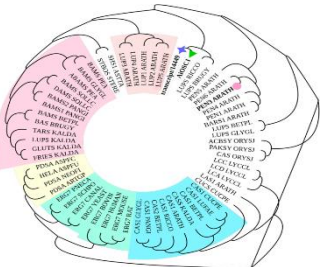
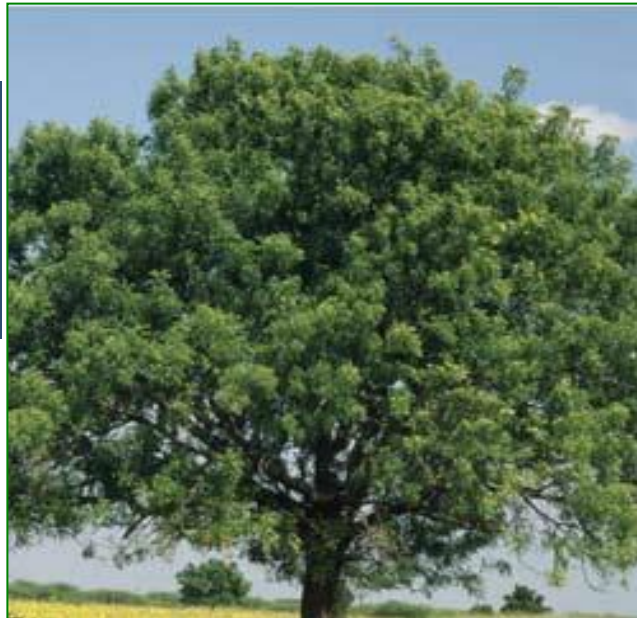
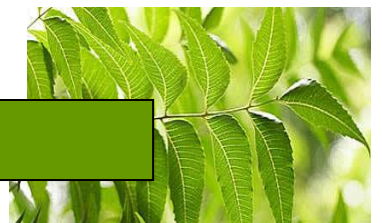


Neem Research Newsletter

Volume 1, Issue 1, 2021



WORLD NEEM ORGANISATION (WNO)



From
The Editor's Desk.....

Azadirachta indica, commonly known as neem, has attracted the attention of researchers globally due to its ever-expanding repertoire of applications in agriculture, human and animal health, energy, environment, green chemistry, pharmaceutical, and cosmetic industry as well as in the manufacture of household products. Due to its remarkable potential for sustainable development, the neem tree is regarded as the 'Tree of the 21st century', 'A tree for solving global problems' and 'A panacea for all diseases'. All parts of the neem tree have been reported to exhibit a wide range of biological activities. The neem tree is a treasure trove of bioactive phytochemicals, one-third of which are tetranortriterpenoids or limonoids. Over the last few years, there has been a remarkable momentum in unravelling the potential of neem in diverse fields. In the last meeting of the Executive Committee of the World Neem Organisation (WNO), publication of a newsletter that would provide a bird's eye view of the progress in neem research was mooted. The newsletter will be uploaded on the WNO website twice a year and will attempt to capture in a nutshell, the research publications on neem. This volume is the maiden venture to showcase the versatility of the neem tree based on research papers published from January 1 2021 to July 31 2021. The abstracts have been condensed and running titles are given to reflect important findings in a concise manner. Illustrations are provided wherever available as well as PMIDs for those readers who wish to delve more deeply. It is my immense pleasure to function as an Editor of the Neem Research Newsletter. I thank Mr. S. Arvinth and Ms. J. Saranya, PhD students, Annamalai University for assistance in preparing this newsletter. Feedback/suggestions are most welcome.

S. Nagini

Core Founding Member, WNO
Chief Scientific Coordinator &
Regional Director, South India



Neem in Agriculture & Aquaculture

Neem-coated urea enhances nitrogen use efficiency of wheat crop

Ghafoor I, Habib-Ur-Rahman M, Ali M, Afzal M, Ahmed W, Gaiser T, Ghaffar A.

Environ Sci Pollut Res Int. 2021, PMID: 33834341

The effects of different types of coated urea fertilizers and their rates on wheat crop under arid climatic conditions of Pakistan were explored. The neem-coated fertilizers showed better results than monotypic urea. The wheat growth and phenology significantly improved by using coated fertilizers. The major problem of groundwater contamination with nitrate leaching was also reduced by using coated fertilizers. These results reveal that coating urea with secondary nutrients, neem oil, and microbes are highly effective techniques for enhancing fertilizer use efficiency and wheat production in calcareous soils and reduced N losses under arid environments.

Neem mixed biochar reduces fertilizer dependency

Kumar A, Singh E, Singh L, Kumar S, Kumar R.

Sci Total Environ. 2021;751:141659. PMID: 32882552

A 60-day trial experiment was carried out for investigating the impacts of sugarcane, neem and bamboo mixed biochar and polyvinyl chloride, polyethylene and polyethylene terephthalate mixed plastic char on physico-chemical properties of soil and growth of *Dendrocalamus strictus* saplings. The application of both biochar and plastic char enhanced the quality of soil (increased soil pH, total organic carbon, available phosphorus and nitrogen), plant height and thereby helped in achieving higher crop yields, making it more suitable for the improvement of agricultural system and reducing the dependency on market-based fertilizers.

Antifungal activity of propyl disulfide from neem in mango fruit

Khan MR, Chonhenchob V, Huang C, Suwanamornlert P.

Microorganisms 2021;9(4):839. PMID: 33920016

Propyl disulfide neem was tested as an alternative against mango's anthracnose disease which shows resistance to the current fungicides. Neem extract significantly inhibited mycelial growth of *Colletotrichum gloeosporioides* and *Colletotrichum acutatum*. Further, the antifungal activity increased with increasing concentrations.

Endophytic fungi from neem inhibit MDR bacteria and phytopathogens

Raihan T, Azad AK, Ahmed J, Shepon MR, Dey P, Chowdhury N, Aunkor TH, Ali H, Suhani S.

Future Microbiol. 2021;16:557-576. PMID: 33998269

Seventeen extracellular metabolites (EMs) of endophytic fungal isolates (EFIs) from different organs of *Azadirachta indica* were isolated and eight of them identified by internal transcribed spacer (ITS) sequencing. The EMs of EFIs inhibited the growth of six multidrug-resistant (MDR) bacterial superbugs and three phytopathogenic fungi. The MDR bacterial superbugs are resistant to six commercial antibiotics of different generations but susceptible to EMs of EFIs. The EMs of the EFIs have promising antimicrobial activity against MDR bacteria and phytopathogenic fungi.

Efficacy of *A. indica* against marine parasitic leech

Venmathi Maran BA, Josmeh D, Tan JK, Yong YS, Shah MD.

***Molecules*. 2021;26(7):1908. PMID: 33805254**

The antiparasitic efficacy of the aqueous extract of the *Azadirachta indica* leaves against *Zeylanicobdella arugamensis* (Hirudinea), a marine parasitic leech, *Z. arugamensis* that not resulted in the mortality of the host fish (Groupers) and also caused economic losses was investigated. *A. indica* aqueous extract was found to be a good source of metabolites (5 flavonoids- myricetin 3-O-galactoside, trifolin, isorhamnetin, quercetin and kaempferol; 4 aromatics- 4-methoxy benzaldehyde, scopoletin, indole-3-acrylic acid and 2,4-quinolinediol; 3 phenolics- p-coumaric acid, ferulic acid and phloretin; and 2 terpenoids- pulegone and caryophyllene oxide) with the potential to act as a biocontrol agent against the marine parasitic leech in aquaculture.

Neem in Animal Husbandry

Neem exhibits bactericidal effect against MDR pathogenic bacteria of poultry

Ali E, Islam MS, Hossen MI, Khatun MM, Islam MA.

***Vet Med Sci*. PMID: 33955693**

The efficacy of neem leaf extract against multidrug resistant (MDR) pathogenic bacteria was determined. The minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of neem leaf extract were 12.5 and 25 mg/ml, respectively for *Pasteurella multocida*, 50 and 100 mg/ml for *Salmonella pullorum* and *Salmonella gallinarum*, 100 and 112.5 mg/ml for *Escherichia coli*. Neem leaf extracts exhibited bactericidal effect against MDR pathogenic bacteria of poultry.

Neem seed oil alters rumen fermentation and nitrogen utilization in sheep

El-Zaiat HM, Alqaisi O, Sallam SM, Al-Marzooqi WS.

***Anim Biotechnol*. 1-9. PMID: 33941033**

The effects of neem seed oil (NSO) on feed intake, ruminal fermentability, feed digestibility, nitrogen balance, and blood parameters in Omani sheep were examined. Sheep fed with high dose showed lower intake, fiber digestibility, lower ruminal acetate proportion, and increased ruminal propionate. There was a linear decrease in ruminal ammonia nitrogen concentration. Emission of predicted methane (CH₄) reduced by 13% for high dose compared to the control. These results suggest that NSO is a potential feed additive that alters rumen fermentation profile, decreased CH₄ production, feed digestibility, and nitrogen metabolism for sheep.

