SAFETY ISSUES & NEEM

Overview

Within certain parameters, ongoing research generally indicates that neem is not likely to cause long-term problems. Those parameters include:

- Use oil externally only
- Do not use neem at all if you are trying to conceive a child (male or female)
- Do not use neem to treat fevers in children

While several reports (detailed below) indicate that neem should be used with caution, others show no side effects even when neem products are used in large quantities or across multiple generations. The most important contraindication is for people trying to conceive a child. Although most current research focuses on using neem oil as a contraceptive, reports on neem's immunostimulatory effects seem to indicate that leaf or bark extract taken internally may make conception less likely.

The US Environmental Protection Agency has designated neem oil as GRAS, or Generally Recognized as Safe, for use in food products and exempted its typical requirement for maximum pesticide residues on agricultural products treated with neem. Other USDA research, available at the Extension Toxicology Network for using neem as a pesticide shows that it is "relatively non-toxic" and caused no significant problems even at the extraordinary high dosages fed to laboratory rats.

However, neem is relatively new in the U.S. and most people here are not familiar with it. As with any medicinal herb, it should be ingested with caution until an individual is sure that he or she will have no adverse effects.

Recent Research

Am J Ther. 2007 Jul-Aug;14(4):369-74.

Fractionated neem leaf extract is safe and increases CD4+ cell levels in HIV/AIDS patients.

Mbah AU, **Udeinya IJ**, **Shu EN**, **Chijioke CP**, **Nubila T**, **Udeinya F**, **Muobuike A**, **Mmuobieri A**, **Obioma MS**.
Department of Pharmacology and Therapeutics, College of Medicine, University of Nigeria, Enugu Campus, Enugu, Nigeria.
http://www.ncbi.nlm.nih.gov/pubmed/17667213?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The safety and effect of an acetone-water neem leaf extract (IRAB) on CD4 cells was investigated in 60 HIV/AIDS patients as part of an ongoing study to determine the influence of neem on immunity and viral load in HIV/AIDS. Patients were confirmed as HIV I or II

positive, as having CD4 cell count, less than 300 cells/microL, and as antiretrovirally naïve. They were given oral IRAB (1.0 g daily for 12 weeks). Clinical and laboratory tests were carried out at baseline and at 4 weekly intervals. Thus, the patients served as their own controls. Sixty patients completed treatment. Fifty (83.33%) were completely compliant with respect to laboratory tests. Increase in mean CD4 cells, 266 cells/microL (159%), for the 50 patients was significant ($P < 0.001$) between baseline and week 12. Erythrocyte sedimentation rate (64 mm/hr at baseline) was 16 mm/hr at week 12, whereas total number of incidences of HIV/AIDS-related pathologies decreased from 120 at baseline to 5. Mean bodyweight, hemoglobin concentration, and lymphocyte differential count increased significantly by 12% ($P < 0.05$), 24% ($P < 0.0001$), and 20% ($P < 0.0001$), respectively. There were no adverse effects and no abnormalities in kidney and liver function parameters. The results support the safety of IRAB in HIV/AIDS, and its significant influence on CD4 cells may be useful in the formulation of multidrug combination therapies for HIV/AIDS. However, its antiretroviral activity is being evaluated in our laboratory.
PMID: 17667213 [PubMed - indexed for MEDLINE]

Trans R Soc Trop Med Hyg. 2005 Oct;99(10):769-74.

Phase I safety study of Praneem polyherbal vaginal tablet use among HIV-uninfected women in Pune, India.

Joshi SN, **Katti U**, **Godbole S**, **Bharucha K**, **B KK**, **Kulkarni S**, **Risbud A**, **Mehendale S**.
National AIDS Research Institute, Epidemiology Department, MIDC, Bhosari, Pune, Maharashtra, India. sjoshi@nariindia.org
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16084547&query_hl=46&itool=pubmed_docsum

Praneem polyherbal formulations containing purified extracts of Azadirachta indica (neem tree) have shown activity against HIV and sexually transmitted disease pathogens in studies in vitro. The product also has contraceptive properties. This has prompted its development as a possible microbicide. We evaluated the safety of Praneem polyherbal tablet use among HIV-uninfected women. Twenty eligible women were enrolled in a Phase I open-label study requiring 14 days of consecutive intravaginal use of Praneem polyherbal tablets. Nine (45%) participants experienced 17 episodes of genital irritation. Transient genital itching was reported by eight (40%) participants, burning micturation by two (10%) and lower abdominal pain, genital burning and intermenstrual spotting by one (5%) each. On colposcopy, petechial haemorrhage was observed in two participants, one on day 7 and the other on day 14, and both were resolved without any treatment. There were no serious adverse events. Praneem polyherbal tablets were found to be safe for once daily intravaginal use for 14 consecutive days in sexually active HIV-uninfected women and a Phase II study may be taken up as a priority.
Publication Types: Clinical Trial, Phase I
PMID: 16084547 [PubMed - indexed for MEDLINE]

Ecotoxicol Environ Saf. 2004 Nov;59(3):332-9.

