

ANTIOXIDANT COMPOUNDS IN NEEM

Overview

Antioxidants are compounds that protect cells against reactive oxygen cells – or free radicals -- in the body. Although they are created as part of the body's normal metabolic functions, free radicals react with other cells and may interfere with their ability to function. Free radicals are believed to play a role in many health conditions, ranging from cancer and atherosclerosis to wrinkles caused by too much sun.

Ongoing research in universities around the world details the antioxidant compounds in neem as well as their impact on animals with chemically induced cancers. A single study reported in [LifeSciences](#) indicates that antioxidant compounds in neem helped to prevent brain damage in rats who had suffered a stroke by enhancing lipid peroxidation and increasing ascorbic acid (Vitamin C) in the brain. Rats pre-treated with neem seemed to complete standard tests, including a water maze, better than the control group.

Unpublished data from Brunswick Laboratories, one of the nation's leading laboratories specializing in the science of antioxidants and oxidative stress, shows that neem is extraordinarily high in antioxidants as measured by the industry-standard ORAC (oxygen radical absorbance capacity).

NUTRIENT	ORAC (oxygen radical absorbance capacity) /gram
Blueberries	62.20
Broccoli	15.90
Cranberry	94.56
Grapefruit	15.48
Neem Bark	476.00
Neem Leaf	357.00
Neem Oil	430.06
Neem/Supercritical Extract (8% in sesame oil)	114
Plums	62.39
Spinach	26.40
Tomatoes	4.6

Recent Research

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Evaluation of *Azadirachta indica* leaf fractions for in vitro antioxidant potential and in vivo modulation of biomarkers of chemoprevention in the hamster buccal pouch carcinogenesis model.

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http://www.ncbi.nlm.nih.gov/pubmed/18442880?ordinalpos=13&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

We evaluated the chemopreventive potential of *Azadirachta indica* (neem) leaf fractions based on in vitro antioxidant assays, and in vivo inhibitory effects on 7,12-dimethylbenz[a]anthracene (DMBA)-induced hamster buccal pouch (HBP) carcinogenesis. In addition we also identified the major constituents in neem leaf fractions by HPLC. Analysis of the free radical scavenging activities and reducing potential of crude ethanolic extract (CEE), ethyl acetate fraction (EAF) and methanolic fraction (MF) of neem leaf revealed a concentration-dependent increase in antioxidant potential that was in the order EAF>MF>CEE. Administration of neem leaf fractions reduced the incidence of DMBA-induced HBP carcinomas at a lower concentration compared to the crude extract. Chemoprevention by neem leaf fractions was associated with modulation of phase I and phase II xenobiotic-metabolising enzymes, lipid and protein oxidation, upregulation of antioxidant defences, inhibition of cell proliferation and angiogenesis, and induction of apoptosis. However, EAF was more effective than MF in terms of antiproliferative and antiangiogenic effects, and expression of CYP isoforms. The greater efficacy of EAF may be due to higher content of constituent phytochemicals as revealed by HPLC analysis. The results of the present study suggest that the antioxidant properties of neem leaf fractions may be responsible for modulating key hallmark capabilities of cancer cells such as cell proliferation, angiogenesis and apoptosis in the HBP carcinogenesis model.

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[Asian Pac J Cancer Prev.](#) 2006 Jul-Sep;7(3):467-71.

Antioxidative and modifying effects of a tropical plant *Azadirachta indica* (Neem) on azoxymethane-induced preneoplastic lesions in the rat colon.

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http://www.ncbi.nlm.nih.gov/pubmed/17059347?ordinalpos=3&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The purpose of the present study was to examine whether Neem leaf (*Azadirachta indica*) has short-term chemopreventive effects on endpoint preneoplastic lesions involved in rat colon carcinogenesis and might also exert antioxidative activity. Forty-two male F344 rats were randomly divided into 6 experimental groups. Groups 1 to 4 were given a subcutaneous injection of azoxymethane (AOM, 20 mg/kg body weight) once a week for 2 weeks. Starting one week before the first injection of AOM, rats in groups 2 to 4 received an aqueous extract of Neem leaf (20, 100, and 250 mg/kg, respectively) by gavage 3 times per week, for 5 weeks. Rats in group 5 also were given the Neem extract by gavage feeding 3 times per week for 5 weeks, while group 6 served as untreated controls. The experiment was terminated 5 weeks

after the start. Dietary feeding of the Neem extract at all dose levels significantly inhibited the induction of aberrant crypt foci (ACF) ($P < 0.0002$), when compared to the AOM-treated group (group 1). In groups 2 to 4, treatment of rats with the Neem extract also significantly decreased the proliferating cell nuclear antigen (PCNA) labeling indices ($P < 0.0006$) of colon epithelium and ACF. Moreover, the Neem extract also showed antioxidative activity. The finding that dietary Neem has possible chemopreventive effects in the present short-term colon carcinogenesis bioassay suggests that longer-term exposure may cause suppression of tumor development.

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[Med Princ Pract.](#) 2006;15(3):219-22.

