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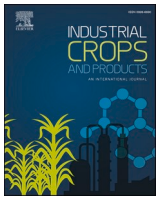

Traditional to modern perspectives on Neem (*Azadirachta indica*): A gateway to bioactive compounds, sustainable agrochemicals and industrial applications

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ABSTRACT

Azadirachta indica (Neem) is miracle tree cultivated in Indian subcontinent for around 4500 years ago owing to its medicinal and pesticidal significance due to its potential life saver phytochemical ingredients and have traditionally been used as folk medicine to treat ailments and as an agrochemicals. Despite several research confirmed that Neem includes a range of active components, a thorough compilation of references and in-depth analysis of the phytochemical profiling, pharmacological potential, traditional applications, agrochemical agents, and industrial uses of this amazing tree is lacking till date. This review attempted to compile an exhaustive review pretaining to systematic research on phytochemistry, biological properties, phytotoxic qualities, and industrial uses that have been compiled from an exhaustive literature search (1921–2025). Evidences from literature suggested that neem tree has ~186 biologically active ingredients especially 'Azadirachtin' isolated from neem plant parts. According to reports, the other bioactive substances with potential biological and medicinal properties are nimbinin and nimbidin. Many Asian and African nations have made commercial utilization of neem for the production of neem-based agrochemicals, pesticides for agriculture and extraction of beneficial compounds for the cosmetics industry. These compounds had an immense potential to treat a number of chronic diseases in plants and animals. The future research is being directed towards utilization of neem for biosynthesis of large-scale production of nanoparticles for theraptutic activities and environmental amelioration.

1. Introduction - rationale and objectives

Botanically, the name of neem was established by Antoine Laurent de Jussieu in 1830 with *Melia azadirach* Linn. as only the species, which he lated named *Azadirachta indica* A. Juss (Troup, 1921; Tewari, 1992), belongs to mahagony family Meliaceae. The family Meliaceae comprises woody pereninials belonging to nearly 50 genera comprising 640 species (Muellner et al., 2005; Stevens, 2012). The genus name has been derived from Persian word, "*Azad-e-darakht-e-Hind*", means 'free tree of India' (Suri, 2001). There are two species of *Azadirachta*: *A. excelsa*, which is endemic to South-East Asia, and *A. indica*, which is native to arid regions of the Indian subcontinent (Lemmens et al., 1995). Although Valerton identified *A. indica* var. *siamensis* in Thailand. The studies of Mabberley (1997) reported that the species does not identify any infraspecific taxa. The *Azadirachta indica* has three subspecies and varieties, *i.e. Azadirachta indica* subsp. *vartakii*; *Azadirachta indica* var. *minor*; and *Azadirachta indica* var. *siamensis* (Lauridsen et al., 1991). Commonly it is known by various other vernacular names as Indian cedar; Indian lilac; margosa tree; neem; Persian lilac; margosa; azad-daraknul-hind, etc.

Neem tree inhabits on various types of soil with preferably alkaline pH, however is sensitive to water stagnation and severe frost that results in tree decline (Tewari, 1992). Neem tree is adapted to wide range of climatic conditions and has been located thriving under sub-humid to semi-arid and arid climatic conditions across Indian subcontinent and

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worldwide (Siddiqui, 1995). Neem is widely distributed outside of its native region as introduced species, mainly in the drier (arid) tropical and subtropical zones of Asia, Africa, the Americas, Australia and the South Pacific islands; however, over 60 % of the entire neem population is found in India (Ram Mohan and Nair, 1993). Neem trees have been reported to successfully thriving in roughly 72 different nations worldwide (Fathima, 2004). It has recently been itroduced in the Caribbean, Central and South America, Australia, Saudi Arabia, the Philippines, Peninsular Malaysia, Singapore, Mauritius and Madagascar (World Agroforestry Centre, 2002). Apart from this, it is considered as an invasive species in Pacific (Australia, Fizi, Hawaii, Mauritius, Marshell Islands) (PIER, 2002) and South American countries (I3N-Brasil, 2014).

From prehistoric times to the present, *A. indica* has been used. The oldest known medical system is said to have been Siddha medicine, which was practiced in south India between 10,000 and 4000 B.C. According to Tamil (Indian) literature, the first medicinal plant to be included in the Siddha system was neem (Kumar and Navaratnam, 2013). According to the Trans-Disciplinary University's bibliographic database, 'neem' has been cited in 448 instances in 20 traditional literature texts and ancient sript concerning with ayurvedia and unani system of medicine (INMEDPLAN, 2018) owing to its immense therapeutic significance. The neem tree is the first medicinal plant mentioned in the *Sidhha* system of medicine, which is regarded as most antiquated traditional medical systems, believed to be more than 10,000 years ago. The 350-year-old palm leaf manuscript conserved at Centre for Traditional Medicine and Research, India reveals the medicinal uses of neem tree. Numerous neem tree formulations are found in books like Agathiyar Gunavagadam Bogar-7000, Agathiyar Vaithya Rathina Surukkam, and Bogar-300 (Srirangarayan et al., 2020). The United Nations has named the divine and amazing neem tree the "Tree of the 21st century" (UNEP, 2012). A report entitled "Neem: A tree for solving global problems" was published by the United States of National Academy of Science (NRC, 1992) which revealed the detailed ideas about its visions and reality of the neem tree with historial background. The neem tree holds a sacred value for Indian people to the extent that 'Neem day' is celebrated on the 1st day of the month of *Chaitra, Gudi Padwa* (April) in South India. Neem tree is a rich source of various valuabe bioactive compounds and secondary metabolites having immense therapeutic benefits besides, excellent biocidal, repellent, phytotaxic properties and many more other uses (Saleem et al., 2018). These chemical ingredients have very less toxicity to the non-targeted creature's especially beneficial insects and bees and are therefore safe to use in agriculture. Thus, pharmaceutical industries are evolving novel neem-based granular or liquid formulations as natural insecticide for use in organic agriculture. The literature cited has revealed that review articles have already been compiled to cover different aspects of *Azadirachta indica* like phytochemicals, pharmacological activities, pesticidal properties, etc. Nonetheless, a thorough compilation of references and in-depth analysis of the phytochemical profiling, pharmacological potential, traditional applications, insecticidal properties, and industrial uses of this amazing tree is lacking till date. Given the immense significance of neem, this review aims to bridge the information gap that exists between academic and industry researchers about the phytochemistry and bioactive potential uses of this miraculous sacred tree.

2. Methodology

The data acquisition for this manuscript involved the searching, screening and selection of relevant scientific literature enriched with the phytochemical, biological and pharmacological properties, along with phytotoxicity, and traditional applications of *A. indica* compiled through different print media (scientific journals) and e-databases, *e.g.*, ebooks (https://www.ebooks.com/en-in/), Google Scholar (https://scholar.google.com/), Science Direct (https://www.sciencedirect.com/), PubMed (https://pubmed.ncbi.nlm.nih.gov/), Scopus (https://www.scopus.com/), ResearchGate (https://www.researchgate.net), and Web of Science (https://www.webofscience.com/wos/). A variety of keywords were used during the literature search, including "*Azadirachta indica*", Neem", "phytochemistry", "ethnomedicial uses", "secondary metabolites", "biological effects", "pharmacological studies", "toxicity", and "traditional uses". Notably, the search encompassed articles published in the timeframe spanning from 1921–2024. The selected papers and e-contents were categorized in view of the general framework of the review (Fig. 1). The collage diagram is presented in Fig. 2 to get the clear visual representation of neem's diverse uses.

3. Traditional applications

Influenced by the traditional folk-lore medicinal properties of neem, the pharmaceutical researchers were the first to take up the task of isolation of active ingredients form neem oil. Adverse effect of the synthetic organic insecticides caused wide concern, not only among the entomologists but also among the environmentalists. This initiated the research in identifying the pesticidal properties of plant origin, and neem is one of the specie being extensively investigated by chemists and biologists worldwide. Some of the medicinal attributes of various parts of neem as mentioned in Ayurveda have been summarized below in Table 1.

There are reports of people eating tender or immature leaves of neem. It is reported that Father of the nation 'Mahatma Gandhi', who had a great regard for the nutritional benefits of greens, frequently made neem-leaf chutney and ate it with pleasure despite its intensely bitter taste. Leaf tea may be dangerous, especially if consumed in abundance over an extended period of time. There have been reports of the finding of a rare "sweet" leafing neem tree (Patrao, 1985). This neem-fruit pulp is a promising substrate for creating methane gas, and it may also serve as a carbohydrate-rich base for other industrial fermentations (Mitra, 1963). The neem tree is regarded as a panacea to cure bodily evils and has been revered as a "Village Pharmacist" (Kumar and Navaratnam, 2013).

4. Phytochemistry

The research on exploring phytochemical constituents of neem was initiated by Indian pharmaceutical chemists in 1919, which led to the identification of acidic principle in neem oil, later designated as 'margosic acid". Later, a systematic chemical research began during mid 1940s, when three active ingredients i.e. nimbin, nimbidin, and nimbinene were isolated (Neem Foundation, 1997). Multiple phytochemicals are thought to be "storehoused" in neem. The chemists of Indian origin, Sen and Banerjee (1931) gave an account of bitter principles and associated compounds present in neem oil. Later on Siddiqui (1942) evolved a method to isolate the crystalline bitter compound nimbin. Various methods and techniques for isolation have been extensively described by (Siddiqui, 1945). Mitra (1963) had also mentioned a detailed account of spaeration of these bitter principles. Soon after the discovery of chemical inhibiting locust feeding (Butterworth and Morgan, 1968), extensive research began, focusing especially on the compound azadirachtin, for its potential insectidial properties. The readers can refer to the exhaustive research article written by Morgan and Mandava (1987), Siddiqui et al. (1988), Kraus (1983), Connolly (1983), Lavie et al. (1971), Morgan and Mandava (1987) and Balandrin et al. (1988) for their significant research in neem as potential insecticide. In addition, the exhaustive literature can be found in the three volumes 'Compendium of Indian Medicinal Plants' (Rastogi and Mehrotra, 1990; 1991; 1995) that provided thorough phytochemistry analyses of neem. Koul et al. (1990), Van der Nat et al. (1991), Tewari (1992), and Govindachari (1992) provided a succinct monographic overview of 'neem' that focused on the noteworthy findings related to phytochemical research. Till date, over 300 phytochemicals have been isolated from its various plant parts (Subapriya and Nagini, 2005). Two major classes of phytochemicals: i) isoprenoids, and ii) non-isoprenoids have

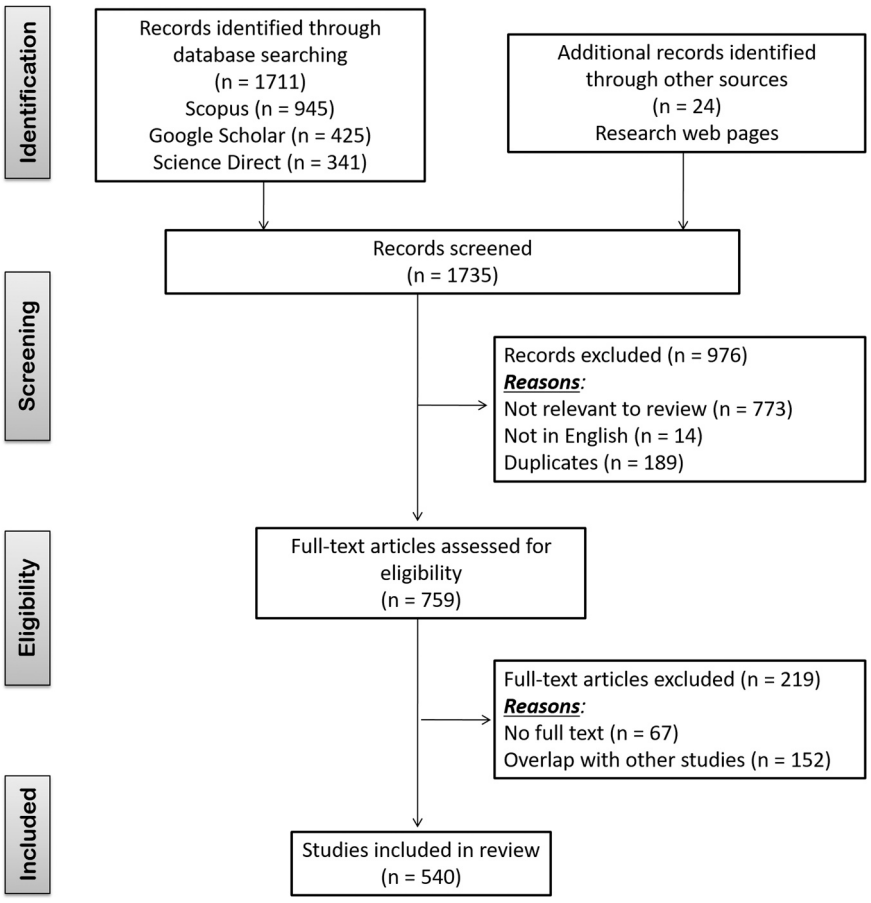

Fig. 1. Flowchart for the review methodology adopted.

been isolated (Biswas et al., 2002). A number of organic compounds have been isolated from various parts of neem, and an attempt has been made to group these compounds based on their origin in different plant parts as summarized in Table 2.

The major limonoid in seed kernel and seed oil is azadirachtin isolated by Butterworth and Morgan (1968) who reported its antifeedant properties, however, ist is also extracted from leaves and immature fruits as well (Azam et al., 2009). Azadirachtin was found in varying concentrations in neem trees growing in varying habitat and climatic conditions (Kaushik et al., 2007; Tewari et al., 2014) and also differs with phenological growth stages (Rangaswamy and Parmar, 1994). This compound was present in both green and yellow fruit, although it was not noticeable until forty days after anthesis. Yakkundi et al. (1995) found azadirachtin in fruit that was nine weeks old. As the fruit grew older, the amount of azadirachtin increased, reaching its peak when the fruit's colour changed from green to yellow at the 19th week. Sidu and Behl (1996) examined the variability in azadirachtin content obtained from the seeds during monsoon and winter season. The yield of azadirachtin-rich fraction from monsoon seed is 1.53 %, while that from winter seed is 1.26 %. Similarity, Gupta et al. (2010) reported varying concentrations of azadirachtin during summer (0.29 %) and winter season's seeds (0.81 %).

4.1. Variability in azadirachtin content

Azadirachtin, a key tetranortriterpenoid found in neem, varies in concentration significantly during different developmental stages of reproductive phenophases (Azam et al., 2009). Understanding these dynamics is crucial for maximizing yields and optimizing harvest strategies for neem-based bioactive products. Azadirachtin, the most potent limonoid in neem, varies significantly across individuals (Dhakad and Kaur, 2024) and environments conditions (Sidhu et al., 2004; Tewari et al., 2014) as presented in Table 3. Understanding the factors influencing its content is essential for optimized extraction and commercial application.

