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Unveiling the Multidisciplinary Nature of Neem: From Tradition to Modern Medicine

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ABSTRACT:

Medicinal plants are essential in both traditional and modern medicine. They have a wide range of applications for physical, emotional, and spiritual well-being, providing valuable contributions to human health, culture, and sustainability. The therapeutic potential of various plants in disease management continues to be actively researched due to their minimal side effects and cost-effectiveness. *Azadirachta indica*, generally known as "neem," has been widely used across Asia for treating various ailments. Renowned for its extensive medicinal properties, it is often referred to as "the versatile tree" used in various forms from different parts of the tree, including the leaves, bark, seeds, fruit, and oil. Neem contains a vast range of phytochemicals, including azadirachtin, nimbin, nimbolide, salannin, and gedunin, which contribute to its medicinal, antimicrobial, and insecticidal properties. These compounds play an important role in the tree's use for various purposes, from traditional medicine to natural pest control. The potent bioactive compounds found in *A.indica* contribute to its remarkable efficacy in preventing and treating numerous infectious and non-infectious diseases, including cancer. The present work highlights the multidisciplinary nature of Neem. Further preclinical & clinical research is needed to validate its therapeutic effects and confirm its safety and effectiveness.

Keywords: Neem, Pharmacological properties, antimicrobial, Agriculture

INTRODUCTION:

The growing recognition of neem long-term benefits in both agriculture and healthcare has led to increased global attention and commercial interest [4]. Neem is a significant plant in traditional medicine, agriculture (as a natural pesticide), and various other industries due to its numerous health and environmental benefits [1]. In Indian mythology and the Puranas, the neem tree (*Azadirachta indica*) is often revered for its medicinal, spiritual, and protective qualities. Neem has been an integral part of Ayurvedic medicine for centuries in the treatment of many diseases [3,4,5]. It is often referred to as "Sarva RogaNivarini," which means "the healer of all diseases" [2]. Ayurveda considers neem as a cooling, detoxifying, and purifying agent for both body and spirit.

Azadirachta indica, belonging to the Meliaceae family and commonly known as neem, nimtree, or Indian lilac, was first identified in India approximately 4,500 years ago. The Latinized name -*A.indica* originates from Persian, meaning "the free tree of India" [5]. Revered for its vast medicinal properties, various parts of the neem tree—including its leaves, flowers, fruits, seeds, and bark—are extensively utilized in traditional healing systems such as Ayurveda, Unani, and Siddha for treating a wide array of ailments, including tumors [1,2,3,4,6,7]. Due to its exceptional therapeutic potential, neem has earned titles such as the "Village Pharmacy" the "Tree of the 21st Century" and "A Tree for Solving Global Problems" [9].

Distribution & Morphology:

Today, neem trees commonly found in India, Pakistan, Bangladesh, and Nepal [10]. *A.indica* can endure temperatures ranging from 50°F to 98°F [1]. It exhibits remarkable resilience to low rainfall and flourishes best in sandy, nutrient-poor soils with a pH between 6.2 and 7 [1]. Predominantly found in dry tropical and subtropical regions, neem trees also grow along sandy riverbanks in Australia

[1]. This fast-growing tree can reach a height of 15–23 meters, featuring a straight trunk with a diameter of approximately 4–5 feet. Its leaves are compound and imparipinnate, consisting of 5–15 leaflets. The tree bears green drupes that ripen to a golden-yellow hue between June and August [10].

In recent years, extensive research has highlighted the rich phytochemical composition of neem, revealing a vast spectrum of biological and pharmacological activities. These include, but are not limited to, anti-inflammatory, antipyretic, antihistamine, antifungal, antibacterial, anti-ulcer, analgesic, anti-arrhythmic, anti-tubercular, anti-malarial, diuretic, spermicidal, anti-arthritic, anti-protozoal, insect-repellent, anti-feedant, and anti-hormonal properties [3,4,5,6,11].

With such an extraordinary range of therapeutic benefits, neem continues to be a subject of global scientific interest and remains a cornerstone of traditional and modern medicine. The purpose of this article to disclose the therapeutic efficiency of neem in the healthcare and agriculture sector based on published preclinical results.