Biochemical effects of vepacide (from Azadirachta indica) on Wistar rats

during subchronic exposure.

Rahman MF, **Siddiqui MK**.
Biochemical Toxicology, Biology Division, Indian Institute of Chemical Technology, Hyderabad 500 007, India. rahman@iict.ap.nic.in
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15388273&query_hl=1&itool=pubmed_docsum

We investigated the effect of Vepacide (from Azadirachta indica), a neem-based pesticide, on acid (AcP) and alkaline (AkP) phosphatase in different tissues of male and female albino Wistar rats. Subchronic doses of Vepacide in coconut oil (80, 160, and 320 mg/kg; maximum volume of 0.2 mL) were administered orally for 45 or 90 days. The administration of Vepacide resulted in a significant increase in AcP and AkP in serum, kidney, lung, and liver tissue (AkP only in liver), whereas a significant decrease of AcP in liver was observed in male and female rats after 45 and 90 days of treatment with moderate and high doses. The alterations in serum, liver, kidney, and lung tissues of both male and female rats caused by this compound were statistically significant, and the changes were also dose and time dependent. The alterations in male rats were not statistically significant when compared with female rats, indicating that there were no sexual differences. The withdrawal study (28 days post-treatment) revealed significant recovery, indicating reversal of the toxic symptoms once the toxicant was removed. There was a high degree of positive correlation between results for serum as compared to those for kidney, lung, and liver (AkP only for liver). However, there was a high negative correlation between AcP results for serum as compared with those for liver. The alterations in these enzymes indicated that lung tissue was the most susceptible, followed by liver and kidney. AcP and AkP are marker enzymes, and their increase in serum, with parallel increases in different tissues, might be due to the increased permeability of plasma membranes. The decrease in liver AcP may be due to the necrosis of cellular tissues. The changes observed in these enzyme activities could be useful as biomarkers of exposure to Vepacide.
PMID: 15388273 [PubMed - indexed for MEDLINE]

J Ethnopharmacol. 2004 Sep;94(1):25-41.

Safety evaluation of neem (Azadirachta indica) derived pesticides.

Boeke SJ, **Boersma MG**, **Alink GM**, **van Loon JJ**, **van Huis A**, **Dicke M**, **Rietjens IM**.
Laboratory of Entomology, Wageningen University, P.O. Box 8031, 6700 EH, The Netherlands.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15261960&query_hl=46&itool=pubmed_docsum

The neem tree, Azadirachta indica, provides many useful compounds that are used as pesticides and could be applied to protect stored seeds against insects. However in addition to possible beneficial health effects, such as blood sugar lowering properties, anti-parasitic, anti-inflammatory, anti-ulcer and hepatoprotective effects, also toxic effects are described. In this study we present a review of the toxicological data from human and animal studies with oral administration of different neem-based preparations. The non-aqueous extracts appear to be the most toxic neem-based products, with an estimated safe dose (ESD) of 0.002 and 12.5 microg/kg bw/day. Less toxic are the unprocessed materials seed oil and the aqueous extracts

(ESD 0.26 and 0.3 mg/kg bw/day, 2 microl/kg bw/day respectively). Most of the pure compounds show a relatively low toxicity (ESD azadirachtin 15 mg/kg bw/day). For all preparations, reversible effect on reproduction of both male and female mammals seem to be the most important toxic effects upon sub-acute or chronic exposure. From the available data, safety assessments for the various neem-derived preparations were made and the outcomes are compared to the ingestion of residues on food treated with neem preparations as insecticides. This leads to the conclusion that, if applied with care, use of neem derived pesticides as an insecticide should not be discouraged.
Publication Types: Review
PMID: 15261960 [PubMed - indexed for MEDLINE]

Toxicology. 2004 May 20;198(1-3):83-90.

Pesticide exposure--Indian scene.

Gupta PK.
Toxicology Consulting Services Inc., C-44, Rajinder Nagar, Bareilly 243122, UP, India.
drpkg_brly@sancharnet.in
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15138033&query_hl=46&itool=pubmed_docsum

Use of pesticides in India began in 1948 when DDT was imported for malaria control and BHC for locust control. India started pesticide production with manufacturing plant for DDT and benzene hexachloride (BHC) (HCH) in the year 1952. In 1958, India was producing over 5000 metric tonnes of pesticides. Currently, there are approximately 145 pesticides registered for use, and production has increased to approximately 85,000 metric tonnes. Rampant use of these chemicals has given rise to several short-term and long-term adverse effects of these chemicals. The first report of poisoning due to pesticides in India came from Kerala in 1958 where, over 100 people died after consuming wheat flour contaminated with parathion. Subsequently several cases of pesticide-poisoning including the Bhopal disaster have been reported. Despite the fact that the consumption of pesticides in India is still very low, about 0.5 kg/ha of pesticides against 6.60 and 12.0 kg/ha in Korea and Japan, respectively, there has been a widespread contamination of food commodities with pesticide residues, basically due to non-judicious use of pesticides. In India, 51% of food commodities are contaminated with pesticide residues and out of these, 20% have pesticides residues above the maximum residue level values on a worldwide basis. It has been observed that their long-term, low-dose exposure are increasingly linked to human health effects such as immune-suppression, hormone disruption, diminished intelligence, reproductive abnormalities, and cancer. In this light, problems of pesticide safety, regulation of pesticide use, use of biotechnology, and biopesticides, and use of pesticides obtained from natural plant sources such as neem extracts are some of the future strategies for minimizing human exposure to pesticides.
PMID: 15138033 [PubMed - indexed for MEDLINE]

Chembiochem. 2004 Apr 2;5(4):408-21.

