

STRESS & NEEM

Overview

Like the shorter section on strokes, the research on stress isn't as comprehensive as it is in other areas, and it is all based on animal studies. However, it's another concern that affects me personally – as well as an enormous percentage of the people I work with. The first two reports are available through the University of the West Indies' outstanding research database, the third abstract originally came from the National Institutes of Health database but doesn't show up in recent searches. We've reprinted here so it remains accessible.

To paraphrase the scientists, that report indicates that small amounts of neem leaf extract (100 or 200 milligrams to kilogram body weight) helped mice significantly outperform mice on rat maze and open field behavior test paradigms – even when compared to diazepam – the active ingredient in Valium. Other research indicates that low doses of neem leaf extracts lower anxiety levels, although researchers have not been able to determine exactly how it works.

Recent Research

1.

Publication Type: Journal Article

UWI Author(s): Young, Ronald; Parshad, Omkar

Author, Analytic: Thaxter, K.A.; Young, Lauriann E.; Parshad, Omkar; Young, Ronald E.; Addae, J.

Author Affiliation, Ana.: Department of Basic Medical Sciences

Article Title: Effects of neem as revealed by somatosensory evoked potentials and the elevated x maze

Journal Title: Society for Neuroscience Abstracts Viewer

Date of Publication: 2003

Volume ID: 859

Issue ID: 2

Abstract:

We previously reported significant decreases in spontaneous motor activity in rats treated with neem (*Azadirachta indica*). We further studied this sedative action of neem using intracortical somatosensory evoked potentials (SEPs) and behaviour in an elevated X maze to differentiate an anxiogenic effect from motor deficiency. In SEP studies, urethane anesthetized Wistar rats (200-250g) were given a steroidal extract of neem leaf (0.07 or 7 mg/kg i.p.), vehicle (1% DMSO/saline), diazepam (1 mg/kg) or no treatment (baseline). Amplitude of wave N1 increased ($p < 0.05$) in neem versus (*vs*) vehicle treated rats and decreased ($p < 0.05$) in diazepam treated rats *vs* baseline. For behavioral studies, rats (100-150g) received neem, vehicle, diazepam (2mg/kg i.p.), sham injection or no treatment (baseline) 1 hr before a 5-min exploration of the X maze. Open arm entries (%) indicated anxiogenesis after high dose ($p < 0.05$; 7mg/kg *vs* 0.07mg/kg neem), and anxiolysis after low dose (0.07 mg/kg). The high-dose rats deposited more fecal boli in the maze ($p < 0.05$) *vs* the vehicle group. Measures of

total and closed arm entries showed that neem treatment did not significantly affect ability to explore the maze. Both doses of neem also increased rearing ($p < 0.05$ vs vehicle). Sham injected rats performed more stretched-attended postures in closed areas of the maze than baseline rats ($p < 0.05$), indicating anxiogenesis due to the injections. Diazepam vs sham injection reduced both rearing and closed arm entries ($p < 0.05$), but increased both % open arm entries and residence time ($p < 0.05$) without affecting total entries. Results suggest that the neem extract has a dose-related effect on anxiety and locomotory/orienting activity of rats in an elevated X maze. At high dose, 7mg/kg neem has cortical stimulatory and anxiogenic effects. CNS correlates may include serotonin and noradrenaline.

Call Number: 5.04

Keywords: neem; azadirachta indica; x maze

2.

Publication Type: Book Chapter

UWI Author(s): Parshad, Omkar; Young-Martin, Lauriann; Young, Ronald

Author, Analytic: Parshad, Omkar; Young, Lauriann E.; Young, Ronald E.

