THE LIVER & NEEM

Overview

Throughout its long history, neem has often been recommended as blood cleanser. The truth of the matter may be it that helps protect the liver from damage, which in turn helps cleanse blood. The studies detailed below are extremely complex, but appear to indicate that neem boosts levels of protective enzymes and decreases level of damaging chemicals, perhaps by functioning as an antioxidant.

Liver weight and function also are often used as the "canary in the mine" to test for adverse effects of chemical compounds and drugs. The largest single gland in the body and the second-largest organ, the liver filters about a quart of blood every minute, detoxifying blood by filtering toxins and other chemicals from it. When possible, it converts toxics to less harmful chemicals through various reactions that typically create free radicals. Antioxidants, like those found in neem as well as vitamins C and E and other natural carotenoids, neutralize the free radicals to prevent damage to the liver (see separate section on antioxidants).

Neem leaf appears to minimize chemically induced liver damage in rats, stabilizing serum levels of serum marker enzymes. Livers of sacrificed rats pretreated with neem leaf show normal lobular structure with minimum damage from the paracetamol. Additionally, many of these reports tie back to cancer, particularly mestasizing cancer, because the liver is often the first organ to be affected. It also plays a key role in controlling cancer, producing critical enzymes like glutathione and other antioxidants.

From a user's perspective, the only report which noted any damage to the liver was a series of tests on subchronic use of a pesticide made of neem oil (which is not recommended for internal use) at extremely high levels, up to 320 mg per kilogram. It also noted that all major organs significantly recovered once the toxins were removed. Optimum dosages for neem in human beings have not been established and large quantities are likely to adversely impact its immunostimulatory 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.

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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]

Food Chem Toxicol. 2007 Mar;45(3):465-71. Epub 2006 Oct 1.

Lack of toxic effect of technical azadirachtin during postnatal development of rats.

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http://www.ncbi.nlm.nih.gov/pubmed/17084955?ordinalpos=4&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

Azadirachtin, a biopesticide has been evaluated for its possible toxic effects during postnatal development of rats over two generations. Rats were fed 100, 500 and 1000ppm technical azadirachtin through diet which is equivalent to 5, 25 and 50mg/kg body weight of rats. Technical azadirachtin has not produced any adverse effects on reproductive function and data were comparable to control animals over two generations. There were no toxicological effect in parent rats as evidenced by clinical signs of toxicity, enzymatic parameters like AST, ALT, ALP, S. bilirubin, S. cholesterol, total protein and histopathology of liver, brain, kidney and testes/ovary. The litters of F(1B) and F(2B) generations were devoid of any morphological, visceral and teratological changes. The percent cumulative loss and growth index of pups were also comparable to respective controls in successive growth period of 0, 4, 7, 14 and 21 days in two generations. There were no major malformations in fetuses while some insignificant minor skeletal variations like missing 5th sternebrae and bipartite thoracic centre found were not compound or dose related. No significant pathomorphological changes were observed in liver, kidney, brain and gonads of F(2B) pups. In conclusion rats fed technical azadirachtin showed no evidence of cumulative effects on postnatal development and reproductive performance over two generations. Absence of any major adverse reproductive effects in adults as well as in

21 days old pups of F(2B) generation suggest the safe use of technical azadirachtin as a biopesticide.
PMID: 17084955 [PubMed - indexed for MEDLINE]

Indian J Physiol Pharmacol. 2006 Jul-Sep;50(3):241-9.

Effect of aqueous extract of neem (Azadirachta indica) leaves on offensive and diffensive gastric mucosal factors in rats.

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http://www.ncbi.nlm.nih.gov/pubmed/17193895?ordinalpos=3&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

Standardized aqueous extract of Neem (Azadirachta indica) leaves (AIE) has been reported to show both ulcer protective and ulcer healing effects in normal as well as in diabetic rats. To study the mechanism of its ulcer protective/healing actions, effects of AIE (500 mg/ kg) was studied on various parameters of offensive acid-pepsin secretion in 4 hr pylorus ligation, pentagastrin (PENTA, 5 microg/kg/hr)-stimulated acid secretion and gastric mucosal proton pump activity and defensive mucin secretion including life span of gastric mucosal cells in rats. AIE was found to inhibit acid-pepsin secretion in 4 hr pylorus ligated rats. Continuous infusion of PENTA significantly increased the acid secretion after 30 to 180 min or in the total 3 hr acid secretion in rat stomach perfusate while, AIE pretreatment significantly decreased them. AIE inhibited the rat gastric mucosal proton pump activity and the effect was comparable with that of omeprazole (OMZ). Further, AIE did not show any effect on mucin secretion though it enhanced life span of mucosal cells as evidenced by a decrease in cell shedding in the gastric juice. Thus, our present data suggest that the ulcer protective activity of AIE may be due to its anti-secretary and proton pump inhibitory activity rather than on defensive mucin secretion. Further, acute as well as sub acute toxicity studies have indicated no mortality with 2.5 g/kg dose of AIE in mice and no significant alterations in body or tissues weight, food and water intake, haematological profile and various liver and kidney function tests in rats when treated for 28 days with 1 g/kg dose of AIE.
PMID: 17193895 [PubMed - indexed for MEDLINE]

In Vivo. 2006 Mar-Apr;20(2):247-51.

Enhancement of immune responses to neem leaf extract (Azadirachta indica) correlates with antineoplastic activity in BALB/c-mice.

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An aqueous plant extract from Azadirachta indica and its chromatographic fraction F1 (neem extract) exerted immunomodulating and antimetastatic activities in BALB/ c-mice. Regular

subcutaneous administration of neem extract yielded significantly increased spleen weight and significant enhancement of peritoneal macrophage activity in the chemiluminescence assay, and activation marker CD-44 expression. The thymus weight and thymocyte counts did not show significant differences in the control and neem extract-treated groups, however, determination of peripheral blood cells revealed significant up-regulations of leukocyte subsets, the lymphocytes and monocytes. Flow cytometric analaysis of lymphocyte supopulations documented increased counts of CD-4 and CD-8 cells and an inreased activation marker expression on lymphocytes (CD-25) and monocytes (MAC-3) in neem-treated mice compared to the control animals. To evaluate the antimetastatic activity of neem extract, sarcoma L-1 cells and lymphosarcoma RAW cells were intravenously inoculated into BALB/c-mice. In these model systems the number of experimental lung and liver metastases decreased relevantly, however, biometrically non-significantly in neem extract-treated animals, as compared to the control mice which received injections of saline solutions. Neem extract can be regarded as an immunomodulating and antimetastatic substance which holds promise for further experimental and clinical investigation.
PMID: 16634526 [PubMed - in process]

Phytother Res. 2006 Mar;20(3):169-77.

