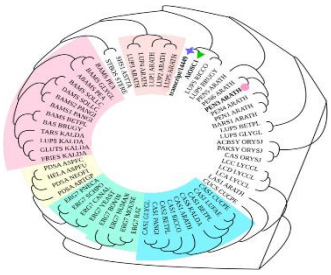
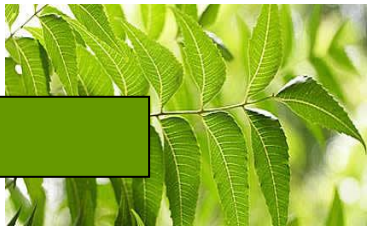
Neem Research Newsletter

Volume 2, Issue 5, 2022





WORLD NEEM ORGANISATION

Happy September! Neem continues to inspire researchers to delve deeper into its immense potential in various fields. Of particular interest is the review on the promising application of neem in extending the post-harvest shelf life of fruits and vegetables. The attenuation of direct short-wave radiation by neem trees has implications in improving the outdoor thermal environment in dense urban settings. Of note, deacetylepoxyazadiradione and gedunin-2-hydroxypropyl-β-cyclodextrin complex were found to exert anti-inflammatory effects. Nimbolide was demonstrated to enhance the antitumor effect of docetaxel and reduce metastases in orthotopic models of prostate cancer. Studies indicate that the antireproductive and antifertility effects of neem could be utilized in rodent depopulation programs in animal agriculture and as a contraceptive to limit the proliferation of stray dogs, known to be reservoirs of the rabies virus in developing countries.

S. Nagini

Core Founding Member, WNO
Chief Scientific Coordinator &

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Acute and Chronic Toxicity of Neem Oil to the Endoparasitoid Palmistichus elaeisis (Hymenoptera: Eulophidae).

Caldeira VZ, Soares AM, Veloso VDSR, Silva SC, Costa SPE, Santos MDM, da Silva MI, Silva MW, Zanuncio CJ.

J Econ Entomol. 2022 Aug 8:toac109. doi: 10.1093/jee/toac109. Online ahead of print. PMID: 35934883

Palmistichus elaeisis Delvare and LaSalle 1993 (Hymenoptera: Eulophidae) and neem oil are two control alternatives for the integrated management of defoliating lepidopterans. The aim of this study was to evaluate the acute and chronic toxicity of neem oil compared to the synthetic insecticide deltamethrin, on the endoparasitoid P. elaeisis, in generations F0, F1, F2, and F3. Females of P. elaeisis were exposed to neem solutions at concentrations of 0, 1.87, 3.75, 7.50, 15.00, 30.00, and 60.00 mg ml-1, to determine the dose-response relationship and estimate the neem LC50. The sublethal effects on the parasitoid P. elaeisis in generations F0 to F3 were evaluated with these same concentrations of neem and 0.033 mg ml-1 of deltamethrin. The neem LC50 was estimated at 3.92 mg ml-1. The LC50 for P. elaeisis is 3.83 times lower than that recommended by the neem manufacturer for pest control, demonstrating high acute toxicity to this natural enemy. The chronic toxicity of both the commercial dose and those below it to P. elaeisis caused low sublethal effects. The correct concentration of neem oil in pest control is important, and its use should be performed with caution in integrated pest management programs using the endoparasitoid P. elaeisis to avoid causing interference between the two pest control techniques.

Natural Plant Extracts: An Update about Novel Spraying as an Alternative of Chemical Pesticides to Extend the Postharvest Shelf Life of Fruits and Vegetables.

Shahbaz MU, Arshad M, Mukhtar K, Nabi BG, Goksen G, Starowicz M, Nawaz A, Ahmad I, Walayat N, Manzoor MF, Aadil RM.

Molecules. 2022 Aug 12;27(16):5152. doi: 10.3390/molecules27165152.PMID: 36014396

Fresh fruits and vegetables, being the source of important vitamins, minerals, and other plant chemicals, are of boundless importance these days. Although in agriculture, the green revolution was a milestone, it was accompanied by the intensive utilization of chemical pesticides. However, chemical pesticides have hazardous effects on human health and the environment. Therefore, increasingly stimulating toward more eco-friendly and safer alternatives to prevent postharvest losses and lead to improving the shelf life of fresh fruits and vegetables. Proposed alternatives, natural plant extracts, are very promising due to their high efficacy. The plant-based extract is from a natural source and has no or few health concerns. Many researchers have elaborated on the harmful effects of synthetic chemicals on human life. People are now much more aware of safety and health concerns than ever before. In the present review, we discussed the latest research on natural alternatives for chemical synthetic pesticides. Considering that the use of plant-based extracts from aloe vera, lemongrass, or neem is non-chemical by-products of the fruits and vegetable industry, they are proved safe for human health and may be integrated with economic strategies. Such natural plant extracts can be a good alternative to chemical pesticides and preservatives.

Implications of Foliar Particulate Matter Deposition on the Physiology and Nutrient Allocation of Dominant Perennial Species of the Indo-Gangetic Plains.

Singh H, Singh P, Agrawal SB, Agrawal M.

Front Plant Sci. 2022 Jul 19;13:939950. doi: 10.3389/fpls.2022.939950. eCollection 2022.PMID: 35928714

The ramifications of different concentrations of foliar particulate matter on the physiology, nutrient stoichiometry, allocation pattern, and their corresponding re-translocation rates were investigated for evergreen (*Mangifera indica* and *Psidium guajava*), semi-evergreen (*Ficus religiosa* and *Azadirachta indica*), and deciduous (*Dalbergia sissoo*) tree species in a simulation experiment over an exposure period of 2 years. Physiological parameters (P_n, g_s, Ci, E, and WUE), nutrient stoichiometry (C: N) in different plant parts, and their allocation pattern for five macro- (C, N, K, Mg, Ca) and five (Zn, Ni, Mn, Cu, Fe) micro-elements at two different concentrations of particulate matter (ambient and elevated) with respect to control (no particulate load) were assessed. Significant differences in nutrient concentrations and their re-translocation rates were observed between the treatments in evergreen species compared to deciduous species. The photosynthetic rate significantly declined with an increase in foliar deposition of particulate matter. Higher variations in C, N, K, Mg, and Zn levels were found compared to other elements under particulate matter stress and the ratio of C/N showed a slight decline in mature leaves except in deciduous tree species. The nutrient stoichiometry revealed that the deciduous species were more tolerant whereas the re-translocation efficiency was maximum for the semi-evergreen tree species. The nutrient allocation was found greater in foliage compared to branch in evergreen and was opposite in semi-evergreen and deciduous tree species. The element re-translocation rate indicated an inconsistent behavior in nutrient recycling under the particulate matter load depending upon the tree species. The study entrenched a critical change in nutrient re-translocation and allocation pattern under the particulate stress in different parts of the tree, suggesting a novel approach for screening the tree species for sustainable plantation and planning of urban areas.

Bacterial inoculants as effective agents in minimizing the non-target impact of azadirachtin pesticide and promoting plant growth of Vigna radiata.

Singh U, Roy P, Sharma S.