Neem--an omnipotent plant: a retrospection.

Brahmachari G.

Natural Product Laboratory, Department of Chemistry, Visva-Bharati University, Santiniketan 731235, West Bengal, India. brahmg2001@yahoo.co.in
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15185362&query_hl=46&itool=pubmed_docsum

Neem (Azadirachta indica A. Juss.) has universally been accepted as a wonder tree because of its diverse utility. Multidirectional therapeutic uses of neem have been known in India since the Vedic times. Besides its therapeutic efficacies, neem has already established its potential as a source of naturally occurring insecticide, pesticide and agrochemicals. Safe and economically cheaper uses of different parts of neem in the treatment of various diseases and in agriculture are discussed in this article. It further deals with the active chemical constituents of various neem formulations. Commercially available neem products are also mentioned along with their respective applications. Furthermore, evaluation of safety aspects of different parts of neem and neem compounds along with commercial formulations are also taken into consideration. Systematic scientific knowledge on neem reported so far is thus very useful for the wider interests of the world community.
Publication Types: Review
PMID: 15185362 [PubMed - indexed for MEDLINE]

J Basic Clin Physiol Pharmacol. 2003;14(4):387-95.

Azadirachta indica adversely affects sperm parameters and fructose levels in vas deferens fluid of albino rats.

Ghosesawar MG, **Ahamed RN**, **Ahmed M**, **Aladakatti RH**.
Post-Graduate Department of Zoology, Karnatak University, Dharwad 580 003, India.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15198309&query_hl=19&itool=pubmed_DocSum

Azadirachta indica treatment for 24 days in albino rats resulted in a decrease in the total sperm count, sperm motility, and forward velocity in vas deferens fluid. The percentage of abnormal sperm increased and the fructose content decreased. As diminished levels of fructose parallel androgen deficiency, we conclude that reduced androgen levels resulting from the anti-androgenic property of A. indica leaves probably influences the physiological maturation of sperm.
PMID: 15198309 [PubMed - indexed for MEDLINE]

Life Sci. 2002 Nov 1;71(24):2845-65.

Gastroprotective effect of Neem (Azadirachta indica) bark extract: possible involvement of H(+)-K(+)-ATPase inhibition and scavenging of hydroxyl radical.

Bandyopadhyay U, **Biswas K**, **Chatterjee R**, **Bandyopadhyay D**, **Chattopadhyay I**, **Ganguly CK**, **Chakraborty T**, **Bhattacharya K**, **Banerjee RK**.
Department of Physiology, Indian Institute of Chemical Biology, 4, Raja S. C. Mullick road, Kolkata 700032, India.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12377267&query_hl=46&itool=pubmed_docsum

The antisecretory and antiulcer effects of aqueous extract of Neem (Azadirachta indica) bark have been studied along with its mechanism of action, standardisation and safety evaluation. The extract can dose dependently inhibit pylorus-ligation and drug (mercaptomethylimidazole)-induced acid secretion with ED(50) value of 2.7 and 2 mg Kg(-1) b.w. respectively. It is highly potent in dose-dependently blocking gastric ulcer induced by restraint-cold stress and indomethacin with ED(50) value of 1.5 and 1.25 mg Kg(-1) b.w. respectively. When compared, bark extract is equipotent to ranitidine but more potent than omeprazole in inhibiting pylorus-ligation induced acid secretion. In a stress ulcer model, it is more effective than ranitidine but almost equipotent to omeprazole. Bark extract inhibits H(+)-K(+)-ATPase activity in vitro in a concentration dependent manner similar to omeprazole. It offers gastroprotection against stress ulcer by significantly preventing adhered mucus and endogenous glutathione depletion. It prevents oxidative damage of the gastric mucosa by significantly blocking lipid peroxidation and by scavenging the endogenous hydroxyl radical ((z.rad;)OH)-the major causative factor for ulcer. The (z.rad;)OH-mediated oxidative damage of human gastric mucosal DNA is also protected by the extract in vitro. Bark extract is more effective than melatonin, vitamin E, desferrioxamine and alpha-phenyl N-tert butylnitrone, the known antioxidants having antiulcer effect. Standardisation of the bioactive extract by high pressure liquid chromatography indicates that peak 1 of the chromatogram coincides with the major bioactive compound, a phenolic glycoside, isolated from the extract. The pharmacological effects of the bark extract are attributed to a phenolic glycoside which is apparently homogeneous by HPLC and which represents 10% of the raw bark extract. A single dose of 1g of raw extract per kg b.w. (mice) given in one day and application of 0.6g raw extract per kg b.w. per day by oral route over 15 days to a cumulative dose of 9g per kg was well tolerated and was below the LD(50). It is also well tolerated by rats with no significant adverse effect. It is concluded that Neem bark extract has therapeutic potential for the control of gastric hyperacidity and ulcer.
PMID: 12377267 [PubMed - indexed for MEDLINE]

Aquat Toxicol. 2002 Mar;56(4):257-73.