5. Biological and pharmacological activities

The bitter constituents present in neem being non-poisonous to man and potentially harmful to lower forms of life (Sarkar et al. 2021 Apr)) might have resulted in its use as a medicine in the Indian subcontinent, that later spread to parts of world. Over 300 compounds have been isolated from different parts of the neem plant out of which one-third of the compounds belong to the limonoid group of natural products, which are the major cause for the biological and pharmacological activities. Neem-based insecticides utilize almost one-third of the botanicals used in agriculture (Isman, 2006). The fact that neem crude extracts outperform than azadirachtin based formulations even at low concentrations (25 mg/lit) (Boursier et al., 2011). Neem seed extracts, even aqueous, have been reported to exhibit biological action towards various target organisms both in the field and in the lab, albeit to differing degrees (Fauziah et al., 2012; Selma et al., 2013).

Neem is one of the most promising medicinal plants showing different pharmaceutical and medicinal activity. Neem extracts are recognised to have a wide range of pharmacological qualities, particularly those that are antibacterial and antifungal (Table 4). Because these qualities are commercially exploited, neem trees have long been used to treat a wide range of ailments due to its rich composition of bioactive compounds like azadirachtin, nimbin, and other limonoids. Parts of the neem tree (pencil thickness twigs) have also been employed as a general

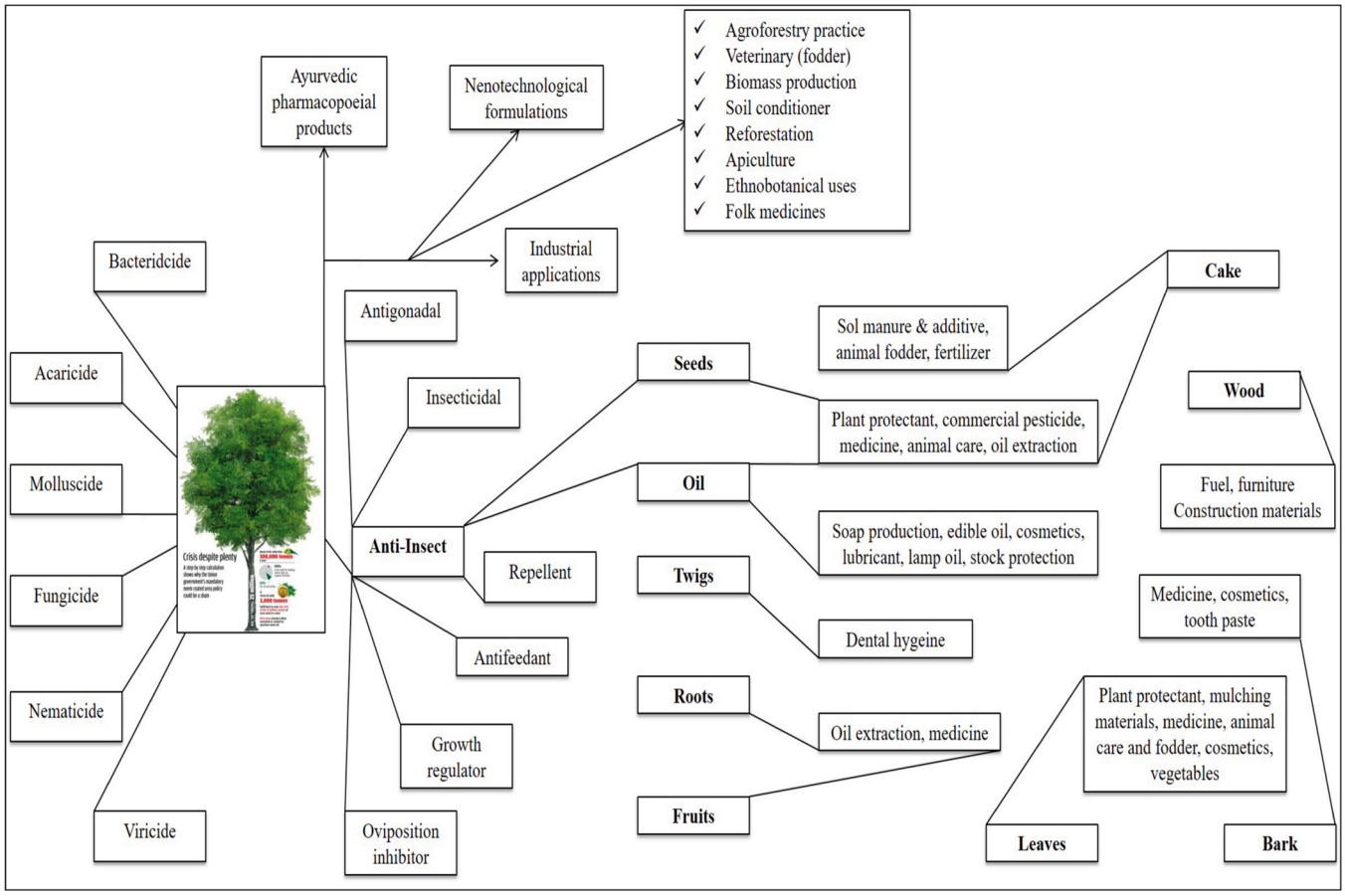

Fig. 2. Summary of diverse uses of neem.

folk remedy; more recently several studies have been undertaken that discovered significant antifertility, anti-inflammatory, antioxidant or free radical scavenging, anti-plaque, antitumor, cardioprotective, dental caries, hepatoprotective, hypoglycemi and hypolipemic activities, immuno-modulatory, nephrotoxicity, neuroprotective, pain killer, skin disorders and wound healing propetties (Table 5). The mechanism behind these properties is discussed in Table 6.

The majority of the biological activities of neem oil are attributed to the triterpenoid nimbin and nimbidin, while the principal component primarily responsible for the poisonous effects on insects is azadirachtin, a complex tetranortriterpenoid limonoid found in neem seeds. Cyclic trisulphide, tetra sulphide and quercetin are the flavonoids which are responsible to affect different biological activities (Maithani et al., 2011; Table 7). Furthermore, it has been discovered that the bioactive components in neem exhibit potential therapeutic benefits via modifying cell signaling pathways (Gupta et al., 2017).

From these bioactive compounds, limonoids including azadirachtin, nimbin, salannin, and gedunin are the important one who are continuously studied in depth insights. Understanding these at the molecular level offers valuable insights into how neem functions as a natural pesticide and therapeutic agent, enriching its pharmacological significance. These compounds act at the molecular level through well-defined biochemical pathways, making neem not only a potent botanical pesticide but also a promising source of pharmaceutical agents.

a) **Azadirachtin** (Insect Hormone Disruptor): Azadirachtin, one of neem's most potent limonoids, interferes with the endocrine system of insects by inhibiting ecdysone receptors, which are responsible for molting and metamorphosis. It also disrupts juvenile hormone regulation, thereby impairing reproduction, feeding behavior, and larval development. Azadirachtin exhibits high specificity to insect targets and is biodegradable, which makes it an excellent candidate for Integrated Pest Management (Koul et al., 2023; Ghosh et al., 2021).

b) **Nimbin and Nimbidin** (Antimicrobial and Anti-inflammatory Agents): Nimbin and its derivative nimbidin act primarily by disrupting microbial cell membranes, leading to increased permeability and cytoplasmic leakage. These compounds also inhibit key inflammatory signaling pathways such as NF-κB and COX-2, reducing the production of pro-inflammatory cytokines. These actions grant neem its strong antimicrobial and anti-inflammatory properties, which are valuable in treating both plant and human infections (Alzohairy, 2021; Kumar et al., 2023).

c) **Gedunin** (Hsp90 Inhibitor): Gedunin targets heat shock protein 90 (Hsp90), a chaperone protein involved in the proper folding of client proteins. By inhibiting Hsp90, gedunin induces protein misfolding, leading to apoptosis in cancer cells and larvae of insect pests. It is also being explored for anticancer, antimalarial, and larvicidal applications due to its ability to destabilize stress response systems (Ali et al., 2023; Devkota and Jha, 2021).

d) **Salannin** (Insect Repellent): Salannin acts on chemoreceptors in insects, inhibiting their ability to detect host plants for feeding and oviposition. This compound functions as a strong repellent and oviposition deterrent, making it suitable for mosquito repellents and stored grain protection systems. Salannin's non-lethal mode of action allows it to work without disrupting the broader ecological balance (Isman, 2020; Pradhan et al., 2023).

e) **Nimbolide** (Anticancer and Antioxidant agent): Nimbolide induces reactive oxygen species (ROS) production in cancer cells, leading to oxidative stress, cell cycle arrest, and apoptosis. It modulates pathways involving p53, caspase-3, and Bax/Bcl-2, highlighting its role in anticancer and antiproliferative activity. Additionally, nimbolide has

Table 1
Ethnomedicinal significance of neem.

Part	Medicinal uses	Literature cited
Leaf	Leprosy, eye problem, epistaxis, intestinal worms, anorexia, biliousness, chicken pox, skin infections, cosmetics, pest repellents, leprosy, intestinal infections, respiratory disorders, constipation, and vegetables	Drabu et al., (2012); Biswas et al., (2002); Kaushik et al., (2002); Anon (1988); Chopra et al., (1956); Kirtikar et al. (1935); Benthal (1933)
Bark	Analgesic, alternative and curative of fever, Pain, malaria, cosmetics, pest repellents, leprosy, intestinal infections, respiratory disorders, constipation, stomachache	Drabu et al., (2012); Patil and Patil (2007); Biswas et al., (2002); Kaushik et al., (2002); Chopra et al., (1956); Kirtikar et al. (1935)
Flower	Bile suppression, elimination of intestinal worms and phlegm, GIT infections	Drabu et al., (2012); Biswas et al., (2002); Kaushik et al., (2002); Chopra et al., (1956)
Fruit	Piles, intestinal worms, urinary disorder, epistaxis, phlegm, eye problem, diabetes, wounds and leprosy, GIT infections	Drabu et al., (2012); Biswas et al., (2002); Kaushik et al., (2002); Chopra et al., (1956)
Twig	Relieves cough, asthma, piles, phantom tumour, intestinal worms, spermatorrhoea, obstinate urinary disorder, diabetes, Pyrexia, increase in appetite, and teeth cleaner	Drabu et al., (2012); Biswas et al., (2002); Kaushik et al., (2002); Chopra et al., (1956); Benthal, (1933)
Gum	Effective in skin diseases like ringworms, scabies, wounds and ulcers, Healing of wounds, scabies, ulcer, tonic, and stimulant	Kaushik et al., (2002); Charles and Charles (1992); Benthal (1933)
Seed pulp	Leprosy and intestinal worms	Kaushik et al., (2002)
Oil	Leprosy and intestinal worms, Cosmetics, pest repellents, leprosy, intestinal infections, respiratory disorders, constipation, soaps, toothpastes, and waxes	Drabu et al., (2012); Biswas et al., (2002); Kaushik et al., (2002); Dastur, (1964), Chopra et al., (1956); Kirtikar et al. (1935); Benthal, (1933);
Root, bark, leaf, flower and fruit	Blood morbidity, biliary afflictions, itching, skin ulcer, burning sensation and leprosy, Fever, headache, rheumatism, chronic syphilitic sores, ulcer, skin disorders, and blood purification	Drabu et al., (2012); Gul et al., (2012); Biswas et al., (2002); Kaushik et al., (2002); Kirtikar and Basu (1975); Chopra et al., (1956); Charles and Charles (1992); Mitra (1963)

Table 2
Phytochemical constituents identified in different plant parts of neem.

Plant part	Extracted or identified compound	Literature cited
Leaves	Cyclic trisulphide, Cycle tetrasulphide	Pant et al., (1986)
	Isoprenoid, flavanone, nonisoprenoids, and meliacin	Garg and Bhakuni (1984)
	Meliatetraolenone and odoratone	Siddiqui et al., (2003)
	Nimbinene, Nimbandiol	Kraus et al., (1981)
	Nimocinol, Nimbocinone, Nimocinolide, Isonimocinolide, Deacetylnimbinolide, Deacetylisonimbinolide, Magosinolide, Isomargosinolide, Isonimbolide, Isolimbolide, Isocoumarins, Coumarin scopoletin, Margocetin, Isofraxidin, Nimbocinolide, Isonombocinolide	Siddiqui et al., (1989); Siddiqui et al., (1987); Siddiqui et al., (1986); Siddiqui, Faizi (1984)
	Nimbin	Narayanan et al., (1964)
	Nimonol	Gopalakrishnan et al., (2002)
	Nimbolide	Bokel et al., (1990)
	Nimbaflavone	Garg and Bhakuni (1984)
	Nimbothalin and n-tridecyl benzene	Sharma et al., (1998)
	Pyronimbic acid	Narayanan et al., (1964)
	Quercetin	Chakraborthy et al., (1989)
	Stigmasterol, terpinen−4-ol, sugiol, 4-cymene, nimbiol, α-terpinene and vitamin E	Nand et al., (2012); Dakshinamurty (1954)
	Steroid, glycoside, flavonoids, triterpenoid, carbohydrate, alkaloids, and antiquinone	Prashanth and Krishnaiah (2014); Rapheal (2012)
	Tetracyclic triterpenes	Siddiqui et al., (1986)
	Zafaral, meliacinanhydride, nimocinol, and isomeldenin	Siddiqui et al., (2004)
	4α, 6α-Dihydroxy-A-homoazadirone	Bruhn et al., (1984)
	22,23-Dihydronimocinol and Desfurano−6-α-hydroxyazadiradione	Siddiqui et al., (2002)
Seed/Fruit	Azadirachtin	Deota et al., (2000); Kraus et al., (1985);
	Azadirachtin M, azadirachtin N, 11-epi-azadirachtin H, Triterpenoid, odoratone, and 2β,3β,4β-trihydroxypregnan−16-one	Luo et al., (2000); Luo et al., (1999)
	Azadirone, Azadiradiaone, Epoxyazadiradoine	Lavie et al., (1971)
	Azadirachtol, Azadirachnol, Nimocin, Nimbocinol, Nimolinone, Nimolicinol, Isonimolicinolide	Siddiqui et al., (1987); Siddiqui et al., (1986); Siddiqui et al., (1985)
	Deacetylazadirachtinol	Kubo et al., (1986)
	Gedunin	Khalid et al., (1989)
	Genistein 7-O-glucoside and (–)-epi-catechin	Kanwal et al., (2011)
	Hydroxyazadiradione	Kraus and Cramer (1978)
	Limocinone, limocin A &B, limocinol, limocinin	Siddiqui et al., (1991)
	Mahmoodin, azadirachtol, and naheedin	Siddiqui et al., (1992)
	Meldenin	Connolly et al., (1968)
	Mohmoodin	Devakumar et al. (1996)
	Nimbin	Devakumar and Mukerjee (1985)
	Nimbinene, 6-Deacetylnimbinene, 6-O-Acetylnimbandiol	Kraus et al., (1981)
	Salannin	Yamasaki et al., (1988)
	Salannolide	Garg and Bhakuni (1984)
	Salimuzzalin, azadirolic acid, azadiradinol, and azadironol	Siddiqui et al., (1998)
	Tetranortriterpene	Gaikwad et al., (1990)
	Vepinin	Narayanan et al., (1969)
	1α,2α-Epoxy−17β-hydroxyazadiradione, 1α,2α-epoxynimolicinol, 7-deacetylnimolicinol, epoxyazadiradione, 17β-hydroxyazadiradione, gedunin, nimbin, and nimolicino	Hallur et al., (2002)
	1α-Methoxy−1,2-dihydroepoxyazadiradione, 1β,2β-diepoxyazardiradione, 7-acetylneotrichilenone, desacetyl−7- benzoylazadiradione 7-desacetyl−7-benzoylepoxyazadiradione, and 7-desacetyl−7-benzoyl-gedunin	Kraus et al., (1981)
	7-Desacetyl−7-benzoylgedunin, 1β,2β-diepoxyazadiradione, 1-αMethoxy−1,2-dihydroepoxyazadiradione	Kraus et al., (1981)
	11-Hydroxyazadirachtin-B, -tigloyl−3-acetylazadirachtinin, 1,2-diacetyl−7-tigloyl−12-hydroxyvilasinin, and 23-desmethyllimocin-B	Kumar et al., (1996)
	17-Epinimbocinol	Gaikwad et al., (1990)