Arch Microbiol. 2022 Aug 13;204(9):555. doi: 10.1007/s00203-022-03162-8.PMID: 35962834

Microbes regulate soil health by negating ecological disturbances, and improve plant productivity in a sustainable manner. Indiscriminate application of pesticides creates a detrimental impact on the rhizospheric microbiota, thereby affecting soil health. Azadirachtin, earlier believed to be an environment-friendly alternative to chemical pesticides, exhibits a non-target impact on microbial communities. This study aimed to employ potent bacteria to promote the growth of mungbean plant (Vigna radiata), and mitigate the non-target impact of azadirachtin. Bacterial strains were isolated by enrichment from mungbean rhizosphere. A plant growth experiment was performed with mungbean, amended with azadirachtin to assess the impact of bacterial bioinoculants on the rhizospheric microbiota. The impact of azadirachtin on rhizospheric bacterial

community was analyzed qualitatively and quantitatively by 16S rRNA PCR-DGGE and qPCR of various markers, respectively. Residual concentration of azadirachtin in the soil was estimated by HPLC. The bacterial inoculants used in combination significantly promoted plant growth and enhanced the diversity and abundance of total bacterial community in the presence of azadirachtin. Further, the abundance of specific bacterial groups (α-Proteobacteria, β-Proteobacteria, Actinobacteria, Acidobacteria, and Firmicutes) were significantly boosted. Compared to the control, the isolates significantly facilitated the reduction in residual concentration of azadirachtin in the mungbean rhizosphere. Bacterial inoculants can serve a tripartite role in reducing the stress imparted by botanical pesticides, together with promoting plant growth and enriching the rhizospheric bacterial community structure.

Effect of slow-release nitrogenous fertilizers on dry matter accumulation, grain nutritional quality, water productivity and wheat yield under an arid environment.

Ghafoor I, Rahman MHU, Hasnain MU, Ikram RM, Khan MA, Iqbal R, Hussain MI, Sabagh AE.Sci Rep. 2022 Aug 30;12(1):14783. doi: 10.1038/s41598-022-18867-5.PMID: 36042362

Slow release nitrogenous fertilizers can improve crops production and reduce the environmental challenges in agro-ecosystem. There is a need to test the efficiency and performance under arid climatic conditions. The study investigates the effect of slow-release fertilizers (urea, neem coated urea (NCU), sulfur coated urea (SCU) and bioactive sulfur coated urea (BSCU)) on the growth, productivity and grain nutritional qualities of wheat crop. Slow-release fertilizers (SRF) with nitrogen levels (130,117,104 and 94 kg ha^{-1}) were applied with equal splits at sowing, 20 and 60 days after sowing (DAS). Research showed that the BSCU with 130 kg ha^{-1} increased dry matter accumulation (1989 kg ha^{-1}) after anthesis and grain yield 4463 kg ha^{-1}. The higher plant height (102 cm) was attained by 130 kg N ha^{-1} SCU while the minimum (77.67 cm) recorded for 94 kg N ha^{-1} as urea source. Maximum grain NPK concentrations (3.54, 0.66 and 1.07%) were recorded by BSCU 130 kg N ha^{-1} application. While, the minimum NPK (0.77, 0.19 and 0.35%) were observed by Urea 94 kg N ha^{-1}. The high irrigation water use efficiency (WUE) recorded (20.92 kg ha^{-1} mm^{-1}) and a crop index of 25.52% by BSCU 130 kg N ha^{-1} application. Research findings show that generally all SRF but particularly BSCU proved effective and can be recommended for wheat crop under arid environment.

Neem in Aquaculture

A blend of Guava, Bitter, and Neem Leaf extracts improves haematology and resistance to co-infection of Streptococcus agalactiae and Aeromonas jandaie but not liver health in Nile tilapia

Abarike ED, Dandi SO, Ampofo-Yebovah A. Fish & Shellfish Immunology Reports, 2022; 100066. https://doi.org/10.1016/j.fsirep.2022.100066

Given the intense interest in the use of herbal extracts to improve fish growth, fish health, and disease resistance in fish in culture systems, in this study, we examined the effects of a blend of Guava, Bitter and Neem leaf extracts (GBNL) (i.e., 1:1:1 for GL, BL, and NL respectively) at different inclusion (i.e. 0 GBNL gkg^{-1}, 1 GBNL gkg^{-1}, 3 GBNL gkg^{-1}, 5 GBNL gkg^{-1}, 7 GBNL gkg^{-1} and 10 GBNL gkg^{-1}) levels on growth, haematology, immunity, liver toxicity and resistance to bacterial co-infections in Nile tilapia. After 8 weeks of feeding, Nile tilapia fed 3 GBNL gkg^{-1} diets showed significant effects in improving weight gain compared to those fed the control diet. GBNL fed fish showed improved health of fish by stimulating significant increases in levels of White blood cells, Red blood cells, Haemoglobin, and Haematocrit in relation to those fed the control diet. Also, the applications of deferent GBNL levels in Nile tilapia diets showed the potential to upregulate the expression of the immune-related genes heat shock protein 70, chicken type lysozymes, and Beta-defensin, with significant effects shown in fish fed 5GBNL gkg^{-1} diets in comparison to the control. The results also indicate that GBNL supplementation can decrease mortalities to co-infection of *Streptococcus agalactiae* and *Aeromonas jandaie* in Nile tilapia with the lowest mortalities of 13.65% and relative per cent survival of 82.57 % in fish fed 5GBNL gkg^{-1}. Despite the potential of GBNL applications in Nile tilapia, findings of this study indicate fish fed the different concentrations of GBNL, particularly with 7 GBNL gkg^{-1} can promote the leaching of the liver enzymes: alanine transaminase, aspartate aminotransferase, and alkaline phosphate into the bloodstream which is suggestive of potential liver damage in Nile tilapia. Histological examinations of a cross-section of the liver tissues of fish fed GBNL showed various injuries including hydropic changes, pyknosis nuclei, erythrocytes congestion and vacuolation with the severest seen in those fed 7 GBNL gkg^{-1}. Taking all of the above into consideration, 5GBNL gkg^{-1} application could improve the health and disease resistance of Nile tilapia; however, prolong use thus after 8 weeks of administration could be injurious to fish liver health.

Neem- Component Analysis

Intensification of total phenolic compounds extraction from Azadirachta indica (Neem**) leaves by ultrasound**

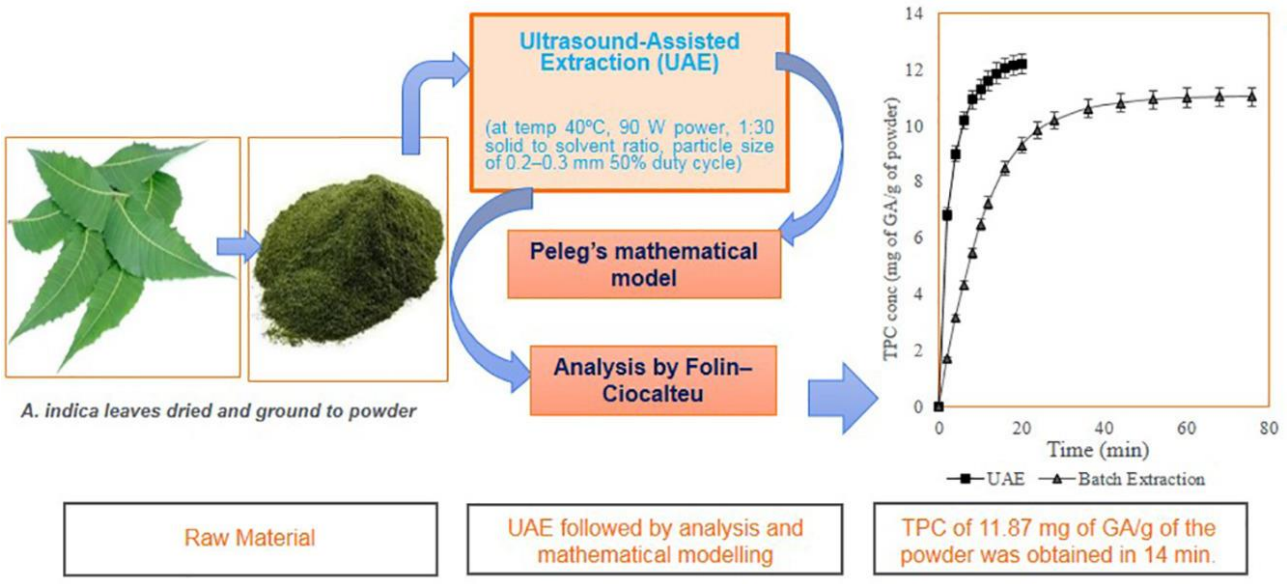
SP Shewale, M Kapadia, VK Rathod

Chemical Engineering and Processing- Process Intensification. 2022; in press. *https://doi.org/10.1016/j.cep.2022.109099*