Author Affiliation, Ana.: Department of Basic Medical Sciences

Title, Analytic: Medicinal plants containing sedative activity with special reference to neem (*Azadirachta indica*, A Juss)

Author, Monographic: Wray, Samuel R.; Hernandez, N.; Parshad, Omkar

Author Role: Editors

Title, Monographic: Brain, function, behaviour, drugs and disease : Neurosciences in the Caribbean

Place of Publication: Kingston, Jamaica

Publisher Name: Medical and Scientific Development Trust and Caribbean Brain Research Organization

Date of Publication: 2000

Page(s): 78-85

Abstract:

With the growing focus on alternative methods of health-care has come a new craze to treat everything, from losing weight to staving off the AIDS virus, with the use of herbs and other natural plants. Consumers in the United States of America spend some US\$6 billion annually on nutritional supplements, herbs, seeds, pollen and oils and the market continues to grow by 29% every year. Most useful sedatives and central nervous system (CNS) depressant drugs available today are the products of plants and herbs. Neem is one such unique plant with numerous medicinal properties. Currently, there has been a spurt in the production of low-cost commercial brands of products based on neem components. For example, a number of new toothpastes, washing soaps and anti-inflammatory compounds are now available. In the present study, the administration of a crude steroidal neem extract clearly demonstrated significant decreases both in the spontaneous motor activity (SMA) and amplitude of the peak twitch force, indicating a tranquillizing effect on rats. This depression of the SMA may be due to an effect of neem on the CNS and/or muscle strength but not on the peripheral nerve conduction. Although, this is a preliminary study and needs further expansion, it is suggested that neem could be a low cost source of an effective sedative in the future.

Keywords: medicinal plants; neem; hypnotics and sedatives.

3.

Anxiolytic Activity of *Azadirachta indica* leaf extract in rats

Indian Journal of Experimental Biology, Vol. 32, July 1994, pp 489-491

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Abstract:

Putative anxiolytic activity of leaf extract of (*Azadirachta indica*), was investigated and compared with that of diazepam in rat plus maze and open field behavior test paradigms of anxiety. Doses (10, 20, 50, 100, 200, 400 and 800 mg/kg) of extract of *A. indica* and diazepam (1 mg/kg) were administered (po) once, 45 min prior to behavioral testing. Lower doses (100 and 200 mg) of *A. indica* leaf extract produced significant antianxiety effects both in plus maze and open field tests. The higher doses of leaf extract (400 and 800 mg/kg) did not show anxiolytic activity. The effects induced by low doses (100,200 mg/kg) of extract were comparable to those induced by diazepam (1 mg/kg).

Azadirachta indica, a Joss. (Meliaceae), commonly known as neem, is found throughout India and is known to have medicinal properties from ancient times. Different parts of the *A. indica* tree have been studied and reported to contain compounds including nimbin, azadirachtin and meliantriol etc. which have a variety of properties ranging from insecticidal to male spermicidal. *A. indica* is known to be beneficial in microbial infections, skin diseases and dental disorders. It has hypoglycemic and antiulcerogenic properties. Alcoholic extracts of leaf have been found to be anti-inflammatory.

Leaf extract – fresh green leaves of *A. indica* were collected during April and May from the University campus and identified by a pharmacognist of Institute's Indian medicine department. Fresh leaves were separated from stem and with the help of pestal and mortar to make a paste then squeezed to get the leaf extract. The extract was directly used during the experimentation. The dose was calculated in terms of weight of green leaves of *A. indica*. The extract was given orally via an orogastric tube 45 min prior to the behavioral testing. (report no longer available online)

[Comp Biochem Physiol C Toxicol Pharmacol](#). 2007 Mar;145(2):236-44. Epub 2006 Dec 16.

Acute lethal and sublethal effects of neem leaf extract on the neotropical freshwater fish *Prochilodus lineatus*.

[Winkaler EU](#), [Santos TR](#), [Machado-Neto JG](#), [Martinez CB](#).

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http://www.ncbi.nlm.nih.gov/pubmed/17251062?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The aim of this study was to determine the toxicity of the aqueous extract of neem leaves, a product extensively used in fish-farms as alternative for the control of fish parasites and fish

fry predators, for the neotropical fish *Prochilodus lineatus*. The 24 h LC(50) of neem leaf extract for juveniles *P. lineatus* was estimated as 4.8 g L(-1); the fish were then exposed for 24 h to 2.5, 5.0 and 7.5 g L(-1) or only clean water (control). Plasma glucose levels were higher in fish exposed to 2.5 g L(-1) and 5.0 g L(-1) neem extract, relative to control, indicating a typical stress response. Neem extract did not interfere with the osmoregulating capacity of the fish, as their plasma sodium, chloride, total protein and osmolarity did not change. The presence of the biopesticide interfered with the antioxidant defense system of *P. lineatus*, as there was a decrease in liver catalase activity at all neem concentrations and the detoxifying enzyme glutathione-S-transferase was activated in fish exposed to 5.0 g L(-1). Fish exposed to all neem extract concentrations exhibited damaged gill and kidney tissue. These results indicate that although neem extract is less toxic to *P. lineatus* than other synthetic insecticides used in fish-farming it does cause functional and morphological changes in this fish species. PMID: 17251062 [PubMed - indexed for MEDLINE]

[J Environ Biol.](#) 2007 Jan;28(1):119-22.