Botanical nomenclature [12](Figure 1)

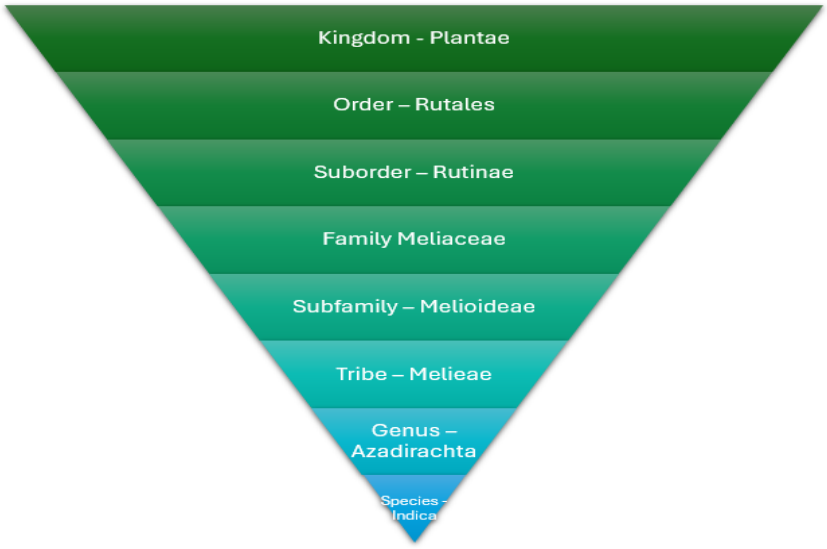

Figure 1: Botanical nomenclature of Neem Plant

Regional names of Margosa:

Neem (*Azadirachta indica*) is widely recognized across India, and it is known by different names in various languages and regions. Here are some of the local names of neem in India(figure 2):

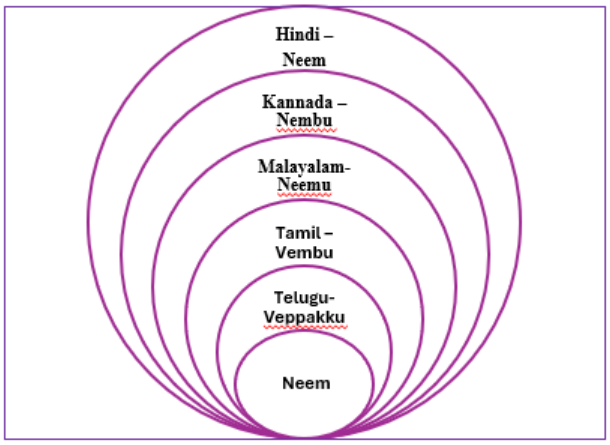

Figure 2: Regional names of Margosa

Each of these names refers to the same plant, but their pronunciation and spelling vary according to the regional language. Neem is deeply ingrained in the culture of India, with each region often having its own traditional uses and beliefs associated with it.

Chemical Constituents:

Azadirachta indica (neem) plays a significant therapeutic role in health management due to the presence of more than 135 bioactive compounds as shown in the table 1. Each and every part of neem tree, including the whole tree, stems, branches, leaves, flowers and fruits, produces different phytochemicals. The most potent constituent is azadirachtin, alongside other key compounds such as nimbolinin, nimbin, nimbidin, nimbidol, sodium nimbinate, gedunin, salannin, and quercetin. Neem leaves contain a diverse range of bioactive ingredients, including nimbin, nimbanene, 6-desacetylnimbinene, nimbandiol, nimbolide, ascorbic acid, *n*-hexacosanol, amino acids, 7-desacetyl-7-benzoylazadiradione, 7-desacetyl-7-benzoylgedunin, 17-hydroxyazadiradione, and nimbiol. Additionally, quercetin and β-sitosterol, two polyphenolic flavonoids extracted from fresh neem leaves, exhibit potent antibacterial and antifungal properties. Neem seeds are also a valuable source of bioactive compounds, including gedunin and azadirachtin, further contributing to its extensive medicinal applications [10,12-17].

Table 1: Neem, chemical constituents & its Pharmacological activities

Part of Neem plant	Active Constituents	Pharmacological Activities
Bark	Nimbidin, Sodium nimbinate, Polyphenols	Antifungal, Antipyretic, Antimalarial
Flowers	Flavonoids, Essential oils	Antioxidant, Antibacterial
Fruit	Margolonone, Isomargolonone	Antibacterial, Antifungal
Gum	Polysaccharides	Anti-inflammatory, Immunomodulatory
Leaves	Nimbin, Nimbidin, Quercetin, Nimbolide	Anti-inflammatory, Antibacterial, Antiviral, Antioxidant
Oil (Neem oil)	Azadirachtin, Nimbin, Fatty acids	Antimicrobial, Antiparasitic, Wound healing
Roots	Polysaccharides, Triterpenoids	Anti-inflammatory, Antimalarial
Seeds	Azadirachtin, Nimbin, Salannin	Insecticidal, Antifeedant, Antifungal

Material and methods:

The process of gathering relevant information on *Azadirachta indica* involved an extensive library search for scholarly articles published in peer-reviewed journals and ethnobotanical textbooks, supplemented by electronic searches through databases such as Google Scholar, PubMed, Web of Science, Scopus, and various other online research platforms.