Neem fruit extract exerts acaricidal effects against mange mites in grower pigs

Pasipanodya CN, Tekedza TT, Chatiza FP, Gororo E.

Trop Anim Health Prod. 2021;53(1):135. PMID: 33483804

The acaricidal activity of neem aqueous fruit extract was evaluated against *Sarcoptes scabiei* var. suis (mange mites) in an on-farm trial using grower pigs. Topical application of 25% aqueous neem fruit extract cured clinical mange on grower pigs 6 weeks post treatment and amitraz-based acaricide after 5 weeks. The results indicated that aqueous neem fruit extracts have acaricidal effects against mange mites and can provide a cheaper, safer, and more eco-friendly alternative for the control of *Sarcoptes* mange in pigs.

Neem extract mitigates methane production and improves fermentation in sheep

Faniyi TO, Adewumi MK, Jack AA, Adegbeye MJ, Elghandour MMMY, Barbabosa-Pliego A, Salem AZM.

Trop Anim Health Prod. 2021;53(2):312. PMID: 33966126

Aqueous and methanolic extracts of neem on ruminal methane production and fermentation characteristics was studied in West African dwarf sheep. Neem extract increased the gas produced, from the insoluble fraction, degradability rate, volume of gas produced at time and time of most rapid change in gas produced. This study suggests that extracts of neem have the potential to mitigate ruminal methane production and improve fermentation characteristics.

Neem influences growth and gene expression in growing calves

Díaz Galván C, Méndez Olvera ET, Martínez Gómez D, Gloria Trujillo A, Hernández García PA, Espinosa Ayala E, Palacios Martínez M, Lara Bueno A, Mendoza Martínez GD, Velázquez Cruz LA.

Front Vet Sci. 2021;7:623710. PMID: 33575280

A polyherbal feed mixture containing neem was evaluated in growing calves during the pre-ruminant to weaning period. The animals treated with the polyherbal mixture showed a quadratic effect on final body weight, daily weight gain, final hip height, and final thoracic girth. The serum IgG increased linearly with the treatment doses. Gene expression analysis confirmed that polyherbal treatment could improve the metabolism of lipids, carbohydrates, proteins, and also immune response.

Neem For Sustainable Energy

Neem biodiesel reduces exhaust emissions and fuel consumption

Datla R, Puli RK, Velayudhan Parvathy C, Varuvel EG.

Environ Sci Pollut Res Int. 2021;28(10):11942-11953. PMID: 32144698

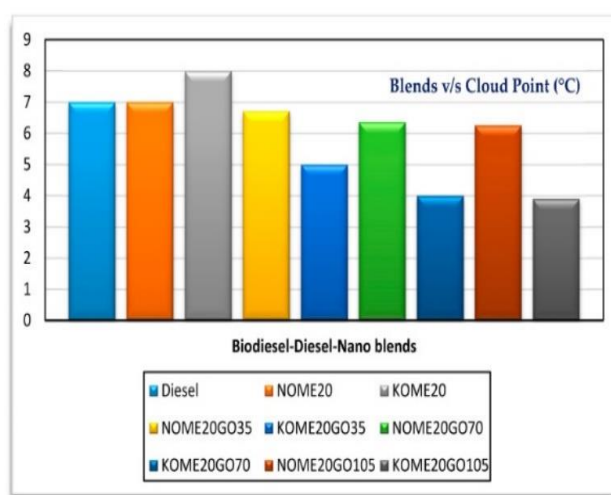
The optimum start of main injection (SoMI) timing on performance, emission, and combustion characteristics of a variable geometry turbocharger (VGT) compression ignition (CI) engine fueled with neem biodiesel blend NB20 with diesel was analysed. Addition of neem biodiesel NB20 blend to diesel fuel decreases exhaust emissions, brake-specific fuel consumption, and improves brake thermal efficiency.

Neem biodiesel-diesel blends display more efficacy than Karanja blends

Khan TMY.

Nanomaterials (Basel). 2021;11(2):417. PMID: 33562116

Biodiesel prepared from feedstocks of Neem oil employing a single step direct transesterification method and acid-base catalysts simultaneously was found to be better in terms of kinematic viscosity, calorific value and cloud point for all its blends with diesel compared to Karanja biodiesel-diesel blends. Higher concentrated B20-nano blends of neem (NOME20GO105) resulted in 31% brake thermal efficiency, reduction of brake-specific fuel consumption (BSFC) by 10% and carbon monoxide (CO) by 27% in 4-stroke variable compression ratio diesel engine.

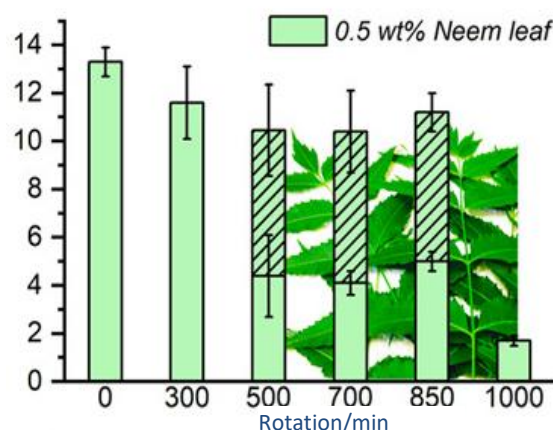


A. indica biopowder inhibits methane hydrates

Kiran BS, Prasad PSR.

ACS Omega. 2021;6(12):8261-8270. PMID: 33817485

Additives are used to eliminate/delay the formation of hydrate plugs during transportation of oil and natural gas in the pipeline network. Natural biopowders, such as *Azadirachta indica* in low dosage (0.5 wt%) act as efficient thermodynamic hydrate inhibitors and kinetic hydrate promoters. The addition of *A. indica* biopowder extract is useful in controlling hydrate formation and a small quantity provides higher inhibition and reduces synthetic chemicals which are toxic and expensive.

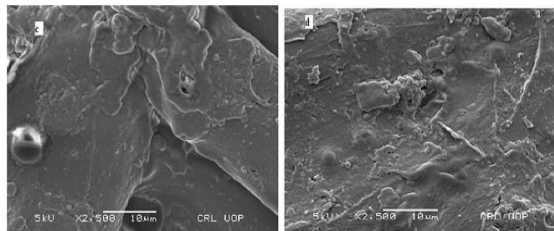


Neem For Sustainable Environment & Green Synthesis

Biosorption of halosulfuron methyl pesticide onto neem seeds powder

Haq AU, Saeed M, Usman M, Zahoor AF, Anjum MN, Maqbool T, Naheed S, Kashif M.
Sci Rep. 2021;11(1):9960. PMID: 33976253

The ability of neem seed powder (NSP) to remove halosulfuron methyl from aqueous media in batch modes was investigated. The point of zero charge of NSP was found to be 6.5 implying that the surface of NSP is positively charged below pH 6.6 and favored anionic sorption. Isotherm results imply that Langmuir was found to be the principal model to explain the removal of halosulfuron methyl and maximum monolayer sorption capacity was determined to be 200 mg g⁻¹. Thermodynamic parameters were negative suggesting that removal of halosulfuron methyl is exothermic and spontaneous at low temperature. These outcomes indicate that neem seed powder may be a valuable, inexpensive and ecofriendly biosorbent for the removal of pesticides.



Neem for green synthesis of zinc oxide coupled cadmium sulfide nanostructures

Rani M, Yadav J, Keshu, Shanker U.J

Colloid Interface Sci. 2021;601:689-703. PMID: 34091316

The leaf extract of *Azadirachta indica* was used to synthesise sunlight active zinc oxide coupled with cadmium sulfide (ZnO@CdS). This nanocomposite was used to remove chlorpyrifos and atrazine pesticides that show high persistence, bioaccumulation, and toxicity in the environment. At moderate dosage and neutral pH, the nanocomposite was found highly efficient for the quantitative removal of pesticides (89-91%) and in suppressing the half-life of pesticides. The applicability of green or alternative photocatalyst for multiple times confirmed its sustainability and high efficiency for environmental and industrial purposes.

Use of neem leaf extract for green synthesis of heterometallic nanocatalysts

Rani M, Keshu, Shanker U.

Environ Sci Pollut Res Int. 2021. PMID: 34189687

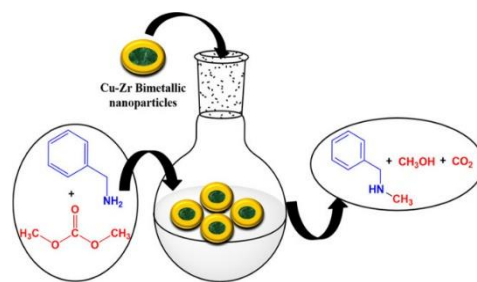
Dyes and phenols are extensively used chemicals in petrochemicals, pharmaceuticals, textile, and paint industries. Due to high persistence, bioaccumulation, and toxicity, their removal from the environment is highly imperative. Leaf extract of *Azadirachta indica* was used for green synthesis of heterometallic oxide (HMO) nanocatalysts such as CuFe₂O₄, CuMn₂O₄, and MnZn₂O₄. HMOs nanocatalysts were used as photocatalysts for removal of 3-amino phenols (3-AP) and eriochrome black T (EBT) from water under sunlight. Substantial degradation (80-95%) of pollutants (50 mgL⁻¹) by HMOs (80 mg) was achieved at neutral pH under sunlight exposure with highest removal by CuFe₂O₄. Overall, green synthesized HMOs nanoparticles with prominent surface characteristics offer a viable alternative photocatalyst for industrial applications.