Toxicity of neem pesticides on a fresh water loach, *Lepidocephalichthys guntea* (Hamilton Buchanan) of Darjeeling district in West Bengal.

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http://www.ncbi.nlm.nih.gov/pubmed/17717997?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

Static renewal bioassay tests were conducted to evaluate the acute toxicity of two neem based biopesticides, applied widely on tea plantation namely, Nimbecidine and Neem Gold either separately as well as, in combination to the fingerlings (mean body length- 4.46 +/- 0.15 cm; mean body weight- 0.49 +/- 0.15g) of a fresh water loach, *Lepidocephalichthys guntea* (Hamilton Buchanan) acclimatized to laboratory conditions prior to experiment. The 96 hours LC50 values for Nimbecidine and Neem Gold and the combination of the two were 0.0135 mgL(-1), 0.0525mgL(-1) and 0.0396 mgL(-1), respectively. The regular water quality analysis showed, that with increasing doses of biopesticides, dissolved oxygen level was lower and other parameters like pH, free carbon dioxide, total alkalinity total hardness, chloride ions of water increased. The fish under toxicity stress suffered several abnormalities such as erratic and rapid movement, body imbalance and surface floating responding proportionately to the increase in concentrations of the toxicant biopesticides. The 96 hours LC50 values proved Nimbecidine more toxic than Neem Gold and the combination of the two biopesticides. PMID: 17717997 [PubMed - indexed for MEDLINE]

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

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

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http://www.ncbi.nlm.nih.gov/pubmed/15473007?ordinalpos=4&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

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.

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PMID: 15473007 [PubMed - indexed for MEDLINE]

[J Herb Pharmacother.](#) 2005;5(4):39-50.

Protective effects of ethanolic neem leaf extract on DMBA-induced genotoxicity and oxidative stress in mice.

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http://www.ncbi.nlm.nih.gov/pubmed/16635967?ordinalpos=3&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

We evaluated the effects of pretreatment with ethanolic neem leaf extract on 7,12-dimethylbenz[a]anthracene (DMBA)-induced genotoxicity and oxidative stress in male Swiss albino mice. The frequency of bone marrow micronuclei, the extent of hepatic lipid peroxidation and the status of antioxidants-reduced glutathione (GSH), glutathione peroxidase (GPx) and glutathione-S-transferase (GST) were used as intermediate biomarkers of chemoprotection. In DMBA-treated mice, the increases in micronuclei and lipid peroxides were accompanied by compromised antioxidant defenses. Pretreatment with ethanolic neem leaf extract (200 mg/kg body weight) significantly reduced DMBA-induced micronuclei and lipid peroxides and enhanced GSH-dependent antioxidant activities. The results of the present study suggest that ethanolic neem leaf extract exerts protective effects against DMBA-induced genotoxicity and oxidative stress by enhancing the antioxidant status.

PMID: 16635967 [PubMed - indexed for MEDLINE]

[Aquat Toxicol.](#) 2004 Apr 28;67(3):239-54.

Some ecological implications of a neem (azadirachtin) insecticide disturbance to zooplankton communities in forest pond enclosures.

