Neem Research Newsletter

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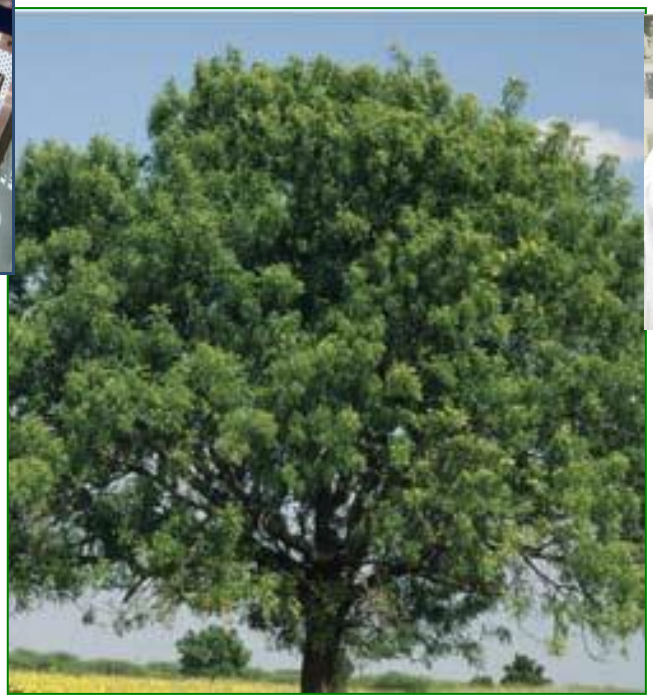

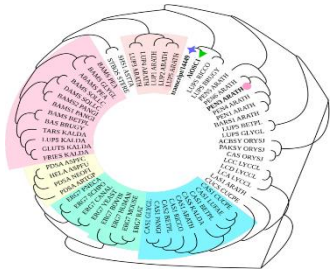

WORLD NEEM ORGANISATION (WNO)

From

The Editor's Desk……

In this issue of the Neem Newsletter, abstracts of research on neem in diverse areas are presented. A nanoferilizer synthesized from marine waste derived $CaCO_3$ nanoparticles formulated with azadirachtin and panchakavya emulsion was found to exhibit synergistic role of fertilizer, pesticide, fungicide and growth regulator in tomato cultivation. A critical review on the composition, uses, and safety of neem leaf flour highlighted its immense potential for food and medicinal purposes. The metabolism and bioactivation profiles of nimbolide was analysed in rats to aid in understanding its safety and activity. A study conducted in the Mandara Mountains in Cameroon to assess the effects of human activities on woody vegetation in gallery forests, revealed neem tree to be one among the 45 species affected by damage caused by human beings.Neem-derived silver nanoparticles were suggested as a safe, efficacious, and eco-friendly alternative in place of conventional therapies to treat periodontal infection based on investigations, and as a potential antibacterial ingredient in formulations for use like mouthwashes and gels for local drug delivery. Neem in combination with triphala were found to be effective substitutes for root canal irrigants. Copper oxide nanoparticles synthesized using ethanolic extracts of neem was reported to be effective against multidrug resistant bacteria. Structure-based discovery identified several neem components as promising agents against schistosomiasis. The neem limonoid, nimbolide was shown to induce death of oral cancer cells. Evaluation of reproductive toxicity of aqueous extract of neem leaf revealed that although neem exhibited low toxicity, sperm motility and viability were affected especially in rats receiving the highest dose.

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Field efficacy of insecticides for suppressing white mango scale insect (*Aulacaspis tubercularis* Newstead) (Hemiptera: Diaspididae) in southwest Ethiopia.

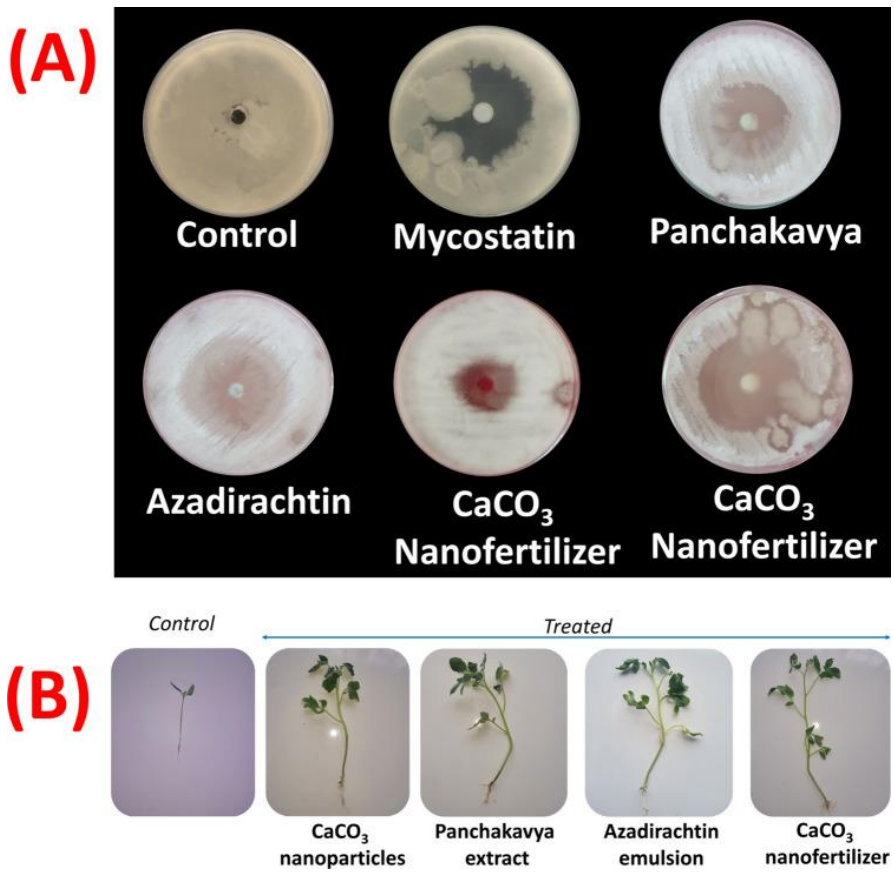
Ebrahim YN.Heliyon. 2024 Sep 19;10(18):e38156. doi: 10.1016/j.heliyon.2024.e38156. eCollection 2024 Sep 30.PMID: 39347434