The current work deals with ultrasound-assisted extraction (UAE) of the total phenolic compounds (TPC) from *A. indica* (Neem) leaves powder. Various process operating parameters have been optimized, including solvent screening, solid/solvent ratio, extraction temperature, particle size, power input, duty cycle, and sound wave frequency. The highest TPC yield of 11.87 mg of GA/g of powder was obtained at a time of 14 min, 70% ethanol as solvent, solid to solvent ratio of 1:30, the particle size of 0.2–0.3 mm, extraction temperature of 40ºC, power input of 90 W, and duty cycle of 50%. The experimental outcomes obtained from the UAE have been matched with stirred batch and Soxhlet extraction of TPC, which shows that ultrasound, was relatively better than the traditional method. The UAE method has efficiently decreased the extraction time (14 min) and marginally improved the TPC yield from *A. indica* leaves. Further, Peleg's mathematical model was studied for the extraction kinetics and to calculate the predicted extraction values of the rate constant, initial rate, and equilibrium concentration for all investigational circumstances. The predicted values obtained from Peleg's mathematical model show a good fit with experimental outcomes.

Graphical Abstract

Experimental and mathematical study of TPC extraction from A. indica leaves by UAE



Role of Azadirachta indica (Neem) and Polyalthia longifolia (Asopalav) trees for improving outdoor thermal environment in unorganized urban settings.

Gajjar HH, Jeyaraman JD, Kaul DS.

Int J Biometeorol. 2022 Aug 2. doi: 10.1007/s00484-022-02340-z. Online ahead of print. PMID: 35918553

This study assesses the effect of native trees in improving the outdoor thermal environment of an educational institute located in the semi-arid city of Ahmedabad, India. The study area was modelled using ENVI-met and validated against the field measurements. Physical properties of 8 species (55 samples) found in the city were collected. Azadirachta indica (Neem) and Polyalthia longifolia (Asopalav) are among the top 10 species found in the city. The campus has limited space availability and green cover, hence adding more trees is not possible. Hence, two separate scenarios of only those two species were developed by replacing the existing trees. The reduction in air temperature, mean radiant temperature and physiological equivalent temperature (PET) against existing scenario by Asopalav trees at a non-shaded site was found to be up to 1.0 °C, 2.2 °C and 2.0 °C whereas by Neem trees was found to be up to 1.1 °C, 2.3 °C and 2.1 °C. This similarity was likely due to their similar crown widths. The attenuation of direct short-wave radiation by Neem trees was more due to higher Leaf Area Density (LAD). Trees with higher LAD and wider crowns are found to be more useful in improving the outdoor thermal environment in dense urban settings with space constraints.

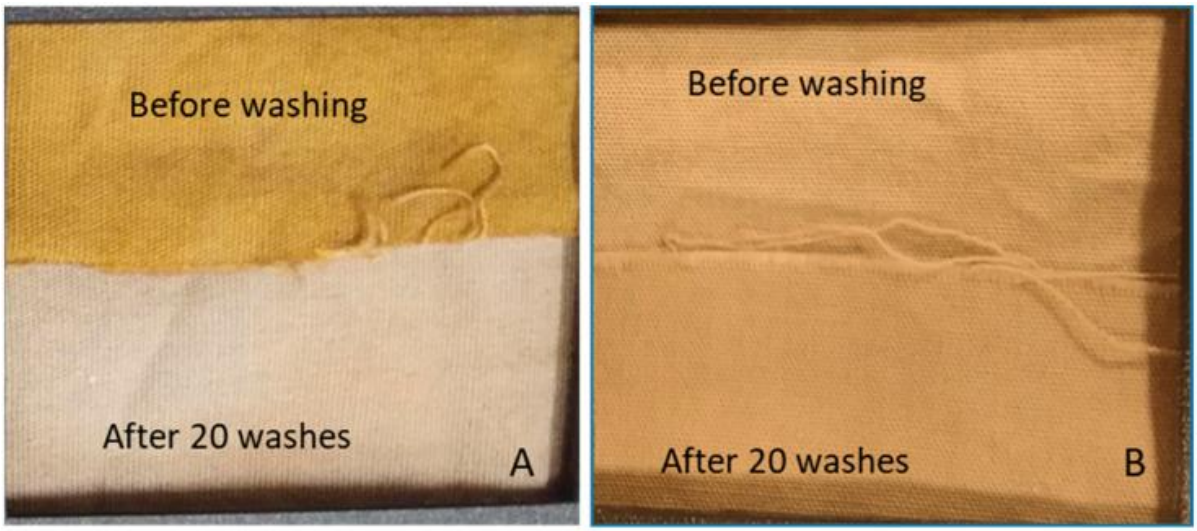
Development of Wash-Durable Antimicrobial Cotton Fabrics by In Situ Green Synthesis of Silver Nanoparticles and Investigation of Their Antimicrobial Efficacy against Drug-Resistant Bacteria.

Jain A, Kongkham B, Puttaswamy H, Butola BS, Malik HK, Malik A.

Antibiotics (Basel). 2022 Jun 27;11(7):864. doi: 10.3390/antibiotics11070864. PMID: 35884119

An environment friendly and wash-durable silver nanoparticle treatment of cotton fabrics was carried out by in situ reduction of silver nitrate using Azadirachta indica leaf extract. The wash durability of the silver nanoparticles treatment on the cotton fabric was improved by pretreating the fabrics by mercerization and by adopting hydrothermal conditions of 120 °C temperature and 15 psi pressure for the in situ synthesis. The silver nanoparticle treated fabrics were characterized using scanning electron microscopy, colorimetric analysis and inductively coupled plasma mass spectroscopy. The coating of silver nanoparticles was seen to be dense and uniform in the scanning electron micrographs of the treated fabrics. An evaluation of the antibacterial efficacy of the silver nanoparticle treated fabric against antibiotic-resistant Gram-positive and Gram-negative strains was carried out. The antibacterial efficacy was found to be the highest against Bacillus licheniformis, showing 93.3% inhibition, whereas it was moderate against Klebsiella pneumoniae (20%) and Escherichia coli (10%). The transmittance data of a UV spectrophotometer (290-400nm) was used for measuring the UV protection factor of the silver nanoparticle treated fabrics. All the silver nanoparticle treated fabrics showed good

antimicrobial and UV protection activity. The treatment was also seen to be durable against repeated laundering. This paper contributes the first report on a novel green synthesis approach integrating mercerization of cotton fabrics and in situ synthesis of nanoparticles under hydrothermal conditions using Azadirachta indica leaf extract for improved wash durability of the multifunctional fabric.



Prediction models for evaluating the impacts of ambient air pollutants on the biochemical response of selected tree species of Haridwar, India.

Goswami M, Kumar V, Kumar P, Singh N.