Neem for green synthesis of Cu-Zr Bimetallic Nanoparticles

Sharma A, Verma K, Kaushal S, Badru R.

ACS Omega. 2021;6(23):15300-15307. PMID: 34151109

Alkylamines are widely used as intermediates or as a whole in biology and medicine in addition to chemistry. Aqueous solutions of *Azadirachta indica* leaf extract was used as a reducing and stabilizing agent for the green synthesis of copper-zirconium bimetallic nanoparticles (Cu-Zr BNPs). The synthesized Cu-Zr BNPs were employed as efficient catalysts for the selective *N*-methylation of aromatic and aliphatic amines with dimethyl carbonate. The analysis of catalytic reusability confirmed that the reported heterogeneous catalyst can be used for five consecutive cycles without much loss in activity. Thus, the current protocol can be considered as a simpler, reproducible, and environmentally benign approach for *N*-methylation of amines.



Neem leaves nanoparticles: a green prospect for dye degradation in wastewater

Sengupta A, Sarkar A.

Ecotoxicology. 2021. PMID: 33905024

A rapid, simple, and environment-friendly method for the biosynthesis of silver nanoparticles (AgNPs) from neem leaves and banana peels was developed. The application of AgNPs as antimicrobials was tested against *Escherichia coli*, *Bacillus subtilis*, *Staphylococcus aureus*, and *Klebsiella* sp. as well as dye degrading agents for wastewater treatment.

Removal of hexavalent chromium by biochar derived from *Azadirachta indica* leaves

Thangagiri B, Sakthivel A, Jeyasubramanian K, Seenivasan S, Dhavethu Raja J, Yun K.

Chemosphere. 2021; 286(Pt 1):131598. PMID: 34325269

This report details the preparation, characterization, and applications of an inexpensive adsorbent obtained from *Azadirachta indica* leaves (Neem biochar (NBC)) and used to remove Cr(VI) from synthetic waste water. Adsorption experiments conducted at various pH levels confirmed that 58.54 mg g⁻¹ of Cr(VI) was removed by NBC at pH 2. The Cr(VI) adsorption on NBC fits the Langmuir-type adsorption isotherm. A fixed-bed column study was conducted to obtain breakthrough curve for the adsorption process, which confirmed that the NBC usage rate was 4.63 g/L. Cr(VI)NBC was reactivated by NaOH treatment, and the reactivated NBC was used as a sorbent to remove fresh Cr(VI) from the synthetic waste water repeatedly. A cost analysis was also performed for the Cr(VI) removal confirmed that the process was less expensive.

Silver nanoparticles synthesized from *Azadirachta indica* leaf extract exhibit higher antimicrobial efficacy than chemically synthesized nanoparticles

Khan K, Javed S.

Sci Prog. 2021;104(2):368504211012159. PMID: 33926312

Silver nanoparticles (Ag-NPs) were synthesized chemically (cAg-NPs) using a chemical reductant and biologically (bAg-NPs) by using aqueous leaf extract of *Azadirachta indica* (neem). The results revealed that bAg-NPs of APS 43 nm were highly antimicrobial against *Escherichia coli* (Gram -ve) and *Staphylococcus aureus* (Gram +ve) compared to cAg-NPs of 8 nm.

Characterization of microRNAs from neem

Paul S, Reyes-Pérez P, Angulo-Bejarano PI, Srivastava A, Ramalingam S, Sharma A.
3 Biotech. 2021;11(6):277. PMID: 34040926

Using a high stringent genome-wide computational-based approach, 44 potential conserved neem microRNAs (miRNAs) belonging to 21 families and their corresponding 48 potential target transcripts were identified. Important targets include Squamosa promoter binding protein-like proteins, NAC, Scarecrow proteins, Auxin response factor, and F-box proteins. A biological network has also been developed to understand the miRNA-mediated gene regulation using the minimum free energy (MFE) values of the miRNA-target interaction. Moreover, six selected miRNAs (*miR156a*, *miR156l*, *miR160*, *miR164*, *miR171*, *miR395*) were validated by qPCR and their tissue-specific differential expression pattern was observed in leaves and stem. Except for *ain-miR395*, all the other miRNAs were found overexpressed in the stem as compared to leaves. This is the first report of neem miRNAs and the findings of the present study will be useful for the functional genomic study of medicinal plants.

Azadirachta indica microRNAs: Genome-Wide Identification, Target Transcript Prediction, and Expression Analyses

Rajakani R, Prakash P, Ghosliya D, Soni R, Singh A, Gupta V.
Appl Biochem Biotechnol. 2021;193(6):1924-1944. PMID: 33523368

MicroRNAs are short, endogenous, non-coding RNAs, with regulatory function. A comprehensive search of miRNAs in the *A. indica* genome by C-mii tool was performed. Overall, 123 miRNAs classified into 63 families and their stem-loop hairpin structures were predicted. The size of the *A. indica* (*ain*)-miRNAs ranged between 19 and 23 nt in length, and their corresponding *ain*-miRNA precursor sequence MFEI value averaged as -1.147 kcal/mol. The gene ontology (GO) annotation revealed the involvement of *ain*-miRNA targets in developmental processes, transport, stress, and metabolic processes including secondary metabolism. Stem-loop qRT-PCR was carried out for 25 randomly selected *ain*-miRNAs and differential expression patterns were observed in different *A. indica* tissues. Expression of miRNAs and its targets shows negative correlation in a dependent manner.

Functional characterization of crucial genes involved in neem limonoid biosynthesis

Pandrea A, Chaya PS, Kumar A, Aarthi T, Mulani FA, Bhagyashree DD, B SH, Jennifer C, Ponnusamy S, Nagegowda D, Thulasiram HV.
Phytochemistry. 2021;184:112669. PMID: 33524856

Limonoids present in neem are responsible for its medicinal, agricultural, and pesticidal properties. To understand limonoid biosynthesis, tissue-specific (kernel, pericarp, leaves, and flower) transcriptome analysis was carried out. The following were identified- one farnesyl diphosphate synthase (AiFDS), one squalene synthase (AiSQS), three squalene epoxidases (AiSQE1, AiSQE2, and AiSQE3), two triterpene synthases (AiTTS1 and AiTTS2), cycloartenol synthase (AiCAS), two cytochrome P450 reductases, and ten cytochrome P450 systems. Comparative tissue-expression analysis indicated that AiFDS, AiSQS, AiSQE3, and AiTTS1 are expressed higher in the kernel than in the other tissues. Expression profile data, phylogeny with triterpene synthases from Meliaceae and Rutaceae families, real-time PCR of different tissues, and transient transformation

revealed the involvement of tirucalla-7,24-dien-3 β -ol synthase (AiTTS1) in limonoid biosynthesis. Mutagenesis studies of AiTTS1 indicated that Y125 and F260 are probably involved in stabilization of dammarenyl cation. A 2.6-fold increase in production of tirucalla-7,24-dien-3 β -ol was observed when AiSQE1 was co-expressed with mutant AiTTS1 in a yeast system. Furthermore, the highly expressed cytochrome P450 reductases and cycloartenol synthase were functionally characterized.

Heterologous overexpression of caffeic acid 3-O-methyltransferase from neem

Narnoliya LK, Sangwan N, Jadaun JS, Bansal S, Sangwan RS.

***Planta*. 2021;253(1):20. PMID: 33398404**

Caffeic acid 3-O-methyltransferase gene from neem (NCOMT) was isolated from neem fruits and heterologously expressed in *E. coli*. The purified recombinant NCOMT enzyme exhibited efficient catalytic conversion of caffeic acid into ferulic acid, a highly potential pharmaceutical compound. NCOMT was also heterologously overexpressed in *Withania somnifera* and *Ocimum* species, to analyze its role in ferulic acid biosynthesis in planta. The analysis of tissue-wide expression of NCOMT gene revealed interesting pattern of transcript abundance reflecting its role in the development of fruit tissues. The study provides insight into the endogenous role of NCOMT in ferulic acid biosynthesis en route to lignin, an important structural component. The study involving NCOMT opens up new dimensions of metabolic engineering approaches for the biosynthesis of potential therapeutically important phytomolecules in heterologous systems.

Role of neem and its active compounds in the regulation of biological pathways

Sarkar S, Singh RP, Bhattacharya G.

***3 Biotech*. 2021;11(4):178. PMID: 33927969**

Neem, a versatile medicinal plant traditionally used to treat different ailments is rich in bioactive compounds. The review article explores the importance of neem extracts and bioactive compounds such as nimbolide, azadirachtin, and gedunin in the regulation of different biological pathways. Research articles up to March 2020 on the role of neem in antioxidant, anti-inflammatory, antiangiogenic, immunomodulatory, and apoptotic activities have been reviewed. Extensive research has been carried out on limonoids such as nimbolide and azadirachtin. Neem can be used to alleviate oxidative stress and inflammation.