Chemomodulatory effects of Azadirachta indica on the hepatic status of skin tumor bearing mice.

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The liver plays an important role in the modulation of the process of carcinogenesis, as it is the primary site for the biotransformation of xenobiotics including carcinogens as well as anticancer drugs. The present study was designed to evaluate the biochemical alterations occurring in the liver of 7,12-dimethylbenz(a)anthracene (DMBA) induced skin tumor bearing male Balb/c mice and their modulation by aqueous Azadirachta indica leaf extract (AAILE). It was observed that skin tumor induction caused hepatic damage characterized by a decreased hepatosomatic index and significantly increased ($p < 0.001$) activities of the hepatic tissue injury marker enzymes, namely alkaline phosphatase, alanine aminotransferase and aspartate aminotransferase. However, upon treatment with AAILE, the above-mentioned alterations, including the increased activities of hepatic tissue injury marker enzymes, were significantly reversed, which signified the hepato-protective efficacy of Azadirachta indica. Increased oxidative stress was also observed in the hepatic tissue of skin tumor bearing mice as revealed by a significant increase ($p < 0.001$) in lipid peroxidation levels and a decrease in reduced glutathione contents and activities of various antioxidant enzymes studied, namely glutathione-S-transferase, glutathione peroxidase and glutathione reductase. The AAILE treatment reduced oxidative stress by decreasing lipid peroxidation levels and enhancing the reduced glutathione contents and activities of various antioxidant enzymes. The activities of the xenobiotic biotransformation enzymes, namely cytochrome P450, cytochrome b5 and glutathione-S-transferase, were found to be decreased in the hepatic tissue of tumor bearing mice. Treatment

with AAILE further caused a decrease in the activity of cytochrome P450 and cytochrome b5, whereas it up-regulated the activity of glutathione-S-transferase. The significance of these observations with respect to the progress of the process of carcinogenesis is explained in the present research article. Copyright 2006 John Wiley & Sons, Ltd.
PMID: 16521106 [PubMed - in process]

Immunopharmacol Immunotoxicol. 2006;28(1):33-50.

Prophylactic dose of neem (Azadirachta indica) leaf preparation restricting murine tumor growth is nontoxic, hematostimulatory and immunostimulatory.

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http://www.ncbi.nlm.nih.gov/pubmed/16684666?ordinalpos=5&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

Significant restriction of growth of Ehrlich's carcinoma was observed following prophylactic treatment on Swiss albino mice with neem leaf preparation (NLP-1 unit) once weekly for four weeks. Toxic effects of this particular dose (1 unit), along with 0.5 unit and 2 units of NLP doses, were evaluated on different murine physiological systems. One hundred percent of mice could tolerate 4 injections of 0.5 and 1 unit NLP doses. Body weight, different organ-body weight ratios and physical behavior of treated mice remained completely unchanged during treatment with different NLP doses. All of these NLP doses were observed to stimulate hematological systems as evidenced by the increase in total count of RBC, WBC and platelets and hemoglobin percentage. As histological changes as well as elevation in serum alkaline phosphatase, SGOT, SGPT were not observed in mice treated with three different doses of NLP, the nonhepatotoxic nature of NLP was proved. The level of serum urea remained unaltered and normal architecture of the cortical and medullary parts of the kidney were also preserved after NLP treatment. Increased antibody production against B16 melanoma antigen was detected in mice immunized with 0.5 unit and 1 unit of NLP. Number of splenic T lymphocytes (CD4+ and CD8+) and NK cells were also observed to be increased in mice injected with 0.5 unit and 1 unit of NLP. However, NLP dose of 2 units could not exhibit such immunostimulatory changes; NLP mediated immunostimulation was correlated well with the growth restriction of murine carcinoma. In other words, tumor growth restriction was observed only when mice were injected with immunostimulatory doses of NLP (0.5 unit and 1 unit).
PMID: 16684666 [PubMed - indexed for MEDLINE]

Asian Pac J Cancer Prev. 2005 Jul-Sep;6(3):263-9.

Quinone reductase inducers in Azadirachta indica A. Juss flowers, and their mechanisms of action.

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We have previously shown that the flowers of neem tree (Azadirachta indica A. Juss, family Meliaceae), Thai variety, strongly induced the activity of glutathione S-transferase (GST) while resulting in a significant reduction in the activities of some cytochrome P(450)-dependent monooxygenases in rat liver, and possess cancer chemopreventive potential against chemically-induced mammary gland and liver carcinogenesis in rats. In the present study, 2 chemicals possessing strong QR inducing activity were fractionated from neem flowers using a bioassay based on the induction of QR activity in mouse hepatoma Hepa 1c1c7 cultured cells. Spectroscopic characteristics revealed that these compounds were nimbolide and chlorophylls, having CD (concentration required to double QR specific activity) values of 0.16 and 3.8 mug/ml, respectively. Nimbolide is a known constituent of neem leaves, but was found for the first time here in the flowers. Both nimbolide and chlorophylls strongly enhanced the level of QR mRNA in Hepa 1c1c7 cells, as monitored by northern blot hybridization, indicating that the mechanism by which these constituents of neem flowers induced QR activity is the induction of QR gene expression. These findings may have implication on cancer chemopreventive potential of neem flowers in experimental rats previously reported.
PMID: 16235984 [PubMed - indexed for MEDLINE]

Cell Biochem Funct. 2005 Jul-Aug;23(4):229-38.

Ethanolic leaf extract of neem (Azadirachta indica) inhibits buccal pouch carcinogenesis in hamsters.