Environ Monit Assess. 2022 Aug 19;194(10):696. doi: 10.1007/s10661-022-10384-2.PMID: 35986107

This study aimed to assess the spatio-temporal impact of selected ambient air pollutants (SO_2, NO_2, PM_{10}, and $PM_{2.5}$) on the biochemical response of four tree species including Neem (Azadirachta indica), Mountain cedar (Toona ciliate), Bottlebrush (Callistemon citrinus), and Guava (Psidium guajava) in the province of Haridwar City, Uttarakhand, India. The study was performed in 2020 and 2021 over three selected sites (S1: institutional; S2: industrial; and S3: urban). Purposely, seasonal data of ambient air pollutants and biochemical parameters (ascorbic acid, carotenoid, chlorophyll, pH, relative water content, and dust load) of selected tree species were collected and analyzed using multiple linear regression (MLR) tool to develop prediction models. The results indicated that biochemical parameters of all tree species were negatively impacted by the polluted ambient air quality in the industrial and urban (S2 and S3) sites as compared to the non-polluted institutional (S1) site. The models were characterized by high prediction performance as indicated by the coefficient of determination (R^2) values greater than 0.80. Moreover, A. indica was found to be more 'tolerant' based on the air pollution tolerance index (APTI) followed by T. ciliate, P. guajava, and C. citrinus. Similarly, the anticipated performance index (API) was reported higher for A. indica (75 to 81.25%) followed by T. ciliate (68.75 to 75.00%), P. guajava (56.25%), and C. citrinus (37.50%), respectively. This study revealed that the selected tree species are being negatively impacted by the induced pollutant exposure in the urban and industrial region of Haridwar, India which needs sufficient mitigation measures to conserve their diversities.

Pyrolysis and kinetic behavior of neem seed biomass using thermogravimetric analysis for the production of renewable fuel

H Krishnaswamy, R Chelliah, RI Ramakrishnan et al.

International Journal of Materials Research https://doi.org/10.1515/ijmr-2021-8514

Renewable fuel is gaining more attention in the current energy crisis, and biomass is one of the potential sources of producing renewable fuel. The objective of the present research is to analyze the pyrolysis and kinetic behavior of neem seed biomass. Pyrolysis and kinetic behavior of neem seed were analyzed using thermogravimetric analysis (TGA) at different heating rates, viz. 5, 10, 15, and 20 K min^{-1}. The kinetic study was conducted on the neem seed using various kinetic models such as Friedman, Kissinger, Flynn–Wall–Ozawa (FWO), and Kissinger–Akahira–Sunose (KAS). Thermodynamic analysis was carried out using the data extracted from the TGA curves. The results showed that the neem seed degraded in three stages, stage I: <100 °C, stage II: 100–550 °C, and stage III: >550 °C. A maximum mass loss of 73.14 % occurred at stage II owing to the loss of cellulose and hemicellulose. The activation energy determined by Friedman, KAS, and FWO models was 5.11–18.64, 10.62–57.41, and 13.77–61.51 kJ mol^{-1}, respectively. Thermodynamic analysis revealed that the pyrolysis of neem seed was an endothermic and spontaneous process. Moreover, the previously reported average activation energy required for the pyrolysis of various seeds and shells was compared with the present study and concluded that the variation in activation energy of neem seed adheres to the outcomes reported earlier.

Evaluation of heavy metal phytoremediation potential of six tree species of Faisalabad city of Pakistan during summer and winter seasons.

Rahman SU, Yasin G, Nawaz MF, Cheng H, Azhar MF, Riaz L, Javed A, Lu Y.

J Environ Manage. 2022 Aug 2;320:115801. doi: 10.1016/j.jenvman.2022.115801. Online ahead of print.PMID: 35930882

Environmental pollution induced by heavy metals has been identified as a leading threat in the modern era. Woody tree species may play a crucial role in the removal of heavy metals from soil and air, thus minimizing pollution potential. The present study was designed to evaluate the phytoremediation potential of six tree species; Azadirachta indica, Cassia fistula, Conocarpus erectus, Eucalyptus camaldulensis, Morus alba, and Populus deltoids, respectively, in the industrial and residential areas of Faisalabad based on the concentrations of lead (Pb), zinc (Zn), cadmium (Cd), and copper (Cu) in their leaves and barks in winter (2018) and summer (2019) seasons. The seasonal contents of heavy metals in both the leaves and barks of these trees decreased in the order of: Zn > Pb > Cu > Cd at both study sites. The highest heavy metal contents were recorded in the leaves and barks of trees grown in the industrial areas as compared to residential areas, with leaves and barks having higher contents of heavy metals in the summer than winter. The tree species exhibited significantly different capacity for heavy metal accumulation, with the accumulation of Cd decreased in the order of: E. camaldulensis > M. alba > C. erectus > A. indica > P. deltoids > C. fistula, and while the order varied for different heavy metals. Overall, M. alba, E. camaldulensis and A. indica performed well in accumulating the targeted heavy metals from the ambient environment. Among the six tree species grown commonly in Faisalabad city, M. alba, E. camaldulensis, and A. indica are recommended for the industrial and residential areas due to their phytoremediation capacity for heavy metals.

Neem For Human Health

Antimicrobial & Anti-inflammatory Effects

Antimicrobial and Anti-Inflammatory Activity of Low-Energy Assisted Nanohydrogel of *Azadirachta indica* Oil.

Kaur S, Sharma P, Bains A, Chawla P, Sridhar K, Sharma M, Inbaraj BS.

Gels. 2022 Jul 11;8(7):434. doi: 10.3390/gels8070434.PMID: 35877519

Plant-based bioactive compounds have been utilized to cure diseases caused by pathogenic microorganisms and as a substitute to reduce the side effects of chemically synthesized drugs. Therefore, in the present study, *Azadirachta indica* oil nanohydrogel was prepared to be utilized as an alternate source of the antimicrobial compound. The total phenolic compound in *Azadirachta indica* oil was quantified by chromatography analysis and revealed gallic acid (0.0076 ppm), caffeic acid (0.077 ppm), and syringic acid (0.0129 ppm). Gas chromatography-mass spectrometry analysis of *Azadirachta indica* oil revealed the presence of bioactive components, namely hexadecenoic acid, heptadecanoic acid, ç-linolenic acid, 9-octadecanoic acid (Z)-methyl ester, methyl-8-methyl-nonanoate, eicosanoic acid, methyl ester, and 8-octadecane3-ethyl-5-(2 ethylbutyl). The nanohydrogel showed droplet size of 104.1 nm and -19.3 mV zeta potential. The nanohydrogel showed potential antimicrobial activity against *S. aureus*, *E. coli*, and *C. albicans* with minimum inhibitory, bactericidal, and fungicidal concentrations ranging from 6.25 to 3.125 (µg/mL). The nanohydrogel showed a significantly (*p* < 0.05) higher (8.40 log CFU/mL) value for Gram-negative bacteria *E. coli* compared to Gram-positive *S. aureus* (8.34 log CFU/mL), and in the case of pathogenic fungal strain *C. albicans*, there was a significant (*p* < 0.05) reduction in log CFU/mL value (7.79-6.94). The nanohydrogel showed 50.23-82.57% inhibition in comparison to standard diclofenac sodium (59.47-92.32%). In conclusion, *Azadirachta indica* oil nanohydrogel possesses great potential for antimicrobial and anti-inflammatory activities and therefore can be used

as an effective agent.

Deacetylepoxyazadiradione Derived from Epoxyazadiradione of Neem (Azadirachta indica A. Juss) Fruits Mitigates LPS-Induced Oxidative Stress and Inflammation in Zebrafish Larvae.

Murugan R, Rajesh R, Guru A, Haridevamuthu B, Almutairi BO, Almutairi MH, Juliet A, Renganayagi S, Gopinath P, Arockiaraj J.