Community-level disruptions among zooplankton of pond mesocosms treated with a neem (azadirachtin) insecticide.

Kreutzweiser DP, **Back RC**, **Sutton TM**, **Thompson DG**, **Scarr TA**.
Canadian Forest Service, Great Lakes Forestry Centre, Sault Sainte Marie, Ont., Canada.
dkreutzw@nrcan.gc.ca
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11856575&query_hl=46&itool=pubmed_docsum

A natural, plant-derived insecticide, neem, is being evaluated as an alternative insect pest control product for forestry in Canada. As part of the process to investigate the environmental safety of neem-based insecticides, a mesocosm experiment was conducted to assess the effects of neem on natural zooplankton communities. Replicate (n=5), shallow (<1 m) forest pond enclosures were treated with Neemix 4.5, at concentrations of 0.035 (the expected

environmental concentration), 0.18, 0.70, and 1.75 mg/l active ingredient, azadirachtin. Zooplankton communities were quantitatively sampled over a 4-month experimental period in treated and control enclosures, and water samples were collected to track azadirachtin concentrations. Concentrations in water declined linearly with estimated DT(50) values of 25-29 days. Trends in abundance over time among populations of cladocerans, copepods, and rotifers were found to differ significantly among treatments. At the two highest test concentrations, adverse effects were obvious with significant reductions in several cladoceran species, and near elimination of the three major copepod species present. More subtle effects at the two lowest test concentrations were determined by comparing the community structure of enclosures across treatment levels and over time through an analytical process based on the multivariate statistical software, PRIMER. Significant effects on community structure were detected at both of these lower concentrations, including the expected environmental concentration of 0.035 mg/l azadirachtin. Differential responses among species (some increases, some decreases) caused detectable disruptions in community structure among zooplankton of treated enclosures. Perturbations to zooplankton communities were sufficient to cause measurable differences in system-level metabolism (midday dissolved oxygen concentrations) at all but the lowest test concentration.
PMID: 11856575 [PubMed - indexed for MEDLINE]

Phytother Res. 2002 Mar;16(2):122-6.

LDH profiles of male and female rats treated with Vepacide.

Rahman MF, **Siddiqui MK**, **Jamil K**.
Biochemical Toxicology, Biology Division, Indian Institute of Chemical Technology, Hyderabad 500 007, India.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11933112&query_hl=1&itool=pubmed_DocSum

In the present study we investigated the effect of vepacide, a neem-based compound, on the biochemical target enzyme lactate dehydrogenase (LDH) in different tissues of male and female albino Wistar rats treated orally with 80, 160 and 320 mg/kg (low, medium and high doses, respectively) for a period of 90 days. Prolonged administration of vepacide caused a significant increase of LDH activity in serum and lung tissues and a decrease in liver and kidney in both male and female rats when measured after 45 and 90 days of daily treatment. Females were more susceptible than males with regard to serum and kidney LDH showing sexual dimorphism in the treated rats. Recovery was observed in the affected enzyme after 28 days post treatment (withdrawal study). A positive correlation was observed with regard to this enzyme between serum and lung tissues, whereas for serum versus liver and kidney there was a negative correlation. The effect of vepacide was more pronounced in the lung tissue followed by liver and kidney tissues. Necrosis of the liver and kidney tissues was observed but in the lung tissue an increase in the LDH enzyme was seen. Therefore, it was concluded that the increase in LDH could be indicative of a stress adaptive response to the toxicant.
PMID: 11933112 [PubMed - indexed for MEDLINE]

Food Chem Toxicol. 2001 May;39(5):477-83.

Azadirachtin, a neem biopesticide: subchronic toxicity assessment in rats.

Raizada RB, **Srivastava MK**, **Kaushal RA**, **Singh RP**.
Pesticide Toxicology Laboratory, Industrial Toxicology Research Centre, Post Box No. 80, M.G.Marg, -226001, Lucknow, India. intox@itrc.sirnetd.emet.in
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11313114&query_hl=46&itool=pubmed_docsum

Azadirachtin, a biopesticide obtained from neem, was subjected to subchronic toxicological testing to document its safety for use as a pesticide. Azadirachtin technical 12% orally administered to male and female rats at doses of 500, 1000 and 1500 mg/kg/day for 90 days did not produce any signs of toxicity, mortality, changes in tissue weight, pathology and serum and blood parameters. It can be suggested that azadirachtin at the highest dose tested is well tolerated by rats of both sexes. The highest dose, 1500 mg/kg, can be used as a basal dose for the determination of the no-observed-effect level (NOEL) of azadirachtin to calculate its safety margin.
PMID: 11313114 [PubMed - indexed for MEDLINE]

Hum Exp Toxicol. 2001 May;20(5):243-9.