White mango scale (WMS) Aulacaspis tubercularis Newstead (Hemiptera: Diaspididae) is a polyphagous armored scale insect which is considered one of the key pests of mango (Mangifera indica L.) around the world. Mango is widely grown in Ethiopia whereas its production is challenged by WMS in the last decade. Effective formulations that could help manage the scale as part of IPM practice were sought from field experiments at Seka mango farm, Ethiopia in 2019 and 2020 seasons. The study aimed to evaluate the efficacy of some formulations against WMS on mango trees. Randomized complete block designs with three replications were used for the experiments and each tree served as a plot. Allocation of each treatment within each replication was done randomly. The treatments were applied sequentially three times at 14 days interval using motorized Knapsack sprayer coinciding with peak period of natural infestation. Scale numbers before and after each spray were counted using a microscope with LCD. Sum of live crawler, female and male was registered as WMS count data. Results showed that dimethoate, diazinon, imidacloprid & λ-cyhalothrin sprayed alone; dimethoate rotated with imidacloprid & λ-cyhalothrin, chlorpyrifos-ethyl rotated with paraffin, and diazinon rotated with azadirachtin, caused total mortality of the scales. The results also showed that, chlorpyrifos-ethyl, deltamethrin, paraffin oil and λ-cyhalothrin sprayed alone caused percent reduction with range 83-95 % in both seasons. Hence, the study revealed that dimethoate, diazinon, imidacloprid & λ-cyhalothrin applied individually, dimethoate rotated with imidacloprid & λ-cyhalothrin, chlorpyrifos-ethyl rotated with paraffin and diazinon rotated with azadirachtin fully protect mango trees from WMS and significantly superior to other treatments. Therefore, chemical control of A. tubercularis may consider the use of these materials as foliar application and can be used as components for integrated pest management plans for WMS. However, application in the form of rotation is preferred to the alone spray as the former could substantially reduce the likelihood of inducing pesticide resistance. Cost implications and effects of the products on the natural enemy and residual toxicity in fruits need to be studied.

[Organic fertilizer integrated with marine waste derived $CaCO_3$ nanocarrier system: A focus on enhanced yield and quality in tomato cultivation.]

Nallasamy P, Natarajan S.Sci Rep. 2024 Oct 25;14(1):25299. doi: 10.1038/s41598-024-70478-4.PMID: 39455634

Tomatoes are rich in lycopene, β-carotene, ascorbic acid and other mineral sources including phosphorus, potassium, zinc, magnesium and iron. Major constraints in tomato cultivation were high cost, poor cultivation due to adverse weather conditions, pest attacks, microbial infections and nutritional deficiency complications. Conventional fertilizers, pesticides, fungicides and growth regulators are effective at higher concentration, which induces specific toxic effects on soil fertility, plant yield and also affects the health status of humans, animals and soil associated microbes. The use of organic fertilizers to meet the soil nutrient demand increases the acidity of soil affecting plant growth, which turned the focus of researchers towards nanofertilizer. The present study focuses on synthesis of marine waste derived $CaCO_3$ nanoparticles formulated with azadirachtin and panchakavya emulsion to develop a $CaCO_3$ nanofertilizer. $CaCO_3$ nanofertilizer developed through this study was investigated for its material properties and behavioral traits. Further, the in-vitro antifungal impact of the $CaCO_3$ nanofertilizer was examined, and it was sprayed on tomato plants via foliar spray. $CaCO_3$ nanofertilizer effectively inhibited fusarium wilt causing plant fungal pathogen and also exhibited enhanced growth and yield of tomatoes against pest attack and nutritional deficiency with effect to foliar treatment. Also, $CaCO_3$ nanofertilizer enhanced the total carotenoid level and essential nutritional minerals in fruit yield of tomatoes. Overall, fabricated $CaCO_3$ nanofertilizer exhibits synergistic role of fertilizer, pesticide, fungicide and growth regulator in tomato cultivation. It suggests that, $CaCO_3$ nanofertilizer generated from renewable biowaste will become the innovative platform for sustainable agriculture.

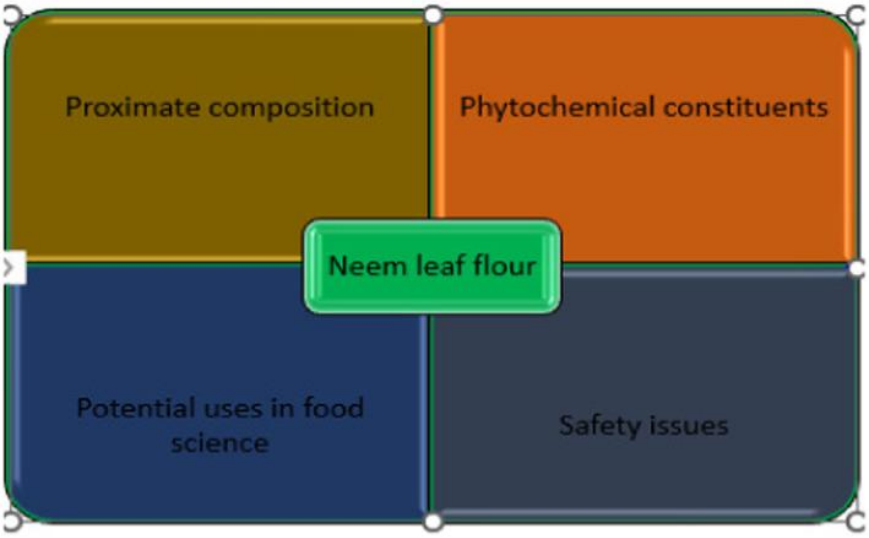


Neem Components

Proximate composition, some phytochemical constituents, potential uses, and safety of **neem** leaf flour: A review.