***Azadirachta indica* A. Juss. In vivo toxicity-An Updated Review**

Braga TM, Rocha L, Chung TY, Oliveira RF, Pinho C, Oliveira AI, Morgado J, Cruz A.

***Molecules*. 2021;26(2):252. PMID: 33419112**

The neem tree is known for its large spectrum of compounds with biological and pharmacological interest. These include, among others, activities that are anticancer, antibacterial, antiviral, and anti-inflammatory. Some neem compounds are also used as insecticides, herbicides, and/or antifeedants. The safety of these compounds is not always taken into consideration and few in vivo toxicity studies have been performed. The current study is a literature review of the latest in vivo toxicity of *A. indica*. It is divided into two major sections- aquatic animals toxicity and mammalian toxicity- each related to neem's application as a pesticide or a potential new therapeutic drug, respectively.

Anticancer Effects

Pharmacoinformatics and molecular dynamics simulation-based phytochemical screening of neem plant against human cancer by targeting MCM7 protein

Ahammad F, Alam R, Mahmud R, Akhter S, Talukder EK, Tonmoy AM, Fahim S, Al-Ghamdi K, Samad A, Qadri I.

Brief Bioinform. 2021. PMID: 33834183

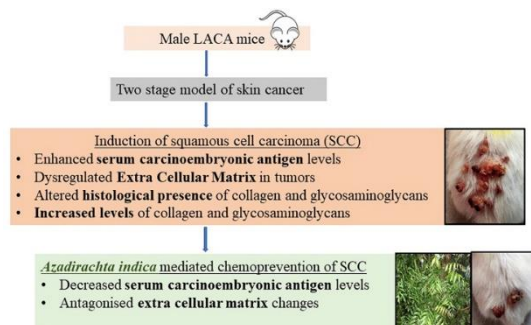
Using molecular docking simulation method, seventy phytochemicals were retrieved and screened from the neem tree against minichromosome maintenance complex component 7 (MCM7) protein, a replication protein overexpressed in several malignant tumours. Based on their binding affinities, four small molecule compounds were identified by molecular docking as potential drug candidates to target MCM7 protein in aggressive malignancies. Analysis of ADMET properties revealed the efficacy and safety, while MD simulations approach on protein-ligand complex structure confirmed the stability of the selected four compounds. These in silico studies provide leads for validation of these compounds as anticancer agents that target the MCM7 protein.

Neem leaf extract modulates extracellular matrix components in murine skin cancer

Chugh NA, Koul A.J

Tradit Complement Med. 2020;11(3):197-208. PMID: 34012866

The modulatory effects of aqueous *Azadirachta indica* leaf extract (AAILE) on extracellular matrix (ECM) components in carcinogen induced cutaneous squamous cell carcinoma (SCC) in mice was explored. Administration of AAILE to 7,12-dimethylbenz(a)anthracene (DMBA) + 12-O-tetradecanoyl phorbol-13-acetate (TPA) treated animals caused a decrease in collagen, glycosaminoglycans and serum CEA levels. AAILE administration antagonised tumor associated ECM alterations which may be contributing to its chemopreventive activity.



Neem leaf glycoprotein inhibits myeloid-derived suppressor cells to enhance T cell immunity in melanoma

Sarkar M, Bhuniya A, Ghosh S, Sarkar A, Saha A, Dasgupta S, Bera S, Chakravarti M, Dhar S, Guha I, Ganguly N, Das T, Banerjee S, Pal S, Ghosh SK, Bose A, Baral R.

Melanoma Res. 2021;31(2):130-139. PMID: 33625102

The immunomodulator, neem leaf glycoprotein (NLGP), was observed to inhibit tumor-resident myeloid-derived suppressor cells (MDSCs) and enhance antitumor CD8+ T cell immunity. Mechanistically, NLGP-mediated rectification of T cell suppressive functions of MDSCs was associated with downregulation of the interleukin (IL)-10/signal transducer and activator of transcription 3 (STAT3) signaling axis within the tumor microenvironment.

Nimbolide induces cell death in T lymphoma cells

Jaiswara PK, Gupta VK, Sonker P, Rawat SG, Tiwari RK, Pathak C, Kumar S, Kumar A. *Environ Toxicol.* 2021;36(4):628-641. PMID: 33274819

The molecular mechanisms of the antitumor potential of nimbolide, a neem limonoid against T cell lymphoma, a neoplastic disorder of thymic origin were explored. The results demonstrate that nimbolide exerts tumoricidal activity against T lymphoma cells via augmentation of apoptosis and reversal of altered cell metabolism (suppression of glycolysis and activation of oxidative phosphorylation).

Epoxyazadiradione induced apoptosis/anoikis in triple-negative breast cancer cells

Lakshmi S, Renjitha J, B Sasidhar S, Priya S.J

J Biochem Mol Toxicol. 2021;35(6):1-17. PMID: 33684251

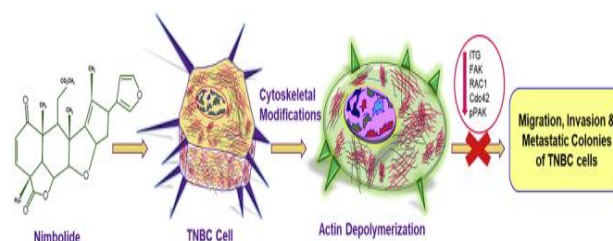
Epoxyazadiradione, a limonoid from neem targets multiple cellular events to induce growth arrest in triple-negative breast cancer cells including mitochondria-mediated apoptosis and anoikis, antimigration, inhibition of colony formation, invasion, cell cycle arrest, interference in cellular metabolism, and inhibition of nuclear factor kappa-B nuclear translocation.

Nimbolide inhibits growth and metastasis of triple-negative breast cancer

Arumugam A, Subramani R, Lakshmanaswamy R.

Mol Ther Oncolytics. 2021;20:596-606. PMID: 33768141

Nimbolide, a major bioactive compound present in neem leaves, was demonstrated to inhibit the growth, migration, invasion, and metastasis of triple-negative breast cancers that are aggressive cancers with no effective treatment options. The mechanism involved alteration of the integrin-focal adhesion kinase pathway and cytoskeletal modifications.

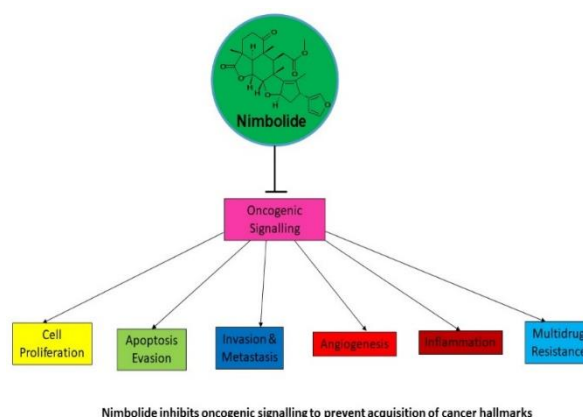


Nimbolide is a promising candidate for the anticancer drug arsenal

Nagini S, Nivetha R, Palrasu M, Mishra R.

J Med Chem. 2021;64(7):3560-3577. PMID: 33739088

Nimbolide, a major limonoid constituent of neem, has attracted increasing research attention owing to its wide spectrum of pharmacological properties, predominantly anticancer activity. Nimbolide is reported to exert potent antiproliferative effects on a myriad cancer cell lines and chemotherapeutic efficacy in preclinical animal tumor models. The potentiality of nimbolide to circumvent multidrug resistance and aid in targeted protein degradation broaden its utility in enhancing therapeutic modalities and outcome. Accumulating evidence indicates that nimbolide prevents the acquisition of cancer hallmarks such as sustained proliferation, apoptosis evasion, invasion, angiogenesis, metastasis, and inflammation by modulating kinase-driven oncogenic signaling networks in addition to influencing the epigenome. Nimbolide, with its ever-expanding repertoire of molecular targets, is a valuable addition to the anticancer drug arsenal.