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We evaluated the chemopreventive effects of ethanolic neem leaf extract in the initiation and post-initiation phases of 7,12-dimethylbenz[a]anthracene (DMBA)-induced hamster buccal pouch (HBP) carcinogenesis. The frequency of bone marrow micronuclei as well as the concentrations of lipid peroxides, ratio of reduced to oxidized glutathione (GSH/GSSG), and the activities of the GSH-dependent enzymes glutathione peroxidase (GPx) and glutathione-S-transferase (GST) in the buccal pouch, liver and erythrocytes were used as biomarkers of chemoprevention. All the hamsters painted with DMBA alone for 14 weeks developed buccal pouch carcinomas that showed diminished lipid peroxidation and enhanced antioxidant status associated with increased frequencies of bone marrow micronuclei. In the liver and erythrocytes of tumour-bearing animals, enhanced lipid peroxidation was accompanied by compromised antioxidant defences. Administration of ethanolic neem leaf extract effectively suppressed DMBA-induced HBP carcinogenesis as revealed by the absence of tumours in the initiation phase and reduced tumour incidence in the post-initiation phase. In addition, ethanolic neem leaf extract modulated lipid peroxidation and enhanced antioxidant status in the pouch, liver and erythrocytes and reduced the incidence of bone marrow micronuclei. The results of the present study, demonstrate that ethanolic neem leaf extract inhibits the development of DMBA-induced HBP tumours by protecting against oxidative stress.

J Exp Clin Cancer Res. 2005 Jun;24(2):223-30.

Modulation of xenobiotic-metabolizing enzymes by ethanolic neem leaf extract during hamster buccal pouch carcinogenesis.

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Chemoprevention by medicinal plants is a promising approach for controlling cancer. There is substantial evidence to indicate that chemopreventive agents exert their anticarcinogenic effects by modulation of phase I and phase II xenobiotic-metabolizing enzymes. Therefore, we examined the chemopreventive potential of ethanolic neem leaf extract (ENLE) on 7,12-dimethylbenz[a]anthracene (DMBA)-induced hamster buccal pouch (HBP) carcinogenesis. Hamsters were divided into four groups of six animals each. The right buccal pouches of animals in Group I were painted with 0.5 per cent DMBA in liquid paraffin three times per week. Animals in Group 2 painted with DMBA as in group 1, received in addition, intragastric administration of ENLE at a concentration of 200 mg/kg bw three times per week on days alternate to DMBA application. Group 3 was given ENLE alone. Animals in Group 4 served as controls. All animals were killed after an experimental period of 14 weeks. Five out of six hamsters painted with DMBA alone developed squamous cell carcinomas in the buccal pouch. The HBP tumours showed an increase in phase I carcinogen activation (cytochrome P450 and b5) and phase II detoxification enzyme (glutathione-S-transferase, DT-diaphorase and NADPH-diaphorase) activities. In the liver of tumour-bearing animals, enhanced cytochrome P450 and b5 levels were accompanied by a decrease in phase II detoxification enzyme activities. Administration of ENLE effectively suppressed DMBA-induced HBP tumours, decreased cytochrome P450 and b5 levels, and enhanced phase II enzyme activities in the pouch and liver. Our results suggest that the modulation of DMBA metabolism is a possible mechanism for the chemopreventive effects of ethanolic neem leaf extract.

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

Biochemical effects of vepacide (from Azadirachta indica) on Wistar rats during subchronic exposure.

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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 Med Food. 2004 Fall;7(3):334-9.

Effects of aqueous extracts of garlic (Allium sativum) and neem (Azadirachta indica) leaf on hepatic and blood oxidant-antioxidant status during experimental gastric carcinogenesis.

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http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15383228&query_hl=1&itool=pubmed_docsum

The modifying effects of aqueous extracts of garlic and neem leaf during the pre-initiation and post-initiation phases of gastric carcinogenesis induced by N-methyl-N'-nitro-N-nitrosoguanidine were investigated in male Wistar rats. The extent of lipid peroxidation and the status of phase II biotransformation enzymes such as glutathione peroxidase and glutathione-S-transferase that use reduced glutathione (GSH) as substrate were used to biomonitor the chemopreventive potential of these extracts. Enhanced lipid peroxidation in the liver and blood of tumor-bearing animals was accompanied by significant decreases in the activities of GSH-dependent antioxidants in the pre-initiation as well as in the post-initiation phases. Our results suggest that the modulatory effects of garlic and neem leaf on hepatic and blood oxidant-antioxidant status may play a key role in preventing cancer development at extrahepatic sites.
PMID: 15383228 [PubMed - indexed for MEDLINE]

Med J Malaysia. 2004 May;59 Suppl B:208-9.

The effect of neem (Azadirachta indica) extract and dietary selenium on distribution of selenium in hepatocarcinogenesis induced rat.

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Neem, Azadirachta indica, is a plant from the family Meliaceae, known as "Pokok Semambu" in Malay community. It has been extensively used in India as traditional Ayurvedic and folklore minedicine for the treatment of various diseases. This study aimed to determine the distribution of selenium in the liver of rats during hepatocarcinogenesis when neem aqueous extract and dietary selenium was supplemented.
PMID: 15468891 [PubMed - indexed for MEDLINE]

Ecotoxicol Environ Saf. 2004 Jun;58(2):194-201.

Genotoxic effects of cadmium chloride and azadirachtin treated singly and in combination in fish.

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http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15157573&query_hl=1&itool=pubmed_docsum

The genotoxic effects of cadmium chloride (CdCl(2)) and azadirachtin (Aza) were assessed singly and conjointly in a fish, Oreochromis mossambicus, with endpoints such as chromosome aberrations, abnormal red cell nuclei, abnormal sperm morphology, and protein content (both qualitative and quantitative) of selected tissues, namely, muscle, heart, eye, brain, gill, liver, spleen, and kidney. The primary objectives were, first, to examine if CdCl(2), a common pollutant, and Aza, a natural product of the neem plant used extensively as an 'ecofriendly' agent for many purposes, had any genotoxic effect of their own on nontarget aquatic organisms of economic importance; and second, if Aza could have any ameliorating effect on CdCl(2)-induced genotoxicity in O. mossambicus tissues. As compared with distilled water-treated controls, both CdCl(2) and Aza induced genotoxicity in O. mossambicus, the former in greater quantity than that produced by Aza. However, Cd-induced toxicity in O. mossambicus appeared to be ameliorated to some extent by Aza.
PMID: 15157573 [PubMed - indexed for MEDLINE]

J Ethnopharmacol. 2004 May;92(1):23-36.