Andersa KN, Tamiru M, Teka TA, Ali IM, Chane KT, Regasa TK, Ahmed EH.Food Sci Nutr. 2024 Jul 17;12(10):6929-6937. doi: 10.1002/fsn3.4336. eCollection 2024 Oct.PMID: 39479641

Globally, there is a growing concern about avoiding using artificial compounds in food ingredients, food preservation, and packaging. Among the parts of the neem tree, leaf flour is one of the most commonly used parts in some countries for food and medicinal purposes and is known for containing several nutrients and phytochemicals. In this review, the proximate composition, phytochemical constituents, potential uses, and safety issues of neem leaf flour are discussed. Neem leaf flour contains high levels of crude protein, total carbohydrate, crude fat, and fiber and moderate amounts of crude fat and ash. In addition, it contains numerous health-promoting phytochemical constituents. Some phytochemicals, such as ascorbic acid, saponin, total alkaloids, carotenoids, total phenols, total flavonoids, and the total antioxidant capacity of neem leaf flour, have been critically discussed. Neem leaf flour has various potential applications in food science, such as preserving foods and preparing food packaging materials. However, researchers' perspectives on its safety are not yet in agreement. In general, the proximate compositions, phytochemical constituents, potential uses, and safety issues of neem leaf flour were compiled and critically reviewed. In addition, research is needed to identify all the toxic substances found in neem leaves and develop methods to eliminate them that hinder their use for various purposes in food. Further research is needed to develop food products from neem leaf flour and evaluate its nutritional value and phytochemical constituents.



Identification of the metabolites of nimbolide in rat by liquid chromatography combined with quadrupole/orbitrap mass spectrometry.

Li K, Jiang L, Wei Y, Li Z.Biomed Chromatogr. 2024 Oct 4:e6012. doi: 10.1002/bmc.6012. Online ahead of print.PMID: 39363690

Nimbolide is a major furanoid compound isolated from Azadirachta indica. The aim of this study was to characterize the metabolites of nimbolide in rats and to propose the metabolic pathways. The metabolites were generated by incubating nimbolide (10 μM) with rat liver microsomes, nicotinamide adenine dinucleotide phosphate (NADPH), and nucleophiles (glutathione [GSH] or N-acetyl-lysine [NAL]) at 37°C for 60 min. For the in vivo study, nimbolide was intravenously administered to rats at a single dose of 10 mg/kg, and the bile and urine were collected. The metabolites were identified by ultra-high-performance liquid chromatography-quadrupole/orbitrap mass spectrometry (UPLC-Q/Orbitrap-MS) using electrospray ionization in positive ion mode. Totally, nine metabolites were detected, and their identities were characterized by accurate MS and MS/MS data. In GSH-supplemented liver microsomes, GSH conjugation was the primary elimination pathway. The furan ring was bioactivated into cis-butene-1,4-dial that can be trapped by GSH. In NAL-supplemented liver microsomes, two NAL conjugates (M4 and M5) derived from cis-butene-1,4-dial were observed. In rat bile and urine, N-acetyl-cysteine, cysteine-glycine, and GSH conjugate were also found. The current study provides an overview of the metabolism and the bioactivation profiles of nimbolide in rats, which aids in understanding its safety and activity.

Neem for Sustainable Environment & Green Synthesis

Impact of Human Activities on Woody Vegetation in Gallery Forests in the Mandara Mountains (Far North, Cameroon).

Fanday H, Tchobsala.ScientificWorldJournal. 2024 Oct 12;2024:9198533. doi: 10.1155/2024/9198533. eCollection 2024.PMID: 39444784

This study was conducted in the Mandara Mountains in Cameroon and aimed to assess the effects of human activities on woody vegetation in gallery forests, based on floristic inventories and observations made by the government. Firstly, the inventories were carried out in 150 plots of 1000 m^2 each, installed on the banks of watercourses following the band of plant formations. In each plot, woody species were counted and those showing at least one sign of degradation were noted. Secondly, the survey was conducted in 18 administrative structures made up of delegations (MINFOF, MINADER, MINEPDED, and MINEPIA) and town halls. One hundred woody species, grouped into 63 genera and 30 families, have been inventoried, in which 45 species showed at least one sign of damage caused by human being. The species most affected are *Anogeissus leiocarpus* (67 stems), *Azadirachta indica* (46 stems), *Diospyros mespiliformis* (43 stems), *Acacia albida* (42 stems), *Andira inermis* (30 stems), *Acacia sieberiana* (23 stems), *Khaya senegalensis* (19 stems), *Ficus sycomorus* (13 stems), and *Acacia polyacantha* (10

stems). The most recurrent activity in the gallery forests is pruning (212 stems), followed by cutting (93 stumps), then picking (71 individuals). However, there are fewer debarked trees (11) and trees with fire trail (6). According to the responses provided, logging (77.78%), agriculture (72.22%), population growth (44.44%), grazing (33.33%), and bush fires (33.33%) are the main causes of the degradation of plant formations in the Mandara Mountains. These main factors could have a negative impact on biodiversity if appropriate integrated management measures are not taken. To maintain these vital ecosystems, an integrated management plan must be put in place, limiting human activities to a minimum.

Green synthesis of graphene oxide and magnetite nanoparticles and their arsenic removal efficiency from arsenic contaminated soil.