Pharmacological properties of Margosa:

Neem has been widely used in traditional medicine for centuries due to its diverse pharmacological properties as shown in Figure 3.. The various parts of the neem tree such as the leaves, bark, seeds, and flowers—contain bioactive compounds with multiple therapeutic effects. Today, a wide range of neem-based formulations are available on the market for managing various ailments. Extensive clinical and pharmacological research has been conducted on different parts of the neem tree, as well as on commercially available neem products. In nearly all cases, the findings have been highly promising.

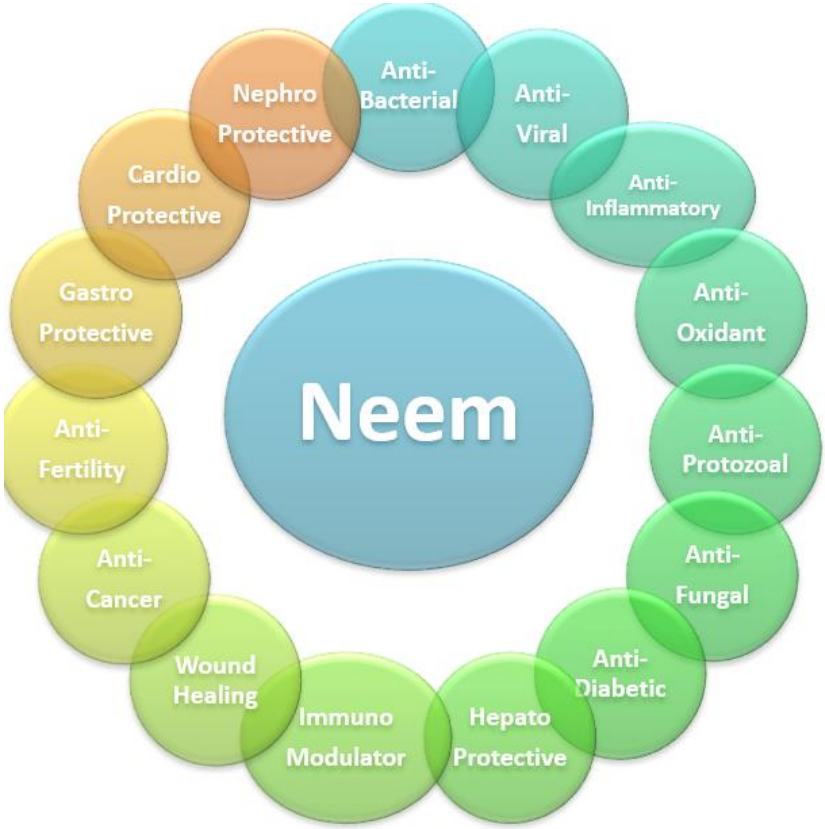

Fig 3: Schematic representation of Neem therapeutic activities.

1.Anti-bacterial activity:

Neem bark and leaf extract has been shown to exhibit antibacterial activity against a wide range of bacteria, including *Staphylococcus aureus, Escherichia coli* [18]. Recent studies suggest that neem contains compounds showing antibacterial activity that can be able to control the foodborn pathogenic organisms. The minimum inhibitory concentration (MIC) of chloroform and ethanol neem leaves extract (NLE) demonstrated greater inhibition against *L. monocytogenes* and *S. aureus, S. mutans* and *C. albicans* microorganisms respectively [19,20].

The results demonstrated that the methanol extract exhibited bactericidal activity against nosocomial strains of *Staphylococcus aureus* and *Pseudomonas aeruginosa*, as well as bacteriostatic activity against the *nosocomial strain of Enterococcus faecalis*. The ethanol extract showed bactericidal effects against nosocomial strains of *E. faecalis* and *P. aeruginosa*, and bacteriostatic activity against the nosocomial strain of *S. aureus*. The ethyl acetate extract displayed bactericidal activity against *S. aureus* and *P. aeruginosa*, and bacteriostatic activity against the nosocomial strain of *S. aureus* and the standard strain of *E. faecalis*. These findings suggest that neem may serve as a potential therapeutic agent in the fight against antibiotic-resistant bacteria.