Nimbolide inhibits oncogenic signalling to prevent acquisition of cancer hallmarks

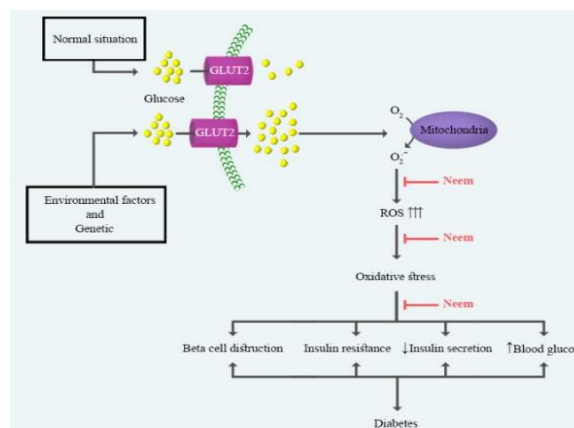
Antidiabetic & lipid lowering effects

The protective effect of *Azadirachta indica* against metabolic syndrome

Yarmohammadi F, Mehri S, Najafi N, Salar Amoli S, Hosseinzadeh H. Iran J

Iran J Basic Med Sci. 2021; 24(3):280-292. PMID: 33995939

Metabolic syndrome is a condition associated with obesity, diabetes, dyslipidemia, and high blood pressure. In this review, the protective effects of neem against the complications of metabolic syndrome with a special focus on mechanisms are discussed. Neem controls hyperglycemia and hypertension through overexpression of transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2) and antioxidant effects. Neem also reduces glucose uptake through up-regulation of glucose transporter 4 (GLUT4) and inhibition of intestinal glucosidases. The anti-hypertensive effects of neem are probably mediated via blockade of calcium channels, up-regulation of endothelial nitric oxide synthase, and extracellular signal-regulated kinases 1/2 signaling pathway. The antioxidant effects play an important role in protective mechanisms of neem against metabolic syndrome and its complications.



Gedunin, a neem limonoid suppresses hyperglycaemia induced oxidative stress

Mazumdar S, Marar T, Devarajan S, Patki J.

Biochem Biophys Rep. 2021;25:100904. PMID: 33490651

In silico findings reveal the strong binding affinity of the neem limonoid gedunin for NADPH oxidase 5 (NOX5) C terminal HSP90 binding site that disrupts NOX5 stability and its ability to generate ROS, leading to restoration of antioxidant enzymes activities. Gedunin was found to suppress hyperglycaemia induced oxidative stress in an *in vitro* RBC model and reversed glucose induced changes including haemoglobin glycosylation and lipid peroxidation. A significant restoration of activities of cellular antioxidant enzymes; superoxide dismutase, catalase and glutathione peroxidase in the presence of gedunin revealed its ability to reduce oxidative stress. These results substantiated gedunin as a bona fide inhibitor of human NOX5 and a ROS scavenging antioxidant with promising therapeutic attributes including its natural origin and inhibition of multiple diabetic targets.

Neem limonoids improve serum amylase and glucose levels in diabetic rats

Ramkumar S, Thulasiram HV, RaviKumar A.

J Food Biochem. 2021;45(4):e13674. PMID: 33634871

Limonoids from the neem tree, azadiradione and gedunin, were found to inhibit the antidiabetic target human pancreatic α -amylase in streptozotocin-induced Sprague-Dawley rats. The neem limonoids induced a significant improvement in body weight, blood glucose levels, serum amylase, and fructosamine levels as well in other serum parameters associated with diabetes with respect to liver and renal functions.

Neem exhibits lipid and uric acid suppressing properties

Mazumder T, Mamun IP, Zaman MS, Islam AKMK, Chowdhury S, Reza MS, Hussain MS.

Biochem Biophys Rep. 2021 Mar 30;26:100990. PMID: 33869811

The comparative anti-obesity efficacy of ethanolic extract of *Azadirachta indica*, *Trigonella foenum-graecum*, *Allium sativum*, and *Zingiber officinale* was investigated in high fat-induced mice. *A. indica* extract contained the highest phenolic and flavonoid content and reduced serum cholesterol, triglyceride, and uric acid than other three extracts.

Antiparasitic effects

A. indica smoke repellency against *Anopheles arabiensis* and *Aedes aegypti*

Wendimu A, Tekalign W.

Heliyon. 2021;7(7):e07373. PMID: 34258465

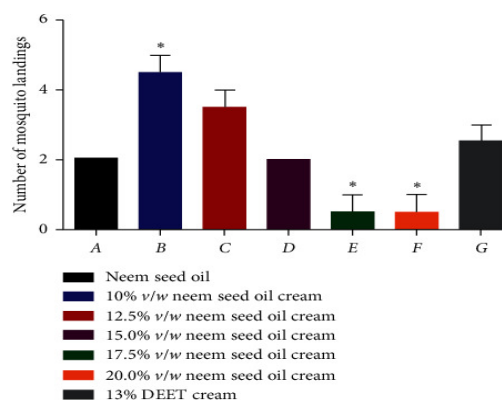
The repellency effect of smoke from burning *Azadirachta indica*, *Eucalyptus camaldulensis* and *Ocimum forskolin* plants to reduce human-mosquito biting activity was investigated. There was a 93.75% reduction of *An. arabiensis* and 92% for *Ae. aegypti*. Overall, plant mixed powders offered significant protection against both mosquito species tested and has the potential to be used as an alternative mosquito control method.

Evaluation of mosquito repellent property of neem seed oil

Aidoo O, Kuntworbe N, Owusu FWA, Nii Okantey Kuevi D.

J Trop Med. 2021;2021:5567063. PMID: 34194510

A natural mosquito repellent was formulated from the oil extracted from *Azadirachta indica*. The oil cream was formulated in concentrations of 10% v/w, 12.5% v/w, 15% v/w, 17.5% v/w, and 20% v/w. Repellency properties of the cream revealed a lasting effect on the mosquitoes. Formulations of 17.5% v/w and 20% v/w neem seed oil cream had an equal repellency effect of 87.5%, whereas the synthetic repellent had a repellency of 75%. Plant-based mosquito repellents promise a healthier approach in controlling mosquito bites, protecting the skin, and preventing malaria.



Azadirachta indica leaf fractions exert antitrypanosomal effects

Tauheed AM, Mamman M, Ahmed A, Suleiman MM, Balogun EO.

Acta Parasitol. 2021; 1-10. PMID: 34156634

Nine column chromatographic, partially purified leaf fractions of *Azadirachta indica* (AIF) were subjected to trypanosome alternative oxidase (TAO) inhibition assay using ubiquinol oxidase assay. The potent TAO inhibitors were evaluated for trypanocidal activities against *T. congolense* in rat model using in vitro, ex vivo, and in vivo assays. Only AIF1, AIF2, and AIF5 significantly inhibited TAO. AIF1 and AIF5 produced significant, dose-dependent suppression of parasite motility. Mice inoculated with 1-2 moribund parasites did not develop parasitaemia. The two fractions significantly lowered parasite burden, with the AIF5 exhibiting highest in vivo trypanocidal effects. AIF1 and AIF5 offer prospects as TAO inhibitor(s) to manage trypanosomiasis, a neglected disease of humans and livestock.

Neem silver nitrate nanoparticles exhibit potential antimalarial activity

Ghazali SZ, Mohamed Noor NR, Mustaffa KMF.

Prep Biochem Biotechnol. 2021; 1-9. PMID: 33890844

Neem-silver nitrate nanoparticles (neem-AgNPs) were synthesized using aqueous extracts of *Azadirachta indica* A. Juss for malaria therapy. The half inhibitory concentration (IC₅₀) of the synthesized neem-AgNPs showed a four-fold IC₅₀ decrease against two lab-adapted *Plasmodium falciparum* strains, 3D7 (chloroquine-sensitive), and W2 (chloroquine-resistant) compared to aqueous neem leaves extract. The results indicate that synthesized neem-AgNPs has a great potential to be used for malaria therapy.

Antiviral effects

Neem (*Azadirachta Indica* A. Juss) Capsules for Prophylaxis of COVID-19 Infection: A Pilot, Double-Blind, Randomized Controlled Trial

Nesari TM, Bhardwaj A, ShriKrishna R, Ruknuddin G, Ghildiyal S, Das A, Pandey AK, Chaudhary N, Soman G, Barde M.

Altern Ther Health Med. 2021. PMID: 33891569

A prospective, randomized, double-blind, placebo-controlled, parallel-design study was undertaken to evaluate the prophylactic effects of neem capsules on persons at high risk of COVID-19 infection (190 healthcare workers at the hospital or relatives of patients with COVID-19 infection). Of the 190 participants, 95 in the intervention group received 50 mg of a proprietary, patent-pending, neem-leaf extract orally in capsules, twice a day for 28 days while 95 in the control group were administered placebo. All the 13 subjects who tested positive during the study were asymptomatic. Of the 154 participants who completed the study per-protocol, 11 tested positive, 3 in the intervention group and 8 in the control group. The probability of COVID-19 infection in participants receiving the intervention was 0.45 times that of participants receiving the placebo, a relative risk of 0.45, with the effectiveness of the intervention being around 55%. Treatment-emergent adverse events in both groups were minimal and were of grade 1 or 2 in severity. Biomarkers and QOL remained stable in both groups. The study found a reduced risk of COVID-19 infection in participants receiving neem capsules, which demonstrates its potential as a prophylactic treatment for the prevention of COVID-19 infection. The findings warrant further investigation in clinical trials.

A computational prediction of SARS-CoV-2 structural protein inhibitors from neem

Borkotoky S, Banerjee M.