Effects of Vepacide (Azadirachta indica) on aspartate and alanine aminotransferase profiles in a subchronic study with rats.

Rahman MF, **Siddiqui MK**, **Jamil K**.
Biology Division, Indian Institute of Chemical Technology, Hyderabad.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11476156&query_hl=1&itool=pubmed_DocSum

The aim of this study was to ascertain the long-term effects of Vepacide, a neem-based pesticide on biochemical profiles. Albino Wistar rats were treated orally with 80 (low), 160 (medium) and 320 mg/kg (high) doses of Vepacide in coconut oil for 90 days. Control rats received the same volume of the vehicle. Vepacide caused increase of aspartate and alanine aminotransferase in serum, kidney and lung, and these enzymes decreased in liver in both male and female rats when measured after 45 and 90 days of treatment. The two-way analysis of variance (ANOVA) showed that the alterations in these enzymes were dose- and time-dependent. Sexual dimorphism was observed when male rats were compared with female rats (Student t-test at $P < 0.05$). Positive correlation was observed with regard to these enzymes between serum, kidney and lung, whereas in the case of serum and liver, a negative correlation was recorded. These enzyme profiles elucidate that they increased in serum with simultaneous decrease in liver, indicating necrosis of liver, whereas in other tissues, the level of enzymes increased, showing an adaptive mechanism due to the chemical stress. The affected enzymes were recovered to normal conditions after 28 days of post-treatment (withdrawal study). Due to the Vepacide treatment, lung was more affected followed by liver and kidney. This study has indicated that these enzymes could be useful as biomarkers for the insult of any toxicant. Besides, they can also help in predictive toxicology.
PMID: 11476156 [PubMed - indexed for MEDLINE]

Cytobios. 2001;106 Suppl 2:151-64.

Genotoxicity of a crude leaf extract of neem in male germ cells of mice.

Awasthy KS.
Department of Zoology, K.K.M. College, Pakur, India.
http://www.ncbi.nlm.nih.gov/pubmed/11545443?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The oral administration of a soxhlated crude ethanolic extract of leaves of neem (Azadirachta indica Ajuss; family Meliaceae) to adult male mice for 6 weeks (one spermatogenic duration) at the rate of 0.5, 1.0 or 2.0 g/kg body weight per day increased the incidences of structural changes and synaptic-disturbances in meiotic chromosomes and also caused more disruptions of meiosis. The extract reduced the sperm count and increased the frequency of spermatozoa with abnormal head morphology. It is suggested that at least one of the constituents of the extract may have interfered with the DNA. The result was chromosome strand breakages, or spindle disturbances, and the regulation of genes responsible for sperm shaping was affected.
PMID: 11545443 [PubMed - indexed for MEDLINE]

Pharmacol Res. 2000 Apr;41(4):419-22.

How safe is neem extract with respect to thyroid function in male mice?

Panda S, **Kar A**.
School of Life Sciences, Vigyan Bhawan, Khandwa Road, Indore, 452 017, India.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10704265&query_hl=1&itool=pubmed_DocSum

In this investigation we attempted to find out the hitherto unstudied adverse effects of neem (Azardirachta indica) leaf extract on the thyroid function of male mice. Neem leaf extract was orally administered in two different doses (40 mg and 100 mg kg(-1)day(-1)for 20 days). The extract exhibited differential effects. While the higher dose decreased serum tri-iodothyonine (T(3)) and increased serum thyroxine (T(4)) concentrations, no significant alterations of levels were observed in the lower dose group, indicating that the high concentrations of neem extract can be inhibitory to thyroid function, particularly in the conversion of T(4)to T(3), the major source of T(3)generation. A concomitant increase in hepatic lipid peroxidation (LPO) and a decrease in glucose-6-phosphatase (G-6-Pase) activity in the higher dosed group also indicated the adverse effect of neem extract despite an enhancement in the activities of two defensive enzymes, superoxide dismutase (SOD) and catalase (CAT). Thus, it appears that the higher concentration of neem extract may not be safe with respect to thyroid function and lipid peroxidation.
PMID: 10704265 [PubMed - indexed for MEDLINE]

Immunol Cell Biol. 1997 Apr;75(2):190-2.

Plant immunomodulators for termination of unwanted pregnancy and for contraception and reproductive health.

Talwar GP, **Raghuvanshi P**, **Misra R**, **Mukherjee S**, **Shah S**.

