of Neem plant (*Azadirachta indica*). *Palestinian Medical and Pharmaceutical Journal*, 2(2): 75–81.

Ghimeray A., Jin C-W., Ghimire B. & Cho D. (2009). Antioxidant activity and quantitative estimation of azadirachtin and nimbin in *Azadirachta indica* A. Juss grown in foothills of Nepal. *African Journal of Biotechnology*, 8(13): 3084-3091.

Ghonmode W., Balsaraf O., Tambe V., Saujanya K., Patil A. & Kakde D. (2013). Comparison of the antibacterial efficiency of neem leaf extracts, grape seed extracts and 3% sodium hypochlorite against E. feacalis - An in vitro study. *Journal of International Oral Health*, 5(6): 61-66.

Giri R.P., Gangawane A. & Giri S. (2019). Neem the wonder herb: A short review. *International Journal of Trend in Scientific Research and Development*, 3(3): 962-967.

Girish K. (2018). Neem (*Azadirachta indica* A. Juss) as a source for green synthesis of nanoparticles. *Asian Journal of Pharmaceutical and Clinical Research*, 11(3): 15-18.

Gupta S.C., Prasad S., Tyagi A.K., Kunnumakkara A.B. & Aggarwal B.B. (2017). Neem (*Azadirachta indica*): An Indian traditional panacea with modern molecular basis. *Phytomedicine*, 34: 14-20.

Habluetzel A., Lucantoni L. & Esposito F. (2009). Azadirachta indica as a public health tool for the control of malaria and other vector-borne diseases. *Indian Journal of Medical Research*, 130(2): 112-114.

Hashmat I., Azad H. & Neem A. (2012). Neem (*Azadirachta indica* A. Juss) - A Nature's Drugstore: An overview. *International Research Journal of Biological Sciences*, 1(6): 76-79.

Islas J.F., Acosta E., Zuca G., Delgado-Gallegos J.L., Moreno-Treviño M.G., Escalante B. & Moreno-Cuevas J.E. (2020). An overview of Neem (*Azadirachta indica*) and its potential impact on health. *Journal of Functional Foods*, 74: 1-13.

Jabeen K., Hanif S., Naz S. & Iqbal S. (2013). Antifungal activity of Azadirachta indica against Alternaria solani. *Journal of Life Sciences and Technologies*, 1(1): 89-93.

James S. & Lond M. (1903). The basil and the neem. *British Medical Journal*, 1(2203): 677.

Jhariya M.K., Raj A., Sahu K. & Paikra P. (2011). Neem- A tree for solving global problem. *Indian Journal of Applied Research*, 3(10): 1-3.

Kar A., Choudhary B.K. & Bandyopadhyay N.G. (2003). Comparative evaluation of hypoglycaemic activity of some Indian medicinal plants in alloxan diabetic rats. *Journal of Ethnopharmacology*, 84(1): 105-108.

Katsayal U.A., Nadabo Y.A., & Isiorho V.J. (2008). Effects of methanol extract of Azadirachta indica leaves on the histology of liver and kidney of wister rats. *Nigerian Journal of Pharmaceutical Sciences*, 7(1): 9-14.

Kaur G., Sarwar Alam M. & Athar M. (2004). Nimbidin suppresses functions of macrophages and neutrophils: Relevance to its antiinflammatory mechanisms. *Phytotherapy Research*, 18(5): 419-424.

Khattak S.G., Gilani S.N. & Ikram M. (1985). Antipyretic studies on some indigenous Pakistani medicinal plants. *Journal of Ethnopharmacology*, 14(1): 45-51.

Khillare B. & Shrivastav T. G. (2003). Spermicidal activity of *Azadirachta indica* (neem) leaf extract. *Contraception*, 68(3): 225-229.

Khosla P., Bhanwra S., Singh J., Seth S. & Srivastava R. (2000). A study of hypoglycaemic effects of *Azadirachta indica* (Neem) in normaland alloxan diabetic rabbits. *Indian Journal of Physiology and Pharmacology*, 44(1): 69-74.

Kumar R., Sharma S. & Devi L. (2018). Investigation of total phenolic, flavonoid contents and antioxidant activity from extracts of *Azadirachta indica* of Bundelkhand region. *International Journal of Life-Sciences Scientific Research*, 4(4): 1925-1933.