Akhtar MS, Jutt DSR, Aslam S, Nawaz R, Irshad MA, Khan M, Khairy M, Irfan A, Al-Hussain SA, Zaki MEA.Sci Rep. 2024 Oct 4;14(1):23094. doi: 10.1038/s41598-024-73734-9.PMID: 39367070

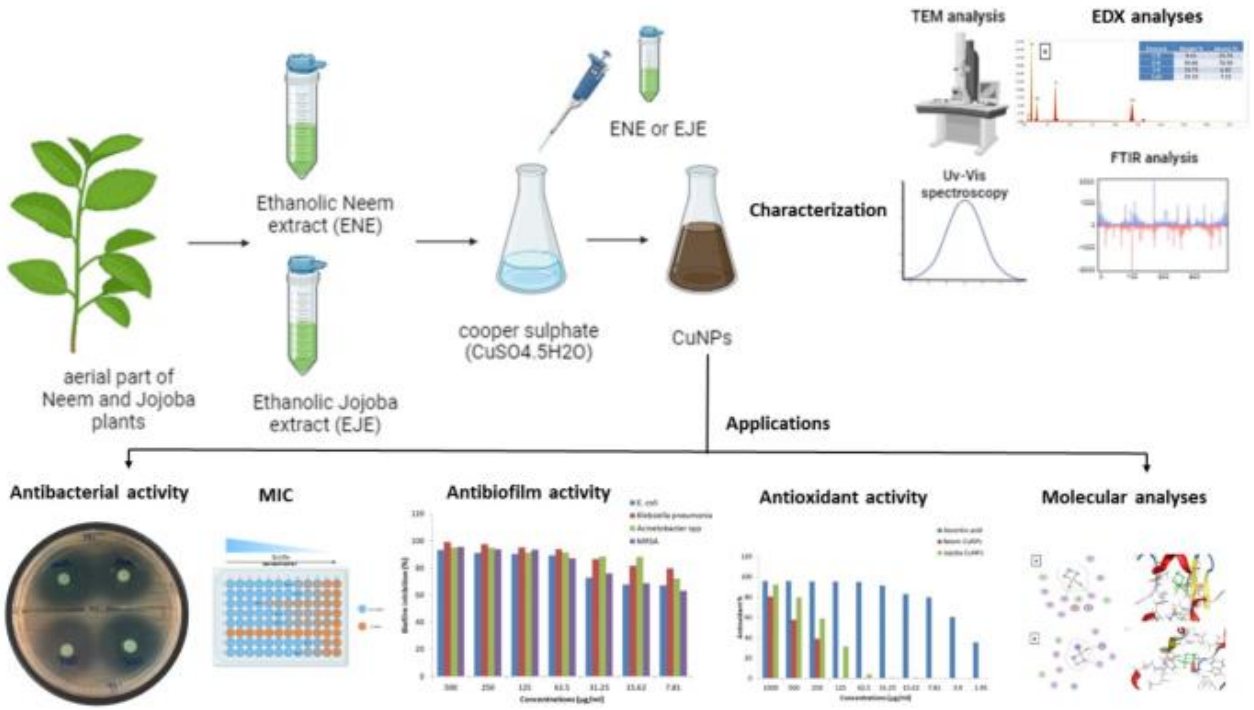
Graphene-based nanomaterials have been proved to be robust sorbents for efficient removal of environmental contaminants including arsenic (As). Biobased graphene oxide (bGO-P) derived from sugarcane bagasse via pyrolysis, GO-C via chemical exfoliation, and magnetite nanoparticles (FeNPs) via green approach using Azadirachta indica leaf extract were synthesized and characterized by Ultraviolet-Visible Spectrophotometer (UV-vis.), Fourier transform infrared (FTIR) spectroscopy, X-ray diffraction (XRD), mean particle size and Scanning electron microscopy (SEM) along with Energy dispersive spectroscopy (EDX) analysis. Compared to cellulose and hemicellulose, the lignin fraction was less in the precursor material. The GOC, bGO-P and FeNPs displayed maximum absorption at 230, 236, and 374 nm, respectively. FTIR spectrum showed different functional groups (C-OH, C-O-C, COOH and O-H) modifying the surfaces of synthesized materials. Graphene based nanomaterials showed clustered dense flakes of GO-C and thin transparent flakes of bGO-P. Elemental composition by EDX analysis of GO-C (71.26% C and 27.36% O), bGO-P (74.54% C and 24.61% O) and FeNPs (55.61% Fe, 4.1% C and 35.72% O) confirmed the presence of carbon, oxygen, and iron in synthesized nanomaterials. Sorption study was conducted with soil amended with different doses of synthesized nanomaterials (10, 50 and 250 mg) and exposed to 100, 300 and 500 ppm of As. Arsenic concentrations were estimated by colorimetry and atomic absorption spectroscopy (AAS). GO-C, bGO-P, and FeNPs showed substantial As removal efficiency i.e., 81 to 99.3%, 65 to 98.8% and 73.1-89.9%, respectively. Green synthesis of bGO-P and magnetite nanoparticles removed substantial amounts of As compared to GO-C and can be effectively deployed for As removal or immobilization. Higher and medium sorbent doses (250 and 50 mg) exhibited greater As removal and data was best fitted for Freundlich isotherm evidencing favorable sorption. Nevertheless, at low sorbent doses, data was best fitted for both models. Newly synthesized nanomaterials emerged as promising materials for As removal strategy for soil nano-remediation and can be effectively deployed in As contaminated soils.

Neem for Human Health

Antibacterial activity of green synthesized copper oxide nanoparticles against multidrug-resistant bacteria.

Khairy T, Amin DH, Salama HM, Elkholy IMA, Elnakib M, Gebreel HM, Sayed HAE.Sci Rep. 2024 Oct 23;14(1):25020. doi: 10.1038/s41598-024-75147-0.PMID: 39443504