J Biomol Struct Dyn. 2021;39(11):4111-4121. PMID: 32462988

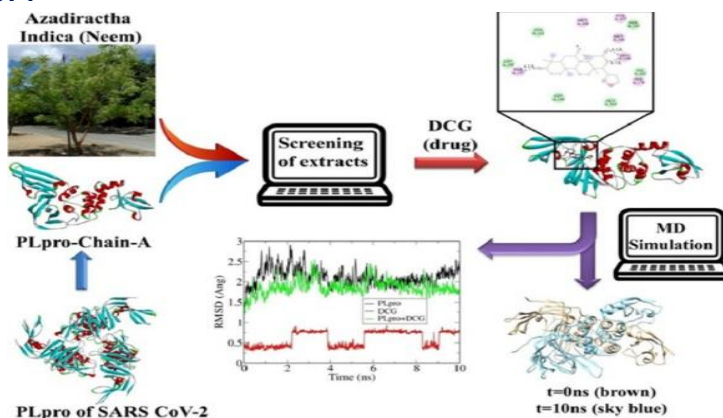
Molecular docking and simulation methods were used to virtually screen 70 compounds from *Azadirachta indica* and identify small molecule inhibitors of SARS-CoV-2 Membrane (M) and Envelope (E) proteins. A few common compounds that bind to critical regions of both structural proteins were identified.

Screening of potential drug from neem extracts for SARS-CoV-2: An insight from molecular docking and MD-simulation studies

Baidya N, Khan AA, Ghosh NN, Dutta T, Chattopadhyay AP.

J Mol Struct. 2021;1227:129390. PMID: 33041371

The inhibitory activity of Neem extracts on Papain like protease (PLpro) of the novel coronavirus SARS-CoV-2 was analysed by molecular docking and molecular dynamics simulation. Of the various compounds in neem, desacetylgedunin found in neem seed showed the highest binding affinity towards PLpro.



COVID-19, prevention and treatment with herbal medicine in the herbal markets of Salé Prefecture, North-Western Morocco

Chaachouay N, Douira A, Zidane L.

Eur J Integr Med. 2021;42:101285. PMID: 33520016

A study was conducted in Salé Prefecture, from March 1st, 2020 to May 31st, 2020 to detail ethnopharmacological information on the medicinal plant species used by 30 herbalists against coronavirus disease. In total, 20 plant species from 20 genera and 14 families had been most frequently used by herbalists for the prevention and treatment of COVID 19. The most mentioned plant was *Eucalyptus globulus*, followed by *Azadirachta indica*, and *Ziziphus lotus*. The most commonly used plant parts for herbal preparations were leaves (28.43%) and seeds (17.5%), and the majority of remedies were prepared through infusion. This study is the first contribution to the ethnopharmacological profile of this Prefecture. It is recommended that the constituents of indigenous species be studied to determine the therapeutic effects and mechanisms of action. However, attention must be paid to the conservation of medicinal species, comprehensively documenting traditional medicinal knowledge as well as conducting phytochemical validation of reported plants.

Molecular docking and ADMET studies of *Azadirachta indica* isolates as potential anti-viral drugs for Covid-19

Adegbola PI, Semire B, Fadahunsi OS, Adegoke AE.

Virus disease. 2021;32(1):1-13. PMID: 33869672

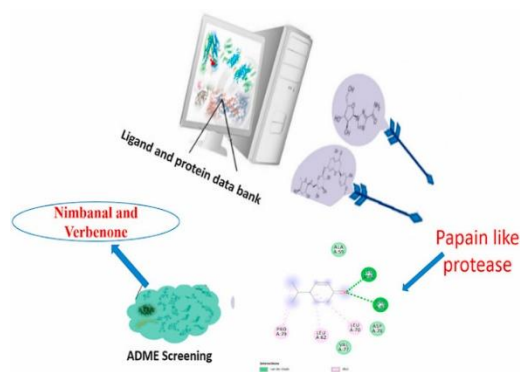
The inhibitory potential of *Azadirachta indica* and *Xylopi aethiopica* isolates against SARS-CoV-2 viral accessory proteins and the host serine protease was investigated by molecular docking and ADMET studies. Although many compounds have good binding affinity for viral and host proteins, based on the ADMET prediction, only azadironic acid, nimbionone, nimbionol and nimocinol all from *A. indica* could serve as potential drug candidates with good pharmacokinetics and toxicity profile. This study gives an insight into potential inhibitors and novel drug candidates for SARS-CoV-2. Future studies will validate azadironic acid, nimbionone, nimbionol and nimocinol against corona virus disease.

Computational prediction of nimbanal as potential antagonist of MERS-CoV

Adegbola AE, Fadahunsi OS, Alausa A, Abijo AZ, Balogun TA, Aderibigbe TS, Semire B, Adegbola PI.

Inform Med Unlocked. 2021;24:100617. PMID: 34075339

Forty-six compounds characterized from *Azadirachta indica*, *Xylopi aethiopica* and *Allium cepa* were docked against Middle East Respiratory coronavirus papain like protease (MERS-CoV-PLpro). Twenty-two of the compounds showed inhibition potential similar to dexamethasone and remdesvir. Of all the compounds, nimbanal and verbenone showed drug likeliness, they did not violate the Lipinski rule neither were they inhibitors of drug-metabolizing enzymes. Both nimbanal and verbenone were further post-scored with MM/GBSA and the binding free energy of nimbanal was comparable to that of dexamethasone. The RMSD, RMSF, torsional angle, and other analysis following simulation further substantiate the efficacy of nimbanal as an effective drug candidate for the management of severe respiratory coronavirus syndrome.



***Azadirachta indica* and *Senna siamea* decoction stimulate CD4+ and CD8+ production in HIV positive patients**

Goni Hamadama O, Leonel Javeres MN, Nyemb N, Mba Fabrice M, Manuela Elsa PT.

***J Toxicol.* 2021;2021:5594505. PMID: 34257647**

A decoction of *Azadirachta indica* and *Senna siamea* was demonstrated to stimulate the production of CD4+ and reduce toxicity caused by antiretroviral therapy (ARTs) in HIV-positive patients. A total of 297 participants aged 18-52 and HIV-positive were divided into 3 groups: Group 1 taking the decoction (250 mL twice daily for 6 months), group 2 on ARTs, and group 3 receiving both decoction and ARTs for antiretroviral (group 3). CD4+ levels were significantly increased by the decoction in group 3. ARTs (Group 2) induced hepatic and renal toxicity and oxidative stress. No signs of toxicity were detected in the other groups. Decoction of *Azadirachta indica* and *Senna siamea* stimulates production of CD4+, is not toxic and also reduces toxicity caused by ARTs.

In-vitro immunomodulatory activity of *Azadirachta indica* against HIV associated chronic CD4+ T-cell activation/exhaustion

Olwenyi OA, Asingura B, Naluyima P, Anywar GU, Nalunga J, Nakabuye M, Semwogerere M, Bagaya B, Cham F, Tindikahwa A, Kiweewa F, Lichter EZ, Podany AT, Fletcher CV, Byrareddy SN, Kibuuka H.

***BMC Complement Med Ther.* 2021;21(1):114. PMID: 33836748**

The immunomodulatory effects of *Azadirachta indica* ethanol: water mixtures against HIV associated chronic CD4+ T-cell activation/exhaustion were investigated. Peripheral blood mononuclear cells isolated from HIV negative (n = 13), viral load < 1000 copies per mL (n = 10) and viral load > 1000 copies per mL (n = 6) study participants from rural Uganda were treated with Staphylococcus enterotoxin B (SEB). Then *A. indica* extract was added to test the potential to inhibit corresponding CD4+ T cell activation. At the final concentration of 0.500 µg/mL of *A. indica*, significantly downregulated CD4 + CD38 + HLA-DR+ expression and also significantly lowered SEB induced % CD4+ T cell HLADR, PD-1 and Tim-3 levels. *A. indica* exhibited in-vitro immunomodulatory potential to inhibit the continuum of SEB induced CD4+ T-cell activation/ exhaustion without impacting general T-cell specific functions such as cytokine secretion.

Bioflavonoids from *Azadirachta indica* inhibit dengue virus serine protease

Dwivedi VD, Bharadwaj S, Afroz S, Khan N, Ansari MA, Yadava U, Tripathi RC, Tripathi IP, Mishra SK, Kang SG.

***J Biomol Struct Dyn.* 2021 Mar;39(4):1417-1430. PMID: 32107969**

Using computational and experimental approaches, the potential of bioflavonoids from *Azadirachta indica* against dengue infection was demonstrated. Molecular docking and molecular dynamics simulations identified kaempferol-3-O-rutinoside, rutin, hyperoside, and epicatechin as potent inhibitors of dengue virus (DENV) serine protease. Antiviral assay showed dose dependent inhibition of DENV-2 infectivity by the selected compounds while maximum 77.7% and 66.2% viral inhibition were recorded for 100 µM kaempferol 3-O-β-rutinoside and 1000 µM epicatechin, respectively without significant cell toxicity. These results suggest the potential of bioflavonoids from *Azadirachta indica* in the development of effective drug against dengue infection.

Orodonal Protection

Neem as root canal irrigant reduces postoperative pain and endotoxin levels

Hosny NS, El Khodary SA, El Boghdadi RM, Shaker OG.