Chemopreventive potential of Azadirachta indica (Neem) leaf extract in murine carcinogenesis model systems.

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http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15099843&query_hl=1&itool=pubmed_docsum

Numerous laboratory studies reveal that various naturally occurring dietary substances can modify the patho-physiological process of various metabolic disorders and can be an effective preventive strategy for various diseases, including cancer. Indian Neem tree, Azadirachta

indica A. Juss. (family: Meliaceae), contains at least 35 biologically active principles and is widely grown all over the tropics. The effect of two different doses (250 and 500 mg per kilogram body weight) of 80% ethanolic extract of the leaves of Azadirachta indica were examined on drug metabolizing Phase-I and Phase-II enzymes, antioxidant enzymes, glutathione content, lactate dehydrogenase, and lipid peroxidation in the liver of 7-week-old Swiss albino mice. Also anticarcinogenic potential of Azadirachta indica leaf extract was studied adopting protocol of benzo(a)pyrene-induced fore-stomach and 7,12-dimethyl benz(a)anthracene (DMBA)-induced skin papillomagenesis. Our primary findings reveal its potential to induce only the Phase-II enzyme activity associated mainly with carcinogen detoxification in liver of mice. The hepatic glutathione S-transferase ($P < 0.005$) and DT-diaphorase specific activities ($P < 0.01$) were elevated above basal level. With reference to antioxidant enzymes the investigated doses were effective in increasing the hepatic glutathione reductase (GR), glutathione peroxidase (GPX), superoxide dismutase (SOD) and catalase (CAT) activities significantly (from $P < 0.005$ to $P < 0.001$). Reduced glutathione measured as non-protein sulphydryl was found to be significantly elevated in liver ($P < 0.005$) and in extrahepatic organs (from $P < 0.005$ to $P < 0.001$) examined in our study. Glutathione S-transferase (GST) and DT-diaphorase (DTD) showed a dose-dependent increase in extrahepatic organs. Chemopreventive response was measured by the average number of papillomas per mouse, as well as percentage of tumor-bearing animals. There was a significant inhibition of tumor burden, in both the tumor model system studied (from $P < 0.005$ to $P < 0.001$). Tumor incidence was also reduced by both the doses of Azadirachta indica extract.

PMID: 15099843 [PubMed - indexed for MEDLINE]

Drug Chem Toxicol. 2004 Feb;27(1):15-26.

Protective effects of ethanolic neem leaf extract on N-methyl-N'-nitro-N-nitrosoguanidine-induced genotoxicity and oxidative stress in mice.

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We evaluated the effects of pretreatment with ethanolic neem leaf extract on N-methyl-N'-nitro-N-nitrosoguanidine (MNNG)-induced genotoxicity and oxidative stress in male Swiss albino mice. The frequency of micronuclei (MN), concentrations of lipid peroxides and the status of the antioxidants, reduced glutathione (GSH), glutathione peroxidase (GPx) and glutathione-S-transferase (GST) were used as intermediate biomarkers of chemoprotection. Animals were divided into four groups of five animals each. Animals in group 1 were given MNNG (40 mg/kg body weight) by intragastric intubation. Animals in group 2 received intragastric administration of ethanolic neem leaf extract at a concentration of 200 mg/kg body weight for 5 days followed by MNNG 1.5 h after the final feeding. Group 3 animals received ethanolic neem leaf extract alone for five days. Group 4 received the same volume of normal saline and served as control. The animals were sacrificed by cervical dislocation 27 h after the carcinogen exposure. In MNNG-treated mice, enhanced lipid peroxidation with compromised

antioxidant defences in the stomach, liver and erythrocytes was accompanied by increase in bone marrow micronuclei. Pretreatment with ethanolic neem leaf extract significantly reduced MNNG-induced micronuclei and lipid peroxides and enhanced GSH-dependent antioxidant activities. The results of the present study demonstrate that ethanolic neem leaf extract exerts protective effects against MNNG-induced genotoxicity and oxidative stress by augmenting host antioxidant defence mechanisms.
PMID: 15038245 [PubMed - indexed for MEDLINE]

J Ethnopharmacol. 2004 Feb;90(2-3):185-9.

Protective role of extracts of neem seeds in diabetes caused by streptozotocin in rats.

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http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15013179&query_hl=1&itool=pubmed_docsum

Effect of petroleum ether extracts of kernel (NSK) and husk (NSH) of neem (Azadirachta indica A. Juss, Meliaceae) seeds on the prevention of oxidative stress caused by streptozotocin (STZ) was investigated. Diabetes mellitus was induced in adult male Wistar rats after administration of STZ (55 mg/kg b.wt., i.p., tail vein).The effect of NSK (2 gm/kg, b.wt.) and NSH (0.9 gm/kg, b.wt.) orally for 28 days was investigated in diabetic rats. Insulin-treated diabetic rats (6 U/kg, i.p., 28 days.) served as positive control. Diabetic rats given normal saline served as diabetic control. Rats that neither received STZ nor drugs served as normal control. Serum creatine phosphokinase (CPK) increased in diabetic rats was significantly decreased on insulin, NSK, and NSH treatments. The decrease in activities of superoxide dismutase (SOD) and catalase (CAT) and increase in lipid peroxidation (LPO) of erythrocytes as observed in diabetes was regained after insulin, NSH, and NSK treatments. However, there was insignificant improvement in SOD, CAT, and LPO of kidney on NSK and NSH treatment. In spite of increased CAT and SOD activities in liver and heart, LPO was also increased in diabetic rats. Insulin, NSH, and NSK treatments significantly protected animals from cardiac damage but not hepatic. Results suggest that NSH and NSK prevent oxidative stress caused by STZ in heart and erythrocytes. However, no such preventive effect was observed on renal and hepatic toxicity.