2.Anti-fungal activity: Neem is also effective against fungal infections, particularly *Candida albicans* and other dermatophytes. Its antifungal properties are attributed to compounds like azadirachtin, which inhibit fungal growth. Invitro antifungal activity of neem leaf extracts on seed borne fungi *Aspergillus , Rhizopus* has documented [22]. Neem leaves and see extracts obtained by ethanol, hexane and petroleum were significantly inhibited the growth of pathogenic fungi *fusarium axysporium, rhizoctonia solani, Alternaria Olani, Sclerotinia sclerotiorum* [23].

Aqueous, ethanolic and ethyl acetate extracts of neem leaves on growth of some human pathogens like *Aspergillus flavus, Aspergillus fumigatus, Aspergillus niger, Aspergillus terreus, Candida albicans* and *Microsporum gypseum* was evaluated [24].The antifungal effect of Malaysian neem leaf extracts against otomycosis causing fungi *Aspergillus niger* and *Candida albicans* by well diffusion method was demonstrated [25].The growth of four soil-borne pathogens of *Cicer arietinum, Fusarium oxysporum* f.sp. *ciceri, Rhizoctonia solani, Sclerotium rolfsii*, and *Sclerotinia sclerotiorum* was inhibited by different parts of neem like leaf, trunk bark, fruit pulp, and oil [26].

Neem seed kernel extracts significantly reduces the multiplication of *Monilinia fructicola, Penicillium expansum, Trichothecium roseum* and *Alternaria alternate* which were isolated from the infected fruit of Prunus salicina/ *Pyrus bertschneideri* [27]. By in vitro tube dilution technique, the antifungal activity of *A.indica* leaves and seeds extracts was tested against *Trichophyton rubrum, Trichophyton mentagrophytes and Microsporum nanum*. The results revealed that there was a significant decrease in growth treated dermatophytes with reference to the untreated fungi [28].

3.Anti-viral activity: Neem extracts interfere with critical stages of the viral lifecycle, such as cell entry and replication. It has been recognized for its broad-spectrum antiviral activity against a range of viruses, including herpes simplex virus (HSV), dengue virus, hepatitis C virus (HCV), poliovirus, influenza, HIV, SARS-CoV-2and coxsackie B virus.

A novel antiherpetic microbicide effect of an aqueous extract of the *Azardirachta indica* bark (NBE) was observed when the extract was pre-incubated with the Herpes simples virus type-1 and also inhibited the glycoprotein-mediated cell–cell fusion and polykaryocytes formation at viral fusion step [29]. Anti-viral, antitumor and cytotoxic activities of crude aqueous extracts of seeds and leaves of neem plant was investigated. It suggests that the crude acidic extract of leaves and seeds and alkaline extract of seeds possesses very remarkable antiviral activity against herpes simplex virus type 1 compared with acyclovir [30].

The current study highlighted the in vitro and in vivo inhibitory effects of the aqueous extract of neem leaves and pure Azadirachtin on the replication of Dengue virus type-2. The suppression of viral replication was evidenced by the absence of Dengue-related clinical symptoms in suckling mice and the lack of the virus-specific 511 bp amplicon in RT-PCR analysis [31].

In vivo results revealed that NLE inhibited the protein petptide of 14 Kda in theserum of Hepatitis-C Patients [32].Two polysaccharides isolated from *A.indica* demonstrated better virucidal effect on initial stage of polio viral replication [33].

Molecular docking analysis revealed three promising compounds Nimbaflavone, Rutin, and Hyperoside derived from neem that demonstrated potential activity against the influenza virus nucleoprotein. Among these, Hyperoside from neem leaf extract, in combination with the drugs LGH, Naproxen, BMS-885838, and BMS-883559, exhibited the most favorable interactions with the conserved residues of the nucleoprotein [34].

HIV related opportunistic pathogens *Staphylococcus aureus ,Pseudomonas aeruginosa , Candida albicans, Cryptococcus neoformans* growth inhibited by Neem plant parts extract against was examined [35].The reduced risk of COVID-19 infection was observed in patients taking neem capsules highlights its potential as a prophylactic treatment for preventing COVID-19 [36].The antiviral effects of neem bark and leaves were conformed on Newcastle Disease Virus in Poultry [37].

4. Anti-protozoal activity:

Neem has demonstrated significant antiprotozoal activity, making it a promising candidate for the treatment of protozoal infections. It can expel parasitic worms from the body, particularly in the intestines. Studies have indicated that neem compounds, particularly limonoids azadirachtin, salannin, deacetylgedunin, gedunin, 17-hydroxyazadiradione and deacetylnimbin exhibit potent effects against toxic to various parasites such as *Plasmodium* [38,39], *Leishmania* [40], *Trypanosoma* [41]and insects also.

Anti-malarial screening of neem leaf and stem bark extracts using *Plasmodium berghei* infected albino mice reduced the level of parasitemia [38]. Leishmanicidal effect was validated using ethyl acetate fraction of neem leaves through cytotoxicity assay [40].