Reproductive Health and Vaccinology Division, International Centre for Genetic Engineering and Biotechnology, Aruna Asaf Ali Marg, New Delhi, India.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9107574&query_hl=46&itool=pubmed_docsum

Neem (Azadirachta indica) seed and leaf extracts have spermicidal, anti-microbial, anti-fungal and anti-viral properties. They are also immunomodulators that induce primarily a TH1 type response. These properties are being exploited to develop two different useful methods of fertility control. Neem extracts given orally at early post-implantation stage terminate pregnancy in rodents and primates. Treatment has no residual permanent effect and fertility is regained in subsequent cycles. The mechanism by which the action occurs is not fully clear. A transient increase in CD4 and more significantly in CD8 cells is noticed in mesenteric lymph nodes and spleen. A rise in immunoreactive and bioactive TNF-alpha and IFN-gamma in draining lymph nodes, serum and foetal-placental tissue is observed. A polyherbal cream and pessary have been developed containing three active ingredients of plant origin. These have synergistic spermicidal properties on human sperm as determined by the Sander Cramer test. Their use before mating has high contraceptive efficacy in rabbits and baboons. Another interesting property is their inhibitory action on a wide spectrum of micro-organisms, including Candida albicans, C. tropicalis, Neisseria gonorrhoeae, the multidrug-resistant Staphylococcus aureus and urinary tract Escherichia coli, Herpes simplex-2 and HIV-1. Phase I clinical trials have been completed in India, Egypt and the Dominican Republic, and indicate the safety of the formulation, its acceptability and beneficial action invaginosis due to infections.
PMID: 9107574 [PubMed - indexed for MEDLINE]

J Pharmacol Exp Ther. 1996 Sep;278(3):1000-5.

The mitochondrial permeability transition: a new pathophysiological mechanism for Reye's syndrome and toxic liver injury.

Trost LC, **Lemasters JJ**.
Department of Cell Biology & Anatomy, School of Medicine, University of North Carolina at Chapel Hill, USA.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=8819478&query_hl=1&itool=pubmed_DocSum

Aspirin, Neem oil, valproic, adipic, benzoic, isovaleric, 3-mercaptopropionic and 4-pentenoic acids are implicated in the pathogenesis of Reye's syndrome, Jamaican vomiting sickness, and related chemical toxicities. These disorders are characterized by hyperammonemia, hypoglycemia, microvesicular steatosis and encephalopathy. The goal of this study was to determine whether chemicals implicated in Reye's-related disorders induce the mitochondrial permeability translation (MPT). The MPT is induced by opening of a high-conductance, cyclosporin-sensitive pore in the mitochondrial inner membrane, causing swelling, depolarization and uncoupling of oxidative phosphorylation. In freshly isolated rat liver mitochondria, unhydrolyzed aspirin (300 microM) did not induce the MPT in the presence of 50 microM CaCl2. Salicylate, the hydrolysis product of aspirin and its active metabolite, was much more potent causing dose-dependent onset of the MPT in a therapeutic range of

concentrations (37.5-300 microM). Similarly, Neem oil and valproic, adipic, benzoic, isovaleric, 3-mercaptopropionic and 4-pentenoic acids induced onset of the MPT. In all cases, cyclosporin A (200 nM), a specific inhibitor of the permeability transition pore, blocked the MPT caused by these inducers. Induction of the MPT by these agents was not caused by mitochondrial depolarization because concentrations of valproic acid and salicylate inducing the MPT had little effect on mitochondrial delta psi. Moreover, equivalent uncoupling caused by 5 nM carbonyl cyanide p-trifluoromethoxyphenylhydrazone did not induce an MPT. These data suggest that induction of the MPT is a common pathophysiological mechanism causing mitochondrial injury in Reye's syndrome and Reye's-related drug toxicities.
PMID: 8819478 [PubMed - indexed for MEDLINE]

Indian J Malariol. 1996 Sep;33(3):139-43.

Preliminary evaluation of safety aspects of neem oil in kerosene lamp.

Valecha N, **Ansari MA**, **Prabhu S**, **Razdan RK**.
Malaria Research Centre (ICMR), Delhi, India.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9014397&query_hl=46&itool=pubmed_docsum

Kerosene lamps containing one per cent neem oil were used for mosquito repellent action in a village near Delhi. The safety aspects of this personal protection method developed by Malaria Research Centre were evaluated by animal studies and clinical examination of population before and after exposure. Single application of neem oil (1%) did not produce skin irritation in rabbits and adverse effect on guinea pigs after exposure to aerosol. Clinical examination of 156 adults and 110 children did not reveal any major adverse effects after one year of exposure to 1% neem oil.
PMID: 9014397 [PubMed - indexed for MEDLINE]

Indian J Med Res. 1995 Aug;102:66-70.

Safety of intrauterine administration of purified neem seed oil (Praneem Vilci) in women & effect of its co-administration with the heterospecies dimer birth control vaccine on antibody response to human chorionic gonadotropin.