Asia Pac J Clin Nutr. 2004;13(Suppl):S170.

The effect of Azadirachta indica on distribution of antioxidant elements and glutathione S-transferase activity in the liver of rats during hepatocarcinogenesis.

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http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15294745&query_hl=1&itool=pubmed_docsum

The liver is often the first organ to be infected by metastasizing cancer. Hepatocarcinogenesis is one of the most prevalent and deadly cancers worldwide, which ranks seventh among cancers in order of frequency of occurrence. Numbers of natural and synthetic antioxidants are known to treat initiation and promotion of chemical carcinogenesis in experimental animal models. The effect of 5% w/v of Azadirachta indica extract in diethylnitrosamine and acetylaminofluorene induced hepatocellular carcinoma, which is a vital mechanism in cancer treatment, was studied in male Sprague dawly rats. The result of microscopic observation of the lesion score during hepatocarcinogenesis revealed that cells of cancer group without treatment were severely necrotic at week 12. However, cells of cancer group with Azadirachta indica treatment appeared nearly normal. The tracking of the elements during hepatocarcinogenesis was done using energy filtering transmission electron microscope (EFTEM). According to EFTEM results, some of antioxidant elements such Na, Ca, and P is highly distributed in Azadirachta indica treated normal and cancer group. However, the distribution is too low in normal control and cancer control group without Azadirachta indica treatment. The obtained results have shown a significant, decrease (P=0.05) of liver cytosol Glutathione S-transferase in cancer control group rats. Meanwhile, treatment with Azadirachta indica caused overall increase in liver GST activity nearly to control group. Distinct evidence from this study contribute that oral administration of 5% Azadirachta indica extract demonstrated anticancer activity by increasing the distribution of antioxidant elements and GST activity may to protect cells in preneoplastic nodules in cancer treated groups. However, there was no evidence of side effects of Azadirachta indica towards normal cells indicating Azadirachta indica as a potential preventive agent for cancer.
PMID: 15294745 [PubMed - in process]

J Ethnopharmacol. 2003 Dec;89(2-3):217-9.

Possible mechanism of hepatoprotective activity of Azadirachta indica leaf extract: part II.

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Hepatoprotective activity of Azadirachta indica leaf extract against paracetamol induced hepatic damage in rats has already been reported. In the present investigation effects of Azadirachta indica leaf extract on blood and liver glutathione, Na+K(+)-ATPase activity and thiobarbutiric acid reactive substances against paracetamol induced hepatic damage in rats have been studied with a view to elucidate possible mechanism behind its hepatoprotective action. It was interesting to observe that Azadirachta indica leaf extract has reversal effects on the levels of above mentioned parameters in paracetamol hepatotoxicity. Possible mechanism behind the results are discussed.
PMID: 14611885 [PubMed - indexed for MEDLINE]

J Agric Food Chem. 2003 Oct 22;51(22):6456-60.

Prenylated flavanones isolated from flowers of Azadirachta indica (the neem tree) as antimutagenic constituents against heterocyclic amines.

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Four prenylated flavanones were isolated from the methanol extract of the flowers of Azadirachta indica (the neem tree) as potent antimutagens against Trp-P-1 (3-amino-1,4-dimethyl-5H-pyrido[4,3-b]indole) in the Salmonella typhimurium TA98 assay by activity-guided fractionation. Spectroscopic properties revealed that those compounds were 5,7,4'-trihydroxy-8-prenylflavanone (1), 5,4'-dihydroxy-7-methoxy-8-prenylflavanone (2), 5,7,4'-trihydroxy-3',8-diprenylflavanone (3), and 5,7,4'-trihydroxy-3',5'-diprenylflavanone (4). All isolated compounds were found for the first time in this plant. The antimutagenic IC(50) values of compounds 1-4 were 2.7 +/- 0.1, 3.7 +/- 0.1, 11.1 +/- 0.1, and 18.6 +/- 0.1 microM in the preincubation mixture, respectively. These compounds also similarly inhibited the mutagenicity of Trp-P-2 (3-amino-1-methyl-5H-pyrido[4,3-b]indole) and PhIP (2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine). All of the compounds 1-4 strongly inhibited ethoxyresorufin O-dealkylation activity of cytochrome P450 1A isoforms, which catalyze N-hydroxylation of heterocyclic amines. However, compounds 1-4 did not show significant inhibition against the direct-acting mutagen NaN(3). Thus, the antimutagenic effect of compounds 1-4 would be mainly based on the inhibition of the enzymatic activation of heterocyclic amines.
PMID: 14558762 [PubMed - indexed for MEDLINE]

Asian Pac J Cancer Prev. 2003 Jul-Sep;4(3):215-23.
Comment in: Asian Pac J Cancer Prev. 2003 Jul-Sep;4(3):167-8.

Ethanolic neem leaf extract protects against N-methyl -N'-nitro-N-nitrosoguanidine-induced gastric carcinogenesis in Wistar rats.

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http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14507242&query_hl=1&itool=pubmed_docsum

We evaluated the effects of ethanolic neem leaf extract on N-methyl-N'-nitro-N-nitrosoguanidine (MNNG)-induced gastric carcinogenesis in Wistar rats. The extent of lipid peroxidation and the status of the antioxidants superoxide dismutase (SOD), catalase (CAT), reduced glutathione (GSH), glutathione peroxidase (GPx), and glutathione-S-transferase (GST) in the stomach, liver and erythrocytes were used as biomarkers of chemoprevention. Animals were divided into four groups of six animals each. Rats in group 1 were given MNNG (150 mg/kg bw) by intragastric intubation three times with a gap of 2 weeks in between the treatments. Rats in group 2 administered MNNG as in group 1, in addition received intragastric

intubation of ethanolic neem leaf extract (200 mg/kg bw) three times per week starting on the day following the first exposure to MNNG and continued until the end of the experimental period. Group 3 animals were given ethanolic neem leaf extract alone, while group 4 served as controls. All the animals were killed after an experimental period of 26 weeks. Diminished lipid peroxidation in the stomach tumour tissue was associated with enhanced antioxidant levels. In contrast to tumour tissue, enhanced lipid peroxidation with compromised antioxidant defences was found in the liver and erythrocytes of tumour bearing animals. Administration of ethanolic neem leaf extract significantly reduced the incidence of stomach tumours, modulated lipid peroxidation and enhanced antioxidant status in the stomach, liver and blood. From the results of our study, we suggest that ethanolic neem leaf extract may exert its chemopreventive effects by modulating lipid peroxidation and enhancing the antioxidant status in the stomach, liver and erythrocytes.
PMID: 14507242 [PubMed - indexed for MEDLINE]

East Mediterr Health J. 2003 Jul;9(4):646-58.