Using plant extracts in the green synthesis of nanoparticles has become an environmentally acceptable approach. In our study, copper oxide nanoparticles (CuO NPs) were synthesized using ethanolic extracts of Azadirachta indica and Simmondsia chinensis. CuO NP formation was confirmed by the change in color and by UV–visible spectroscopy (CuO NPs peaked at a wavelength of 344 nm). TEM images confirmed the semispherical shape of the CuO NPs, with particle sizes ranging from 30.9 to 10.7 nm. The antibacterial activity of these NPs was evaluated by using the agar diffusion method against clinical isolates, including methicillin-resistant Staphylococcus aureus (MRSA), Escherichia coli, Pseudomonas aeruginosa, Acinetobacter spp., Klebsiella pneumoniae, and Stenotrophomonas maltophilia. The minimum inhibitory concentration (MIC) of CuO NPs ranged from 62.5 to 125 µg/ml. In contrast, the antioxidant activity and antibiofilm activity of CuO NPs ranged from 31.1 to 92.2% at 125-500 µg/ml and 62.2-95%, respectively, at 125 -62.5 µg/ml. Our results confirmed that CuO NPs had IC50s of 383.41 ± 3.4 and 402.73 ± 1.86 at 250 µg/mL against the HBF4 cell line. Molecular docking studies with CuO NPs suggested that penicillin-binding protein 4 (PBP4) and beta-lactamase proteins (OXA-48) strongly bind to S. aureus and K. pneumoniae, respectively, with CuO NPs. Our study confirms the promising use of CuO NPs in treating pathogenic bacteria and that CuO NPs could be possible alternative antibiotics. This study supports the pharmaceutical and healthcare sectors in Egypt and worldwide.



Comparative Evaluation of Antimicrobial Efficacy of Silver Nanoparticles Infused with *Azadirachta indica* Extract and Chlorhexidine Against Red-complex Pathogens.

Krishnappan S, Ravindran S, Balu P, Ilangovan K, Sathiyaseelan S, Pandraveti RR.J Contemp Dent Pract. 2024 Jun 1;25(6):547-553. doi: 10.5005/jp-journals-10024-3672.PMID: 39364821

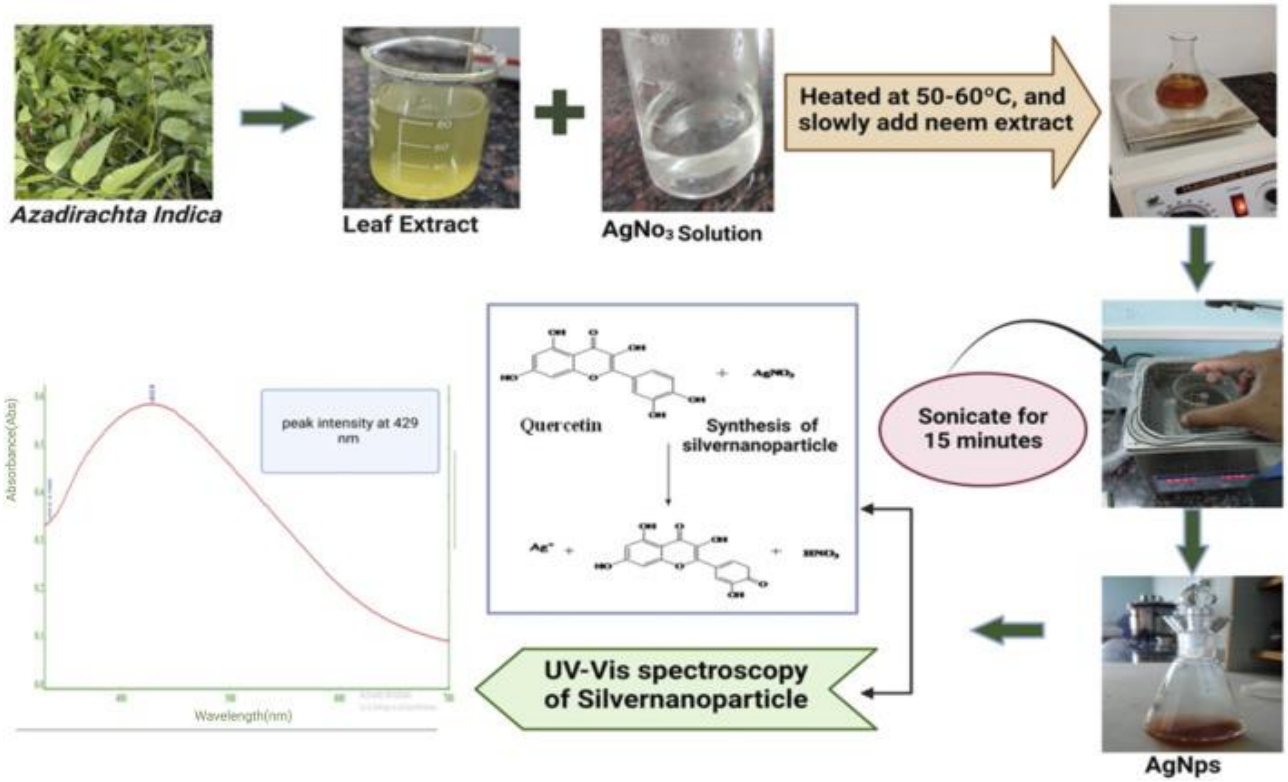
Aim: The present study aimed to evaluate the antimicrobial efficacy of silver nanoparticles infused with *Azadirachta indica* extract and chlorhexidine against red-complex periopathogens. **Materials and methods:** Neem leaf extraction was done followed by standardization to the synthesis of neem-infused silver nanoparticles and fractionation of compounds done by using thin layer chromatography to separate the mixture of neem leaf extract. Characterization of neem-infused silver nanoparticles was done by scanning electron microscopy and UV-Visible spectroscopy. The compound identified in neem-infused silver nanoparticles was gedunin which was confirmed by Fourier transform infrared spectroscopy and nuclear magnetic resonance spectroscopy. Determination of antibacterial activity done by disc diffusion, minimum inhibitory concentration (MIC), and minimum bactericidal concentration (MBC) methods. Group I-99% ethanolic extract, group II-neem-infused silver nanoparticles (NAgNPs), group III-chlorhexidine. **Results:** The relative inhibitory zone value for *Tannerella forsythia* (180) in neem-infused silver nanoparticles (group II) was greater when compared with other periopathogens *Porphyromonas gingivalis* (133) and *Treponema denticola* (160) than 99% ethanolic extract (group I), chlorhexidine (group III). Neem-infused silver nanoparticles (group III) showed superior antimicrobial activity against *T. forsythia* (19.3 ± 31.1547) and *T. denticola* (18±0) when compared with *P. gingivalis* (17.6 ± 0.5774). On evaluating MIC and minimum bacterial concentrations, *P. gingivalis* is more resistant than other pathogens in neem-infused silver nanoparticles (group III). **Conclusion:** Neem-infused silver nanoparticles exhibited superior antibacterial activity as compared with gold-standard chlorhexidine against red-complex periodontal pathogens. For MIC and MBC all the three periopathogens were effective but *P. gingivalis* was more resistant. **Clinical significance:** Antibiotics are effective against many drug-resistant bacteria. As a ready-made medicine, they can be used to treat many infections. Silver nanoparticles in drug delivery systems generally increase solubility, stability, and biodistribution, thereby increasing their effectiveness. Green synthesis using plant extracts as precursors to synthesize nanoparticles has proven to be environmentally non-hazardous combined with remarkably improved efficacy against bacterial and viral diseases. So neem-infused silver nanoparticles can be utilized as a drug delivery system. Hence, it can be used as a potential antibacterial ingredient in formulations for periodontal use like mouthwashes and gels for local drug delivery.