Comparison of free radical scavenging activity of Siamese neem tree (*Azadirachta indica* A. Juss var. *siamensis* Valetton) leaf extracts prepared by different methods of extraction.

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OBJECTIVE: The aim of this study was to investigate the antioxidant activity of the aqueous extracts of leaves of Siamese neem tree (*Azadirachta indica* A. Juss var. *siamensis* Valetton) from several extracting and drying methods using 2,2-diphenyl-1-picrylhydrazyl (DPPH)-scavenging assay. **MATERIALS AND METHODS:** The leaves of Siamese neem tree were extracted using percolation, decoction, maceration, soxhlet extraction, freeze drying or spray drying methods. The extract was tested for antioxidant activity using DPPH-scavenging assay. Thin-layer chromatography of the extract from decoction was also investigated. **RESULTS:** The freeze drying method gave the highest yield (51.50%, w/w) of crude extract, while decoction gave the most effective DPPH-scavenging activity (EC(50): 31.4 microg/ml). Thin-layer chromatography analysis was used to screen the leaf extract obtained using decoction, and the chromatogram showed spots corresponding to quercetin and rutin flavonoids which exhibited antioxidant activities (EC(50): 2.29 and 34.67 microg/ml, respectively). **CONCLUSION:** Siamese neem tree leaf extracts possessed free radical scavenging activity against the DPPH radical. The most active extract was obtained with the leaf decoction method. It showed antioxidant activity with EC(50) of 31.4 microg/ml. Copyright 2006 S. Karger AG, Basel.

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[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.

[Mol Cell Biochem.](#) 2006 Feb;283(1-2):47-55.

Inhibitory effects of *Azadirachta indica* on DMBA-induced skin carcinogenesis in Balb/c mice.

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Male Balb/c mice were divided into four groups on the basis of their respective treatments wherein mice of Group I served as controls. For induction of skin tumors, mice of Group II and IV were injected sub-cutaneously with 7,12-dimethylbenz(a)anthracene (DMBA). Mice of Group III and IV were administered aqueous *Azadirachta indica* leaf extract (AAILE) thrice a week throughout the experiment. After 14 weeks of the first DMBA injection, Group II and IV mice developed tumors. In the tumor-bearing mice that received AAILE (Group IV), a significant reduction in mean tumor burden and tumor volume was observed. The tumors were confirmed to be papillomas and interestingly, the extent of hyper-chromatia was observed to be much more in skin tumors of Group II mice vis a vis the mice receiving AAILE. An increase in

the extent of lipid peroxidation was observed in tumorous tissue of Group IV when compared to that of Group II mice. Glutathione (GSH) content and the activities of GSH-based antioxidant enzymes viz. glutathione peroxidase (GPx) and glutathione reductase (GR) increased significantly in the skin tissues of all the groups of mice when compared to control counterparts. Catalase activity was found to decrease significantly in the skin of mice, which received AAILE treatment only (Group III). Activity of super-oxide dismutase (SOD) decreased significantly in all the tumorous tissues (Group II and IV mice). In light of the above observations, the role of AAILE in inhibition of DMBA-induced skin carcinogenesis is discussed in the present study.

[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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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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Antioxidant activity of Siamese neem tree (VP1209).

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Leaves, fruits, flowers and stem bark extracts from the Siamese neem tree (*Azadirachta indica* A. Juss var. *siamensis* Valetton, Meliaceae) were assessed for antioxidant activity in vitro using the 1,1-diphenyl-2-picryl hydrazyl (DPPH) scavenging assay, total antioxidant activity and inhibition of lipid peroxidation in Chago K1 cancer cell culture by the thiobarbituric acid reactive substances (TBARS) method. The results showed that leaf aqueous extract, flower and stem bark ethanol extracts exhibited higher free radical scavenging effect on the DPPH assay with 50% scavenging activity at 26.5, 27.9 and 30.6 microg/ml, respectively. The total antioxidant activity of these extracts was found to be 0.959, 0.988 and 1.064 mM of standard trolox, respectively. At 100 microg/ml, the flower ethanol and leaf aqueous extracts significantly decreased malondialdehyde (MDA) levels (46.0 and 50.6%, respectively) by the TBARS method. The results suggest that extracts from leaf, flower and stem bark of the Siamese neem tree have strong antioxidant potential. This report supports the ethnomedical use of young leaves and flowers of this plant as a vegetable bitter tonic to promote good health. PMID: 15848028 [PubMed - indexed for MEDLINE]

[Life Sci.](#) 2005 Feb 4;76(12):1325-38. Epub 2005 Jan 18.

Neuroprotective effect of *Azadirachta indica* on cerebral post-ischemic reperfusion and hypoperfusion in rats.