Kumar V.S. & Navaratnam V. (2013). Neem (*Azadirachta indica*): Prehistory to contemporary medicinal uses to humankind. *Asian Pacific Journal of Tropical Biomedicine*, 3(7): 505-514.

Kumari A., Kumar R., Maurya S., Choudhary J. & Kumar S. (2013). Antifungal efficacy of aqueous extracts of neem cake, Karanj cake and vermicompost against some phytopathogenic fungi. *The BioScan- An International Quarterly Journal of Life Sciences*, 8(2): 671-674.

Kumari S.A., Patlolla A.K. & Madhusudhanachary P. (2022). Biosynthesis of silver nanoparticles using *Azadirachta indica* and their antioxidant and anticancer effects in cell lines. *Micromachines*, 13(9): 1-11.

Mahfuzul Hoque M., Bari M., Inatsu Y., Juneja V. & Kawamoto S. (2007). Antibacterial activity of guava (*Psidium guajava* L.) and neem (*Azadirachta indica* A. Juss.) extracts against foodborne pathogens and spoilage bacteria. *Foodborne Pathogens and Disease*, 4(4): 481-488.

Maji S. & Modak S. (2021). Neem: Treasure of natural phytochemicals. *Chemical Science Review and Letters*, 10(39): 396-401.

Mondall N., Mojumdar A., Chatterje S., Banerjee A., Datta J., & Gupta, S. (2009). Antifungal activities and chemical characterization of Neem leaf extracts on the growth of some selected fungal species in vitro culture medium. *Journal of Applied Sciences and Environmental Management*, 13(1): 49-53.

Mosaddek A.S. & Rashid M.M.U. (2008). A comparative study of the anti-inflammatory effect of aqueous extract of Neem Leaf and dexamethasone. *Bangladesh Journal of Pharmacology*, 3(1): 44-47.

Mukherjee A.K., Doley R. & Saikia D. (2008). Isolation of a snake venom phospholipase A2 (PLA2) inhibitor (AIPLAI) from leaves of *Azadirachta indica* (*Neem*): Mechanism of PLA2 inhibition by AIPLAI *in vitro* condition. *Toxicon*, 51(8): 1548-1553.

Nishan M. & Subramanian P. (2014). Pharmacological and non-pharmacological activity of *Azadirachta indica* (Neem) – A review. *International Journal of Biosciences*, 5(6): 104-112.

Nunes X.P., Silva F.S., Almeida J.R.G.D.S., Barbosa Filho J.M., de Lima J.T., de Araújo Ribeiro L.A. & Júnior L.J.Q. (2012). Biological oxidations and antioxidant activity of natural products. In: *Phytochemicals as nutraceuticals – Global approaches to their role in nutrition and health*. IntechOpen, London, pp. 1–20.

Osunwoke Emeka A., Olotu Emamoke J., Allison Theodore A. & Onyekwere Julius C. (2013). The wound healing effects of aqueous leave extracts of *Azadirachta indica* on Wistar rats. *Journal of Natural Sciences Research*, 3(6): 181-186.

Othman F., Motalleb G., Lam Tsuey Peng S, Rahmat A, Basri R, & Pei Pei C. (2012). Effect of Neem Leaf Extract (*Azadirachta indica*) on c-Myc Oncogene Expression in 4T1 Breast Cancer Cells of BALB/c Mice. *Cell Journal (Yakhteh)*, 14(1): 53-60.

Patil S., Chaudhari R. & Nemade M. (2022). *Azadirachta indica* leaves mediated green synthesis of metal oxide nanoparticles: A review. *Talanta Open*, 5: 1-10.

Prashant G.M., Chandu G.N., Murulikrishna K.S. & Shafiulla M.D. (2007). The effect of mango and neem extract on four organisms causing dental caries: *Streptococcus mutans*, *Streptococcus salivavius*, *Streptococcus mitis*, and *Streptococcus sanguis*: An *in vitro* study. *Indian Journal of Dental Research*, 18(4): 148-151.

Rahmani A. & Aly S. (2015). *Nigella sativa* and its active constituents thymoquinone shows pivotal role in the diseases prevention and treatment. *Asian Journal of Pharmaceutical and Clinical Research*, 8(1): 48-53.

Sadekar R.D., Kolte A.Y., Barmase B.S. & Desai V.F. (1998). Immunopotentiating effects of Azadirachta indica (Neem) dry leaves powder in broilers, naturally infected with IBD virus. *Indian Journal of Experimental Biology*, 36(11): 1151-1153.