(continued on next page)

Table 2 (*continued*)

Plant part	Extracted or identified compound	Literature cited
Seed oil	Azadirachtin	Banerji et al., (1987)
	Nimbin and nimbidin	Kaushik (2002)
	Tignic acid (5-methyl−2-butanic acid)	Uko and Kamalu (2001)
Flower	Azharone, azadirone, and isoazadironolide	Siddiqui et al., (2009)
	Flowerine, flowerone, Omethylazadironolide, diepoxyazadirol, trichilenone acetate	Subramanian and Rangaswamy (1947)
	Flowerine, flowerone, o-methylazadironolide, and diepoxyazadirol	Nakahara et al., (2002)
	Kaempferol, thiomyl alcohol, melicitrin, benzyl alcohol, benzyl acetate	Ara et al., 1989a
	Nimbosterol (β-Sitosterol), β-D-glucoside	Ayer et al., (1986)
	Prenylated flavonoids	Banerji et al., (1987)
	Sesquiterpenes	Siddiqui et al., (2003)
	3-prenylnaringenin	Garg and Bhakuni (1984)
	4-(2-hydroxyethyl) phenol	Nkengfack et al., (1989)
Stem bark	Nimbionone, Nimbionol, Nimosone, Nimbosone, Nimbiol, Methyl-nimbionone	Van der Nat et al. (1989)
	Nimbione, Nimbinone, Nimbonone, Nimbonolone, Margolone, Margolonone, Isomargolonone	Siddiqui et al., (1988)
	Nimbosodione, Nimbisonol, demethylnimbionol, Margosone, Margosolone	Ara et al., 1989a; Ara et al., (1990)
	Polysaccharides G1A, G1B	Van der Nat et al. (1991)
	Polysaccharides G2A, G3A, NB−2 Peptidoglucan	Fujiwara et al., 1984; Fujiwala et al., (1982)
Root bark	Nimbidiol	Kraus et al., (1981)
	Nimbolicin, nimbilin, nimolinin, margocin, margocinin	Ara et al., (1990); Ara et al., 1989a
	Nimbilicin, Nimbocidin	Majumdar et al., (1987)
Heartwood	Nimbosterol, β-sitosterol-β-D-glucoside, 24-Methylenecycloartenol	Banarji et al., (1977)
Wood oil	Nimbosterol, Cycloeucalenol, 24-Methylenecycloartenol	Singhal and Mudgal (1984); Sinha and Gulati (1968);
Sap (Stem exudates)	Nimbosterol, 24-Methylenecycloartenol, Nimbin, Azadirone,	Anon (1985)
Gum	Aldobiuronic and aldotriuronic acids	Pattabiraman, Lakshmi (1968)

Table 3
Azadirachtin content variation and influencing factors in neem.

Aspect	Particulars	References
Fruit Development Stage	Early (1–9 weeks): Azadirachtin content is negligible or undetectable.	Govindachari et al., (1992); Schmutterer, (1995)
	Mid (9–17 weeks): Azadirachtin begins to accumulate, peaking (~0.38 % w/w) at ~17th weeks (green-yellow fruits).	Govindachari et al., (1992)
	Late (>17 weeks): Azadirachtin slightly declines (~0.29 % w/w by 19th week).	Schmutterer, (1995)
Phenological Influence	Azadirachtin is highest in fully mature, yellow fruits.	Azam et al., (2009)
Genetic Variation	Azadirachtin content varies by provenance (e.g., 556.9–3030.8 mg/kg kernel across Indian genotypes).	Siddiqui et al., (2003); Gupta et al., (2010)
Environmental Influence	Semi-arid regions show higher azadirachtin levels than sub-humid ones; overall climate impact is debated.	Tewari and Singh, (2000); Srivastava and Parmar, (2011)
Associated Compounds	Other limonoids (e.g., salannin, nimbin) also increase with fruit ripening; azadiradione and epoxyazadiradione are higher in unripe fruits.	Koul and Isman, 1991
Post-Harvest Storage	Up to 45 % degradation in azadirachtin occurs over 6 months under poor storage (light, humidity).	Langhans et al., (1996); Thakore, Srivastava (2017) May 26)
Optimal Harvest Period	Best yield obtained when fruits are harvested between weeks 16–18.	Govindachari et al., (1992)
Utilization Strategy	Select high-yielding genotypes; apply proper drying and storage methods to retain compound stability.	Siddiqui et al., (2003); Langhans et al., (1996)
Extraction methods	Pressurized Liquid Extraction (PLE) seems to be a feasible method for recovering azadirachtin rich concentrates from defatted neem seed kernel.	Jadeja et al., (2011)
Post-Extraction Processing	Purification techniques, storage conditions, and the presence of other compounds in the extract can affect azadirachtin content and its stability.	Fernandes et al., (2019)

hepatoprotective and antioxidant benefits, making it a potential lead compound for drug development (Yadav and Singh, 2023; Sharma et al., 2022).

f) **Quercetin** (Flavonoid with Antioxidant Activity): Quercetin, a flavonoid found in neem leaves, targets tyrosine kinases and inflammatory signaling pathways while acting as a potent free radical scavenger. It exhibits antioxidant, anti-inflammatory, and antiviral effects, contributing to neem's utility in both human therapeutics and plant defense mechanisms (Nasrullah et al., 2021; Mehta et al., 2022).

g) **Neem Oil** (Broad-spectrum Bioactivity): Neem oil, a complex mixture of various limonoids and fatty acids, exhibits multi-target action. It inhibits fungal spore germination, reduces pest enzyme activity, and deters feeding and oviposition across a wide range of insects. This broad-spectrum activity makes neem oil valuable in fungal disease control, acaricidal applications, and organic crop protection (Rao et al., 2023; FAO, 2021).

6. Clinical efficacy of neem

Several clinical trials have been reported (Akbar, 2020) to test the efficacy of neem extracts on patients suffering from diabetes and other ailments related to digestive system. It was found that the aqueous and

Table 4
Antimicrobial potential of neem.

Anti-bacterial potential		
Targeted Microorganisms	**Potent Extract**	**Literature cited**
Bacillus anthracis and *E. coli*	Leaf aqueous	Jagtap and Chavan (2016)
Staphylococcus aureus and *E. faecalis*		Geethashri et al., (2014)
Bacillus cereus, B. subtilis, Listeria, Monocytogenes, Staphylococcus aureus, C. perfringens, Micrococcus, S. typhimurium and *Escherichia coli*	Leaf methanolic	Yehia (2016)
Staphylococcus aureus, E. faecalis and *S. mutans*		Mistry et al., (2014)
Staphylococcus aureus and *S. pyogens, E. coli, Pseudomonas aeruginosa* and *Klebsiella neumoniae*		Vijayaram et al., (2016)
Staphylococcus aureus, P. aeruginosa, E. coli and *K. pneumonia*		Tirumalasetty et al., (2014)
Xanthomonas campestris		Britto et al., (2011)
Escherichia faecalis, S. aureus, P. mirabilis, E. coli, P. aeruginosa and *K. pneumonia*	Leaf ethanolic	Mohamed and Omer (2015)
Staphylococcus aureus and *E. coli*		Ravi et al., (2015)
Staphylococcus aureus		Sarmiento et al., (2011)
Staphylococcus aureus, E. coli and *P. aeruginosa*		Azman et al., (2016)
Streptococci, Staphylococci, Lactobacilli, Enterococci, Bacilli and *Mycobacterium bacilli*		Sundaram et al., (2016)
Bacillus cereus	Leaf ethanolic, aqueous and chloroform	Rajasekaran (2008)
Staphylococcus aureus and *P. aeruginosa*	Leaf acetone and ethanolic	Ajayi et al., (2016)
Leuconostoc and *Campylobacter jejuni*	Leaf ethyl acetate	Serrone and Nicoletti (2013)
Staphylococcus aureus, B. subtilis, E. coli and *P. aeruginosa*	Leaf polar and nonpolar extracts	Prashar et al., (2012)
Bacillus subtilis, S. aureus, S. epidermitis, P. aeruginosa, S. typhi, Pseudomonas and *K. pneumoniae,*	Leaf pure ethanolic, acetonic, and methanolic	Irshad et al., (2011)
Bacillus subtilis, E. coli, P. vulgaris, P. aeruginosa, S. typhimurium and *K. pneumonia*	Leaf petroleum and chloroform	Priadarshini et al., (2013)
Bacillus subtilis, E. faecalis, S. epidermis, E. aerogene, E. cloacae and *S. typhimurium*	Leaf pure nimbolide	Farooqui et al., (2014)
Staphylococcus aureus, E. coli, P. aeruginosa, Enterobacter and *K. pneumonia*		Amin and Khan (2011)
Staphylococcus aureus, Pseudomonas species, Vibrio cholera, V. parahaemolyticus, Klebsiella spp., *E. coli,* and *Salmonella*	Leaf oil, aqueous, and methanolic	Farjana et al., (2014)
Staphylococcus aureus, B. pumilus, E. coli, P. aeruginosa and *Salmonella typhimurium*	Leaf methanolic and ethanolic	Maragathavalli et al. (2012b)
Antifungal potential		
Basidiobolus haptosporus, B. ranarum, Aspergillus fumigatus, Geotrichum candidum and *Candida albicans*	Leaf aqueous	Nwosu and Okafor (1995)
Draba graminea		Paul and Sharma (2002)
Puccinia arachidis and *Mycosphaerella berkeleyi*		Ghewande (1989)
Pleomorphomonas oryzae		Amadioha (2000)
Wheat seed mycoflora		Khan and Kumar (1990)
Alternaria solani	Leaf methanolic	Jabeen (2013)
Puccinia arachidis		Suresh et al., (1997)
Draba graminea	Leaf decoction	Bhatti (1986)

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Table 4 (*continued*)

Anti-bacterial potential		
Aspergillus and *Rhizopus* spp.	Leaf aqueous alcoholic	Mondali et al., (2009)
Colletotrichum lindemuthianum	Seed ethanolic and aqueous	Amadioha (1998)
Monilinia fructicola, Penicillium expansum, Trichothecium roseum and *A. alternata*	Seed ethanolic	Wang et al., (2010)
Fusarium oxysporum	Crude seed extract	Agbenin and Marley (2006)
Pleomorphomonas Oryzae	Aqueous seed oil	Amadioha (2000)
Aspergillus spp.	Essential oil and seed aqueous	Paul and Sharma (2002)
Aspergillus fumigatus and *A. niger*	Seed oil	Bansod and Rai (2008)
Aspergillus niger, A. flavus, F. oxysporum, F. moniliforme, F. nivale, F. semitectum, Drechslera hawaiiensis and *A. alternata*	Seed acetonic and n-hexane	Sitara et al., (2008); Niaz et al., (2008)
Cochliobolus miyabeanus	Seed Ethanol/oil	Amadioha (2002)
Aspergillus solani	Fruit methanolic	Jabeen (2013)
Phytophthora infestans	Whole tree decoction	Mirza et al., (2000)
Aspergillus flavus, A. fumigatus, A. niger, A. terreus, C. albicans and *Microsporum gypseum*	Whole tree - aqueous, ethanol, ethyl acetate of	Mahmoud et al., (2011)
Penicillium digitatum	Whole tree -methanolic	Suleiman (2011)
Aspergillus spp.	Whole tree-aqueous	Satish et al., (2007)

Source: Saleem et al#, (2018)

alcoholic extracts of neem seeds had potential effects on lowering blood glucose levels of type-2 diabetic patients significantly (Waheed et al., 2006). Neem leaf aqueous extract also lowered serum TC and LDL-C, and significantly increased triacylglycerol and HDL-C of Nigerian patients suffering from Malaria (Njoku et al., 2001). Additionally, it was discovered that 30 mg bark extract twice daily for 10 weeks administration resulted in a significant reduction in gastric acid secretion and its pepsin activity, and after 10 weeks, the duodenal ulcers were nearly completely healed (Bandyopadhyay et al., 2004). Neem mouthwash reduced plaque-induced gingivitis (Chatterjee et al., 2011 and Sharma et al., 2008), and reduced ability of some Streptococci to colonize over tooth surface (Wolinsky et al., 1996), and the gel treatment dramatically decreased the bacterial count and plaque index (Pai et al., 2004). Volunteers were given around 90 % protection against Anopheles mosquito bites for 12 hours by applying 2 % neem oil mixed with coconut oil to exposed skin (Mishra et al., 1995 and Sharma et al., 1993). Application of a paste of neem leaves and turmeric cured 97 % of 814 patients of scabies between 3 and 15 days of treatment (Charles and Charles, 1992). In comparison to Culex, burning 1 % neem oil mixed with paraffin dramatically decreased the number of Anopheles mosquitoes that bit human volunteers (Sharma and Ansari, 1994). Due to its enomous medicinal potential, several preclininal and clinical trials have been carried out (Table 8 & 9).

7. Neem as agrochemical agent

Neem-based agrochemicals are gaining significant traction in sustainable agriculture due to their natural, eco-friendly properties. Neem often referred to as the "village pharmacy," has a long history of use in agricultural practices. Their eco-friendly and sustainable nature makes them highly appealing in modern agriculture, particularly in organic farming systems and integrated pest management. The development and use of neem-based products continue to expand, offering farmers a safer and more sustainable alternative to conventional chemical pesticides and fertilizers. Here are the primary applications of neem-based agrochemicals in greater detail (Table 10).

Azadirachtin (a natural compound from the neem tree) and synthetic

Table 5
Biological and medicinal attributes of neem.