A dose-dependent anti-trypanosomal effect of aqueous extracts from the bark of neem was observed in *Trypanosoma brucei rhodesiense*-infected mice. The treatment delayed the appearance of parasites in the circulation, reduced parasitemia levels, and improved packed cell volume [41].

5.Anti-inflammatory and Analgesic properties:

Neem contains compounds like azadirachtin and nimbidin, which have anti-inflammatory effects by modulating inflammatory pathways, such as cyclooxygenase (COX) and lipoxygenase (LOX) enzymes.It has been used in treating conditions like arthritis, swelling, and other inflammatory disorders due to its ability to reduce pain and inflammation.

Significant anti-inflammatory action of neem seed oil and bark reduced the carrageenan induced paw edema in albino rats [42] and long Evans rats [43]. Ethanol extract of neem bark on Swiss Albino mice was tested for Analgesic properties using hot plate and acetic acid induced writhing methods [44]. Whereas alcoholic extract of Neem root bark extract proven for weak central and peripheral analgesic activity [44].

6. Anti-oxidant activity:

Due to the presence of flavonoids, alkaloids, and other polyphenolic compounds, neem has strong antioxidant properties which help to neutralize free radicals in the body, reducing oxidative stress and lowering the risk of chronic diseases such as cancer, cardiovascular diseases, and neurodegenerative disorders.

The extract of *Azadirachta indica* flowers demonstrated significant antioxidant activity, including DPPH, hydrogen peroxide (HRSA), and phosphor molybdenum radical scavenging, metal ion chelation, and superoxide anion scavenging. These effects are attributed to the presence of phenolic compounds and flavonoids in the extract [45] and ethanolic extract of neem leaves was also reported for anti oxidant property [46]. In another hand , the potency of *Azadirachta indica* as a good source of natural antioxidant compounds was demonstrated by 1,1-Diphenyl-2-picryl-hydrazyl radical scavenging and Ferric-Reducing Antioxidant Power Assay [47].

7.Anti-diabetic activity:

Neem offers significant potential as a natural therapeutic agent for managing diabetes. Its bioactive compounds help regulate blood sugar levels, improve insulin sensitivity, reduce oxidative stress, and improve lipid profiles. *Azadirachta indica* serves as a valuable alternative in the management of diabetes mellitus, demonstrating the ability to reduce elevated blood glucose levels in alloxan-induced diabetic rats [48].

The therapeutic potential of limonoids azadiradione and gedunin from the neem seed coat and kernel has been reported to inhibit pancreatic α-amylase activity, which suggests potential antidiabetic properties [49]. Antidiabetic potentials of methanolic extracts of neem seeds on the Streptozotocin-induced Wistar Rats have been validated [50].Decrease in serum lipid levels, blood glucose and activities of serum enzymes like alkaline phosphatase , acid phosphatase , lactate dehydrogenase ,liver glucose 6-phosphatase and HMG CoA reductase were assessed for neem kernel powder which suggests a significant antidiabetic and antihyperlipidemic effect of neem [51].

Neem leaves and seeds have shown anti-diabetic effects by improving insulin sensitivity [52], reducing blood sugar levels, and protecting pancreatic beta cells. Some studies suggest the hypoglycemic action of neem was due to its ability to regulate carbohydrate metabolism [53] and enhanced the insulin action.

8. Hepatoprotective Properties:

Neem has hepatoprotective (liver-protecting) effects. It has been used in traditional medicine for treating liver disorders such as hepatitis and cirrhosis. Neem helps in detoxifying the liver, reducing liver enzyme levels, and protecting liver cells from damage.

Nimbolide found to possess hepatoprotective effect against carbon tetrachloride (CCl4) induced liver toxicity in rats [54]. Administration of biosynthesized nano selenium (BSN) derived from *Azadirachta indica* leaf extracts to the mice infected with *E. papillata* exhibited notable increase in parameters like glutamic-pyruvic transaminase ,glutamic-oxaloacetic transaminase , alkaline phosphatase , and direct bilirubin during in help mitigate oxidative damage [55].

9. Anti-cancer activity:

Neem exhibits anticancer properties due to its ability to induce in cancer cells and inhibit the proliferation of tumors. The cytotoxic activity of crude aqueous, acidic neutral extracts from seeds and leaves revealed significantly inhibited the Ehrlich ascites carcinoma cell line growth [30]. Compounds found in neem bark, leaves, flowers, and seed oil have demonstrated chemopreventive properties, apoptotic activity, immunomodulatory effects, and the ability to induce p53-independent apoptosis [56].