Int Endod J. PMID: 33884661

A prospective, double-blinded, randomized controlled trial was conducted to assess the effect of Neem versus 2.5% sodium hypochlorite (NaOCl) as root canal irrigants on the intensity of postoperative pain and amount of endotoxins following root canal treatment of mandibular molars with necrotic pulps. Fifty healthy patients with mandibular molars with necrotic pulps were randomly assigned to two equal groups. In the intervention group, root canals were irrigated using Neem; whilst 2.5% NaOCl was used in the control group. Neem and 2.5% NaOCl were not significantly different in terms of reducing the intensity of postoperative pain during all follow-up periods except at 24 h following instrumentation where Neem was associated with less pain intensity. Both irrigants significantly reduced endotoxin levels but were not effective in eliminating endotoxins completely from root canals of mandibular molars with necrotic pulps.

Synergistic effect of plant extracts on endodontic pathogens isolated from teeth with root canal treatment failure

Arora S, Saquib SA, Algarni YA, Kader MA, Ahmad I, Alshahrani MY, Saluja P, Baba SM, Abdulla AM, Bavabeedu SS.

Antibiotics (Basel). 2021;10(5):552. PMID: 34065139

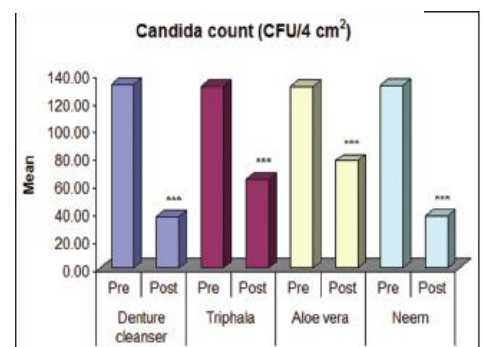
The synergistic antimicrobial activity of extracts obtained from *Salvadora persica* (Miswak), *Commiphora molmol* (myrrh) and *Azadirachta indica* (neem) in combination with commercial antimicrobial agents: penicillin, tetracycline, ofloxacin and fluconazole on endodontic pathogens isolated from teeth with root canal treatment failure such as *Enterococcus faecalis*, *Streptococcus mitis*, *Actinomyces naeslundii* and *Candida albicans* was evaluated. All the three plant extracts were effective against all the experimental pathogenic microorganisms. Maximum antimicrobial activity was displayed by *A. indica* against *Enterococcus faecalis*. Plant extracts in conjunction with various antimicrobials can be valuable aids in combating relatively resistant endodontic microorganisms leading to failure even in treatment procedures following required protocols.

Anticandidal efficacy of neem on heat polymerized acrylic resin

Ojah P, Luniyal C, Nair C, Astekar M, Pal A, Chopra M.

J Indian Prosthodont Soc. 2021;21(2):167-172. PMID: 33938866

The anticandidal efficacy of Triphala, aloe vera, Neem, and denture cleanser on heat polymerized acrylic resin was evaluated. The pre- to post-reduction in mean Candida count was found highest in Denture cleanser followed by Neem, Triphala, and aloe vera. Both Denture cleanser and Neem showed significant reduction in the mean Candida count when compared to Triphala and aloe vera. However, reduction in the mean Candida count of both Denture cleanser and Neem was found statistically similar. Neem can be used as a cost-effective anticandidal modality instead of denture cleanser.



Graph 1: Comparison of pre and post mean candida count of four groups. ***P < 0.001 - as compared to pre

Mouthwash containing neem leaf reduces gingivitis and plaque

Buakaew W, Sranujit RP, Noysang C, Sangouam S, Suphrom N, Thongsri Y, Potup P, Usuwanthim K.

***Plants (Basel)*. 2021;10(6):1153. PMID: 34204096**

Mouthwashes containing leaf extracts of the medicinal plants *Citrus hystrix* DC. (KL), *Moringa oleifera* Lam. and *Azadirachta indica* A. Juss. were assessed for oral healthcare and gingivitis adjunctive treatment on 47 subjects with gingivitis. Results showed that gingival index and plaque index, significantly decreased in participants rinsing with herbal mouthwash twice daily for two weeks compared to placebo group, with accumulative reduction percentages of both *Staphylococcus* spp. and *Candida* spp. indicating their potential as oral healthcare products.

Oral hygiene efficacy of a novel herbal toothpaste containing zinc

Nandlal B, Sreenivasan PK, Shashikumar P, Devishree G, Bettahalli Shivamallu A.

***Int J Dent Hyg*. 2021. PMID: 33866666**

A clinical investigation examined the effects of brushing with a test toothpaste containing natural ingredients i.e., Clove (*Syzygium Aromaticum*), Aloe Vera (*Aloe Barbadensis*), Amla (*Emblica Officinalis*), Neem (*Azadirachta Indica*), Tulsi (*Ocimum Basillicum*) and Honey (from *Apis Mellifera*) along with zinc salts and fluoride in comparison to a dentifrice formulated with fluoride alone on dental plaque and gingivitis over a 6-month period on 180 subjects. At 3 month and 6 month examination, the test toothpaste exhibited progressive reductions in plaque, gingival and bleeding scores as compared to control toothpaste. Routine oral hygiene with the test toothpaste formulated with herbal ingredients and zinc demonstrated a clinical adjunctive improvement in oral hygiene and parameters of gingival health as compared to brushing with a fluoride toothpaste.

Effects of a novel herbal toothpaste on salivary lactate dehydrogenase

Sreenivasan PK, Kakarla VVP, Sharda S, Setty Y.

***Clin Oral Investig*. 2021;25(5):3021-3030. PMID: 33064207**

A double-blind clinical investigation examined the effects of brushing with a test toothpaste containing natural ingredients, i.e., clove (*Syzygium aromaticum*), aloe vera (*Aloe barbadensis*), amla (*Emblica officinalis*), neem (*Azadirachta indica*), tulsi (*Ocimum basillicum*), and honey (from *Apis mellifera*), and 0.96% zinc (zinc oxide, zinc citrate) and 0.76% SMFP (1000 ppm F) in a calcium carbonate base formulated with natural ingredients (Ved Shakti, Colgate Palmolive India) and a fluoride toothpaste containing 0.76% SMFP (1000 ppm F) in a calcium carbonate base (Colgate Cavity Protection, Colgate Palmolive;) on salivary lactate dehydrogenase (LDH) as a measure of mucosal cellular integrity in conjunction with the assessments of dental plaque and gingivitis representing oral hygiene parameters. Brushing with a novel herbal toothpaste demonstrated significant reductions in salivary LDH representing improvements in cellular integrity with concurrent reductions in dental plaque and gingivitis as compared to the control dentifrice.

Neem catechin exhibits antibiofilm and anti-quorum sensing activities

Lahiri D, Nag M, Dutta B, Mukherjee I, Ghosh S, Dey A, Banerjee R, Ray RR.

***Appl Biochem Biotechnol*. 2021;193(6):1617-1630. PMID: 33496925**

Catechin obtained from the phytoextract of *Azadirachta indica* was demonstrated to inhibit dental biofilm and protect against plaque-forming bacteria. Catechin also reduced quorum sensing in *Alcaligenes faecalis* and *Pseudomonas gingivalis* dental biofilm-forming strains.

Wound Healing

Plant leaves extract irrigation on wound healing in diabetic foot ulcers

Jayalakshmi MS, Thenmozhi P, Vijayaraghavan R.

Evid Based Complement Alternat Med. 2021;2021:9924725. PMID: 34055026

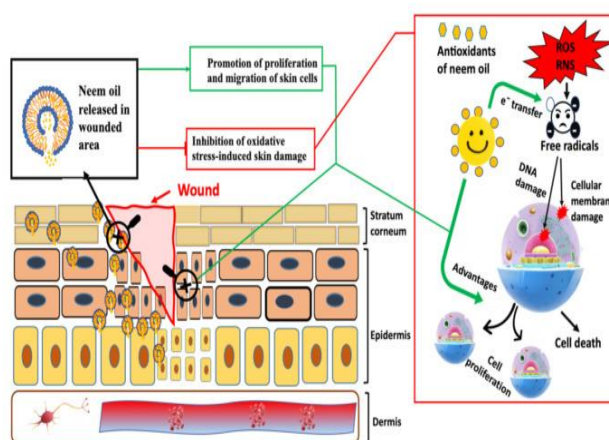
The efficacy of neem leaves extract on wound healing in diabetic foot ulcer (DFU) was evaluated. Reduction of wound healing score and other wound variables improved significantly in the neem leaves extract group. Neem leaves extract irrigation for foot ulcers is considered to be safe as it did not cause any complication. It can be used as an alternative to normal saline in managing DFU.

Neem oil loaded phospholipid vesicles to promote wound healing

Manca ML, Manconi M, Meloni MC, Marongiu F, Allaw M, Usach I, Peris JE, Escribano-Ferrer E, Tuberoso CIG, Gutierrez G, Matos M, Ghavam M.