Sustainable synthesis of silver nanoparticles from **Azadirachta indica**: antimicrobial, antioxidant and in silico analysis for periodontal treatment.

Barik B, Satapathy BS, Pattnaik G, Bhavrao DV, Shetty KP.Front Chem. 2024 Oct 15;12:1489253. doi: 10.3389/fchem.2024.1489253. eCollection 2024.PMID: 39473563

Introduction: This study explores potential application of silver nanoparticles (AgNPs) to treat periodontal infection using *Azadirachta indica* leaf extract. The eco-friendly green

synthesis process uses *Azadirachta indica* as a natural stabilizer and reducer, allowing AgNPs to be formed. **Methods:** Experimental AgNPs were characterized through transmission electron microscopy (TEM), Fourier-transform infrared spectroscopy (FTIR), Zeta potential, ultraviolet-visible spectroscopy (UV-Vis) etc. The antimicrobial, antioxidant potential of AgNPs was tested to identify its efficacy against periodontal infections. **Results and discussion:** AgNPs were found spherical, nanosized (86 nm), with negative surface charge (-26.9 mV). TEM study depicted clear formation of discrete nanosize particles with smooth surface texture. Results showed strong antibacterial and anti-oxidant action of experimental AgNPs, preventing biofilm growth and bacterial viability. A higher binding affinity was observed between Quercetin and the selected protein, which is implicated in bacterial growth and biofilm formation on teeth. The study suggests that *Azadirachta indica* derived AgNPs could be a safe, efficacious, and eco-friendly alternative in place of conventional therapies to treat periodontal infection. Future *in vivo* studies are however warranted.



Comparative Evaluation of Microbial Reduction Using Silver Diamine Fluoride, Azadirachta indica (**Neem**) and Sodium Hypochlorite as Root Canal Irrigants after Biomechanical Preparation in Uniradicular Canals: An In Vivo Study.

Raj S, Sharma A, Dhinsa K, Saha S, Yadav G, Sharma P.Int J Clin Pediatr Dent. 2024 Jun;17(6):625-629. doi: 10.5005/jp-journals-10005-2862.PMID: 39391141

Background: It is difficult to completely eradicate microorganisms from the infected root canal system. Intracanal irrigants seem necessary for eradication of infected tissues and microorganisms in addition to mechanical debridement. Continuous use of chemical antimicrobial agents leads to serious side effects. Therefore, the need arises for alternative agents to overcome the disadvantages of their chemical counterparts. **Aim:** To evaluate

and compare the antimicrobial efficacy of three endodontic irrigants against clinically isolated bacteria found in root canals containing necrotic pulp. **Materials and methods:** Preirrigation sample were collected using sterile paper points and sent for microbial count. Chemomechanical preparation was performed, and the root canals were irrigated with 5 mL of test samples. After 3 days, the patient was recalled, and a postirrigation sample was collected and sent for microbial count. **Result synthesis:** Both 3.8% silver diamine fluoride (SDF) and 3% sodium hypochlorite (NaOCl) showed a superior capacity to sterilize the root canals compared to the neem group. **Conclusion:** The use of SDF as an endodontic irrigant is feasible as it effectively removes the microbes present in the canal. **Clinical significance:** Silver diamine fluoride has not been shown to be cytotoxic or carcinogenic, unlike NaOCl, suggesting it could be used as a potential endodontic irrigant. However, few studies have evaluated the antimicrobial efficacy of SDF as an endodontic irrigant.

Assessment of Antimicrobial Efficacy of Triphala, **Neem**, and Chlorhexidine Root Canal Irrigants.

Mohanty S, Nanda S, Das AC, Sahoo NR, Sahany SK, Panda S, Sahoo R.J Pharm Bioallied Sci. 2024 Jul;16(Suppl 3):S2176-S2178. doi: 10.4103/jpbs.jpbs_124_24. Epub 2024 May 13.PMID: 39346266

Introduction: Complete eradication of microorganisms from the root canal and three-dimensional obturation of the canal space are necessary for a successful root canal therapy. In root canal failures, *Enterococcus faecalis* is the most often detected bacterium. Microorganisms can be eliminated with the aid of chemical irrigation. **Objectives:** The current research was conducted to evaluate the antimicrobial effect of triphala, neem, and chlorhexidine root canal irrigants. **Materials and method:** Mueller-Hinton agar plates were inoculated with the *E. faecalis* (ATCC) bacterial culture after it had been cultured overnight in brain heart infusion (BHI) broth. Agar well diffusion was used to measure antibacterial inhibition. After being introduced to their appropriate wells in agar plates, the three research irrigants were incubated for 24 hours at 37°C. Every well's bacterial inhibition zone was noted. After tabulating the results, statistical analysis was done. **Result:** When triphala and A. indica extract (neem) were added to chlorhexidine, the highest inhibitory zone against *E. faecalis* was observed. **Conclusion:** The herbal remedy triphala and the extract from *A. indica* exhibited an inhibitory zone when tested against *E. faecalis*. As a result, these irrigants might be utilized as a substitute for root canal irrigants.