Activities	Salient findings	Literature cited
Antifertility	Flower extract reduced the number of ova sheds in morning of estrus in rats fed with the alcoholic extract of Neem flower	Gbotolorun et al., (2008)
	Intra-vas administration of seed oil resulted in a blockage of spermatogenesis without affecting testosterone production	Upadhyay et al., (1993)
Anti-inflammatory	Animals treated with 100 mg kg^{-1} dose of fruit skin extract and azadiradione exhibited significant anti-inflammatory activities	Ilango et al., (2013)
	Seed oil showed increased inhibition of edema with the progressive increase in dose from 0.25 to 2.0 mL kg^{-1} body weight	Naik et al., (2014)
Antioxidant or free radical scavenging	Extracts from leaf, flower, and stem bark possess higher antioxidant activity	Sithisarn et al., (2005); Dhakal et al., (2016)
	Ethanolic extracts of flowers and seed oil were found to possess greater free radical scavenging activity	Nahak and Sahu (2011)
Anti-plaque	Commercially available dental gel (mouth wash) containing chlorhexidine gluconate (0.2 % w/v) leaf extract has significantly reduced the plaque index and bacterial count	Pai et al., (2004)
Antitumor	Leaf extract considerably reduced the incidence of 7,12-dimethylbenz (a)anthracene induced hamster buccal pouch carcinomas and tumor burden	Elumalai et al., (2012)
	The progression of MNU-induced mammary tumours was suppressed by leaf extract, and treatment was also found successful in lowering the burden of tumour and continued to suppress for long duration after the cease of the treatment	Sharma et al., (2014)
	In PC−3 and LNCaP cells, leaf extract exhibits 50 % inhibition at a dosage of 100 μg/mL	Metwally et al., (2014)
Cardioprotective	Leaf extract shows equipotent hardioprotective activities as compared to Vitamin E	Peer et al., (2008)
Dental caries	Pencial thickness branch when shewed has been found useful in treatment of dental caries	Lekshmi et al., (2012)
Hepatoprotective	Leaf extract reduced elevated levels of Aspartate aminotransferase, Alanine aminotransferase, and gamma-GT. In addition to this, paracetamol-induced liver necrosis was reduced as observed macroscopically and histologically	Bhanwra et al., (2000)
	Leaf extract prevents and cure the hepatotoxic damage caused by antitubercular drugs	Kale et al., (2003)
Hypoglycemic, hypolipemic activities	Crude extract of neem leaves contains strong hypoglycemic as well as hypolipemic activity in addition to hepatoprotective and hypertensive actions	Sunarwidhi et al., (2014)
	After four hours, a substantial 54 % decrease in blood sugar was observed when root bark extract was administered at a dose of 800 mg kg^{-1} compared to the control	Patil et al., (2013)
Immuno-modulatory	Applying leaf infusion at a concentration of 50 mL L^{-1} of fresh drinking water has been shown to	Durrani et al., (2008)

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Table 5 (*continued*)

	effectively enhance antibody growth performance	
Nephrotoxicity	Leaf extract has showed strong protective effects against cisplatin-induced nephrotoxicity as this extract exhibits antioxidant, anti-inflammatory and other free radical-scavenging actions	Abdel Moneim et al. (2014)
Neuroprotective	Leaf extract has been tested for neuroprotective benefits, and the reversible effects of cisplatin have been found effective	Abdel Moneim (2014)
Pain killer	The leaves' hot infusion when applied on bruises, sprains, and swollen glands relieves pain and have an anodyne effect	Siddiqui (1995)
Skin disorders	Seed oil applied directly reduce skin dryness, skin itchiness and redness	Ogbuewu et al., (2011)
	Stem bark paste or sometimes leaf decoction is used in treating several skin disorders including ringworm, alopecia, eczema, urticaria and scabies	Ogbuewu et al., (2011)
Wound healing	Wounds were significantly reduced by the leaf aqueous extract	Chundran et al., (2015)
	The aqueous extracts of neem leaves are believed to have wound-healing properties that function biochemically through neovascularization and inflammatory response	Osunwoke et al., (2013)

insecticides differ significantly in effectiveness, environmental impact, and sustainability. It has a multi-faceted mode of action, which makes it especially effective as a biopesticide. It doesn't kill insects instantly, but instead disrupts key biological processes. The effectiveness, environmental impact, and sustainability of azadirachtin and synthetic insecticides is hereby provided in Table 11.

Neem is thought to be the most dependable source of environmentally acceptable non-phytotoxic agrochemicals with 'green chemistry', having a good shelf life and efficient against control of a variety of insect-pests. Even though first report on pesticidial property of neem was reported in India in 1928, only after 30 years later systematic research work on neem was initiated. Only azadirachtin exhibits pesticidal activity, and it's possible that some insects like green peach aphid, *Myzus persicae* developed resistance to it (Feng and Isman, 1995). However, Azadirachtin improved the efficacy of other biopesticides (Trisyono and Whalon, 2000; Dara, 2015). There are now primarily two kinds of neem-based products on the market. In the first case, azadirachtin is added in a standardised amount combined with other substances to create an azadirachtin-rich, long-lasting product. In the other product type, azadirachtin-rich neem oil is fortified further with azadirachtin. Apart from azadirachtin, the mixture contains numerous other naturally occurring chemicals found in neem oil. This kind of solution can fight a pest problem, and even if the pests become resistant to one of the active ingredients. Using these principles, herbicide and pesticide companies are preparing many more products of neem for management and control of diseases and insect-pests (Roychoudhury, 2016). Azadirachtin is the major limonoid for pest control and is exceptionally effective at low concentrations (<20 g a.i. per acre) (Walter, 1999). In azadirachtin-based formulations, the content of this limonoid varies from 0.09 % azadirachtin to 4.5 % in the US and 300–1500 ppm in India. Neem oil is used in approximately 100 pesticide products (Roychoudhury, 2016). Till date, the neem products have been found effective against 450–500 species of insect-pests found infesting the field crops worldwide (Schmutterer and Singh, 1995; Table 12). Neem and its derivatives have been tested in the Indian subcontinent against 12 nematodes, 103 insect species, and numerous harmful fungi (Singh and Kataria, 1991; Arora and Dhaliwal, 1994). Alam (1993) suggested that biologically active metabolites of neem plant controlled more than 400 species of insect pests of signifcant food crops and 16 plant parasitic nematodes including mosquitoes, without harming beneficial insects like bees (Nicoletti et al., 2016). Besides, neem formulations made up of neem kernels controlled more than 105 insect pests of 10 orders in commercial crops (Roychoudhury, 2016).

Various types of neem extracts having azadirachtin as major ingredient are known to act on different insect-pests suppressing thier growth as presented in Fig. 3 (Mordue et al. 2000; Benelli et al., 2015; Kilani--Morakchi et al., 2021). Various parts of neem also showed acute toxicological effects on small animals and pests of stored grains (Table 13). The insecticidal efficacy of neem against about 350 species of arthropods, 12 species of nematodes, 15 species of fungi, three viruses, and two species of snails and one crustacean species are reported (Nigam et al., 1994; Ogbuewu et al., 2011; Agbo et al., 2019) but still a very few products have been formulated. Now a day's products derived from leaves and seed kernels are becoming popular in plant protection programmes for cotton, wheat, rice and other cultivated field crops. Neem derived pesticides such as Nimbecidine or Achook @ 1.0 litre per acre have been found effective and economical in controlling whitefly in cotton, and stem borer and leaf folder in rice. Recently, PAU homemade neem extract has been recommended @ 1200 mL/acre against cotton whitefly and 2000 mL/acre against wheat aphid (Dhakad et al., 2021; Fig. 4).

Neem products play a critical role in Integrated Pest Management (IPM) by offering eco-friendly, multipurpose, and target-specific pest control solutions. Its wide-ranging biological activities, ecological safety, and biodegradability make it an effective alternative to conventional synthetic pesticides. Below is a detailed explanation of how neem contributes to IPM and the benefits of reducing dependency on synthetic chemical pesticides (Table 14).

8. Phytotoxic efficacy

The leaf extracts and its formulations act as a broad-spectrum phtotoxic, herbicidal and allelopathic activity (Sindhu et al., 2005; Rickli et al., 2011). It discourages feeding by insects by making plants unpalatable that likely suppresses the insect's appetite. However, if the insect still infests the neem sprayed crop, the endotoxin within the neem sprayed leaves inhibits insect ability to moult and lay eggs (Mordue and Blackwell, 1993). Neem is also known to posssess "systemic" effect unlike most of the synthetic insecticides. The neem-based sprays on crop plants are systemic and uptake through their roots and leaves (Mordue et al. 2000). These systemic properties enable to control the periodic pest population like leaf miners. The way that various orders of insects behave and react to azadirachtin varies significantly. Depending on the species, Lepidoptera exhibit effective antifeedant potentiality ranging from less than 1–50 ppm when exposed to azadirachtin. With up to 100 % antifeedancy being obtained at 100–600 ppm, Coleoptera, Hemiptera, and Homoptera are less behaviorally susceptible to azadirachtin than are other aphid species, such as the strawberry aphid. The sensitivity of the Orthoptera varies greatly from that of the polyphagous *Schistocerca gregaria* (Mordue et al. 2000).

For instance, desert locust (*S. gregaria*), migratory locust (*Locusta migratoria*), rice plant hoppers (*Nilaparvata lugens*) and *Sogetella furcifera*, the leaf folder (*Cnaphalocrocis medinalis*), the ear cutting caterpillar (*Mythimna separata*), etc. that are often migratory and cause huge losses in crop yields (Ketkar, 1976; Saxena, 1989) showed repellent and anti-feedant effects of neem. For the majority of the insect species that have been studied thus far, feeding has been reported to be inhibited by neem seed kernel extracts at concentrations ranging from 0.001 % to 0.4 % (Singh, 2000). The Neem derivatives cause growth inhibitory effects in developmental phases of various insect-pests causing mortality due to the susceptivitlity of insect-pests against neem formulations (Table 15). The larvae of various lepidopterous and coleopterous pests

Table 6
Biological mechanism of neem for antibacttirial, antifungal and anticancer properties.

Antibacterial mechanism		
Inhibition of bacterial growth and reproduction	Neem extracts, particularly those rich in azadirachtin, inhibits bacterial growth by disrupting cell wall synthesis, altering membrane permeability, and inhibiting bacterial metabolism followed by check in reproduction ability.	Ravva and Korn (2015); Alzohairy (2016)
Disruption of Bacterial Cell Membranes	Neem compounds can damage the bacterial cell membrane, leading to leakage of cellular contents and cell death	Jerobin et al. (2015); Wylie and Merrell (2022)
Biofilm Disruption	Neem extracts can effectively disrupt bacterial biofilms, which are communities of bacteria encased in a protective matrix, making them more resistant to antibiotics	Quelemes et al. (2015), Mahmoud et al. (2024)
Targeting DNA Gyrase	Some studies suggest that neem extracts can inhibit DNA gyrase, an enzyme essential for DNA replication in bacteria, thereby hindering bacterial growth	Mahmoud et al. (2024)
Antifungal Mechanisms		
Inhibition of Fungal Growth	Neem extracts exhibit antifungal activity by inhibiting the growth of various fungal species, including those that cause skin infections, nail infections, and systemic infections	Motallebi and Negahban (2024), Baby et al. (2022)
Cell Wall Disruption	Neem compounds can disrupt the fungal cell wall, making it more permeable and less resistant to other antifungal agents.	Pavela (2016), Kale et al. (2024)
Inhibition of Spore Germination	Neem extracts can inhibit the germination of fungal spores, preventing the spread of fungal infections	Anjali et al. (2013)
Anticancer Mechanisms		
Inhibition of Proliferation and Induction of Apoptosis	Neem extracts can induce apoptosis (programmed cell death) in cancer cells and inhibit their proliferation, reducing tumor growth and induction of apoptotic cell death in cancer.	Subapriya et al. (2005), Chitta et al. (2014)
	Downregulated Bcl−2 expression and upregulated Bim, caspase−8, and caspase−3 expression which leads apoptosis induction effects in target organ.	
Regulation of Cell Signaling Pathways	Neem extracts can modulate the activity of various cell signaling pathways, including NF-κB, which plays a role in cancer development and progression	Alzohairy (2016)
Attenuation of Angiogenesis	Neem extracts can inhibit angiogenesis, the formation of new blood vessels, which is essential for tumor growth and metastasis	Mahapatra et al. (2012), Lavanya Uppuluri et al. (2015)
Modulation of Tumor Microenvironment	Neem extracts can modulate the tumor microenvironment by reducing inflammation and promoting the cytotoxic activity of immune cells	Hao et al. (2014)
Activity of various tumour suppressor genes (e.g., p53, pTEN)	Upregulated the proapoptotic genes including p53, Bcl−2-associated X protein (Bax), Bcl−2-associated death promoter protein (Bad) caspases, phosphatase and tensin homolog gene (pTEN), and c-Jun N-terminal kinase (JNK).	Arumugam et al. (2014)
	Expression of proapoptotic genes, such as caspase−8 and caspase−3, and suppressed the expression of Bcl−2 and mutant p53 in the 7,12-dimethylbenz(a)anthracene-induced cancer cells.	Subapriya et al. (2006)
	Downregulated cell survival proteins, including I-FLICE, cIAP−1, cIAP−2, Bcl−2, Bcl-xL, survivin, and X-linked inhibitor of apoptosis protein, and upregulated the proapoptotic proteins p53 and Bax	Gupta et al. (2011)

Table 7
Biological and medicinal attributes of important ingredients of neem.