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http://www.ncbi.nlm.nih.gov/pubmed/15063074?ordinalpos=6&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

A neem-based insecticide, Neemix 4.5, was applied to forest pond enclosures at concentrations of 10, 17, and 28 microg l(-1) azadirachtin (the active ingredient). At these test concentrations, significant, concentration-dependent reductions in numbers of adult copepods were observed, but immature copepod and cladoceran populations were unaffected. There was no evidence of recovery of adult copepods within the sampling season (May to October). The ecological significance of this disturbance to the zooplankton community was examined by determining biomass as a measure of food availability for higher predators, plankton community respiration, dissolved oxygen (DO) concentrations, and conductivity as functional indicators of ecosystem stress, and zooplankton food web stability as a measure of effects on trophic structure. The selective removal or reduction of adult copepods was sufficient to measurably reduce total zooplankton biomass for several weeks mid-season. During the period of maximal impact (about 4-9 weeks after the applications), total plankton community respiration was significantly reduced, and this appeared to contribute to significant, concentration-dependent increases in dissolved oxygen and decreases in conductivity among treated enclosures. The reductions in adult copepods resulted in negative effects on zooplankton food web stability through eliminations of a trophic link and reduced interactions and connectance. Comparing the results here to those from a previous study with tebufenozide, which was selectively toxic to cladocerans and had little effect on food web stability, indicates that differential sensitivity among taxa can influence the ecological significance of pesticide effects on zooplankton communities.

PMID: 15063074 [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/pubmed/15013179?ordinalpos=8&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

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.

PMID: 15013179 [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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http://www.ncbi.nlm.nih.gov/pubmed/15038245?ordinalpos=7&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

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]

[Inflammopharmacology](#). 2004;12(2):153-76.

Mechanism of antiulcer effect of Neem (*Azadirachta indica*) leaf extract: effect on H⁺-K⁺-ATPase, oxidative damage and apoptosis.

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http://www.ncbi.nlm.nih.gov/pubmed/15265317?ordinalpos=5&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The mechanism of the antiulcer effect of Neem leaf aqueous extract to block gastric lesions in rat has been studied with emphasis on acid secretion, oxidative damage and apoptosis. The extract dose-dependently inhibits gastric lesions induced by restraint-cold stress, indomethacin and ethanol. In stress ulcer model, it is more effective than ranitidine but less effective than omeprazole. It also dose-dependently blocks pylorus ligation and mercaptomethylimidazole-induced acid secretion. In the pylorus-ligation model, it is less effective than omeprazole but as effective as ranitidine. It inhibits H⁺-K⁺-ATPase activity in vitro in concentration-dependent manner to inhibit acid secretion. Oxidative membrane damage by hydroxyl radical (*OH) as measured by lipid peroxidation in stress ulcer is significantly blocked by leaf extract. Stress-induced apoptotic DNA fragmentation is also protected. The extract also prevents *OH-mediated mucosal DNA damage in vitro by scavenging the *OH. Neem leaf extract, thus, offers antiulcer activity by blocking acid secretion through inhibition of H⁺-K⁺-ATPase and by preventing oxidative damage and apoptosis.

PMID: 15265317 [PubMed - indexed for MEDLINE]

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

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

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http://www.ncbi.nlm.nih.gov/pubmed/12889539?ordinalpos=9&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

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.

PMID: 12889539 [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](#).

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http://www.ncbi.nlm.nih.gov/pubmed/12377267?ordinalpos=10&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

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 butylnitron, 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]

[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/pubmed/11933112?ordinalpos=11&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

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. Copyright 2002 John Wiley & Sons, Ltd.

PMID: 11933112 [PubMed - indexed for MEDLINE]

[J Exp Bot.](#) 2001 May;52(358):919-31.

Viability loss of neem (*Azadirachta indica*) seeds associated with membrane phase behaviour.

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http://www.ncbi.nlm.nih.gov/pubmed/11432909?ordinalpos=13&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

Storage of neem (*Azadirachta indica*) seeds is difficult because of their sensitivity to chilling stress at moisture contents (MC) > or =10% or imbibitional stress below 10% MC. The hypothesis was tested that an elevated gel-to-liquid crystalline phase transition temperature (T_m) of membranes is responsible for this storage behaviour. To this end a spin probe technique, Fourier transform infrared microspectroscopy, and electron microscopy were used. The in situ T_m of hydrated membranes was between 10 degrees C and 15 degrees C, coinciding with the critical minimum temperature for germination. During storage, viability of fresh embryos was lost within two weeks at 5 degrees C, but remained high at 25 degrees C. The loss of viability coincided with an increased leakage of K^+ from the embryos upon imbibition and with an increased proportion of cells with injured plasma membranes. Freeze-fracture replicas of plasma membranes from chilled, hydrated axes showed lateral phase separation and signs of the inverted hexagonal phase. Dehydrated embryos were sensitive to soaking in water, particularly at low temperatures, but fresh embryos were not. After soaking