Saleem S., Muhammad G., Hussain M.A. & Bukhari S.N. (2018). A comprehensive review of phytochemical profile, bioactives for pharmaceuticals, and pharmacological attributes of *Azadirachta indica*. *Phytotherapy Research*, 32(7): 1241-1272.

Shrivastava D. & Swarnkar K. (2014). Antifungal Activity of leaf extract of Neem (*Azadirachta indica* Linn). *International Journal of Current Microbiology and Applied Sciences*, 3(5): 305-308.

Sithisarn P., Supabphol R. & Gritsanapan W. (2005). Antioxidant activity of Siamese neem tree (VP1209). *Journal of Ethnopharmacology*, 99(1): 109-112.

Sohail M., Rehman M., Hussain S.Z., Huma Z., Shahnaz G., Qureshi O.S., Khalid Q., Mirza S., Hussain I. & Webster T.J. (2020). Green synthesis of zinc oxide nanoparticles by Neem extract as multi-facet therapeutic agents. *Journal of Drug Delivery Science and Technology*, 59: 1-11.

SriRamaMurthy K., Pullaiah, T., Bahadur B. & Krishnamurthy K. (2017). *Ethnobotany of the Neem Tree (Azadirachta Indica A. Juss): A Review*. Ethnobotany of India: The Indo-Gangetic Region and Central India, Apple Academic Press, pp. 573-599.

Srivastava S.K., Agrawal B., Kumar A. & Pandey A. (2020). Phytochemicals of *Azadirachta indica* source of active medicinal constituent used for cure of various diseases: A review. *Journal of Scientific Research*, 64(1): 385-390.

Subapriya R. & Nagini S. (2005). Medicinal properties of Neem Leaves: A review. *Current Medicinal Chemistry. Anti-Cancer Agents*, 5(2): 149-146.

Sujarwo W., Keim A.P., Caneva G., Toniolo C. & Nicoletti M. (2016). Ethnobotanical uses of neem (*Azadirachta indica* A.Juss.; *Meliaceae*) leaves in Bali (Indonesia) and the Indian subcontinent in relation with historical background and phytochemical properties. *Journal of Ethnopharmacology*, 189: 186-193.

Tibebu A., Haile G. & Kebede A. (2017). Review on medicinal value and other application of neem tree: Senior seminar on animal health. *Arch. Journal of Immunology and Vaccines*, 2(2): 16-24.

Tiwari V., Darmani N., Yue B. & Shukla D. (2010). *In vitro* antiviral activity of neem (*Azardirachta indica* L.) bark extract against herpes simplex virus type-1 infection. *Phytotherapy Research*, 24(8): 1132-1140.

Tripathi P. & Singh A. (2020). *Acacia nilotica*, *Albizia saman*, *Azadirachta indica*: *Ethanobotany and Medicinal Uses.* Modern Research in Botany, Book Publisher International, Hooghly, West Bengal, India, 1, pp. 96-103.

Uzzaman S. (2020). Pharmacological activities of Neem (*Azadirachta indica*): A review. *International Journal of Pharmacognosy and Life Science*, 1(1): 38-41.

Weldegerima B. (2009). Review on the importance of documenting ethnopharmacological information on medicinal plants. *African Journal of Pharmacy and Pharmacology*, 3(9): 400-403.

Yadav R.N.S. & Agarwala M. (2011). Phytochemical analysis of some medicinal plants. *Journal of Phytology*, 3(12): 10-14.

Yerima M., Jodi S., Oyinbo K., Maishanu H., Farouq A., Junaidu A., Al-Mustapha M. & Shinkafi A. (2012). Effect of neem extracts (*Azadirachta indica*) on bacteria isolated from adult mouth. *Nigerian Journal of Basic and Applied Sciences*, 20(1): 64-67.

Zambri N., Taib N., Latif F. & Mohamed Z. (2019). Utilization of neem leaf extract on biosynthesis of iron oxide nanoparticles. *Molecules*, 24(20): 1-12.

Zeenat F., Ravish M.S., Ahmad W. & Ahmad I. (2018). Therapeutic, phytochemistry and pharmacology of *Azadirachta indica*: A review. *International Journal of Unani and Integrative Medicine*, 2(1): 20-28.