Exploring the potential of chitosan polyherbal hydrogel loaded with AgNPs to enhance wound healing - A triangular study.

Zahra D, Shokat Z, Sufyan M, Chaudhary Z, Ashfaq UA.Int J Biol Macromol. 2024 Oct 5:135896. doi: 10.1016/j.ijbiomac.2024.135896. Online ahead of print.PMID: 39374716

Hydrogel wound dressings provide a moist environment, which promotes the formation of granulation tissue and epithelium in the wound area, accelerating the wound healing process. There have been numerous approaches to skin wound management and treatment, but the limitations of current methods highlight the need for more effective

alternatives. A Chitosan polyherbal hydrogel integrated with AgNPs was synthesized to assess its wound-healing potential both in vitro and in vivo. The AgNPs were synthesized using Calotropis procera leaf extract and characterized via X-ray diffraction analysis (XRD), Scanning electron microscopy (SEM), and Fourier Transform Infrared Spectroscopy (FT-IR). In swelling kinetic analysis, the hydrogel's weight reached its maximum at 8 h of incubation and began to decrease from 12 h up to 72 h (49 % ± 6.04). The hydrogel formulation demonstrated strong antimicrobial potential against E. coli and S. aureus with an inhibition zone of 18 mm and 25 mm, respectively. Furthermore, in mice studies, the formulation exhibited significant wound size reduction within 12 days, supported by histopathology analysis revealing higher angiogenic potential compared to commercial hydrogels. The concentrations of IL-6 and TNF-α in CS-polyherbal/AgNPs hydrogel were 500 pg/ml and 125 pg/ml, respectively. Additionally, a network pharmacology approach identified 11 chemical constituents in Aloe vera, Azadirachta indica, and Alternanthera brasiliana extracts, along with 326 potential targets, suggesting the superior wound healing properties of this formulation compared to commercially available hydrogels.

Structure-Based Discovery of Phytocompounds from **Azadirachta indica** as Potential Inhibitors of Thioredoxin Glutathione Reductase in Schistosoma mansoni.

Onile OS, Raji O, Omoboyede V, Fadahunsi AI, Onile TA, Momoh AO, Olukunle S, Nour H, Chtita S.Cell Biochem Biophys. 2024 Oct 7. doi: 10.1007/s12013-024-01577-2. Online ahead of print. PMID: 39373903

Schistosomiasis, a parasitic disease caused by Schistosoma species such as S. haematobium, S. mansoni, and S. japonicum, poses a significant global health burden. The thioredoxin glutathione reductase (TGR) enzyme, crucial for maintaining the parasite's redox balance and preventing oxidative stress, has been identified as a promising target for anti-schistosomal drug development. This study aims to identify potential TGR inhibitors from Azadirachta indica phytochemicals using molecular modeling approaches. We screened 60 compounds derived from A. indica bark and leaves through molecular docking to assess their binding affinity, followed by the evaluation of binding-free energies for the most promising candidates. Drug-likeness and pharmacokinetic properties were assessed, and molecular dynamics simulations were conducted to explore the conformational stability of the protein-ligand complexes. Our findings revealed that several A. indica compounds exhibited significantly lower docking scores (up to -9.669 kcal/mol) compared to the standard drug praziquantel (-4.349 kcal/mol). Notably, Isorhamnetin, Isomargolonone, Nimbaflavone, Quercetin, and Nimbionol demonstrated strong interactions with TGR, although Isorhamnetin showed potential mutagenicity. Further binding free energy calculations and molecular dynamics simulations confirmed the stability of Isomargolonone, Nimbionol, and Quercetin as potential TGR inhibitors. In conclusion, these findings suggest that Isomargolonone, Nimbionol, and Quercetin warrant further experimental validation as promising candidates for anti-schistosomal therapy.

Development and In Vitro characterization of Azadirachta Indica Gum grafted polyacrylamide Based pH-Sensitive Hydrogels to improve the Bioavailability of Lansoprazole.

Mustafa MA, Hussain HR, Khan JA, Ahmad N, Bashir S, Asad M, Shah HS, Khan AA, Malik A, Fatima S, Yousaf AM, Nazir I.Chem Biodivers. 2024 Oct 15:e202401434. doi: 10.1002/cbdv.202401434. Online ahead of print.PMID: 39404191

The present study intended to develop a pH-responsive hydrogel based on Neem gum (Ng) to improve Lansoprazole (LSP) oral bioavailability. pH-responsive hydrogel formulations (F1-F9) were prepared using different Ng ratios, Acrylamide (AAm), and methylene-bis-acrylamide (MBA). The formulated hydrogels were characterized through FTIR, thermal analysis, swelling ratio, SEM, sol-gel ratios, In-Vitro drug release, and cytotoxicity analysis. Azadirachta Indica was extracted to produce a powder containing 21.5 % Ng. Prepared hydrogels showed maximum swelling at pH 7.4, whereas the swelling at an acidic pH was insignificant. LSP-loaded hydrogel demonstrated a regulated release of LSP for up to 24 h and indicated a Super Case II transport release mechanism. During the cytotoxic evaluation, the delivery system showed minimal cytotoxicity towards normal cells, while percent cytotoxicity was carried out for a longer duration (up to 96 h). The present study revealed Azadirachta indica gum-based pH-responsive hydrogel as a promising technique for precisely delivering LSP.

Nimbolide Induces Cell Apoptosis via Mediating ER Stress-Regulated Apoptotic Signaling in Human Oral Squamous Cell Carcinoma.