dry embryos at 5 degrees C (4 h) plus 1 d of further incubation at 25 degrees C, the axis cells were structurally disorganized and did not become turgid. In contrast, cells had a healthy appearance and were turgid after soaking at 35 degrees C. Imbibitional stress was associated with the loss of plasma membrane integrity in a limited number of cells, which expanded during further incubation of the embryos at 25 degrees C. It is suggested that the injuries brought about by storage or imbibition at sub-optimal temperatures in tropical seeds whose membranes have a high intrinsic T_m (10-15 degrees C), are caused by gel phase formation. PMID: 11432909 [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.

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http://www.ncbi.nlm.nih.gov/pubmed/11476156?ordinalpos=12&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

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]

[J Exp Bot](#). 2000 Mar;51(344):635-43.

A study of water relations in neem (*Azadirachta indica*) seed that is characterized by complex storage behaviour.

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Neem (*Azadirachta indica*) seed is reputed to have limited tolerance to desiccation, to be sensitive to chilling and imbibitional stress, and to display intermediate storage behaviour. To understand this behaviour the properties of water in seed tissues were studied. Water sorption isotherms showed that at similar relative humidity (RH), the water content was consistently higher in axes than in cotyledons, mainly due to the elevated lipid content (51%) in the cotyledons. Using differential scanning calorimetry, melting transitions of water were observed at water contents higher than 0.14 g H₂O g⁻¹ DW in the cotyledons and 0.23 g H₂O g⁻¹ DW in the axes. Beside melting transitions of lipid, as verified by infrared spectroscopy, changes in heat capacity were observed which shifted with water content, indicative of glass-to-liquid transitions. State diagrams are given on the basis of the water content of seed tissues, and also on the basis of the RH at 20 degrees C. Longevity was considerably improved, and the sensitivity to chilling/subzero temperatures was reduced when axis and cotyledons were dehydrated to moisture contents < or = of approximately 0.05 g H₂O g⁻¹ DW. However, longevity during storage at very low water contents was limited. A possible mechanism for the loss of sensitivity to chilling/subzero temperatures at low water contents is discussed. The results suggest that dry neem seeds in the glassy state have great potential for extended storability, also at subzero temperatures.

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[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/pubmed/10686579?ordinalpos=15&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

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.

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Effects of stress on gamma glutamyl transpeptidase (GGT) activity in lymphoid system of rats: modulation by drugs.

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http://www.ncbi.nlm.nih.gov/pubmed/9332165?ordinalpos=16&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

Effects of stress and its modulation by adaptogens were evaluated on gamma glutamyl transpeptidase (GGT) activity in different tissues of the lymphoid system in rats. Restrain stress (RSx5) suppressed the GGT activity in different tissues of lymphoid system viz. the lymphocyte, the spleen, the thymus and the macrophage, and the maximum effect was seen in the spleen. Chlordiazepoxide, a prototype anti-stress agent, which did not alter GGT activity per se, reversed the effect of RS on this enzyme activity in tissues of lymphoid system studied. Azadirachta indica (AI, Neem), an indigenous adaptogen stimulated the GGT activity per se and nearly normalised RS induced suppression of GGT in lymphoid system. The observed suppression of GGT activity in lymphoid system by stress and its modulation by natural and synthetic adaptogens indicates that GGT could be a consistent cellular/biochemical marker of stress responsiveness and stress-induced immunomodulation.

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The gastric antiulcer effects of the leaves of the neem tree.

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The antiulcer effect of aqueous extracts of the leaves of the neem tree was investigated in rats exposed to 2-h cold-restraint stress or given ethanol orally for 1 h. Extracts were administered in doses of 10, 40, or 160 mg leaf/kg body weight, either as single- or five-dose pretreatment regimens. Neem dose-dependently reduced gastric ulcer severity in rats subjected to stress and also decreased ethanol provoked gastric mucosal damage. The extract appeared to prevent mast cell degranulation and to increase the amount of adherent gastric mucus in stressed animals. These effects may explain, at least in part, the mode of the antiulcer action of neem.

PMID: 8316589 [PubMed - indexed for MEDLINE]

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