Compound name	Source	Biological activities	Literature cited
Ascorbic acid	Foliage	Immunomodulator	Chojnacka et al., (2021)
Azadirachtin	Seeds	Antimalerial	Jones et al., (1994)
	Embryo, rind	Anticancer, antiviral drug, Antimalarial drug	Kharwar et al., (2020)
Azadiramide A	Seeds	Breast cancer	Zhu et al., (2018)
Azadirone	Plant embryos, rind	Antimalarial drug, insecticidal	Chianese et al., (2010); Lin et al., (2021)
Azadiradione/Nimolicin	Neem oil	Neurodegenerative diseases	Nelson et al., (2016)
Catechin	Rind	Antibacterial, antiviral drug	Chojnacka et al., (2021)
Cyclic trisulphide and tetrasulphide	Leaf	Antifungal	Pant et al., (1986)
Epicatechin	Seeds	Immunomodulatory, anti-oxident	Atawodi and Atawodi (2009)
Epoxyazadiradione	Seeds	Anti-inflamatory, Anticancer	Alam et al., (2012); Kumar et al., (2018)
Gallic acid	Rind	Antibacterial, antiviral drug, antioxidant, immunomodulator	Gupta et al., (2019); Chojnacka et al., (2021); Tristantini et al., (2021))
Gallic acid, (-) epicatechin and catechin	Bark	Anti-inflammatory	Van der Nat et al. (1991)
		Immunomodulatory	Van der Nat et al. (1991)
Gedunin	Plant embryos	Antimalarial drug, antifungal, antiviral drug, and antiparasitic	Veeraragavan et al., (2020)
Mahmoodin	Seed oil	Antibacterial	Devakumar et al. (1996)
Margolonone	Rind	Antiviral drug, antibacteria	Gupta et al., (2019)
Margolone, margolonone and isomargolonone	Bark	Antibacterial	Lakshmi et al., (2015)
Meliantriol	Leaves, Seeds	Antifeedent	Jacobson (1995)
Nimbandiol	Foliage	Antiviral drug	Ogidigo et al., (2022)
Nimbidin	Seed oil	Anti-inflammatory	Bhargava et al., (1970)
		Antiarthritic	Pillai and Santhakumari (1981a)
		Antipyretic	David (1969)
		Hypoglycaemic	
		Antigastric ulcer	
		Spermicidal	Sharma and Saxena (1959)
		Antifungal, Antibacterial	Murthy and Sirsi (1958)
		Diuretic	Bhide et al., (1958)
Nimbidol	Plant embryos, foliage	Anti-inflammatory	Kharwar et al., (2020); Sultana et al., 2007
Nimbin	Plant embryos, foliage	Antiviral drug, anti-inflammatory, insecticidal	Dwivedi et al., (2016)
Nimbinin	Plant embryos	Antiviral drug	Veeraragavan et al., (2020)
Nimbiol	Plant embryos, foliag	Antiviral drug	Balkrishna et al., (2021)
Nimbocinol	Plant embryo, foliage	Antiviral drug	Baildya et al., (2021)
Nimbolide	Foliage	Antimalarial drug, antibacterial	Brahmachari (2004)
Nimbolin A	Foliage	Anti-termite	Severino et al., (2007)
Nimbolinin	Plant embryos	Antibacterial, anti-inflammatory	Akihisa et al., (2017)
Nimbosterol (β-Sitosterol)	Seed oil	Antifungal	Govindachari et al., (1998)
Nimolinone	Plant embryos, foliage	Anticancer	Mahapatra et al., (2011)
NB−2 Peptidoglucan	Bark	Immunomodulatory	Van der Nat et al. (1987)
N-Hexacosanol	Foliage	Antidiabetic	Narimatsu et al., (2007)
Polysaccharides G1A, G1B	Bark	Antitumour	Fujiwara et al., (1982)
Polysaccharides G2A, G3A	Bark	Anti-inflammatory	Fujiwara et al., (1984)
Quercetin	Seeds, Bark	Antifungal, antibacterial, anti-oxident activity	Sharad, Kapur (2021); Sultana et al., 2007
Salannin	Plant embryos	Insecticidal	Mitchell et al., (1997)
Salannol	Seeds	Inhibition of larval growth	Koul et al., (2004)
Sodium nimbidate	Seed oil	Anti-inflammatory	Bhargava et al., (1970);
17-Hydroxyazadiradione	Foliage	Antiviral drug, antimalarial drug, antifungal	Ogidigo et al., (2022);
6-Deacetyl nimbinene	Foliage	Anticancer	Mahapatra et al., (2011)
7-Deacetyl−7-benzoylgedunin	Foliage	Antiviral drug	Vardhan, Sahoo (2020)
7-Desacetyl−7-benzoylazadiradione	Foliage	Antidiabetic	Veeraragavan et al., (2020)

Table 8
Preclinical trials of neem.

Preclinical trial	Parts	Extract	Model used	Literature cited
Anti-diabetic activity	Seed kernels	Aqueous extract	Human blood cells	Martinez et al., (2014)
		Seed oil	Albino rats	Nagashayana et al., (2014)
		Ethanolic extract	Rats	Akter et al., (2013)
		Ethanolic extract	Rats	Akinola et al., (2010)
		Ether extract	Wistar rats	Gupta et al., (2004)
		Seed oil	Rabbits	Khosla et al., (2000)
	Flower	Ethanolic extract	Wistar albino rats	Jayasree et al., (2013)
	Fruit extract	Aqueous extract	Rabbits	Rao et al., (2012)
	Roots	Aqueous extract	Rats	Atangwho et al., (2010)
Anti-feedant activity	Seed	Pure seed oil	*Hericium abietis*	Thacker et al., (2003)
Anti-fertility activity	Seed	Seed oil	Albino mice	Roop et al., (2005)
		Azadirachtin	*Locusta migratoria*	Rembold and Peter (1981)
	Leaf	Aqueous	Male rat	Deshpande et al., (1980)
Anti-helmintic /Anti-melanogenesis activities	Seed	Crude powder and aqueous extract	Sheep	Iqbal et al., (2010)
Anti-inflammatory activity	Leaves	Methanol, ethyl acetate, and n-hexane	Mice	Dinda and Kumar (2011)
		Ethanolic extract	Albino mice	Zaman et al., (2009)
		Aqueous extract	Rats	Mosaddek and Rashid (2008)
	Seed	Methanolic fraction	Wistar rats	Pereira et al., (2012)
	Stem bark	Methanolic extract	Mice	Akihisa et al., (2009)
Anti-leishmaiases activity	Leaf	Ethanol, dichloromethane and aqueous extract	*Leishmania amazonensis*	Carneiro (2012)
Anioxident activity	Leaf and Root bark	Aqueous extract	Wistar rats	Bhajonia et al., (2016)
		Methanolic extract	Albino mice	Kiranmai et al., (2011)
		Methanolic extract	Rat	Thakurta et al., (2007)
		Aqueous extract	Mice	Haque, Baral (2006)
			Rat	Dorababu et al., (2006)
Anti-nociceptic activity	Root/ stem/ leaf, and seed	Ethanolic extract	Rats	Khanam et al., (2011)
Anti-pyretic activity	Leaves	Ethanolic extract	Rats	Zaman et al., (2009)
Analgesic activity	Root bark	Alcoholic extract	Wistar rats	Patil et al., (2011)
Insecticidal/ pesticidal activity	Leaves	Aqueous extract	Rhizobacteria	Sarawaneeyaruk et al., (2015)
			Cotesia plutellae, Dinoptera collaris	Charleston et al., (2005)
	Seed	Aqueous extract	Cassava and maize plants	Umeh and Ivbijaro (1999)
		Seed oil	*Callosobruchus maculatus*	Ivbijaro (1990)
		Methanol	Cowpea pest	Egho and Ilondu (2012)
		Powder	*Pristimantis glandulosus*	Nukenine et al., (2011)
	Leaves and seed	Mixture of ethanol and chloroform	Natural foods	Jaglan et al., (1997)
Larvicidal activity	Whole	Oil extract	Fall armyworm	
		Methanolic	*Anopheles stephensi*	Batabyal et al., (2007)
	Leaf	Petroleum ether	Mosquito larvae	
		Ether and *n*-hexane	*Anopheles stephensi*	
	Fruit	Ethanolic extract	*Aedes aegypti*	
	Seed	Petroleum ether	Mosquitoes	George and Vincent (2005)
Molluscicidal/ Cercericidal activity	Whole	Aqueous extract	*Biomphalaria pfeifferi*	Mwonga et al., (2015)
		Water, methanol and ethyl acetate extracts	Biomphalaria pfeifferi, Schistosoma mansoni	Michael et al., (2013)
		Methanolic extract	*Forficula auricularia, Indoplanorbis exustus*	Alam et al., (2011)
		Crude extract	*Aganosma marginata, Colotis aurora*	Ebenso, (2003)
	Seed	Methanolic extract	Golden apple snail	Massaguni and Latip (2015)
Nematicidal Activity	Whole	Ethanol and ethyl acetate extract	*Haemonchus contortus*	Costa et al., (2007)
	Leaves	Dry powder	Emerald ash borer	Mckenzie et al., (2010)
	Seed	Ethanolic extract	Rat	Sharma et al., (2014)
		Aqueous extract	*Aedes aegypti*	Ndione et al., (2007)
Neuroprotective activity	Seed	Aqueous extract	Rat	Peer et al., (2007)
	Whole tree	Powder	Rat	Yanpallewar (2005)
	Leaf	Seed oil	Aphids	Lowery and Isman (1995)
Neuroprotective activity	Seed	Ethanolic extract	Rat	Sharma et al., (2014)
	Whole tree	Powder	Rat	Yanpallewar (2005)
	Leaf	Aqueous extract	Rat	Peer et al., (2007)

Table 9
Clinical trials of various parts of neem.

Biological activity	Plant part used	Administration route	Duration of study	Dose	Literature cited
Acute renal failure	Leaves	Oral and intravaginally	–	–	Kadiri et al., (1999)
Acute toxicity	Neem oil	Oral	2 days	12 mL	Sinniah et al., (1982)
Allergenic effect	Pollen	Skin prick test	Once	–	Chakraborty et al., (1998)
Antidiabetic	Leaves	Oral	–	2 tablets	Alam et al., (1990)
Antiplaque	Leaves	Oral	6 weeks	25 mg/g	Pai et al., (2004)
Antiulcer	Bark	Oral	10 weeks	30–60 mg twice a day	-
Encephalopatic	Neem oil	Oral	Once	5 mL	Lai et al., (1990)
Gingival inflammation and antiplaque	Leaves	Oral	30 days	25 % extract	Botelho et al., (2008)
Gastric secretion and gastroduodenal ulcer	Bark extract	Oral	10 days	30 mg twice daily	-

Table 10
Primary applications of neem-based agrochemicals: approach towards sustainable agriculture.

Applications	Detailed Role	Contribution to Sustainable Agriculture	References
1. Natural Insecticide	Azadirachtin disrupts hormonal systems in pests and works as antifeedant, growth regulator, and sterilant. Effective against > 200 insect species.	• Reduces synthetic insecticide use • Minimizes resistance • Safe for beneficial insects	Isman (2020). Elumalai et al. (2021)
2. Biopesticide for Fungal Diseases	Neem oil and extracts inhibit fungal pathogens like powdery mildew, rusts, and blights.	• Eco-safe fungicide • Reduces chemical residues • Enhances plant immunity	Rao et al. (2023), Okigbo and Nmeka (2020)
3. Nematode Suppression	Neem seed cake inhibits egg hatching and larval development of root-knot nematodes.	• Natural alternative to toxic nematicides • Improves soil and root health • Promotes crop resilience	Singh et al. (2021), Subramanian et al. (2022)
4. Soil Amendment	Neem cake improves nitrogen retention and boosts microbial life. Acts as a nitrification inhibitor.	• Enhances soil fertility • Reduces nutrient leaching • Supports long-term sustainability	Pathak (2020), Yadav et al. (2023)
5. Plant Growth Promotion	Neem extract promotes seed germination, root elongation, and photosynthetic activity.	• Boosts yield without chemicals • Improves drought/ stress tolerance • Supports early plant vigor	Sontakk and Kadam (2022), Jain et al. (2024)
6. Herbicidal Properties	Neem oil inhibits weed seed germination and seedling growth through allelopathic effects.	• Natural weed control • Reduces reliance on glyphosate • Preserves soil biodiversity	Chandel et al. (2021), Devkota and Jha (2020)
7. Antibacterial & Antiviral	Active compounds target bacterial pathogens (e.g., Xanthomonas) and inhibit viral replication (e.g., TMV).	• Safer disease control • Reduces need for antibiotics • Preventive plant care	Alzohairy (2021), Mohamedy et al. (2023)
8. Repellents for Storage & Livestock	Neem oil used to repel grain pests (weevils), ticks, fleas, and other livestock parasites.	• Safe pest control • Reduces fumigant/ chemical use • Low cost for smallholder farmers	Ghosh et al. (2022), Boeke et al. (2021)
9. Post-Harvest Preservation	Neem oil sprays delay fruit ripening and prevent microbial spoilage in bananas, tomatoes, and mangoes.	• Reduces food spoilage • Increases shelf life • Prevents synthetic coatings	Pradhan et al. (2021), Dhembare (2020)
10. Integrated Pest Management (IPM)	Fits into IPM as a low-toxicity, multi-target botanical pesticide with synergistic potential.	• Reduces chemical dependence • Prevents pest resurgence • Enhances agroecosystem resilience	Isman (2020), Koul (2023)

like *Plutella xylostella*, *Spodoptera frugiperda*, *Helicoverpa zea*, *Pectinophora gossypiella*, *Epilachna varivestis* and *Ephestia kuehniella* when fed on neem laden food showed their inability to complete various developmental stages (Saxena, 1993). In addition to interfering with insect growth and development, neem compounds have an adverse effect on insect vigour, longevity, and fertility. Neem chemicals have reportedly been shown to have the ability to sterilise female *E. varivestis* and *Leptinotarsa decemlineata*, while *N. lugens*males failed to reach reproductive

Table 11
Superiority of azadirachtin over synthetic insecticide.

Aspect	Azadirachtin	Synthetic Insecticides	Reference
Effectiveness			
Mode of Action	Acts as an insect growth regulator, repellent, antifeedant, reproduction inhibitor and cause cellular and enzymatic disruption	Usually neurotoxic or systemic; kills on contact or ingestion.	Chaudhary et al. (2017); Kilani-Morakchi et al. (2021); Tamaš et al. (2024)
Speed	Slower and act gradually, often over days.	Fast-acting on insects and kills within hours.	Safir et al. (2024); Wang et al. 2024Wang et al. 2024
Target Range	Narrow-spectrum targeting on specific insect species	Broad-spectrum affecting a wide range of insect species.	Su et al. (2023); Ngegba et al. (2022)
Resistance	Lower risk of resistance due to multiple modes of action.	High resistance potential due to overuse of single compounds.	Safir et al. (2024); Almadiy et al. (2025)
Environmental Impact			
Non-target Species	Generally safe for beneficial insects (e.g. bees, predators, parasitoids) when used properly.	Harmful to beneficial insects, pollinators, birds, and aquatic life.	Kumar et al. (2015); Quintero et al. (2025); Souza et al. (2025)
Persistence	Biodegradable; breaks down quickly in the environment.	Persistent; residues can remain in soil, water, and crops.	Reddy et al. (2025); Zhang et al. (2025)
Bioaccumulation	Minimal to none.	Can accumulate in the food chain, especially organophosphates and chlorinated compounds.	Murussi et al. (2016); Meijer et al. (2021)
Human Toxicity	Low toxicity to humans and mammals.	Varies; many are toxic to humans (e.g., organophosphates, carbamates).	European Food Safety Authority, (2011); Fernandes et al. (2019)
Sustainability			
Renewability	Derived from neem seeds—a renewable plant resource.	Petrochemical-based; non-renewable inputs.	Yadav, (2022); Wylie and Merrell, (2022)
Production Impact	Eco-friendly, low-energy extraction processes.	Energy-intensive manufacturing, often with toxic byproducts.	Chatterjee et al. (2023); Sadiq et al. (2023)
Use in IPM	Ideal for Integrated Pest Management (IPM); compatible with biological controls.	Often disrupt IPM by killing natural predators.	Gupta, (2022); Adusei and Azupio, (2022)
Regulatory Trends	Favored under organic and eco-friendly agriculture.	Increasingly regulated or banned due to environmental concerns.	Juma et al. (2022); Chakraborty et al. (2023); Isman, (2023); Fusar Poli and Fontefrancesco, (2024)

maturation. Surprisingly, when the neem extract was used at higher concentrations, most female insects were found unable to emit normal male eliciting hormones/signals (Saxena, 1993). A substantial reduction in fertility was seen when *E. dodecastigma* beetles were fed on leaves of ribbed gourd treated with different concentrations (0.01–0.5 %) of neem seed kernel extracts (Islam and Islam, 1988). Ovicidal action of neem products has also been reported in several insect species including *Corcyra cephalonica*, *Earias vittella* and *S. litura* (Arora and Dhaliwal, 1994).