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We assessed the effect of *Azadirachta indica* (*A. indica*), a plant that has been reported to possess antioxidant, anti-inflammatory and anxiolytic properties, on cerebral reperfusion injury and long term cerebral hypoperfusion. When blood flow to brain region that has undergone critical period of ischemia is re-established, additional injury is to be expected from the reperfusion. In the present study, bilateral common carotid artery (BCCA) occlusion for 30 min followed by 45 min reperfusion resulted in increase in lipid peroxidation, superoxide dismutase (SOD) activity and fall in total tissue sulfhydryl (T-SH) groups. *A. indica* pretreatment (500 mg/kg/day x 7 days) attenuated the reperfusion induced enhanced lipid peroxidation, SOD activity and prevented fall in T-SH groups. Moreover, *A. indica* per se increased brain ascorbic acid level, which was unchanged during reperfusion insult. Long-term cerebral hypoperfusion induced by permanent BCCA occlusion has been reported to cause behavioral and histopathological abnormalities. In the present study, as tested by open field paradigm and Morris' water maze, a propensity towards anxiety and disturbances of learning/memory were observed in animals subjected to hypoperfusion for 2 weeks. *A. indica* (500 mg/kg/day x 15 days) significantly reduced these hypoperfusion induced functional disturbances. Reactive changes in brain histology like gliosis, perivascular lymphocytic infiltration, recruitment of macrophages and cellular edema following long term hypoperfusion were also attenuated effectively by *A. indica*. We conclude that our study provides an experimental evidence for possible neuroprotective potentiality of *A. indica*.

PMID: 15670613 [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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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.

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[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=57&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.

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[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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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.

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[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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http://www.ncbi.nlm.nih.gov/pubmed/15468891?ordinalpos=8&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

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 medicine 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.
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[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 sulphhydryl 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.
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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.

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[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]

[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/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12889539&query_hl=1&itool=pubmed_docsum

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.

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[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.

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http://www.ncbi.nlm.nih.gov/pubmed/12377267?ordinalpos=14&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.

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[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. Copyright 2000 John Wiley & Sons, Ltd. PMID: 10861977 [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]

[J Ethnopharmacol.](#) 1999 Nov 1;67(2):189-95.

Chemopreventive potential of neem (*Azadirachta indica*) on 7,12-dimethylbenz[a]anthracene (DMBA) induced hamster buccal pouch carcinogenesis.

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http://www.ncbi.nlm.nih.gov/pubmed/10619383?ordinalpos=20&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The inhibitory effect of the aqueous extract of neem (*Azadirachta indica* A. Juss.) on 7,12-dimethylbenz[a]anthracene (DMBA) induced buccal pouch carcinogenesis was investigated in Syrian male hamsters. All hamsters painted on their buccal pouch with DMBA for 14 weeks developed squamous cell carcinoma. Administration of neem leaf extract effectively suppressed oral carcinogenesis initiated with DMBA as revealed by the reduced incidence of neoplasms. Lipid peroxidation, glutathione (GSH) content and the activities of glutathione peroxidase (GPx), glutathione S-transferase (GST) and gamma-glutamyl transpeptidase (GGT) were used to biomonitor the chemopreventive potential of neem. Lipid peroxidation was found to be significantly decreased, whereas GSH, GPx, GST and GGT were elevated in the oral mucosa of tumour bearing animals. Our data suggest that neem may exert its chemopreventive effects in the oral mucosa by modulation of lipid peroxidation, antioxidants and detoxification systems.

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[Contraception.](#) 1996 Dec;54(6):373-8.

Mechanism of action of NIM-76: a novel vaginal contraceptive from neem oil.

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http://www.ncbi.nlm.nih.gov/pubmed/8968666?ordinalpos=21&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The present study was undertaken to elucidate the mechanism of spermicidal action of NIM-76, a fraction isolated from neem oil. The spermicidal activity of NIM-76 was confirmed using a fluorescent staining technique. NIM-76 was found to affect the motility of the sperm in a dose-dependent manner. Supplementation of pentoxifylline, which is known to enhance the motility of the sperm, could not prevent the spermicidal action of NIM-76. There was a gradual leakage of cytosolic LDH from the sperm in the presence of NIM-76. Electron microscopic studies revealed the formation of pores and vesicles over the sperm head, indicating the damage to the cell membrane. Membrane fluidization studies did not reveal any significant change in the fluidity of sperm cell membrane structure.

PIP: Neem oil, an extract of a native plant of India, has been demonstrated to have anti-fertility, anti-implantation, and abortifacient properties. An active fraction, termed NIM-76, was extracted that eliminates its abortifacient properties while retaining spermicidal activity.

This fraction kills all human sperm in vitro in under 20 seconds at a concentration of 25 mg/ml. With increases in NIM-76 concentrations from 10 to 1000 mcg/ml, there was a linear decrease in percentages of motile as well as progressively motile sperm with time; also recorded were decreases in percentages of rapid, medium, and slow moving sperm, mean track speed, progressive velocity, mean linearity, and lateral head displacement and an increase in the percentage of static sperm. Electron microscopy revealed the formation of pores and vesicles over the sperm head, indicating damage to the cell membrane. Membrane fluidization studies did not reveal any significant change in the fluidity of sperm cell membrane structure. Since calcium supplementation did not relieve the sperm from the spermicidal action, it was determined that NIM-76 does not cause any depletion of intracellular calcium. The capability of NIM-76 to selectively kill sperm without affecting normal cells makes it a highly desirable potential vaginal contraceptive agent.
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