Apoptosis in prostate cancer cells, decreases anti-apoptotic protein Bcl-2 expression was studied for ethanolic NLE by a dose-dependent increase in DNA fragmentation, Western blot analysis concludes that NLE potential therapeutic agent for prostate cancer treatment [57]. Methanolic extracts of neem fruit mesocarp and epicarp exhibited dose-dependent antiproliferative effects on PC-3, MCF-7, and Caco-2 cell lines. In PC-3 cells, the mesocarp extract showed downregulation of the anti-apoptotic BCL2 gene and upregulation of P53 and BAX, which discloses the anti-tumor potential of neem fruit [58].

10.Immunomodulatory activity:

Neem has immunomodulatory properties, meaning it can either enhance or suppress the immune system depending on the body's needs. It is used to boost immunity in cases of chronic infections or immunodeficiencies.

After administration of neem oil through intra peritoneal (i.p.), a peak in leukocyte infiltration were observed in mice. Additionally, peritoneal macrophages displayed increased phagocytic activity and upregulated expression of MHC class II antigens. Neem oil treatment also stimulated the production of gamma interferon. Spleen cells exhibited a significantly enhanced lymphocyte proliferative response when challenged in vitro with Concanavalin A (Con A) or tetanus toxoid (TT), compared to controls. These findings suggest that neem oil functions as a non-specific immunostimulant, selectively enhancing cell-mediated immune (CMI) responses to subsequent mitogenic or antigenic stimuli [59].The hydro-alcoholic extract of neem bark exhibits superior antibacterial and immunomodulatory properties, making it a potential therapeutic option for treating endometritis in repeat-breeding crossbred cows [60].The anti-leishmanial properties of ethyl acetate fraction neem leaf extracts (EAF) demonstrated leishmanicidal activity, as confirmed by a cytotoxicity assay against the promastigote stage [61].

A bioactive compound or fraction derived from neem NIM-76, enhanced mitogen-induced lymphocyte proliferation was stimulated, these findings emphasizes that Immunomodulatory effects of *A.indica* through cell-mediated mechanisms by activating macrophages and lymphocytes [62].

11. Wound Healing and Skin Benefits:

Neem oil and neem extract are commonly used for wound healing due to their antimicrobial and anti-inflammatory properties. They promote tissue regeneration and help in the treatment of wounds, cuts, burns, and other dermatological disorders [69] like eczema, acne [69], and psoriasis. Neem leave extracts promotes wound healing activity in rats [63,64] and diabetic foot ulcer patients [65].In vitro studies supports that neem seed oil aid the healing of topical wounds by inhibiting the growth of methicillin resistant *S. aureus* strains [66].

The in vivo wound healing studies of topical neem hydrogels (N-HG), with and without silk fibroin (N-SF-HG) was carried out. The results indicated that N-SF-HG treatment accelerates the regeneration of the injured area more effectively [67].The beneficial effects of the herbal ingredients like neem and turmeric in Himalaya's Purifying Neem Face Wash , showed their effectiveness in preventing and reducing mild-to-moderate acne without any observed side effects were evaluated [68].Screening of neem oil Compounds using the PubChem database revealed that neem oil as a potential target for STAT1, CSK, CRABP2, and SYK genes in the treatment of Acne vulgaris [69].Topical application of Neem-Tulsi-Heena oil combined therapy in Psoriasis patients better results were observed [70].

12. Gastroprotective Effects:

Neem has been shown to protect the gastrointestinal system by preventing ulcers, reducing acid secretion by inhibiting H+ K+-ATPase (proton pump) activity [73] and promoting gastric mucosal protection. This property is used in the treatment of conditions like gastritis, acid reflux, and peptic ulcers.

The aqueous NLE reduced the severity of gastric ulcers [74-79] in a dose-dependent manner in rats exposed to stress, and decreased gastric mucosal damage caused by ethanol. The extract appeared to inhibit mast cell degranulation and enhance the production of adherent gastric mucus in stressed animals. These effects may partially account for the antiulcer properties of neem. The anti-ulcer effects of aqueous neem leaf extracts were evaluated in rats subjected to 2-hour cold-restraint stress and oral administration of ethanol for 1 hour. Results showed that neem extract reduced the severity of stress-induced gastric ulcers in a dose-dependent manner and also lessened ethanol-induced gastric mucosal damage. Not only that the extract appeared to prevent mast cell degranulation and increased the quantity of adherent gastric mucus in stressed animals. These actions likely contribute to the anti-ulcer properties of neem [71].