Although a number of herbivores have been observed feeding on neem leaves despite its insecticidal qualities (Pirani, 1994; Siddiqui, 1995), only a small number of these herbivores cause significant damage (Tewari, 1992). The majority of insects that use neem as a host plant are sucking insects. There are at least 20 known species of sucking pests, belonging to nine different families (Tewari, 1992; Gupta, 1993; Pirani, 1994). Besides, phytotoxic substances in Neem leaves showed allelopathic activity. Though various neem extract showed the persicidal behabious on field crops but if the neem extracts used at the time of seed sowing, it showed allelopathic behavior due to azadirachtin, nimbin nimbolide, nimbic acid, salannin, and other phenolic compounds (Table 16).

9. Industrial applications of neem

9.1. Small scale uses

Several neem-based pesticidial formulas are provided in Wealth of India (1948) for use by small-scale farmers. The easy recipes included applying neem oil to the tree trunk, making a spray oil emulsion, utilising dish soap, or combining a paste made from grounded neem kernels and water, then sifting the mixture through a rough cloth. Feuerhake and Schmutterer (1985) combined crude neem kernel extract with propyl gallate benzophenone and glycol ether to create an affordable, standardised product for small-scale fanners. In the ‘Neem Mission in India’, Ketkar (1989) suggested a number of straightforward neem preparations for small-scale farmers to utilise. Olaifa et al. (1993) developed a technique to extend the shelf life of an emulsifiable concentrate from neem oil by combining an aqueous extract of Tetrapkmatetrapera with 0.1 % propyl paraben and 0.1 % octylgallate. Vijayalakshmi et al. (1995) recommended the freshely preparted neem emulsion without heaing any plant part directly to the crop fields in morning and evening hours. To propare this, neem seed, leaves, etc. might be soaked overnight and then strained through a thick cloth in the morning to make a spray. This might be highly beneficial for the non-cereal crop ripening in March and April, as aphid attacks are so widespread, especially in mustard fields, that these insects are visible in the air, even in metropolitan areas, suspended like dust particles. Vijayalakshmi et al. (1995) further added that jute bags should be dried after 15 minutes of immersion in a 10 % neem kernel emulsion. It is customary in the villages to regularly plaster tiny storage bins, floors, and huts with mud or clay. Neem seed or oil emulsion can be added to the mud mixture in place of water for this mud plastering to deter pests. In addition, the cereals are placed in the gunny bags with dried neem leaves to repell the misquitos (https://www.echocommunity.org/en/resources/d7cd259f-eb9e-4a04-bc17-b26bdaf7e42d).

Wounding the bark allows resin to be "tapped" out of the trunk. This high-protein substance cannot be used in place of polysaccharide gums like gum arabic. Nonetheless, it is commonly employed as "neem glue" in South Asia and may have value as a food additive (Anderson et al., 1972). After hydrogenation, neem can be utilised to produce high melting stearin and olein. Oil was hydrogenated under high pressure by Kane and Kulkarni (1954). A technique for edible neem oil has been devised by lidert (1994) in which crude oil is treated with an alkaline solution or hydrogen peroxide and subjected to distillation or chromatography that contained traces of sulphur. As a byproduct of the neem oil industry, neem cakes are utilised as a natural insecticide, fertiliser, and

Table 12
Effectiveness of neem based formulations against insect-pest in field crops.

Crop/plant	Insect-pest	Neem treatment	Literature cited
Food crops			
Rice	Brown plant hopper, Yellow Stem borer (Scirpophaga incertulas)	Multineem 300 ppm @ 2.5 L ha−1	Dash et al., (2019)
	Yellow stem borer (73.13 %), Green leaf hopper (75.12 %), Gall midge (69.93 %), Dead heart and white ear head (69.26 %), thrips (79.73 %), and leaf folder (85.57 %)	Handi Ausadha pot mixture (5:l fermeted cow urine+ 1 kg fresh cow dung+ 1 kg karanj leaves + 1 kg neem leaves + 1 kg calotropis leaves and 50 g Gaur @ 20 mL L−1)	Mohapatra (2018)
	Brown plant hopper (*Nilaparvata lugens*)	Nimbecidine @ 5 mL L−1 W, 5 mL L−1 of Neem oil	Choudhary et al., (2017)
Wheat	Wheat aphid (*Raphalosi phumpadi*)	Neem Seed Kernel Extract	Matharu and Tanwar (2019)
	Wheat aphid (*Raphalosi phumpadi*)	(Indoneem) 1500 ppm @ 1200 mL ha−1 3 % Neem oil and neem seed	Bushra et al., (2014)
Maize	*Sitophilus zeamais*,	Local Neem	Khanal et al., (2019)
	Corn ear worm (*Heliothis armigera*)	Aqueous Neem extract @300 L ha−1	Udo and Ibanga (2019)
	Maize aphid (*Rhophalosiphum maidis*)	Neem leaf extract @ 2 mL L−1	Alam et al., (2019)
	Fallarmyworm (*Spodoptera furgiperda*)	Neem oil and seed cake	Shaiba et al., (2019)
	Maize weevil	Neem seed kernel powder	Suleiman and Yusuf (2011)
Sorgham	Sorghum shoot fly (*Atherigona soccata* Rondani)	2 % Neem oil	Joshi et al., (2016)
Wheat, sorghum, rice, and sugarcane	Pink stalk borer and Sugarcane borer	Neem seed oil	Bruce et al., (2004)
Cereal crops	Locust	Neem seed karnel suspension (0.1 %)	Pradhan et al., (1962)
Cultivated crops	*Helicoverpa armigera*	Neem oil	Ahmad et al., (2015)
Cultivated crops	*Helicoverpa armigera*	PONNEEM (neem + pongamia oil, 1:1 rate)	Packiam et al., (2015)
Pulses / Oilseed crops			
Chickpea	*Helicoverpa armigera*	5 % Neem seed kernel extract	Kumar et al., (2019)
Greengram	*Callosobruchus maculatus*	Neem leaf powder	Gupta et al., (2015)
Cowpea	Cowpea thrips (*Megolurothipss jostedti*)	Neem + Metarhizium anisople	Raoul et al., (2019)
	Cowpea pod borer	Neem seed kernel power, leave extract and neem oil	Muhammad et al., (2018); Sokam et al., (2015)
	Spodoptera eridania (southern armyworm)	Neem oil (0.35 % and 0.7 %)	Rodrigues et al., (2015)
	Maruca vitrata	Multinucleopolyhedrovirus + neem oil	Sokam et al., (2015)
	Cowpea bruchid	Neem seed kernel extract	Ekeh et al., (2013)
	Giant coreid bud	Neem seed oil and neem seed kernel extract	Wudil et al., (2013); Ahmed et al., (2009)
Common bean	*Bemisia tabaci*	Neem oil	Ogah (2013)
Garden pea	Pea aphid	Neem seed kernel extract	Melesse, Singh (2012)
Cotton	Cotton pest	*Beauveria bassiana* + neem oil	Togbe et al., (2015)
Fruit crops			
Kinnow mandarin	*Penicillum digitatum* and *P. italicum*	Neem essential oil	Jhalegar et al., (2015)
Western white pine	*Zootermopsis angusticollis* (damp wood termite)	Neem oil	Fatima and Morrell (2015)
Cashew nut	*Toxoptera odinae*	Neem oil	Ambethgar, 2015b
	Ferrisia virgate	Neem oil	Ambethgar, 2015b
Coconut	*Aceria guerreronis*	Neem oil	Balaji and Hariprasad (2015)
Stone fruit	*Monilinia fructicola*	Neem oil	Lalancette and McFarland (2015)
Watermelon	*Aphis gossypii*	Neem oil	Ahmad et al., (2015)
Fruit, vegetable/ field crops (apples, corn)	Spiny brown bug	Neem seed oil and neem seed kernel extract	Mbonu (2005); Ahmed et al., (2009)
Apples and grapes	Leaf hopper	Neem seed kernel extract	Ahmed et al., (2007)
Vegetable crops			
Potato	Colorado potato beetle	Neem oil and karanja oil in ratio of 1:1, 1.4 L in 500 L water ha−1 (0.3 %).	Kovarikova and Pavela (2019)
	Colorado potato beetle	Neem oil and karanja oil in ratio of 1:1, 1.4 L in 500 L water ha−1 (0.3 %).	El-Wahab et al., (2019)
Tomato	Tomato fruit worm	Neem seed oil	Muhammad and Kashere (2021)
	Root knot Nematode	Neem cake, leaves, and refined product “aza” 0.1 % w/w	Illakwahhi and Srivastava (2019)
	Whitefly and leaf miner	Neem oil	Chavan et al. (2015)
	Tuta absoluta	Neem seed oil	de Almeida-Marques et al., (2014)
	Root knot Nematode	Neem cake, leaves, and refined product “aza” 0.1 % w/w	Javed et al., (2007)
	Tomato leaf miner (*Tuta absoluta*)	Neem cake, leaves, and refined product “aza” 0.1 % w/w	Javed et al., (2007)
Brinjal	*Leucinodes arbonalis*	Neem oil	Rakibuzzaman et al., (2019)
	Shoot and fruit borer	Neem oil	Singh and Sachan (2015)
Cabbage	Cabbage aphid	Neem oil (1 %)	Pissinati and Ventura (2014)
	Plutella xylostella	3 % concentration of Neem	Ahmad et al., (2019)
Cauliflower	*Spodoptera litura*	Neem oil (58.26 % and 57.89 %), neem seed kernel extract (54.83 % and 55.24 %), neem leaf extract (50.70 % and 51.42 %)	Singh et al., (2019)

(*continued on next page*)

Table 12 (*continued*)

Crop/plant	Insect-pest	Neem treatment	Literature cited
Okra	Jassid, White fly	2 % Neem seed extract	Aziz and Khoso (2019)
	Bemisia tabaci	Neem	Salem and Abdel-Moniem (2015)
	Whitefly	Mineral oil + neem oil	Sridharan et al., (2015)
	White fly, Jassid and Fruit borer	Neem seed kernel extract 5 %	Ketkar (2000)
	Root-knot nematode	Soaking Okra seeds for 20–30 minutes in 5 % aqueous solution of neem cake against root-knot nematode	Ketkarb (2000)
Eggplant/ cucumber	Flower bud thrip	Neem seed kernel power, neem leave extract, and neem oil	Ogah (2013); Sokam et al., (2015)
Cucumber	Two spotted spider mite (*Tetranychus urticae* Koch), *Aphis gossypii* Glov.	Neem extract	Saleem et al., (2019)
Pumpkin	Red pumpkin beetle	Neem seed kernel extract 5 %	Ketkar (2000)
Ginger	Rhizome rot	Neem leaf powder @ 500 g m−2	Ketkar (2000)
Coriander	Coriander aphid (*Hyadaphis coriandari*)	Kernel (5 %), neem cake (5 %), neem oil (3 %) and neem leaf extract (5 %)	Kumari and Yadav (2002)
Others			
Pepper, beans, and potato	European corn borer	Neem seed kernel extract	Ahmed et al., (2009); Shannag et al., (2015)
Carrot, sweet potato, and okra	Southern armyworm	Neem seed oil	Shannag et al., (2015)
Jasmine	Eriophyid mite	Neem oil (30 mL/L)	Devi et al., (2015)

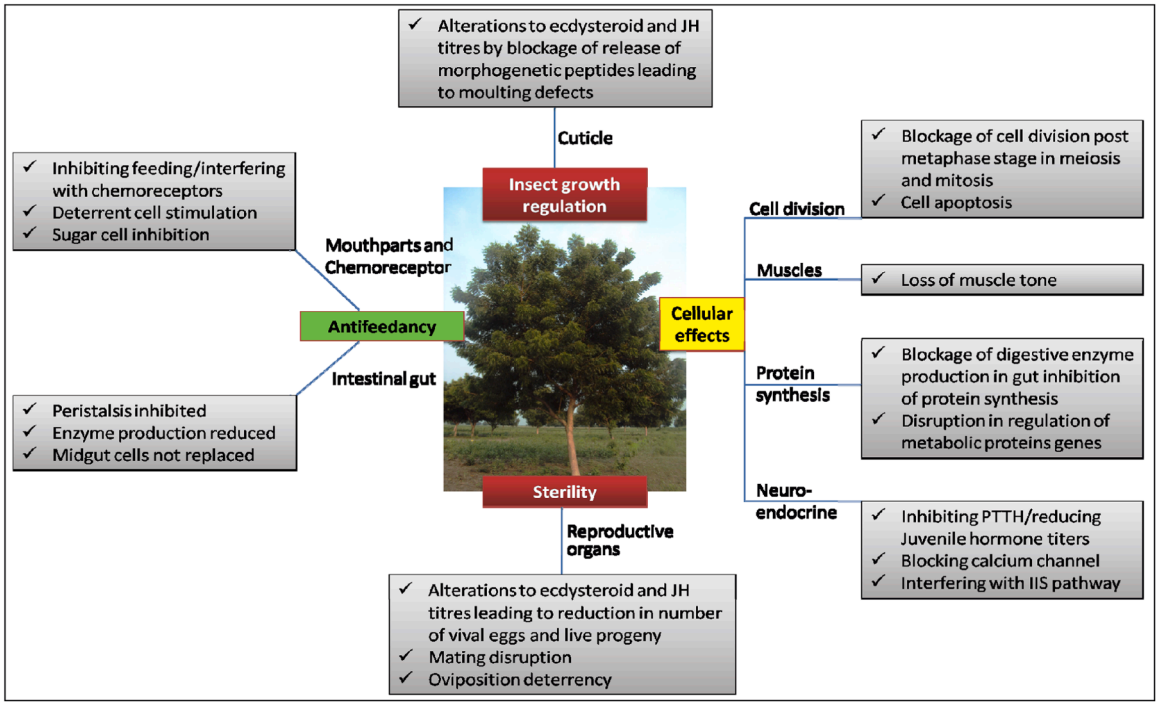


Fig. 3. The overall effects of azadirachtin against insect-pests.

animal feed ().