Talwar GP, **Pal R**, **Singh O**, **Garg S**, **Taluja V**, **Upadhyay SN**, **Gopalan S**, **Jain V**, **Kaur J**, **Sehgal S**.
International Centre for Genetic Engineering & Biotechnology, New Delhi.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=8834816&query_hl=46&itool=pubmed_docsum

Praneem Vilci (PV), purified neem oil was reported to exercise a reversible antifertility effect after a single intrauterine instillation in rodents and primates without any adverse effects. After toxicology, drug regulatory and ethical clearances, a phase I clinical trial was conducted on PV. Eighteen healthy tubectomised women were enrolled to evaluate the safety of a single intrauterine instillation of PV and to determine the effect of its co-administration on anti-hCG response to the heterospecies dimer (HSD) hCG vaccine. Eight women received PV alone and ten women were given the HSD-hCG vaccine in addition. Base-line and post-treatment

haematological and biochemical profiles were determined as also the mid-luteal serum progesterone. Endometrial biopsies were examined to assess ovulatory status and the effect of intrauterine treatment with PV on the endometrium. Anti-hCG antibody titres were estimated in women who were concurrently immunized with the HSD vaccine. No untoward reaction was observed in any woman. Menstrual pattern and ovulatory status remained unaltered. Endometrial biopsy after PV instillation in one woman showed non-specific endometritis but she remained asymptomatic. Mild eosinophilia was seen in two women and this reverted to normal on its own. All women receiving PV and the HSD vaccine generated antibodies against hCG. Our data show that intrauterine administration of PV is safe and does not prevent the antibody response to HSD-hCG vaccine.
Publication Types: Clinical Trial Controlled Clinical Trial
PMID: 8834816 [PubMed - indexed for MEDLINE]

West Indian Med J. 1994 Sep;43(3):71-4.

Effect of aqueous neem (Azadirachta indica) extract on testosterone and other blood constituents in male rats. A pilot study.

Parshad O, **Singh P**, **Gardner M**, **Fletcher C**, **Rickards E**, **Choo-Kang E**.
Department of Physiology, U.W.I., Jamaica.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=7817539&query_hl=19&itool=pubmed_DocSum

Effect of oral administration of crude aqueous neem extract on serum testosterone and other blood constituents was studied in the male Wistar rats for 10 weeks. The neem treatment resulted in significant decreases ($p < 0.01$) in total testosterone, total bilirubin and K+ in serum. There were also increases ($p < 0.05$) in packed cell volume, mean corpuscular haemoglobin concentration, red blood cell, white blood cell and lymphocyte counts without showing any cytotoxic effects in the body.
PMID: 7817539 [PubMed - indexed for MEDLINE]

Food Chem Toxicol. 1993 Apr;31(4):297-301.

Toxicological studies on debitterized Neem oil (Azadirachta indica).

Chinnasamy N, **Harishankar N**, **Kumar PU**, **Rukmini C**.
National Institute of Nutrition, Indian Council of Medical Research, Jamai-Osmania, Hyderabad.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=8477918&query_hl=19&itool=pubmed_DocSum

Azadirachta indica, popularly known as 'Neem' in India, is widely grown all over the tropics. The seed contains 45% oil and is a minor oil of considerable potential. Neem oil is bitter and inedible. Recently, a method has been developed to completely remove the bitter and odoriferous principles and leave a bitterless, odourless and colourless oil. The nutritional and chemical evaluation of debitterized neem oil (NO) was reported earlier (C. Rukmini, Food Chemistry 1987, 26, 119). We report here a three-generation study, carried out according to WHO/FDA protocol in groups of 15 male and 15 female rats fed a diet containing 10% NO or

groundnut oil (GNO). Reproductive toxicology was monitored for three generations. The results obtained in both the matings in all the three generations did not show any adverse effects on the reproductive parameters studied in rats fed NO and were similar to those observed in rats fed GNO. The mean organ weights and the histopathological evaluation of all the organs were similar to those of the control (GNO-fed) rats. A mutagenicity test of NO was also found to be negative in Ames test as reported earlier (K. Polasa and C. Rukmini, Food and Chemical Toxicology 1987, 25, 763). These studies indicate that NO devoid of all the bitter and odoriferous principles, may be recommended as safe for consumption by humans.
PMID: 8477918 [PubMed - indexed for MEDLINE]

Singapore Med J. 1990 Oct;31(5):463-5.

Margosa oil poisoning as a cause of toxic encephalopathy.

Lai SM, **Lim KW**, **Cheng HK**.
Department of Paediatrics, Tan Tock Seng Hospital, Singapore.http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=2259944&query_hl=19&itool=pubmed_DocSum

Margosa Oil is an extract of the seed of the Neem tree and is widely used as a traditional medicine by Indians in India, Sri Lanka, Burma, Thailand, Malaysia and Indonesia. Used mainly for external applications, it is often administered orally to neonates and infants regularly in small amounts. Margosa Oil causes toxic encephalopathy particularly in infants and young children. The usual features are vomiting, drowsiness, tachypnea and recurrent generalised seizures. Leucocytosis and metabolic acidosis are significant laboratory findings. Management is aimed primarily towards the control of convulsions although supportive management is equally important. Prognosis is usually good but fatalities and neurological deficits have been reported. We report here two infants with Margosa Oil poisoning presenting with encephalopathy.
PMID: 2259944 [PubMed - indexed for MEDLINE]

Acta Paediatr Jpn. 1990 Aug;32(4):462-8.