Operational use of neem oil as an alternative anopheline larvicide. Part B: Environmental impact and toxicological potential.

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http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15748062&query_hl=1&itool=pubmed_docsum

This study was conducted to investigate the preliminary environmental and mammalian toxicology of neem oil, temephos and chlorpyriphos-methyl/fenitrothion. Culex pipiens, Daphnia magna and Gambusia affinis were used to study environmental impact. A high level of toxicity was observed, with slight differences between organisms. The emulsifiers individually also displayed toxicity towards the tested organisms. Up to 90 days daily oral crude neem oil treatment (5 g/kg body weight) of laboratory mice did not cause any significant changes in weekly body weight gain, nor in serum liver damage indicators, direct bilirubin or total bilirubin. Blood parameters of treated mice up to 90 days were not statistically different from those of control mice. Neem oil could be used as an environmentally friendly alternative to the traditional chemical anopheline larvicides.

Pharmazie. 2003 Jul;58(7):512-7.

Chemoprotective effects of ethanolic extract of neem leaf against MNNG-induced oxidative stress.

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We evaluated the modifying effects of ethanolic extract of neem leaves (Azadirachta indica A. Juss) on oxidative stress induced by the potent gastric carcinogen N-methyl-N'-nitro-N-

nitrosoguanidine (MNNG) in male Wistar rats. The extent of lipid peroxidation and the status of the antioxidants superoxide dismutase (SOD), catalase (CAT), reduced glutathione (GSH), glutathione peroxidase (GPx) and glutathione S-transferase (GST) were used as intermediate endpoints of chemoprevention. Three different concentrations of ethanolic neem leaf extract (100, 200 and 400 mg kg(-1) body weight) were administered by intragastric intubation (i.g) for five consecutive days followed by MNNG (i.g) 1.5 h after the final administration. Enhanced lipid peroxidation was accompanied by compromised antioxidant defences in the stomach, liver and erythrocytes of MNNG-treated rats. Pretreatment with ethanolic neem leaf extract at a dose of 200 mg/kg body weight (bw) significantly lowered the concentration of lipid peroxides and increased antioxidant levels. Our results demonstrate that neem leaf exerts its chemoprotective effects on MNNG- induced oxidative stress by decreasing lipid peroxidation and enhancing the antioxidant status.

Indian J Exp Biol. 2003 Jun;41(6):636-40.

Lowering of blood sugar by water extract of Azadirachta indica and Abroma augusta in diabetes rats.

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Combination (1:1) of water extract of dried powder of root and leaves (200 mg/kg body wt) of A. augusta and A. indica respectively was administered orally to alloxan diabetic rats once a day for 8 weeks. This treatment caused significant lowering of blood sugar in fasted as estimated by glucose tolerance test. The treatment resulted in a significant reduction in serum lipids. Aqueous extract also decreased the formation of lipid peroxides estimated as thiobarbituric acid reactive substance, (TBARS), and increased antioxidants (superoxide dismutase, catalase, glutathione peroxidase and glutathione transferase) in erythrocytes. There was reduction in LPO as TBARS in heart, liver, kidney, and muscles. It also prevented decrease in body weight. Present study showed that Abroma augusta roots and A. indica leaves when given together as water extract had hypoglycaemic action and had better effect than given alone.

Phytomedicine. 2003;10(5):391-6.

Effect of Azadirachta indica on paracetamol-induced hepatic damage in albino rats.

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http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12834004&query_hl=1&itool=pubmed_docsum

Azadirachta indica, a plant used widely in Ayurveda, has been reported to have anti-inflammatory, immunomodulatory and adaptogenic properties. The present study evaluates its hepatoprotective role. Fresh juice of tender leaves of Azadirachta indica (200 mg/kg body wt. p.o.) inhibited paracetamol (2 g/kg body wt. p.o.)-induced lipid peroxidation and prevented

depletion of sulfhydryl groups in liver cells. There was an increase in serum marker enzymes of hepatic damage (aspartate transaminase, alanine transaminase and alkaline phosphatase) after paracetamol administration. Azadirachta indica pretreatment stabilized the serum levels of these enzymes. Histopathological observations of liver tissues corroborated these findings.

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

LDH profiles of male and female rats treated with Vepacide.

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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]

Asian Pac J Cancer Prev. 2002;3(3):231-238.

Chemopreventive Potential of Neem Flowers on Carcinogen-Induced Rat Mammary and Liver Carcinogenesis.

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We have previously reported that dietary neem flowers (Azadirachta indica A. Juss var. siamensis Valeton) caused a marked increase in glutathione S-transferase (GST) activity in the liver, while resulting in a significant reduction in the activities of some hepatic P450-dependent monooxygenases. These results strongly indicate that neem flowers may have chemopreventive

potential. In the present study, we examined the inhibitory effects of neem flowers on 9,10-dimethyl-1,2-benzanthracene (DMBA)-induced mammary gland carcinogenesis in female Sprague Dawley rats and on aflatoxin B(1)(AFB(1))-induced hepatocarcinogenesis in male Wistar rats. Young animals were fed with AIN-76 purified diets containing either 10-12.5% ground freeze-dried neem flowers for 1 week prior to, during, and for 1 week after the administration of each carcinogen. Interestingly, it was found that neem flowers resulted in a marked reduction of the incidence of mammary gland (about 35.2%) and liver tumors (61.7% and 80.1% for benign and malignant tumors, respectively). Furthermore, the multiplicity of tumors per rats was also lower in the neem flower groups, i.e. those for mammary gland tumors and benign and malignant liver tumors were reduced to 44.0%, 87.9% and 88.9%, respectively. These results clearly demonstrated that neem flowers contain some chemopreventive agents capable of inhibiting AFB(1) and DMBA induced liver and mammary gland carcinogenesis in rats.
PMID: 12718580 [PubMed - as supplied by publisher]

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.