Chem Biodivers. 2022 Aug 26:e202200041. doi: 10.1002/cbdv.202200041. Online ahead of print.PMID: 36026548

Reactive oxygen species (ROS) produced by cell metabolism have a duplex role in oxidation and inflammation reactions which involve cell damage or repair responses. Excess ROS production has detrimental effects on the survival of cells. We examined the protective effect of a semi-natural compound NF2 (deacetylepoxyazadiradione), for its protective activity against free radical-mediated stress and inflammatory response to lipopolysaccharide (LPS) using zebrafish larvae. Preliminary antioxidant assays indicated an increase in scavenging of free radicals from NF2 than NF1 (Epoxyazadiradione) in a concentration-dependent manner. Cell cytotoxicity was determined using rat myoblast cell lines (L6), and more than 95 % of cell viability was obtained. Zebrafish developmental toxicity test indicated that NF2 is not toxic even at 150 μM. The percentage of ROS, lipid peroxidation, nitric oxide and apoptosis were reduced significantly in NF2 treated LPS-stressed zebrafish larvae. The reduced number of employed macrophages on NF2 treatment was observed in neutral red dye-marked macrophage localization images. Relative expression of antioxidant genes in zebrafish larvae after treatment with NF2 is significantly increased. The RT-PCR quantification of antioxidant and anti-inflammatory gene expression indicated decreased relative folds of pro-inflammatory cytokines, iNOS and increased relative folds of mitochondrial antioxidant genes (GR, GST and GPx) in LPS stressed zebrafish larvae after treatment with NF2. From the overall obtained results, it can be concluded that NF2 reduced the oxidative stress and inflammatory response by scavenging free radicals caused by LPS.

A novel gedunin-2-hydroxypropyl-β-cyclodextrin inclusion complex improves anti-nociceptive and anti-inflammatory activities of gedunin in rodents.

Ologe MO.

Niger J Physiol Sci. 2022 Jun 30;37(1):9-19. doi: 10.54548/njps.v37i1.2.PMID: 35947833

Gedunin is a bioactive compound, obtained from Entandrophragma angolense (EA), which has limited therapeutic usefulness due to poor aqueous solubility and first-pass effects. Cyclodextrins are cyclic oligosaccharides that form complexes with poorly soluble compounds, thus enhancing their pharmacological activity. In this article, we evaluated the pharmacological activities of gedunin-2-hydroxypropyl-β-cyclodextrin complex (GCD) in rodents. The antinociceptive activity of GCD (50, 100, 200 mg/kg) and Gedunin (50mg/kg) was tested in acetic acid-induced writhing and formalin-induced paw licking in mice. The anti-inflammatory activity was investigated in carrageenan-induced paw oedema and air pouch inflammation models in rats. Leucocytes counts, Tumour Necrosis Factor-alpha

(TNF-α) level, nitric oxide, malondialdehyde, reduced glutathione, and myeloperoxidase enzyme activities were assessed in the air pouch exudate. The GCD (200mg/kg) significantly decreased writhing response, reduced licking duration and decreased oedema compared with gedunin and control. Exudate volume and leucocyte count were significantly reduced by GCD (200 mg/kg), it decreased myeloperoxidase activity and inhibited TNF-α release. The carrageenan-induced GSH depletion, increased malondialdehyde and nitrite levels were significantly reversed by GCD (200 mg/kg) relative to gedunin and control. The GCD complex demonstrated significant antinociceptive and anti-inflammatory activities relative to gedunin alone via mechanisms associated with inhibition of oxidative stress and inflammation in rodents.

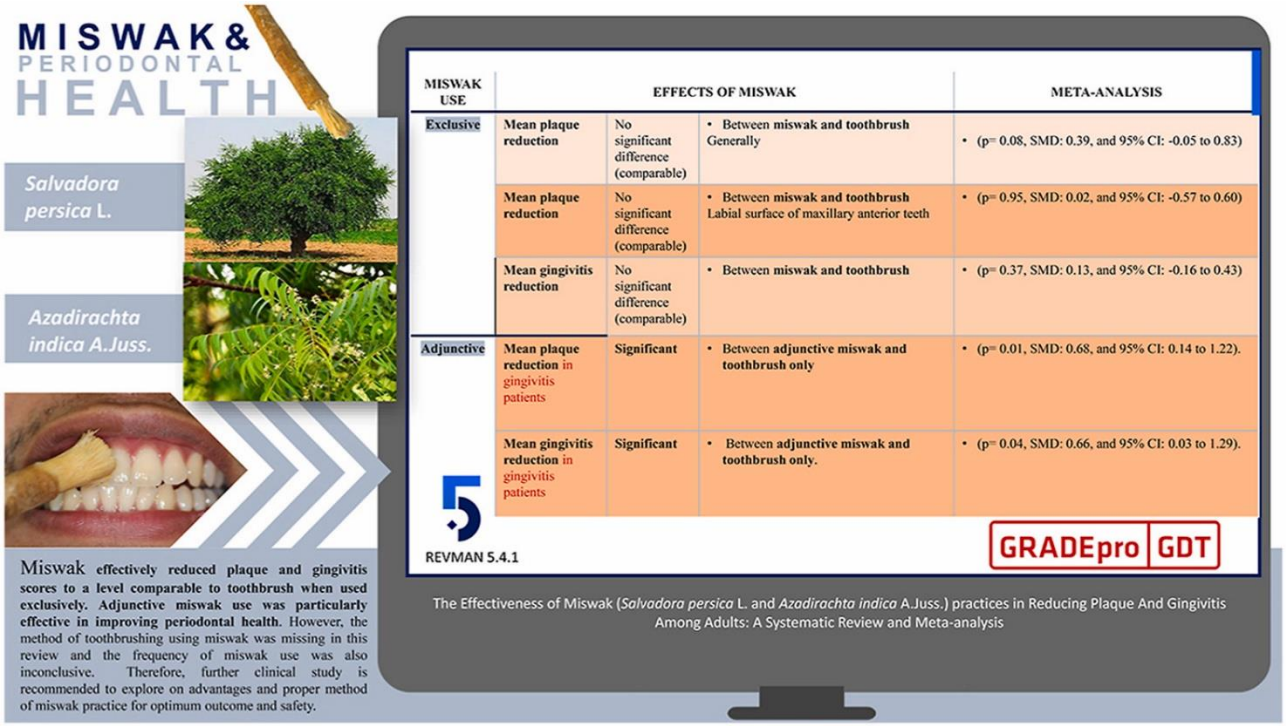
Orodental Protection

The effectiveness of miswak (Salvadora persica L. and Azadirachta indica A.Juss.) practices in reducing plaque and gingivitis among adults: A systematic review and meta-analysis.

Ramli H, Nor Aripin KN, Mohd Said S, Mohamad Hanafiah R, Mohd Dom TN.

J Ethnopharmacol. 2022 Aug 6;298:115598. doi: 10.1016/j.jep.2022.115598. Online ahead of print.PMID: 35944735

Ethnopharmacological relevance: Salvadora persica L. and Azadirachtaindica A.Juss. are listed within the most common sources of miswak or chewing stick that widely used among Western Asia and Muslim populations worldwide. Miswak use in conjunction with toothbrush (adjunctive) has become apparent among the adults. Furthermore, miswak has been reported to have mechanical and pharmacological activities, and benefits to the oral health, by many studies. **Aim of the study:** To assess the effectiveness of miswak in maintaining periodontal health among adults. **Materials and methods:** We searched for randomised controlled trials (RCTs) investigating the effect of miswak published in PubMed, EBSCOHOST (Dentistry & Oral Sciences), SCOPUS, and Cochrane Database for Systematic Review (CDSR) from inception to May 08, 2022. The primary outcomes of interest were changes in the periodontal health measured with plaque and gingivitis scores as well as subgingival bacteria load. The quality of evidence was assessed using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach while the estimates of effect were pooled using a random-effects model. **Results:** Ten eligible articles were identified, of which 9 could be analysed quantitatively. The remaining report was included as part of the qualitative analysis. The meta-analysis showed that miswak was comparable with the toothbrush in reducing the mean plaque score (p= 0.08, SMD: 0.39, and 95% CI: -0.05 to 0.83) and mean gingivitis score (p= 0.37, SMD: 0.13, and 95% CI: -0.16 to 0.43). Even higher certainty of evidence for the effect of miswak on mean plaque reduction on labial surface of anterior teeth. However, the adjunctive effect of miswak was significantly more superior for reducing plaque (p= 0.01, SMD: 0.68, and 95% CI: 0.14 to 1.22) and gingivitis score (p= 0.04, SMD: 0.66, and 95% CI: 0.03 to 1.29). **Conclusions:** Miswak effectively reduced plaque and gingivitis scores to a level comparable to toothbrush when used exclusively. Adjunctive miswak use was particularly effective in improving periodontal health. However, the included studies inadequately reported on the method of toothbrushing using miswak and the frequency of miswak use. Therefore, further clinical studies are recommended to explore on the advantages and proper method of miswak practice for optima outcome and safety.