Evaluation of the possible role of glucose, carnitine, coenzyme Q10 and steroids in the treatment of Reye's syndrome using the margosa oil animal model.

Sinniah D, **Sinniah R**, **Baskaran G**, **Pathmanathan R**, **Yamashita F**, **Yoshino M**.
Department of Paediatrics, Faculty of Medicine, University of Malaya, Kuala Lumpur.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=2288230&query_hl=1&itool=pubmed_DocSum

Glucose and steroids have been used in the treatment of children with Reye's syndrome, while carnitine and coenzyme Q10 have been the subject of some recent studies which suggest that these agents may have a role in the treatment of Reye's syndrome and Reye-like syndrome due to margosa oil poisoning. Because of the paucity of causes of Reye's syndrome seen at any one centre, the clinical variability of the disease, and limited knowledge of definite aetiologic factors, controlled clinical trials are not easy to carry out or to interpret in human cases. These caveats were overcome by evaluation of these four treatment modalities in an established

margosa-oil-induced animal model of Reye's syndrome. Effectiveness of the treatment modalities was determined from clinical response and histopathologic parameters (grading of light microscopic fatty changes and ultrastructural changes in the hepatocytes). Results show that carnitine per se produces a small improvement in survival, but statistically, more significant benefit is seen with glucose administration. Carnitine plus 10% dextrose appears to produce better results. Evaluation of coenzyme Q10 and carnitine on histopathologic parameters in the liver after a sublethal dose of margosa oil showed no obvious ameliorating effect on liver pathology. Steroids (dexamethasone/methylprednisolone) had no beneficial effects in reducing mortality, affecting glycogen storage or lipid accumulation. Changes in the mitochondria, ribosomes and endoplasmic reticulum were unaltered from the groups treated with margosa oil alone. While glucose and carnitine supplements appear to be beneficial, the other modes of therapy do not seem to hold much promise in the treatment of Reye-like syndrome in the margosa-oil-induced animal model.
PMID: 2288230 [PubMed - indexed for MEDLINE]

Newsl Inter Afr Comm Tradit Pract Affect Health Women Child. 1990 May;(9):10.

Ritual hot baths (wankan-jego) in Zaria, Nigeria.

Mabogunje OA.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12157981&query_hl=46&itool=pubmed_docsum

PIP: Among the Hausa-Fulani women of Zaria, Nigeria, "cold" or "sanyi" is thought to be a common cause of illnesses, and especially edema (swelling) during pregnancy. The traditional treatment for these illnesses is a hot bath. The new mother or mother-to-be sleeps in an overheated room and must take baths in very hot water, called "wankan- jego," to keep out the cold. The birth attendant uses a bundle of leafy twigs from tamarind or neem trees to splash hot water over the women's body. This splashing hides the real temperature of the hot water over the women's body. This splashing hides the real temperature of the hot water so that she does not feel it, but it may actually be 82 degrees centigrade. Severe scalds often result from, such baths. Women confined during childbirth in the hospital and then discharged are still often subjected to the "wakan-jego" after they return home. Their thighs, buttocks and breasts are the most susceptible areas where these hot-water scald burns are the worst, sometimes even resulting in their nipples being sloughed off, thus making the mother unable to lactate. Since most deliveries in the Zaria region still take place at home and most patients with childbirth complications come to the hospital only as a last resort, it is possible that scald injuries are underreported and the total morbidity and mortality rate may be much higher, both of mothers and babies. Understanding this cultural ritual is necessary to devise effective countermeasures, like encouraging hand testing the bath water for its safety before commencing the baths. Better still, since all the scalded patients in the groups studied were illiterate housewives, formal education could disprove the need for these traditional and harmful hot baths to chase away the "cold" that has been falsely believed to be the cause of childbirth illnesses. [full text]
PMID: 12157981 [PubMed - indexed for MEDLINE]

J Ethnopharmacol. 1989 May;25(3):281-93.

Biochemical and histological studies of reproductive organs in cyclic and ovariectomized rats supporting a non-hormonal action for neem oil.

Tewari RK, Pathak S, Prakash AO.
Laboratory of Reproductive Biology, School of Studies in Zoology, Jiwaji University, Gwalior, India.

Subcutaneous administration of neem oil to cyclic rats caused significant damage to the luminal epithelium of the uterus and to the uterine glands. It also decreased glycogen and total protein contents in the ovary and uterus, while the activity of acid phosphatase in these organs was increased significantly. Studies in ovariectomized rats revealed that the administration of neem oil decreased protein and glycogen content and increased acid phosphatase activity in the uterus whereas its conjoint administration with estradiol dipropionate or progesterone did not cause significant changes relative to those seen with the steroids per se. Histological studies in ovariectomized rats also supported the relatively inert action of neem oil when given with hormones. It was concluded that the histological and biochemical alterations observed were due to the toxicological potential of the neem oil rather than to hormonal properties.
PMID: 2747262 [PubMed - indexed for MEDLINE]