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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]

Phytother Res. 2000 Jun;14(4):291-3.

Garlic and neem leaf extracts enhance hepatic glutathione and glutathione

dependent enzymes during N-methyl-N'-nitro-N-nitrosoguanidine (MNNG)-induced gastric carcinogenesis in rats.

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http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10861977&query_hl=1&itool=pubmed_DocSum

The protective effect of garlic (Allium sativum L.) and neem leaf (Azadirachta indica A. Juss.) was investigated on hepatic lipid peroxidation and antioxidant status during N-methyl-N'-nitro-N-nitrosoguanidine (MNNG)-induced gastric carcinogenesis in male Wistar rats. Enhanced lipid peroxidation in the liver of tumour-bearing animals was accompanied by significant decreases in the activities of glutathione peroxidase (GPx), glutathione-S-transferase (GST), gamma-glutamyl transpeptidase (GGT) and reduced glutathione (GSH) levels. Administration of garlic and neem leaf extracts significantly lowered lipid peroxidation and enhanced the hepatic levels of glutathione and glutathione dependent enzymes. We speculate that garlic and neem leaf significantly alter cancer development at extrahepatic sites by influencing hepatic biotransformation enzymes and antioxidants.
PMID: 10861977 [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?

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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]

Cell Biochem Funct. 2000 Mar;18(1):17-21.

Modulatory effects of garlic and neem leaf extracts on N-methyl-N'-nitro-N-

nitrosoguanidine (MNNG)-induced oxidative stress in Wistar rats.

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http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10686579&query_hl=1&itool=pubmed_DocSum

The effects of garlic and neem leaf extracts on lipid peroxidation and antioxidant status during administration of N-methyl-N'-nitro-N-nitrosoguanidine (MNNG), a carcinogenic nitrosamine were evaluated in male Wistar rats. Extracts of garlic and neem leaf were administered orally for five consecutive days before intraperitoneal injection of MNNG. Enhanced lipid peroxidation in the stomach, liver and circulation of MNNG-treated rats was accompanied by a significant decrease in glutathione (GSH) and the activities of glutathione peroxidase (GPx), glutathione-S-transferase (GST) and gamma glutamyl transpeptidase (GGT). Administration of garlic and neem leaf extracts significantly decreased the formation of lipid peroxides and enhanced the levels of antioxidants and detoxifying enzymes in stomach, the primary target organ for MNNG, as well as in the liver and circulation. The results of the present study suggest that garlic and neem may exert their protective effects by modulating lipid peroxidation and enhancing the levels of GSH and GSH-dependent enzymes.
PMID: 10686579 [PubMed - indexed for MEDLINE]

Indian J Physiol Pharmacol. 2000 Jan;44(1):64-8.**Effect of Azadirachta indica (Neem) leaf aqueous extract on paracetamol-induced liver damage in rats.**

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http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10919097&query_hl=1&itool=pubmed_DocSum

The effect of aqueous leaf extract of Azadirachta indica (A. indica) was evaluated in paracetamol induced hepatotoxicity in rats. Liver necrosis was produced by administering single dose of paracetamol (2 g/kg, p.o.). The liver damage was evidenced by elevated levels of serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transpeptidase (gamma-GT) and by histopathological observations of liver sections. Aqueous A. indica leaf extract (500 mg/kg, p.o.) significantly ($P < 0.01$) reduced these elevated levels of AST, ALT and gamma-GT. Paracetamol induced liver necrosis was also found to be reduced as observed macroscopically and histologically.

J Environ Sci Health B. 1998 Jul;33(4):425-38.
The effect of subacute administration of a neem pesticide on rat metabolic enzymes.

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http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9674151&query_hl=1&itool=pubmed_DocSum

Acute toxicity of a neem pesticide (Vepacide-Tech) was studied in male Wistar rats by oral (single) intubation for 7 days. Vepacide was found to be moderately toxic to rat based on LD50 value. Subacute toxicity of Vepacide-Tech was also studied in male rats by oral (multiple) intubation of low (80 mg Kg-1 day-1), medium (160 mg Kg-1 day-1) and high dose (320 mg Kg-1 day-1) for 90 days. High dose caused a significant decrease in Cytochrome P-450 (Cyt. P-450) concentration at 45 and 90 days and the medium dose caused same effect at 90th day in liver and lung. Kidney showed similar effect at 90 days by the three doses. Cytochrome b5 (Cyt. b5) concentration was significantly decreased in liver, lung and kidney at 45 and 90 days at medium and high doses. Brain Cyt.b5 concentration was decreased on 90th day at high dose. Cytochrome P-450 reductase (Cyt.P-450 reductase) concentration was decreased significantly in liver and brain at 45 and 90 days, respectively at medium and high doses. The withdrawal study (28 days) has shown significant recovery. These results demonstrate that low levels exposure of Vepacide may have significant effect on the xenobiotic detoxification mechanism of different tissues of rat.

Mutat Res. 1998 Jun 18;402(1-2):247-58.
Antimutagenic and anticarcinogenic potentials of some Thai vegetables.