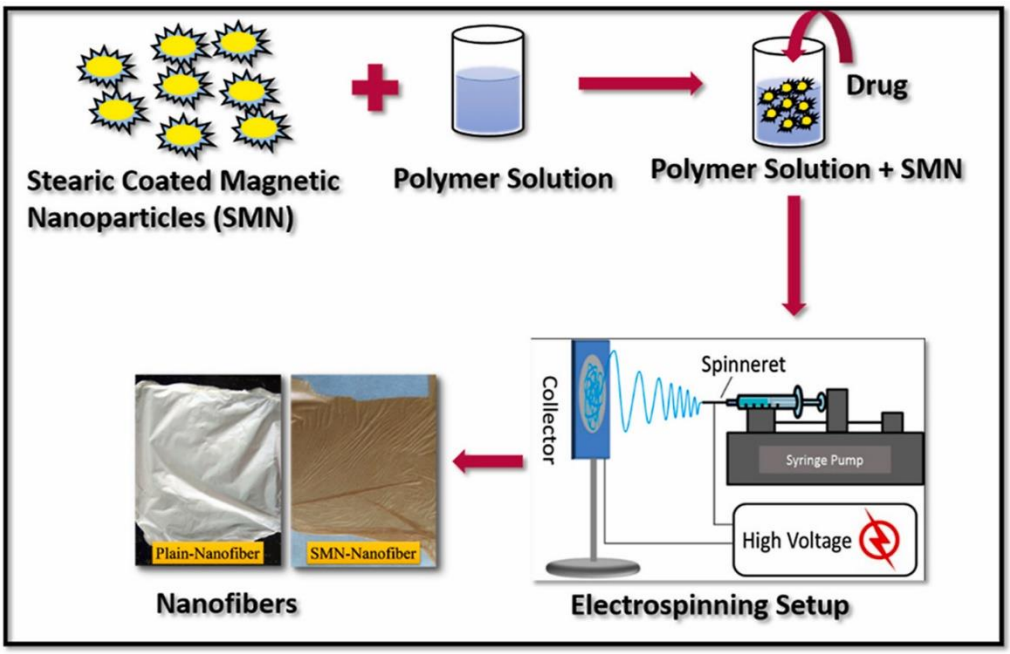
Anticancer Effects

Blend of neem oil based polyesteramide as magnetic nanofiber mat for efficient cancer therapy

PR Patel, A Singam, A Dadwal et al

J Drug Delivery Science & Technol 2022; 75:103629

Stearic acid-coated magnetic nanoparticles (SMN) and FU (5-Fluorouracil) were immobilized in the blends of neem oil-based polyesteramide and fabricated as nanofiber mat (NM) for controlled release of FU under the influence of an external magnetic field for targeted drug delivery to treat cancer efficiently. Analyzed the surface morphology of the fibers using E-SEM, it was observed that the fibers were smooth with the diameter ranging from 250 to 450 nm. TEM studies showed the uniform distribution of SMN in the nanofibers. The physicochemical properties of NM and raw materials were analyzed using FTIR, TGA, and XRD. The results suggested that the polymers were well blended. *In-vitro* FU release studies of the NMs recorded a significant difference in the cumulative percentage of FU release from SMN-NMs. The SMN-NMs released 95% of FU in 4 h, whereas, NMs released 83% of FU in 24 h. The cell viability assay for the NM was evaluated in the L929 mouse fibroblast cells, where >75% of cells were viable. The hemolysis assay for the developed SMN-NF showed <5% of hemolysis, which indicated the NMs were safe for application. The anti-cancer activity of FU loaded SMN-NF was analyzed in the MCF-7 cancer cell line, which recorded more than 50% cell death within 24 h. From SQUID analysis, we found that the 10% SMN were superparamagnetic in nature, the magnetization at 30 kOe was observed to be 4.3 emu/g. Based on the *in vitro* results, we concluded that the developed SMN-NMs are recommended for *in vivo* studies to understand their efficacy for the targeted drug delivery to treat cancer.

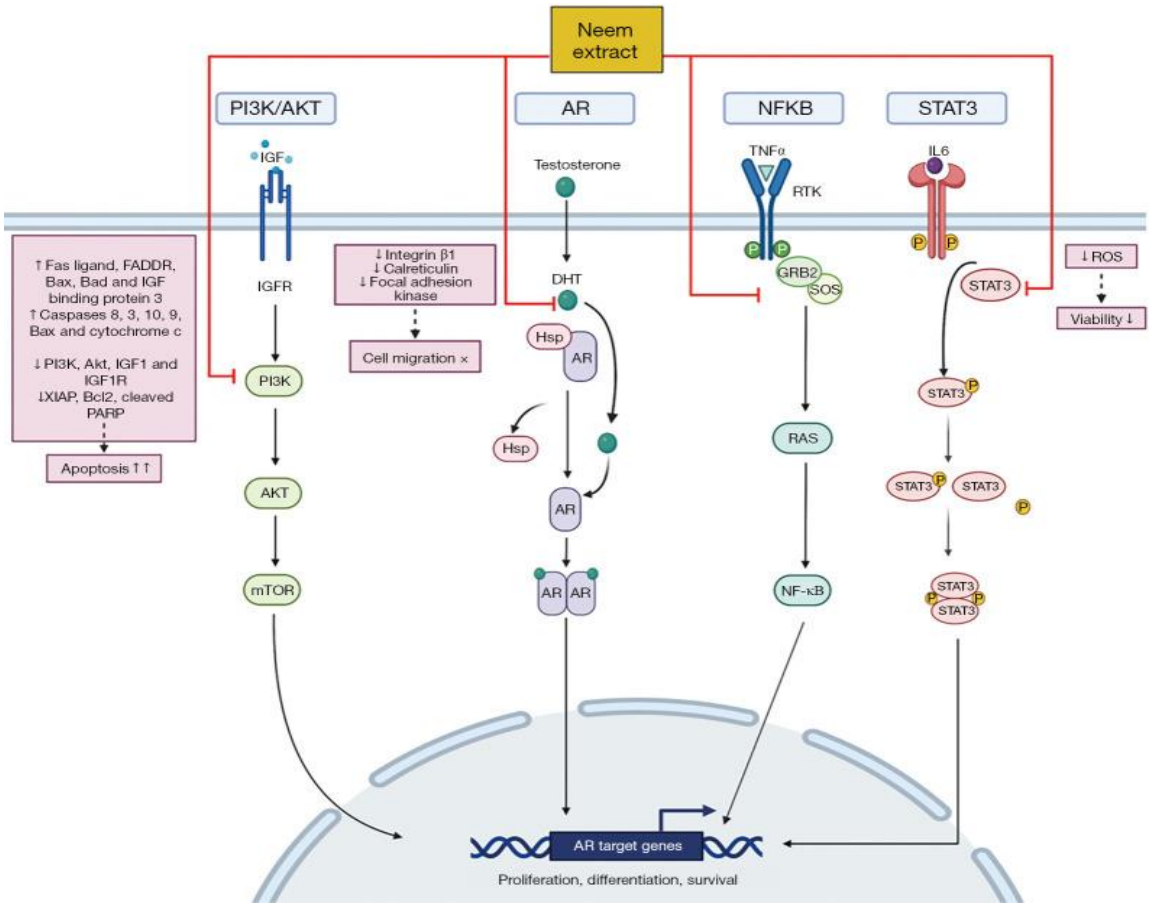


Exploring the therapeutic potential of Neem (*Azadirachta Indica*) for the treatment of prostate cancer: a literature review.