9.2. Commercial uses

Mitra (1963) put forth the notion to add neem oil to soap; soap producers gradually began adding up to 15 % of neem oil to the blend of fatty oils, along with other oils like coconut and cottonseed. Mehtra (1997) provided an example of how to saponify neem oil and then mill it, which extracts the majority of the colour and scent. Renuka and Ramani (1989) experimented with neem cake as a source of bio-gas, whereas Bansal and Juneja (1989) investigated the performance of neem oil as supplement for a diesel engine fuel. Neem oil has been successfully substituted for salt and considered best green material for curing of hides and skins in leather processing (Preethi et al., 2006). Because of the high tannin content and the presence of several complex triterpene glycosides, the aqueous neem leaf extract was found to be an outstanding potential corrosion inhibitor (Nahle et al., 2010). Anbumani and Singh (2010) evaluated the viability of using neem oil in place of diesel, and found that engines running at a 20 % blend with neem seed oil performed better to pure diesel.

Neem is heavily exploited by the Ayurvedic medicinal industry in India. In several cosmetic preparations, including face creams, nail polishes, oils, shampoos, and conditioners, neem oil and powdered neem leaves are used (Anon, 2020). The neem-based product for skin care creams (Chandrasekar and Sivagami, 2018), and heel crack-repairing lotion (Patil et al., 2020) were formulated and evaluated. It is also suggested to apply neem-based bath oil shortly after swimming to remove the final traces of chemicals and salts left on the body (Puri,

Table 13
Toxicological studies of neem extracts against small animals.

Plant part used	Nature of extract	Test animal	Literature cited
Leaves	Ethanolic	Wistar rats	Kanagasanthosh et al., (2015)
	Methanolic	Diamondback moth	Sharma and Singh, (2014)
	Hexane	Diamondback moth	Sharma and Singh, (2014)
	Aqueous	Rats	Bakr (2013)
	Aqueous	Mrigal carp fist	Saravanan et al., (2011)
Flowers	Methanolic	Rats	Kupradinun et al., (2010)
Seeds	Aqueous	Rats	Bakr (2013)
	Aqueous	Red flour beetle	Islam and Talukder (2005)
Seed kernel	Seed kernel	Cockerel chicks	Uko and Kamalu (2006)
Neem oil	Neem oil	*Podisus nigrispinus*	Zanuncio et al., (2016)
	Bioneem oil	Zebra fish	Maranho et al., (2014)
	Bioneem oil	*Daphnia magna*	Maranho et al., (2014)
	Neem oil	Kunming mice	Deng et al., (2013)
	Neem oil	Kunming mice	Deng et al., (2013)
Stem bark	Ethanolic	Wistar rats	Ashafa et al., (2012)

2006). *In-vitro* tests revealed that a novel shampoo based on neem seed extract was significantly more successful at killing lice on the head than those containing permethrin (Heukelbach et al., 2006). An herbal shampoo preparations are been manufactured with neem extract as chief ingredient (Kumari et al., 2022b). Due to hair growth and nourishment, neem oil is said to prevent baldness and graying of hair (Suman et al., 2022). The neem hair oil possesses anti-lice and anti-dandruff properties (Baby, A.R., Freire, T.B., Marques, Gd.A., Rijo, P., Lima, F.V., Carvalho, J.C.Md, Rojas, J., Magalhães, W.V., Velasco, M.V.R., Morocho-Jácome, A.L. 2022. Azadirachta indica (Neem) as a Potential Natural Active for Dermocosmetic and Topical Products: A Narrative Review. Cosmetics 9, 58.). The use of neem-based body care products, i.e. body soaps and lotions are increasingly becoming popular due to its anti-inflammatory and antiseptic properties (Musa et al., 2019; Hashim et al., 2023). In Europe and India, neem-based toothpaste is commonly used (Aneesa and Gayathri, 2016). The neem oil, neem extract or the neem fibers from bark have been incorporated as ingredients in some of the toothpastes and dental floss has also been prepared from the neem twig that is beneficial for general maintenance of oral hygiene (Lakshmi et al., 2015).

9.3. *Commercially available formulations*

In India, several pharmaceuticals containing neem have been brought to market (Ketkar and Ketkar, 1995). There have also been other skin care products created; among these include 'Clean 'N' Care' (pimples), 'Curoline' (antiseptic skin cream), 'Neemcure' (antiseptic product against skin diseases, piles, burns, wounds and injury) and 'Greneem' (a blood purifier that helps with bacterial and viral infections, acne, and skin problems) (Parmar et al. 1996). Other neem-based products, which have been marketed in India for various purposes such as cosmetics (Neemtulsi, Neemal, Licika, etc.), soap (Feu Drop, Homacol, Kutir Neem Sandal Soap, Parashais Limda Soap), shampoo (Margosa Neem), toothpaste and tooth powder (Neem, ORA Neem Gel) are quite popular. In Karachi, Pakistan, M/S Hamdard Co. is marketing a tooth powder 'Nimodent'. In addition, several products are being manufactured as manures and fertilizers (Neem Manure, Humi-Gold, Wellgro, Godrej NESU, Nimin, Neemax, etc.) and cattle and poultry feed (Pasutone). Neem based several products are available worldwide are AZA-Direct, Neemix 4.5, Fortune Aza 3 % EC, Azamax, Neemazal Technical, Ecosense, Safer Brand 3 in 1, Garden Spray, AzatinX, Azact CE, Triact 70 EC, BioNeem, Shubhdeep Neem Oil, DalNeem, OzoNeem Oil and NeemDrop which are being used as agrochemicals ().

With the commercialization of neem-based compound 'azadirachtin' under the trade name *Margosan*-O and its clearance by the US Environmental Protection Agency (EPA) had initiated a new era of organic bio-based pest controlling agents in 1983 (Larson, 1987). Azatin (Agri-Dyne Technologies, USA), Bioneem and Neemesis (Ring Corp., USA), Safer's ENI (Safer Ltd., Canada), RD-repelin (ITC Ltd., India), Neem Guard (Gharda Chemicals, India), Neemark (West Coast Herbochem, India) and Neemazal (Trifoliop M.GmBN, Germany) are some of the early commercial preparations of neem products. Pest Control (India) Pvt Ltd, Godrej Agrovet and SPIC Foundation are the main producers of

Fig. 4. Preparation and application of PAU homemade neem extract (Dhakad et al., 2021).

Table 14
Role of neem in Integrated Pest Management and its benefits in reducing dependency on synthetic chemical pesticides.

IPM Component	Role of Neem	Benefits in Reducing Chemical Pesticide Use	References
Botanical Insecticide	Neem compounds (e.g., azadirachtin) act as insect growth regulators, antifeedants, repellents, and oviposition deterrents.	• Reduces synthetic insecticide use • Slows pest resistance • Eco-friendly and biodegradable	Isman (2020), Ghosh et al. (2021)
Fungicidal Action	Neem oil inhibits fungal spore germination and mycelial growth, effective against common plant pathogens.	• Minimizes use of chemical fungicides • Low toxicity to non-target organisms	Ali et al. (2023), Elumalai et al. (2021)
Nematicidal Properties	Neem seed cake and oil suppress root-knot nematodes and other soil-dwelling parasites.	• Natural alternative to synthetic nematicides • Enhances soil health and fertility	Kundu et al. (2022)
Selectivity and Safety	Neem is selective—harmless to beneficial insects like bees, ladybirds, parasitoids, and earthworms.	• Preserves natural pest predators • Maintains ecological balance	Alzohairy (2021), Rani et al. (2022)
Resistance Management	Neem's multifaceted mode of action makes it hard for pests to develop resistance.	• Supports longevity of pest control strategies • Reduces pesticide overuse	Koul et al. (2023)
Synergy with Other IPM Tools	Neem can be combined with biocontrol agents, pheromone traps, and mechanical controls in IPM systems.	• Reduces total pesticide load • Encourages diversified pest management	Srinivasan (2022)
Post-Harvest Pest Control	Neem oil is used in grain storage to repel pests like weevils and beetles.	• Avoids toxic fumigants • Maintains food quality and safety	Boeke et al. (2020)
Environmental and Human Health Safety	Neem is biodegradable, with low toxicity to humans and animals.	• Reduces environmental pollution • Safer for applicators and consumers	FAO IPM Guidelines (2021), Yadav et al. (2023)

Table 15
Susceptability of insect-pests for the neem-based formulations.

Pests	Extent of control	Recommended neem formulation (s)
Beetle larvae, butterfly and moth caterpillars	Excellent	Aqueous neem extracts
Stalkborers	Good	Aqueous neem extracts and neem cake, neem powder
True bugs, plant- and leaf-hoppers grass hoppers	Good	Neem oil, neem kernel extracts
Grass hoppers	Good	Neem oil
Adult beetles	Good/fair	Aqueous neem extracts, neem cake powder, leaves, neem oil
Thrips, fruit flies, scale insects, mealybugs	Fair/poor	Neem oil, aqueous neem extracts
Mites	Fair/poor	Alcoholic extracts
Aphids and whiteflies	Good/fair	Neem oil
Plant parasitic nematodes	Good	Neem cake, neem leaves

Source: https://infonet-biovision.org/natural-pest-control/plant-extract-neem

neem pesticides in India. Chennai-based EID Parry (I) Ltd is one of India's top exporters. Under a joint venture with an Indian company, Thermal Trilogy is the leading manufacturer of neem pesticides in the United States (Roychoudhury, 2016). Over 100 products have been marketed as pesticides in India (Gahukar, 1998). As of right now, about 40 products based on neem have either full or provisional registration in India (Walia et al., 2002). Table 17 lists some of the neem-based agrochemicals and fertilizers recognized commercial and available in market (Benuzzi and Ladurner, 2018; Khosravi and Sendi, 2013; Kilani-Morakchi et al., 2021).

10. Applications of neem in nanotechnology

Low financial and environmental expenses are associated with a novel green synthesis process called plant-based nanoparticle (NP) synthesis. Developments in nanoparticle engineering have had a major effect on the medicinal, therapeutic and fabric industries in recent years. Polymeric nanofibers combined with herbal extracts, like neem, have

Table 16
Allelopathic properties of neem-based products.

Crop/plant	Neem Treatment	Literature cited
Bur Marigold and little hogweed	Aqueous extract of leaves	Huda et al., (2022)
Morning glory	Neem seed oil	Andradea and Marquesa (2021)
Cucumber, chilli and brinja	Aqueous leaves extract of leaves	Khanam et al., (2020)
Cowpea and chickpea	Aqueous extracts of leaves	Jagtap et al., (2016)
Mung, Cow pea, Jowar and Wheat	Aqueous extracts of leaves	Kasarkar and Barge (2016)
Lettuce, alfalfa, timothy, crabgrass, ryegrass, barnyard grass and jungle rice	Aqueous, methanol extract of leaves	Kato-Noguchi et al., (2014)
Cowpea	Aqueous extract of fresh leaves	Lawan et al., (2011)
Garden cress, lettuce	aqueous methanol extract of neem leaves	Salam and Kato-Noguchi (2010)
Cockscomb, creeping thistle, crabgrass, Wild mustard, lettuce and ryegrass	n-hexane-, acetone- and water-soluble extracts of shoots	Ashrafi et al., (2008)
Congress grass	Aqueous extract of dry leaves	Shafique et al. (2005)
Alfalfa, carrot, radish, rice, sesame, weeds like cockspur grass, oval-leafed pondweed, and Indian jointvetch	Aqueous extract of leaves and bark	Xuan et al., (2004)
Wheat and barley	Neem leafleachate and aqueous extract	Walia et al., (2002)

Table 17
Neem-based applications and formulations.

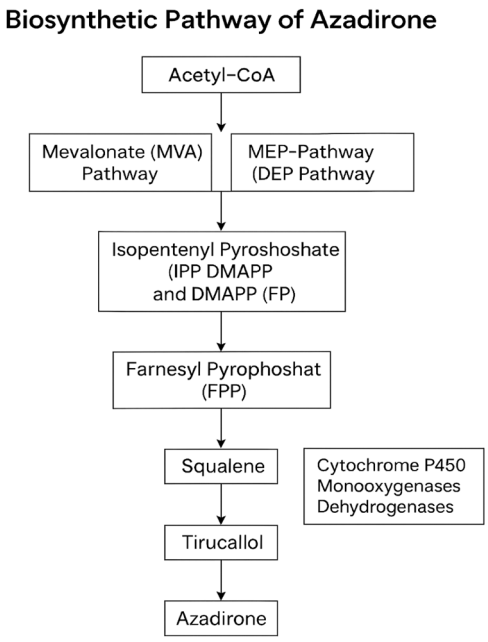
S. N.	Products	Manufacturer	S. N.	Products	Manufacturer
Agrochemical applications					
1	Achook	Godrej Agrovet Ltd., India	28	Neem Azal TS	Trifolio-M GmbH, Germany
2	Agroneem plus	Agro logistic systems Inc, USA	29	Neemarin	AZA-Direct Gowan company LLC, USA
3	Azact CE Neem oil	EPP Ltd., Brazil	30	Neemark	West Coast Herbochem Ltd., India
4	AZA-Direct	Gowan Company,USA	31	NeemDrop	Neem India Products Ltd., India
5	Azagro	India MART, India	32	NeemGold	Southern Petrochemical Industries Ltd., India
6	AzaGuard	BioSafe systems, USA	33	Neemfol	Gassin Pierre, India
7	Azamax	UPA Ltd., Brazil	34	Neemgurad	Gharda Chemicals Ltd., India
8	AzaPRO	CANN-CARE, Japan	35	Neemitaf	Rallis Indian Ltd., India
9	Azasol	ARBORJET Inc., USA	36	Neemix	Certis, USA
10	Azatin XL	OHP Inc., USA	37	Neemnath	Nath Seed Ltd., India
11	Bioneem	Zuari Industries Ltd., India	38	Neemol	Ramson Agrotech Pvt. Ltd., India
12	BioNeem	Woodstream Corporation, USA	39	Neemolin	Khatau Agrotech Ltd., India
13	DalNeem	Dalquim Ltd., Brazil	40	Nemstar	Universal Pesticides & Chemicals Industries, India
14	Debug TRES	AGROLogistic systems, USA	41	Nimbasol	Nimba Foods & Chemicals Pvt. Ltd., India
15	Econeem	Margo Biocontrols Pvt. Ltd., India	42	Nimbecidine	T. Stanes & Co., India
16	Ecosense	Agro Logistic Systems Inc., USA	43	OzoNeem Oil	Ozone Biotech, India
17	EcoZin plus	AMVAC chemical Corp., USA	44	Ornazin	SEPRO Corporation, USA
18	Fortune Aza	Fortune Biotech Ltd., USA	45	Peekrakshak	Yawalkar Pesticides Pvt. Ltd., India
19	Gronim-T	National Tree Grower Co-operative Ltd., India	46	Rakshak	Murkumbi Bioagro Pvt. Ltd., India
20	Kranti	Pragati Glyxal Pvt. Ltd., India	47	RakshakGold	Murkumbi Bioagro Pvt. Ltd., India
21	Margocide	Monofix Agro Products Ltd., India	48	RD−9 Repelin	Indian Tobacco Co. Ltd., India
22	Margosom	Som Phytopharma (India) Ltd., India	49	Reconeem	Ramson Agrotech Pvt. Ltd.,India
23	MOLT-X	BIOWORKS Inc., USA	50	Safer Brand 3 in 1 Garden Spray	Woodstream Corp., Canada
24	Multineem	Karnataka Agro Chemicals, India	51	Shubhdeep Neem Oil	King Agro Food, India
25	Multiplex	Multiplex Fertilizers Pvt. Ltd., India	52	Sukrina	Conster Chemicals Pvt. Ltd., India
26	Neemactin	Wockhardi (Biostadt Agrisciences), India	53	Triact 70 EC	Certis Company, USA
27	Neemazal	EID Parry (India) Ltd., India	54	Uttamneem	Chambal Fertilizers & Chemicals Ltd., India
Fertilizer applications					
1	Fortuneem Coat	Fortune Biotech, USA	6	Ozoneem Coat	Ozone Biotech, India
2	Plan “B” Organics – Neem Cake	Plan “B” Organics, USA	7	Parker Neem Coat	Parker Neem, India
3	Fortuneem Cake	Fortune Biotech, USA	8	Neem Urea Guard	Neemex, India
4	Bio Neem Oil Foliar	FUSA Fertilizers, USA	9	Ozoneem Cake	Ozone Biotech, India
5	Neem Cake	Unibell Corporation, Russia			

been developed; this work has demonstrated potential for biomedical applications and highlights the adaptability of nanotechnology in integrating herbal components into a range of delivery systems. A number of alternative formulations have been developed in recent decades, including integrating natural bioactives with nanotechnological systems, as a result of extensive attempts to find successful treatments (Manconi et al., 2018). According to reports, the bioreduction of neem extract nanoparticles is an inexpensive, environmentally friendly, and green synthesis process that produces nanoparticles with good medicinal and commercial potential (Girish, 2018). The incorporation of plant biomolecules into metal oxide based nanoparticles enhances their toxicity towards microorganisms, hence preventing ecological pollution and allowing them to withstand degradation (Huma et al., 2024).