Oral administration of the lyophilized NBE led to inhibition of acid secretion and peptic activity, along with a reduction in gastric juice volume in patients suffering from acid-related disorders and gastro duodenal ulcers. This research output reflects the anti-secretory and antiulcer effects of neem [72].

13.Cardioprotective Effects:

Some studies suggest that neem may support heart health by reducing cholesterol levels, lowering blood pressure [81] and improving circulation, thus helping to prevent cardiovascular diseases [80]. Neem seed protein hydrolysates (NSPHs) were evaluated for their superoxide radical scavenging and ACE inhibitory activities. The findings suggest that NSPH fractions may have potential applications in managing oxidative stress-related conditions, including hypertension [80].

Blood pressure lowering effects in a was reported. Shift in the Ca^{+2} concentration response curves to right side vaso relaxation was observed when isolated rabbit aorta ring preparations treated with of the crude extracts of *A.indica*, which possibly explains its

antihypertensive activity [81]. Neem possesses blood-purifying properties. It helps detoxify the bloodstream by eliminating harmful toxins that can compromise the function of vital organs such as the liver and kidneys [82].

14. Nephroprotective activity:

Neem exhibits protective effects on the kidney [86] by reducing oxidative stress, enhancing antioxidant enzyme activity, antiurolithiatic activity, improving renal function markers [85], and mitigating histopathological damage in various models of nephrotoxicity [83].

Methanolic leaves extract of *Azadirachta indica* effectively rescues the kidney oxidative damage, down regulates the caspase-3 and caspase-9 and Bax genes on induced nephrotoxicity and oxidative stress in rats. This finding conforms that neem as a potential candidate for protection of nephrotoxicity [83]. The ameliorating effects of extracts of *Cinnamomum cassia* and *Azadirachta indica* against nephrotoxicity in rats exposed to sublethal doses of Titanium Dioxide nanoparticles were demonstrated [84].

The protective effects of the polyphenol-rich fraction (PRF) derived from the methanol extract of *Azadirachta indica* against hypertension and cardiorenal dysfunction induced by N^{ω}-Nitro-L-Arginine Methyl Ester (L-NAME) in rats, significantly reduced oxidative stress indicators (malondialdehyde and protein carbonyl levels),normalized serum nitric oxide (NO) bioavailability, and up-regulated the expression of nuclear factor erythroid 2–related factor 2 (Nrf2) [85].Significant decrease the level of calcium, oxalate , phosphate , Creatine, uric acid and urea was reported in ethylene glycol-induced urolithiasis animals after administration of herbal suspension containing alcoholic extracts of fruit of *Tribulus terrestris*, root of *Boerhavia diffusa* and leaves of *Azadirachta indica*. Histopathology supported that formulation exhibits significant anti-urolithiatic activity [87].

15. In Dental practice:

Neem supports oral health through its antibacterial, anti-inflammatory, and antioxidant properties. It helps prevent plaque, tooth decay, gum diseases, and promotes healing, making it valuable in dental care products.

The dried chewing sticks of *Azadirachta indica* showed maximum zone of inhibition in contrast to organisms responsible for dental caries like *Streptococcus mutans, Streptococcus mitis, Streptococcus salivarius,* and *Streptococcuss anguis* , which uncovers the antimicrobial activity of neem [88]. Some studies explore neem-based formulation to evaluate anti-microbial activity. For example, *Azadirachta indica* (neem) mouth rinse reduced the gingival, plaque, bleeding indexes and growth of cariogenic bacteria. These results revealed the good efficacy in the treatment of periodontal disorders [89].

A double-blind crossover study was conducted to evaluate the effect of Neem Mouthwash on Plaque and Gingivitis was evaluated using Silness and Loe plaque index (PI) and Loe and Silness gingival index (GI). The results conclude that neem mouthwash with greater advantage in maintaining oral hygiene and preventing the onset and spread of oral diseases [90]. Gel containing neem for the prevention of gingivitis was investigated clinically. Observations of this study, state that anti-inflammatory action of neem gel can be effectively used as an adjunct to mechanical plaque control in prevention of plaque and gingivitis [91].

16.Anti-fertility effect:

Neem has been traditionally used for its anti-fertility effects. Certain neem extracts like neem oil [94] exhibited the spermicidal and contraceptive properties [95], and may interfere with implantation [96], making it a potential natural agent for pregnancy termination or prevention.

Oral treatment with neem seed extract for six days in primates resulted in a decrease in chorionic gonadotropin and progesterone levels, along with the presence of blood in vaginal smears, indicating the anti-fertility property of neem [92]. Additionally, oral administration of purified neem extracts led to pregnancy termination in both rodents and primates, confirming its abortifacient potential [93]. Intrauterine application of neem oil led to pre-implantation block in female wistar rats was demonstrated [96].