Batra N, Kumar VE, Nambiar R, De Souza C, Yuen A, Le U, Verma R, Ghosh PM, Vinall RL.

Transl Med. 2022 Jul;10(13):754. doi: 10.21037/atm-22-94.PMID: 35957716

Background and objective: Multiple studies have demonstrated the medical potency of plant extracts and specific phytochemicals as therapeutics for prostate cancer (PCa) patients. Of note, the Neem plant known for its role as an antibiotic and anti-inflammatory is underexplored with an untapped potential for further development. This review focuses on extracts and phytochemicals derived from the Neem tree (Latin name; *Azadirachta indica*), commonly used throughout Southeast Asia for the prevention and treatment of a wide array of diseases including cancer. To date, there are more than 130 biologically active compounds that have been isolated from the Neem tree including azadirachtin, nimbolinin, nimbin, nimbidin, nimbidol, which have demonstrated a wide range of biological activities including anti-microbial, anti-fertility, anti-inflammatory, anti-arthritic, hepatoprotective, anti-diabetic, anti-ulcer, and anti-cancer effects. Very few scientific reports focus on the benefits of Neem in PCa, even though this herb has been used to prevent the disease and its progression for years in complementary and alternative medicine. **Methods:** We used the search engines like PubMed, InCommon and Google using the key words: "Neem", "Cancer", "Prostate Cancer" and related words to find the information and data within the time frame from 1980-2022 for our article study. **Key content and findings:** Here, we provide an overview of Neem extracts and phytochemical derivatives with a focus on their known potential and ability to inhibit specific cellular signaling pathways and processes which drive PCa incidence and progression. **Conclusions:** The information presented here indicate that Neem and its derivatives have a therapeutic potential for the treatment of PCa when used as a single agent or in combination with conventional chemotherapeutics.



***Azadirachta indica* A. Juss Fruit Mesocarp and Epicarp Extracts Induce Antimicrobial and Antiproliferative Effects against Prostate (PC-3), Breast (MCF-7), and Colorectal Adenocarcinoma (Caco-2) Cancer Cell Lines through Upregulation of Proapoptotic Genes.**

Ibrahim OHM, Mousa MAA, Asiry KA, Alhakamy NA, Abo-Elyousr KAM.

Plants (Basel). 2022 Jul 30;11(15):1990. doi: 10.3390/plants11151990.PMID: 35956468

Effective alternative strategies and methodological approaches are critically necessary for cancer prevention and therapy. In this study, we investigated the antitumor potential of neem fruit mesocarp and epicarp extracts. The chemical composition of the derived extracts was characterized using GC-MS. Data were collected on the antimicrobial activity of the extracts in addition to the cytotoxicity effect evaluated against PC-3, MCF-7, and Caco-2 cancer cell lines, compared with the normal Vero cells. Cell-cycle arrest, apoptosis, and expression of apoptosis-related genes were assessed on PC-3 cells. Both extracts had significant antiproliferative effects on all tested cell lines in a dose-dependent manner, with the mesocarp extract being more potent. Both extracts also showed high antibacterial and antifungal activities. These results were related to the chemical constituents of the extracts identified by the GC-MS analysis. The extract of neem fruit mesocarp caused cell-cycle arrest at G2/M phase of PC-3 cells. The cytotoxicity of neem mesocarp extract is strongly correlated with the induction of apoptosis, where it caused downregulation of the antiapoptotic BCL2 gene but upregulation of the proapoptotic P53 and BAX genes. This study showed that neem fruit extract is potential anticancer material in the future.

Nimbolide enhances the antitumor effect of docetaxel via abrogation of the NF-κB signaling pathway in prostate cancer preclinical models.

Zhang J, Jung YY, Mohan CD, Deivasigamani A, Chinnathambi A, Alharbi SA, Rangappa KS, Hui KM, Sethi G, Ahn KS.

Biochim Biophys Acta Mol Cell Res. 2022 Aug 22:119344. doi: 10.1016/j.bbamcr.2022.119344. Online ahead of print. PMID: 36007677

Prostate cancer is the second most frequent type of cancer that affects men. Docetaxel (DTX) administration is the front-line therapy for patients with advanced prostate cancer and unfortunately, half of these patients develop resistance to DTX due to its ability to activate the NF-κB pathway. The combinational effect of DTX and nimbolide on proliferation, apoptosis, activation of NF-κB, DNA binding ability of NF-κB, and expression of NF-κB-targeted gene products was investigated. The antitumor and antimetastatic effect of DTX or NL alone or in combination was also examined. The co-administration of NL and DTX resulted in a significant loss of cell viability with enhanced apoptosis in DTX-sensitive/resistant prostate cancer cells. NL abrogated DTX-triggered NF-κB activation and expression of its downstream antiapoptotic factors (survivin, Bcl-2, and XIAP). The combination of NL and DTX significantly reduced the DNA binding ability of NF-κB in both cell types. NL significantly enhanced the antitumor effect of DTX and reduced metastases in orthotopic models of prostate cancer. NL abolishes DTX-induced-NF-κB activation to counteract cell proliferation, tumor growth, and metastasis in the prostate cancer models.

Antidiabetic Effects

The Anti-Diabetic Effect of Neem Leaves (Azadirachta indica,) in Alloxan-Induced Diabetic Rats

Adel A. Abdel Moaty, Emad A. El-Kholie, Rasha A. Adarous

J Home Economics. 2022, vol 32(no 2): pp19-31

The traditional medicinal herb neem (Azadirachta indica) may contribute intriguing bioactive compounds to the present diet in many countries. Herbal substances are being used as medicinal agents. This study evaluated the effects of different concentrations of neem leaves powder 2.5 and 5% and ethanolic extract 250 and 500 mg/kg body weight on diabetic rats. Thirty-six white male albino rats weighing 140±10g were divided into six groups of six rats each. Diabetic rats were infected with alloxan (150 mg/kg body weight). The following tests were performed: glucose, serum liver functions (ALT, AST, and ALP), T.G., T.C., LDL-c, HDL-c, VIDL-c, and kidney functions (urea, uric acid, and creatinine). HPLC was also used to determine the phenolic components in neem leaves. The findings showed that rats given neem leaves powder or extract improved their serum glucose levels, liver functions, kidney functions, and lipid profile. The best results were obtained with 500 mg/kg neem leaf extract. As a result of the findings, it is suggested that neem leaves contain numerous phytochemicals and can be used as an antioxidant to lower glucose levels in diabetic rats, apart from the fact that it offers multiple health advantages

Bone Lesions in a Young Dog and a NEEM (Azadirachta indica) Spray as the Only Preventive Measure against Leishmaniasis: A Case Report

G De Feo, G Lubas, S Citi, C Puccinelli, RA Papini

Zoonotic Dis. 2022, *2*(3), 95-110; https://doi.org/10.3390/zoonoticdis2030010

As the spread of canine leishmaniasis (CanL) is increasing throughout the world, the need for effective agents to prevent its transmission has intensified. In this case report, an intact 1.5-year-old male French bulldog was presented for treatment of severe, sudden, and constant lameness on his right hindlimb, which had started approximately four months previously and was unresponsive to routine nonsteroidal anti-inflammatory drugs. A Neem oil-based product was sprayed three times a week on the dog's coat for about fourteen months as the only prophylactic measure against CanL. The orthopedic examination revealed grade 3–4 lameness and marked atrophy of the thigh muscles with swollen and painful right stifle joint. The radiological investigation showed polyostotic periosteal proliferation at both hindlimbs. The diagnosis of CanL was established by examination of fine-needle aspiration of lymph nodes (left prescapular, right and left popliteal) and immunofluorescence antibody testing. A leishmanicidal therapeutic protocol was prescribed. Within ten days of starting the therapy, the dog was significantly less lame, and eight months later radiographic examination revealed complete regression of the bone lesions. Some owners resort to a naturalistic approach for CanL prevention, also using products that have not been clinically evaluated. Neem oil is thought to prevent sandfly bites in dogs. Some laboratory and field studies have identified Neem oil as a possible alternative herbal drug that is repellent to sandflies. However, the clinical, laboratory, and radiographic findings clearly show that the Neem oil spray formulation used in this case report was not an effective means of CanL prevention. There is no clinical evidence in support of Neem oil-based products for the protection of dogs against CanL transmission. As Neem oil has previously been shown to be somewhat volatile, this case report suggests that even though it is a very effective repellent against sandflies, in practice, its effect on the dogs' coat was only short-lived.