Antioxidants (Basel). 2021;10(5):670. PMID: 33923127

Neem oil was incorporated in liposomes and hyalurosomes modified by adding argan oil and so called argan-liposomes and argan-hyalurosomes. In vitro studies using representative cells of the skin (keratinocytes and fibroblasts) underlined the ability of argan-liposomes and argan-hyalurosomes, to counteract hydrogen peroxide induced oxidative stress as well as proliferation and migration of cells ensuring rapid and even complete closure of the wound.

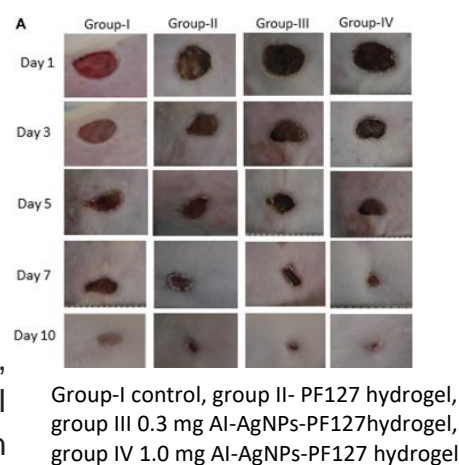


Silver nanoparticles from neem exhibit antibacterial and wound healing properties

Chinnasamy G, Chandrasekharan S, Koh TW, Bhatnagar S.

Front Microbiol. 2021;12:611560. PMID: 33679635

Azadirachta indica (AI) as an alternate source of antibiotic compounds was investigated. Aqueous extracts of leaves were used to synthesize silver nanoparticles (AI-AgNPs). The antibacterial activity of AI-AgNPs (1,000 µg/mL) was confirmed against *Bacillus cereus*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*. Higher bacterial suppression by AI-AgNPs in comparison with AI-extract was further divulged by prominent damage to the bacterial cell walls, disintegration of cell membranes and outflow of intercellular content as evident in SEM images. AI-AgNPs were loaded on PF127 (biocompatible-biodegradable polymer) to form a viscous, spreadable, hydrogel that demonstrated enhanced antibacterial properties. Application of AI-AgNPs-PF127 hydrogel on wound sites in mice, significantly increased the wound contraction rate. These studies present a simple green route to synthesize AI-AgNPs with enhanced antibacterial and free-radical scavenging efficacy; and AI-AgNPs-PF127 hydrogel as a low-toxic, eco-friendly delivery vehicle with potential in wound healing.



Other Health Effects

Nimbolide ameliorates pancreatic inflammation and apoptosis in acute pancreatitis

[Bansod S, Godugu C.](#)

Int Immunopharmacol. 2021; 90:107246. PMID: 33310297

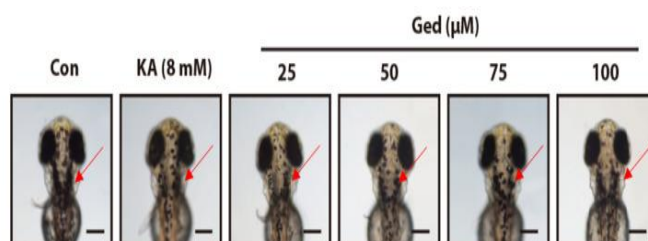
The protective effects of nimbolide on cerulein-induced pancreatic inflammation and apoptosis. Nimbolide ameliorated the severity of acute pancreatitis as shown by reducing pancreatic edema, levels of amylase, lipase, myeloperoxidase. Nimbolide suppressed pancreatic inflammation and apoptosis via SIRT1 activation.

Gedunin, a neem limonoid exhibits anti-melanogenic activity

[Jeon HJ, Kim K, Kim C, Kim MJ, Kim TO, Lee SE.](#)

Plants (Basel). 2021;10(2):330. PMID: 33572083

Gedunin, a neem limonoid was shown to exert anti-melanogenesis activity as revealed by reduction of alpha-melanocyte stimulating hormone (α -MSH) and tyrosinase activity in B16F10 mouse melanoma cells as well as in a zebrafish model for melanogenesis in vivo. Gedunin exerted anti-melanogenic effect at a much lower concentration (100 μ M) compared to the positive control, kojic acid (8 mM).



Hence, gedunin is an attractive candidate for anti-melanogenesis reagents used in the cosmetic industry for skin whitening.

Potential benefits of phytochemicals from *Azadirachta indica* against neurological disorders

[Sandhir R, Khurana M, Singhal NK.](#)

Neurochem Int. 2021;146:105023. PMID: 33753160

This review is an attempt to cover the neuroprotective properties of various phytochemicals from Neem along with their mechanism of action so that the potential of the compounds could be realized to reduce the burden of neurodegenerative diseases.

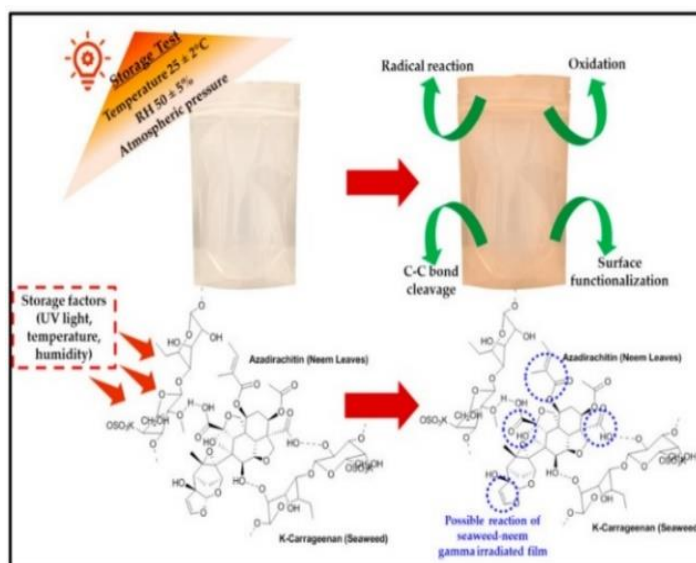
Neem: Applications in Industry

Potential use of irradiated seaweed-neem biocomposite film for packaging

Oyekanmi AA, Kumar USU, H P S AK, Olaiya NG, Amirul AA, Rahman AA, Nuryawan A, Abdullah CK, Rizal S.

Polymers (Basel). 2021;13(10):1664. PMID: 34065404

Irradiated seaweed-neem biocomposite films were synthesized and the storage functional properties investigated. Neem leaves' extracts with (5% w/w) were incorporated into the matrix of seaweed biopolymer and the bio-composite film irradiated with gamma radiation. The irradiated films exhibited improved functional properties at 1.5 kGy radiation dosage. The tensile strength, tensile modulus, and toughness increased, while the elongation decreased. The film had an optimum storage stability under ambient conditions, and the hydrophobic properties were retained until nine months of the storage period. The films displayed antimicrobial activities against *Staphylococcus aureus*, and *Bacillus subtilis* which improved after the incorporation of neem leaves extract and gamma irradiation. The fabricated irradiated seaweed-neem bio-composite film could be used as an excellent sustainable packaging material due to its effective storage stability.



Application of Azadirachta indica extract for preservation of meat products

Hamad GM, Mohdaly AAA, El-Nogoumy BA, Ramadan MF, Hassan SA, Zeitoun AM.

Appl Biochem Biotechnol. 2021. PMID: 34028665

A study conducted in Egypt subjected 75 samples of selected meat products to mycological examination and detection of aflatoxin B1 (AFB1) and ochratoxin A (OTA) residues. Aqueous neem leaf extracts, individually and in combination with *Salvia farinacea* extract, was tested on the growth of human pathogens *Aspergillus parasiticus* and *Aspergillus flavus* producing AFB1 as well as *Aspergillus ochraceus* and *Aspergillus niger* which produce OTA residues. The results confirmed the convenient and safe use of *S. farinacea* and *A. indica* extract and their combination as natural antifungal and antioxidant agents. The combined extract could be used as a natural preservative in food processing to control or prevent contamination.

Application of neem extract as meta-biomordant for cotton dyeing

Habib N, Adeel S, Ali F, Amin N, Khan SR.

***Environ Sci Pollut Res Int.* 2021 May 27. PMID: 34043165**

The demand for natural dyes has increased worldwide due to their therapeutic usage and other food, textiles, agriculture, engineering, and medical applications. Arjun bark (*Terminalia arjuna*) is a herbal natural colorant for cotton dyeing. Application of neem extract as meta-bio-mordant rendered excellent color strength besides making the coloration process more exo-friendly, viable, greener. Additionally, color strength was improved with various tonal effects from red to reddish brown shades.

Neem inhibits corrosion of carbon steel-reinforced concrete structures

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The construction industry requires novel green inhibition strategies for the conservation and protection of carbon steel-reinforced concrete structures. The effect of *Azadirachta indica* leaf extract (Neem) as a potential corrosion inhibitor of carbon steel in reinforced concrete under corrosion in saline simulated media was evaluated. The results suggest that Neem treatment did not alter the concrete integrity after different temperature conditions, slump, weight alteration, air content, compressive strength, and chloride-ions penetration. The long-term corrosion protection of 95% was reached after 182 days of evaluation. These findings open up a new promising "green" road to the conservation of carbon steel in reinforced concrete for the construction industry.