The potential therapeutic benefits of various metals combined with neem plant component extract were assessed. For examples, silver nanoparticles (Ag-NPs) for antioxidant activity and cytotoxicity efficacy (Kumari et al., 2022b), Iron oxide nanoparticles (Fe_3O_4-NPs) as a reducing and stabilizing agent (Zambri et al., 2019), Copper oxide nanoparticles (CuO-NPs) for antibacterial, antioxidant and cytotoxicity (Revathi, Thambidurai 2019), Cerium oxide nanoparticles (CeO_2-NPs) for antioxidant, anti-inflammatory, antibacterial and angiogenic properties (Ashraf et al., 2024), Magnesium oxide nanoparticles (MgO-NPs) for petrochemical properties (Moorthy et al., 2015), Manganese oxide nanoparticles (Mn_3O_4-NPs) for Kinetic studies (Sharma et al., 2015), Zink oxide nanoparticles (ZnO-NPs) for electronic properties (Saleem et al., 2022), etc.

10.1. Biosynthtic pathway of azadirone

Azadirone is a tetranortriterpenoid and a crucial intermediate in the biosynthesis of azadirachtin, nimbin, and other neem limonoids. The biosynthesis begins with isoprenoid precursors via the mevalonate (MVA) and/or methylerythritol phosphate (MEP) pathways. These precursors (IPP and DMAPP) form squalene, which cyclizes to produce tirucallol - a common triterpenoid skeleton in neem. Through a series of oxidation, cyclization, and rearrangement steps, tirucallol is transformed into azadirone. Enzymes such as cytochrome P450 monooxygenases, oxidosqualene cyclases, and dehydrogenases are implicated in these transformations. Azadirone acts as a precursor for azadirachtin and structurally similar bioactive compounds (Dhandapani et al., 2022).



10.2. Neem genomics: unlocking biosynthetic potential

The genome of *A. indica* has been sequenced (Krishnan et al., 2012) to understand the genetic basis of its bioactive compound production. A high-quality chromosome-level genome assembly revealed tha the genome Size of approximately 281 Mb, anchored to 14 chromosomes. The gene content of around 25,767 protein-coding genes have been identified with 115 Mb of repetitive DNA, constituting a significant portion of the genome. Further, the Terpene synthase (TPS) and cytochrome P450 (CYP450) genes are organized into clusters, particularly on chromosome 13, indicating a specialized region for terpene biosynthesis. These genomic insights provide a foundation for further research into the biosynthesis of azadirone and other triterpenoids in neem, which could have implications for agricultural and medicinal applications.

The draft genome of neem (first reported in 2015) spans ~280 Mbp and has enabled the identification of numerous genes linked to limonoid biosynthesis, defense, and secondary metabolism (FAO Biopesticide Report, 2022). Recent genomic advancements in *Azadirachta indica* (neem) have significantly enhanced our understanding of its genetic framework, particularly concerning the biosynthesis of bioactive compounds like azadirachtin (Table 18).

11. Miscellaneous uses

The leaves with bitter and astringent flavor are used in the preparation of soups and curries with other vegetables (Lemmens et al., 1995). Neem leaves are usually given to the goats and camels as green fodder, used as mulch in kitchen gardening and as a green manure (Webb et al., 1984). Neem, in Asia, is the suitable tree component like agro-forestry tree species. In the northern regions of India during the hot summer months, it has been observed that the temperature beneath the neem trees is approximately 10°C lower than the ambient temperature (Ogbuewu et al., 2011). The neem tree has been considered as an ecologically sustainable in providing habitat to domesticated cattle and goats and other forest animals by improving micro-climate and conservation of uncultivated and wastelands. According to Saxena (2015), even a fairly modest assessment of the intangible "environmental service" the neem tree provides over its lifetime at $10 per month would result in an astounding value of US $30,000 to $36,000.

Quantifiable benefits and tangible economic uses of neem tree include biomass production, timber, seed, and nectar. Neem wood is hard and resistant to termite infestation, borers and fungal attack. Thus, wood is suitable for making carts, tool handles, farm implements, toys, carts, axles; packaging cases, ornamental ceilings, fence posts; in manufacturing of ships and boats due to its insect repellent properties (Tewari, 1992). Dried neem wood is extensively utilized and considered as a good fuel wood in Ghana and after partial burning yields good quality charcoal as well (Vietmeyer, 1992). Since neem is a resilient tree, it is perfect for reforestation initiatives as well as the rehabilitation of degraded coastal areas and semi-arid and arid lands (Maramorosch, 1999). In Saudi Arabia neem plantation when full grown is expected to provide shade to about two million pilgrims (Ahmed et al., 1989). In Chad, neem constitutes about 17 % of the tree cover (Ohabuike, 1995). Countries from Somalia to Mauritania, neem plantations on waste lands have been helping to prevent the spread of the Sahara Desert and invasion of weeds (Vietmeyer, 1992).

12. Potential risks of using neem-based products

Research indicates that neem products can have adverse effects on human health in the long term, particularly when consumed orally or used improperly. Several of the studies have been undertaken that intentional or accidental consumption of neem-based products may cause mild to severe vomiting, drowsiness, seizures, metabolic acidosis, coma or even death in severe cases, if left untreated. Ingestion of neem oil has been linked severely toxic to Children's health both as infants and young. Cases have reported symptoms like vomiting, metabolic acidosis, seizures, and encephalopathy after consuming doses ranging from 5 to 30 mL of neem oil. Notably, a study documented a 35-year-old woman who experienced neurological and psychotic symptoms after ingesting 60 mL of neem oil (Suresh et al., 2021; Bantubilli et al., 2022; Shrestha et al., 2024).

Oral consumption of neem oil poses severe risks adults that may

Table 18
Advances in neem genomics.

Advances	Details	References
Genome Sequencing and Assembly	• Neem's genome sequenced using Illumina, PacBio, and Hi-C technologies. • High-quality genome assembly (281 Mb across 14 chromosomes) with genes related to secondary metabolite biosynthesis identified.	Krishnan et al. (2016); Du et al. (2022)
Secondary Metabolite Biosynthesis Pathways	• Key genes involved in azadirachtin biosynthesis identified, such as terpene synthases (TPS) and cytochrome P450s (CYPs). • Transcriptomic analyses have shown gene expression variations under different conditions.	Du et al. (2022); Zhang et al. (2020)
Functional Genomics and Gene Regulation	• Transcriptomic profiling and genome-wide studies help identify regulatory networks and genes controlling terpenoid production and stress responses.	Bhambhani et al. (2017); Kumar et al. (2023)
Biotechnological Applications	• Metabolic engineering in microorganisms for azadirachtin production; potential for synthetic biology to scale production of neem bioactives.	Zhang et al. (2020); Du et al. (2022)
Genetic Diversity and Conservation	• Genetic diversity studies provide insights into neem's populations, aiding conservation and the development of varieties with beneficial traits.	Krishnan et al. (2016)

include potential adverse effects including low blood sugar levels, diabetes and reproductive failure and may lead to kidney failure (Subramaniam et al., 2024). Unprescribed consumption of neem-based products has demonstrated antifertility properties in both men and women. Studies have observed reversible effects on reproduction following sub-acute or chronic exposure to neem-based products. Moreover, internal consumption of neem extract during pregnancy is discouraged due to potential risks, including miscarriage (Mishra and Vuppu, 2023). Some individuals may experience allergic reactions to neem, such as contact dermatitis. It's advisable to conduct a patch test before extensive topical application (Singh et al., 2021; Ghose et al., 2025). Before incorporating neem products into your health regimen, especially for oral consumption, seek advice from a qualified healthcare professional. Particular care should be taken when considering neem use in children, pregnant or breastfeeding women, and individuals with underlying health conditions. Avoid exceeding suggested dosages and durations of use to minimize potential risks. While neem offers various health benefits, understanding and respecting its potential adverse effects are crucial for safe use.

13. Toxicological profile of neem-based products: safety assessment in humans and non-target organisms

Toxicological studies on neem-based products have investigated their safety for humans and non-target organisms. For humans, the acute Toxicity tests conducted in rats and rabbits with neem oil for 24 h reported that LD_{50} (lethal dose for 50 % of subjects) was 14 mL/kg in rats and 24 mL/kg in rabbits. The target organs included the lungs and central nervous system (Gandhi et al., 1988). Studies on subchronic toxicity of neem oil in mice revealed that oral administration of neem oil at doses up to 1600 mg/kg/day did not produce significant toxicity. Target organs included the liver, kidneys, and testes. The No-Observed-Adverse-Effect Level (NOAEL) was determined to be 177 mg/kg/day (Wang et al., 2013). Similarly, subchronic toxicity of Azadirachtin in rats at doses up to 1500 mg/kg/day for 90 days did not produce signs of toxicity (Raizada et al., 2001).

For non-target organisms, the toxicity of Margosan-O on aquatic invertebrate exhibited varying response to different species. For example, the 48-hour EC_{50} for *Culex* spp. was 105 mg/L, while for *Hyalella azteca*, it was 71 mg/L. Concentrations of 20–30 mg/L caused growth inhibitory effects in *Culex* spp. and *Chironomus riparius* larva. Higher concentrations affected growth and reproduction in *H. azteca* and *D. magna*. These findings suggest that while Margosan-O can be effective against target pests, its use may have some non-target effects on aquatic organism (Scott and Kaushik, 1998). Likewise, the toxicity of neem-based insecticides on aquatic animals revealed that azadirachtin showed less toxicity than neem-based insecticides like Neemix™ and Bioneem™ on various species tested, including crayfish, white shrimp, grass shrimp, blue crab, water fleas, oyster, freshwater snails, and mosquitoe. However, the study highlighted that neem-based insecticides could have varying degrees of toxicity depending on the formulation and specie (Goktepe, 1999).

While neem-based products, including neem oil and azadirachtin, have demonstrated low acute and subchronic toxicity in humans, their safety can vary based on the formulation and exposure level. In non-target organisms, especially aquatic species, neem-based insecticides can exhibit varying degrees of toxicity, indicating the need for careful application to minimize environmental impact. Further studies are essential to establish comprehensive safety profiles and guidelines for the use of neem-based product.

14. Conclusions and future perspectives

Azadirachta indica has gained a worldwide attention due to its several known traditional applications with broad-spectrum of medicinal and pharmacological characteristics. A number of phytochemicals and bioactive ingredients have been identified and isolated the from different plant parts of neem tree for commercial manufacturing of neem-based products like agrochemicals, pesticides, herbal and cosmetic products. The scientific studies provide an insight on the use of *A. indica* with different solvent preparations for therapeutic benefits. Several clinical trials have been reported the efficacy of neem-based extracts on chronic diseases of small animals and are also being utilized in the treatment of human ailments. Owing to its superior antimicrobial qualities, scientists are exploring secondary metabolites and are directing their efforts in creating innovative, affordable, and safe medications for use in agriculture and health sciences. Azadirachtin-based agrochemical such as pesticides, herbicides and weedicides are being potentially used in integrated pest and weed management techniques, particularly in organic and agroecological farming systems. Several commercial products containing neem-based formulation and ingredients have been developed and marketed worldwide. Besides, neems is helful in restoring the soil quality through afforestation on degraded landscapes, hence acts as soid-conditioner and provide the woody biomass in form of timber for contruction works.

There are certain legal obstacles curtailing widespread and efficient utilization of neem-based products. There is need to resolved these limitations with the government legislative interventions. Lack of infrastructure for mass scale product manufacturing and a shortage of quality neem seeds hinder the manufacturing of neem-based agrochemicals and organic fertilizers. The poor stability of seeds under field conditions due to high rate of photodegradation, short residence time with lower efficacy rates, weakens the efficient utilization of neem compared to inorganic pesticides for pest control in agricultural crops.

Owing to these limitations, scientists must focus on the development of high yielding varieties and standardize the process for extracting high-quality neem oil. In addition, efforts must be directed to identify the novel bioactive ingredients and evaluate their mode of action in integrated insect-pest management practices. To increase the bioavailability of neem and its parts, large-scale plantations on wastelands, roadsides, community areas, etc., should be planned to maintain a steady supply of raw materials to boost industrial consumption of neem. Fruit collecting, seed drying, and seed storage procedures should be strengthened to prevent fungal and soil contamination of the seeds and extracted compounds. Quality standards for neem seed kernel oil and leaf concentrates should be framed by Bureau of International Standards imposing strict guidelines. The review concludes with implications that neem has enormous potential for treating a wide range of illnesses and disorders through the creation of pertinent herbal formulations that is significant for pharmaceutical and ayurveda-based industries.

CRediT authorship contribution statement

Dhakad Ashok: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Choudhary Raman:** Writing – review & editing, Supervision, Resources, Methodology, Data curation. **Kumar Rahul:** Writing – review & editing, Supervision, Resources, Methodology, Formal analysis. **Khan Salman:** Writing – review & editing, Visualization, Methodology, Formal analysis, Data curation, Conceptualization. **Singh Simrat:** Writing – review & editing, Visualization, Resources, Methodology, Investigation, Data curation. **Poonia Pawan:** Writing – review & editing, Validation, Resources, Methodology, Data curation.

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Declaration of Competing Interest

The authors declare no conflicts of interest.

Data Availability

No data was used for the research described in the article.

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