Effect of Dietary Inclusion of *Azadirachta indica* and *Moringa oleifera* Leaf Extracts on the Carcass Quality and Fatty Acid Composition of Lambs Fed High Forage Total Mixed Rations.

Webb EC, Hassen A, Olaniyi MO, Pophiwa P.

Animals (Basel). 2022 Aug 11;12(16):2039. doi: 10.3390/ani12162039.PMID: 36009629

There is an increased interest in the use of medicinal plants as alternatives to antibiotic growth promoters and as agents for methane production mitigation. This study investigated the effects of *Azadirachta indica* and *Moringa oleifera* feed additives on the carcass and meat quality of lambs. Forty South African Mutton Merino lambs, weighing between 29 and 43 kg, were randomly assigned to four treatment groups (n = 10 lambs/treatment) and fed a basal total mixed ration (TMR) containing soybean meal (17%), yellow maize (28%), Alfalfa hay (20%), Eragrostis curvula hay (22.2%), molasses (6.0%), wheat offal (5%), urea (0.8%) and vitamin premix (0.5%) on a DM basis. The

dietary treatments: TMR diet (control); TMR diet with *A. indica* leaf extract (*A. indica* leaf extract at a dosage of 50 mg per kg of feed: neem); TMR diet with *M. oleifera* leaf extract (*M. oleifera* leaf extract at a dosage of 50 mg per kg DM of feed: moringa); TMR diet with monensin (at a dosage of 50 mg monensin sodium per kg of feed: positive control). After an adaptation period of 10 days to the experimental conditions, the lambs from all treatment groups were fed ad libitum with the experimental diets. The lambs were slaughtered at a live weight of 60-65 kg after a 23 week trial period. The plant extract dietary additives had no significant effects on the carcass characteristics of the lambs. In comparison to monensin, supplementing with moringa leaf extracts resulted in a higher proportion of C18:1n9c (45.0% ± 0.57 vs. 40.5% ± 0.80; *p* < 0.05), total MUFAs (47.3% ± 0.66 vs. 42.6% ± 0.87; *p* < 0.05), and UFA:SFA ratio (1.01 ± 0.03 vs. 0.85 ± 0.03; *p* < 0.05), which may be beneficial for human health. Our results suggest that natural feed additives, such as *A. indica* and *M. oleifera* leaf extracts, can be included in lamb diets without compromising meat fatty acid composition. The negative economic impacts of such technologies on animal production and farm profitability should not be expected.

Acaricidal Properties of Four Neem Seed Extracts (*Azadirachta indica*) on the Camel Tick *Hyalomma dromedarii* (*Acari: Ixodidae*).

Gareh A, Hassan D, Essa A, Kotb S, Karmi M, Mohamed AEH, Alkhaibari AM, Elbaz E, Elhawary NM, Hassanen EAA, Lokman MS, El-Gohary FA, Elmahallawy EK.

Front Vet Sci. 2022 Jul 22;9:946702. doi: 10.3389/fvets.2022.946702. eCollection 2022.PMID: 35937305

Tick infestation remains one of the major health problems that affect the productivity and comfort of camels. The control of ticks mainly relies on using chemical acaracides. Limited information is available on the potential benefits and activity of various neem extracts on *Hyalomma* ticks. The present study investigated the acaricidal activity of neem seed extracts at different concentrations against developmental stages of the camel tick *Hyalomma dromedarii* in comparison to Butox and diazinon. The acaricidal activity of three extracts, namely, hexane extract (HE), methyl chloride extract (MCE), and methanol extract (ME), of neem seeds (*Azadirachta indica*) were tested at varying concentrations of 5, 10, 15, and 20% on engorged *H. dromedarii* female ticks at days 1, 3, 5, 7, 12, 16, 20, 28, 37, and 43 after treatment (DPT). Interestingly, results of applying different neem seed extracts to engorged *H. dromedarii* female ticks showed that the most effective extract was hexane at concentration 20%, causing 100% mortality at 1st day post-application, while methanol extract at 20% and dichloromethane extract at 20% caused the death of all ticks at 28th day posttreatment as compared to Butox® 5.0 and Diazinon-60, which resulted in mortality of all ticks at 3 and 5 DPT, respectively. In addition, no mortality was reported with the application of aqueous extract (AE), which served as the control group. Furthermore, the neem hexane extract exhibited high efficacy against reproductive performance of female ticks, whereas no fertility or oviposition was reported at all of their concentrations. Additionally, no hatchability occurred using all neem extracts, except the aqueous extract, which showing no effect. In the present study, larvae responded more rapidly to the plant extracts, whereas mortality of all larvae was recorded at 24 h after treatment with 5% hexane. Taken together, this study pointed out that the acaricidal effect of hexane extract of neem seeds was more effective and could be economically used for controlling *H. dromedarii* ticks.

Reproductive Effects of Medicinal Plant (Azadirachta Indica) Used as Forage and for Ethnoveterinary Practices: New Insights from Animal Models

UJ Njoga, IF Jaja, OS Onwuka, SU Ilo, IG Eke, KO Abah

Challenges, 2022. https://doi.org/10.3390/ challe13020040

In some African and Asian countries, Azadirachta indica (AI) has been fed to livestock for decades and traditionally used to treat certain animal and human diseases. Recently, there are suspicions that the plant may possess anti-reproductive properties and concerns that the continued use of AI as forage or for folkloric medicine may detrimentally affect reproduction in the subjects. To address these challenges, this work determined the reproductive and fertility effects of a methanolic seed extract of AI (MSEAI) using adult female albino rats (AFARs) as an experimental model. Sixtyfour AFARs were randomly assigned into four groups (A–D) of sixteen rats each. Group A was the control while groups B, C and D were treated daily with 50, 100 and 200 mg/kg of MSEAI respectively, for 28 consecutive days via oral gavage. Blood samples were collected for hormonal and biochemistry assays. Ovarian samples from the experimental rats were harvested for histopathological studies. Thereafter, the remaining experimental rats were bred, and certain fertility indices determined. The mean serum FSH and LH levels were significantly decreased ($p \leq 0.05$) in the 100 and 200 mg/kg groups. The histopathological studies revealed massive follicular degeneration in the 100 and 200 mg/kg treatment groups. The fertility indices indicated that the post-implantation survival index was 100% in the control and 0% in the 200 mg/kg treatment group. No abortion occurred in the control and 50 mg/kg groups, but 25% and 100% of the pregnant does aborted in the 100 and 200 mg/kg treatment groups, respectively. Considering that high doses (100 mg/kg and 200 mg/kg) of MSEAI had significant anti-reproductive and antifertility properties, the use of AI as forage or for ethnoveterinary medicine in breeding females may adversely affect their reproductive potentials. However, the antireproductive and antifertility effects could be utilized in rodent depopulation programs in animal agriculture and as a contraceptive to limit the proliferation of stray dogs, known to be reservoirs of the rabies virus in developing countries. Moreover, the MSEAI could be further refined for human use as an effective, cheap, eco-friendly and acceptable alternative to synthetic/modern contraceptives, the use of which is limited in developing nations due to superstitious beliefs and their multiple side effects.