Peng BY, Wu CY, Lee CJ, Chang TM, Tsao YT, Liu JF. Environ Toxicol. 2024 Oct 27. doi: 10.1002/tox.24436. Online ahead of print.PMID: 39462890

Human oral squamous cell carcinoma (OSCC) poses a significant health challenge in Asia, with current therapeutic strategies failing to improve the survival rates for OSCC patients sufficiently. To elucidate the effects of Nimbolide on OSCC cell proliferation and apoptosis, we performed a series of experiments, including cell proliferation assays, annexin V/PI assays, and cell cycle analysis. We further investigated nimbolide's role in modulating endoplasmic reticulum (ER) stress, reactive oxygen species (ROS) production, and mitochondrial dysfunction using flow cytometry. Additionally, Western blotting was used to detect apoptosis-related protein expression. Our findings reveal that nimbolide exerts its anti-proliferative effects on OSCC cells by inducing apoptosis. The nimbolide increased intracellular ROS levels and acceleration of cellular calcium accumulation, respectively promoting endoplasmic reticulum stress and cancer cell apoptosis. Furthermore, nimbolide activates the caspase cascade by altering the mitochondrial membrane potential and apoptotic protein expression, thereby inhibiting the viability of tumor cells. Our data show that Nimbolide suppresses tumor growth through the induction of ROS production, ER stress, and mitochondrial dysfunction, resulting in apoptosis in OSCC cells. Overall, our study highlights nimbolide as a potential natural compound for OSCC therapy.

Therapeutic Applications of **Neem** (Azadirachta indica): A Narrative Review.

Mehnaz S, Shamsi Y, Akhtar MW, Mohanty S, Ahmad S.Adv Mind Body Med. 2024 Fall;38(4):14-18.PMID: 39447127

It is no surprise that nature has provided us with many therapeutic compounds for thousands of years. Throughout history, plants and their derivatives have been used orally and locally to treat most of the diseases. In addition to providing a wealth of health benefits, Azadirachta indica stands out among all of them as one of the most universal and prolific trees. Since antiquity, this medicinal plant has been used in the Unani System of Medicine as well as in other traditional systems of medicine (Ayurveda, Homeopathic, Chinese, and European "Materia Medica") to treat a wide range of diseases. Almost every part of the tree can be used as medicine, including its leaves, flowers, seeds, fruits, roots, and bark, both locally and systemically after being properly processed in pharmaceutical industries. Apart from treating various skin ailments like dermatitis, eczema, acne, and fungal and bacterial infections, it also exhibits anti-malarial, anticancer, antifertility, antioxidant, antidiabetic, anti-inflammatory, hepatoprotective, neuroprotective, and wound healing properties. In modern times, it is also used in cosmetics, toiletries, and pharmaceutical products. The purpose of this review is to gather all the information available about Azadirachta indica, including its distribution, botanical description, commercial use, and medicinal properties.

Neem- Toxicity

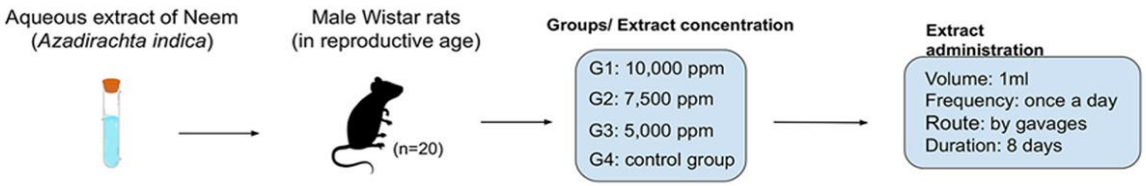
Natural pesticide, **Azadirachta indica** A.Juss. (Neem), disrupted reproductive parameters of male rats.

Cardoso CA, Valim Parca A, Facciotti PR, Machado LC, de Oliveira VC, Severi-Aguiar GDC, Martins DDS.J Ethnopharmacol. 2024 Oct 12:118927. doi: 10.1016/j.jep.2024.118927. Online ahead of print. PMID: 39401664

Ethnopharmacological relevance: Neem (Azadirachta indica A.Juss.) is native to India and belongs to the Meliaceae family. It has been used for centuries in Eastern medicine, and more recently, as a natural pesticide. Although the use of bioinsecticides is supported by organic food production, further research is needed on each formulation, particularly on their effects on organisms. **Aim of the study:** This study evaluated the reproductive toxicity of an aqueous extract of neem leaves in male Wistar rats of reproductive age after eight days of exposure. **Materials and methods:** For this study, 20 rats were divided into four groups of five animals each and treated with different concentrations: Group 1 received 10,000 ppm, Group 2 received 7,500 ppm, Group 3 received 5,000 ppm, and Group 4 served as the control, received distilled water. The animals were observed for eight days for any clinical signs of toxicity. Semen quality, including sperm motility and viability, was analyzed. **Results:** No significant differences in physiological changes were observed between treatments. However, sperm motility and viability were affected in a concentration-dependent manner, with the group that received the highest dose exhibiting

inviable spermatozoa. **Conclusion:** The data suggested that the administered doses had low toxicity. Nevertheless, concerns regarding reproductive toxicity remain because motility and sperm viability are negatively affected at the highest dose. Although bioinsecticides are widely used in organic food production, further research on each formulation, particularly regarding their long-term effects on organisms, is required.

METHODS



FINDINGS

Physiological changes	Semen evaluation			Hematological parameters	Evaluation of target organs
	Quality	Motility	Viability		
No signs of intoxication (posture, spasms, piloerection, stress, salivation) No significant difference: - weight - temperature - feed consumption - water consumption	No significant difference: - viscosity - color - pH	Sperm motility is concentration dose-dependent G1: Immobility G2: Non-progressive mobility G3: Progressive mobility G4: Progressive mobility	Spermatic viability is concentration dose-dependent G1: 89,2% inviable G2: 94,8% viable G3: 98,2% viable G4: 98,6% viable	No significant difference for all hematological parameters	No significant morphological changes or wet mass values. Normal cytoarchitecture for all groups in the target organs

CONCLUSION: Neem aqueous extract administered orally for 8 days at the dose of 10,000ppm influences the reproductive capacity of the animals, by the alteration of motility and viability of spermatozoa, suggesting a contraceptive action.