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Fifteen kinds of commonly consumed Thai vegetables were sequentially extracted with hexane, chloroform and methanol, and then tested for antimutagenic activities against direct-acting (AF-2 and NaN3) and indirect-acting (AFB1 and B(a)P) mutagens using Ames' Salmonella mutagenicity test with Salmonella typhimurium TA100 as tester strain. It was found that only the methanol extract of neem leaves contain weak antimutagen inhibiting the mutagenicities of both direct-acting mutagens. Interestingly, all vegetables studied were found to contain chemical compounds, mainly nonpolar ones, capable of inhibiting the mutagenicity of AFB1, while only some vegetables contain chemical compounds capable of inhibiting the mutagenicity of B(a)P, which is also an indirect-acting mutagen. Studies on anticarcinogenic potentials demonstrated that Thai bitter gourd fruits, but not sweet basil leaves, at the concentration of 6.25% and 12.5% in the diet, partially inhibited DMBA-induced mammary gland carcinogenesis in female Sprague-Dawley rats when fed to the animals 2 weeks prior to DMBA. Results in the present study therefore demonstrated that most Thai vegetables contain antimutagens inhibiting the mutagenicity of some indirect-acting mutagen, particularly AFB1. The mechanism of their antimutagenicity may probably be the inhibition of the activity of metabolic-activating enzymes in rat liver homogenates. Very interestingly, our results clearly reveal that Thai bitter gourd fruits, which possess Phase II enzymes inducing property, as well as the ability to reduce Phase I enzyme activities in rat liver, contain some anticarcinogens or chemopreventive agents. However, sweet basil leaves that possess both Phase I and Phase II enzyme-inducing properties may not contain any anticarcinogen, at least against DMBA-induced mammary gland carcinogenesis.
PMID: 9675301 [PubMed - indexed for MEDLINE]

Food Chem Toxicol. 1998 Jun;36(6):475-84

Effects of neem flowers, Thai and Chinese bitter gourd fruits and sweet basil leaves on hepatic monooxygenases and glutathione S-transferase activities, and in vitro metabolic activation of chemical carcinogens in rats.

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http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9674955&query_hl=1&itool=pubmed_DocSum

The objectives of this study were to determine the effects of feeding of four vegetables commonly consumed in Thailand, namely, flowers of the neem tree (Azadirachta indica var. siamensis), fruits of Thai and the Chinese bitter gourd (Momordica charantia Linn.) and leaves of sweet basil (Ocimum basilicum Linn) on the levels of phase I enzymes, which include cytochrome P450 (P450), aniline hydroxylase (ANH) and aminopyrine-N-demethylase (AMD) as well as the capacity to activate the mutagenicities of aflatoxin B1 (AFB1) and benzo[a]pyrene (BaP), and to induce the phase II enzymes [i.e. glutathione S-transferase (GST)] in rat liver. It was found that feeding of the diets containing 12.5% neem flowers and Thai bitter gourd fruits for 2 weeks strongly enhanced GST activity, 2.7- and 1.6- fold of the pair-fed control values, respectively, while resulting in a marked reduction of the levels of

most phase I reactions. Fruits of the Chinese bitter gourd, which is in the same species as Thai bitter gourd, had no effect on GST activity but decreased AMD activity and the in vitro metabolic activation of AFB1 and BaP. On the other hand, however, dietary sweet basil leaves caused a significant increase in the levels of both GST and all phase I enzymes. Results in the present study clearly demonstrate that neem flowers and Thai bitter gourd fruits contain monofunctional phase II enzyme inducers and compounds capable of repressing some monooxygenases, especially those involved in the metabolic activation of chemical carcinogens, while sweet basil leaves contain compounds, probably bifunctional inducers, capable of inducing both phase I and phase II enzymes and Chinese bitter gourd fruits contain only compounds capable of repressing some monooxygenases. These results therefore suggest that neem flowers and Thai bitter gourd fruits may possess chemopreventive potential, while those of Chinese bitter gourd fruits and sweet basil leaves are uncertain.
PMID: 9674955 [PubMed - indexed for MEDLINE]

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

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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.
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Modulation of humoral and cell-mediated immune responses by Azadirachta indica (Neem) in mice.

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The effects of A. indica (AI, Neem) were evaluated on tests of humoral and cell-mediated immune responses after 3 weeks of oral AI (leaf extract) treatment in ovalbumin immunized mice. At the dose levels tested, AI (10, 30 or 100 mg/kg), had no appreciable influence on different organ (liver, spleen, thymus)/body weight indices, when compared to controls. In tests for humoral immune responses, AI (100 mg/kg) treated mice had higher (1) IgM and IgG levels, and (b) anti-ovalbumin antibody titres, when compared to the vehicle treated group. In tests for cell-mediated immune responses, there was an enhancement (%) of (a) macrophage migration inhibition, and (b) footpad thickness after AI (100 mg/kg) treatment. These results are discussed in light of the possible immunopotentiating effects of AI.
PMID: 8979510 [PubMed - indexed for MEDLINE]

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Purified neem (Azadirachta indica) seed extracts (Praneem) abrogate pregnancy in primates.

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http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=8773426&query_hl=1&itool=pubmed_DocSum

The use of neem (Azadirachta indica) seed extracts (Praneem) given orally for abrogation of pregnancy in subhuman primates is described. Oral administration of Praneem was initiated after confirmation of pregnancy using Leydig cell bioassay estimating rising levels of chorionic gonadotropin (CG) in the blood from day 25 onwards of the cycle and continued for six days. Termination of pregnancy was observed with the appearance of blood in the vaginal smears and decline in CG and progesterone. Pregnancy continued in the control animals treated with peanut oil at the same dose. The effect was observed in both baboons and bonnet monkeys. The treatment was well tolerated; blood chemistry and liver function tests had normal values. The animals regained their normal cyclicity in the cycles subsequent to Praneem treatment.
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Plant products as protective agents against cancer.

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Out of various spices and leafy vegetables screened for their influence on the carcinogen-detoxifying enzyme, glutathione-S-transferase (GST) in Swiss mice, cumin seeds, poppy seeds, asafoetida, turmeric, kandathipili, neem flowers, manathakkali leaves, drumstick leaves, basil leaves and ponnakanni leaves increased GST activity by more than 78% in the stomach, liver and oesophagus, - high enough to be considered as protective agents against carcinogenesis. Glutathione levels were also significantly elevated in the three tissues by these plant products. All of them except neem flowers, significantly suppressed (in vivo) the chromosome aberrations (CA) caused by benzo(a)pyrene in mouse bone marrow cells. Multiple CA and exchanges reflecting the severity of damage within a cell were significantly suppressed by these nine plant products. The results suggest that these nine plant products are likely to suppress carcinogenesis and can act as protective agents against cancer.