17. In Agriculture field:

Neem and its products are biodegradable, non-toxic to beneficial insects like bees and earthworms. It is safe for humans, animals and ideal for organic and sustainable farming practices [101].

Neem oil-based nano-pesticide contributes to sustainable agriculture [98] by acting as a natural pesticide, fertilizer, and soil enhancer, supporting eco-friendly and chemical-free farming practices due to its natural pesticidal [97], insecticidal [102], fungicidal [104], and soil-enriching properties. Neem cake, the residue left after oil extraction, used as an organic fertilizer because it enhances soil fertility and controls soil-borne pests and nematodes [103], improves nitrogen availability by inhibiting nitrification, thus reducing fertilizer loss. Neem-based products inhibit the growth of pests, insect species including aphids, whiteflies [99], and caterpillars, fungal infections in plants like powdery mildew, rust, and black spot.

Neem products were tested for their efficiency in reducing transmission of vector of tomato leaf curl gemini virus disease [99]. Results of another experiment suggest that applying neem leaf powder as a soil amendment at the appropriate rate and time could effectively help control cucumber mosaic virus in cowpea plant [100].

Summarized pharmacological properties of Neem:

Table:2

No.	Activity	Main Effects	Key Compounds/Extracts	Target Organisms/Systems
1	Anti-bacterial	Inhibits bacterial growth	Methanol, ethanol, ethyl acetate extracts	S. aureus, E. coli, L. monocytogenes, P. aeruginosa, E. faecalis
2	Anti-fungal	Inhibits pathogenic fungi	Ethanol, hexane, petroleum, aqueous extracts	Aspergillus spp., Candida albicans, Fusarium spp., Sclerotinia spp.
3	Anti-viral	Blocks virus entry/replication	Aqueous extracts, Azadirachtin, Nimbaflavone, Hyperoside	HSV, Dengue virus, HCV, Influenza, SARS-CoV-2, Poliovirus
4	Anti-protozoal	Anti-malarial, anti-leishmanial, anti-trypanosomal	Azadirachtin, Salannin, Gedunin	Plasmodium, Leishmania, Trypanosoma
5	Anti-inflammatory & Analgesic	Reduces swelling and pain	Azadirachtin, Nimbidin	Arthritis, inflammatory disorders
6	Anti-oxidant	Neutralizes free radicals	Flavonoids, polyphenolics	General oxidative stress, chronic diseases
7	Anti-diabetic	Lowers blood glucose, improves insulin sensitivity	Limonoids (Azadiradione, Gedunin)	Diabetes mellitus
8	Hepatoprotective	Protects liver from toxins	Nimbolide, BSN (biosynthesized selenium)	Liver disorders (hepatitis, cirrhosis)
9	Anti-cancer	Induces apoptosis, inhibits tumors	Ethanolic/methanolic extracts, crude aqueous extracts	Cancer cell lines (prostate, breast, colon)
10	Immunomodulatory	Boosts immune responses	Neem oil, NIM-76, ethyl acetate fractions	Chronic infections, immunodeficiencies
11	Wound Healing & Skin Benefits	Promotes tissue regeneration	Neem oil, hydrogels, ethanol extracts	Wounds, acne, psoriasis
12	Gastroprotective	Prevents ulcers, reduces acid secretion	Aqueous NLE	Gastritis, peptic ulcers
13	Cardioprotective	Lowers BP, antioxidant effect	NSPHs, crude extracts	Cardiovascular health, hypertension
14	Nephroprotective	Protects kidneys from oxidative damage	Methanolic extracts, polyphenol-rich fraction (PRF)	Nephrotoxicity, oxidative stress

Conclusion:

Neem (*Azadirachta indica*) has displayed significant therapeutic potential across a wide range of pharmacological activities, as supported by various research studies. Its bioactive compounds exhibit potent antibacterial, antifungal, antiviral, anti-inflammatory,

antioxidant, antimalarial, antidiabetic, hepatoprotective, and anticancer properties. These effects make neem a valuable natural resource for the development of novel therapeutic agents. The traditional use of neem in Ayurvedic and folk medicine and scientific evidence, suggesting a strong basis for its continued exploration in modern medicine.

Despite extensive research, the full potential of neem remains underexplored. Future research should focus on isolating novel compounds, understanding their specific molecular mechanisms, developing standardized extracts, and conducting more clinical studies to validate therapeutic claims. Advanced biotechnological approaches and nano formulations could further enhance neem's applications in modern medicine, agriculture, and environmental sustainability.

Thus, neem continues to be a promising natural resource with vast opportunities for future scientific exploration.

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