ULCERS & NEEM

Overview

Right about the time Vioxx and Celebrex became front-page news, a series of reports came out of India and Hong Kong indicating that neem extracts, specifically neem bark extracts, have potent antiulcer properties.

Vioxx and Celebrex, called cox-2 inhibitors, had been hailed as life-saving drugs because they did not cause the gastrointestinal irritation and bleeding that may occur with other pain relievers, like aspirin or ibuprofen. Called non-steroidal anti-inflammatory drugs (often abbreviated as NSAIDs), they may damage the protective mucous layer of the stomach, allowing stomach acids necessary for digestion to further injure the stomach's lining.

In one of the few clinical trials among humans using neem, a A 2004 clinical study at the Indian Institute of Clinical Biology indicates that neem bark causes significant decreases in gastric acid secretion (77%), as well as gastric secretion volume (63%) and pepsin activity (50%). Multiple cases of duodenal ulcers were almost completely healed (as confirmed by barium x-ray or endoscopy) at doses of 30 to 60 mg of neem bark twice daily for 10 weeks. One case of esophageal ulcer and one case of gastric ulcer healed completely when treated at a dose of 30 mg of neem bark twice a day for six weeks. Parameters for toxicity, including sugar, urea and hemoglobin levels, remained within normal range, suggesting no adverse effects on other organs.

Previous animal studies published in Inflammopharmacology had shown that neem bark works by protecting the stomach's mucous lining and preventing oxidative damage by blocking lipid peroxidation and scavenging the free radicals that are a major cause of ulcers.

From the perspective of patients with chronic pain, particularly senior adults suffering from arthritis, the studies may indicate that neem bark used in combination with NSAIDs could be an effective alternative for people faced with the choice of an increased risk of heart attack from cox-2 inhibitors or the potential gastrointestinal injuries from NSAIDs alone.

In addition to its gastro-protective compounds, neem has traditionally been used as an anti-inflammatory treatment with some more recent researching confirming that use. Compounds found in neem compare favorably with cortisone acetate and hydrocortisone according to a study published in the Journal of Indian Medical Research (not available online), which notes that neem may gain efficacy over a period of one to three weeks when treating inflammatory conditions such as arthritis.

And finally, neem bark has traditionally been used as an analgesic with at least one animal study in the Indian Journal of Experimental Biology indicating that it may affect both central and peripheral mechanisms and complex neural pathways. Anecdotal reports from users,

particularly people suffering with chronic pain, suggest that it can be as effective as aspirin in treating joint pain and carpal tunnel syndrome.

Recent Research

Life Sci. 2004 Oct 29;75(24):2867-78.

Clinical studies on the effect of Neem (Azadirachta indica) bark extract on gastric secretion and gastroduodenal ulcer.

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We have shown earlier that Neem (Azadirachta indica) bark aqueous extract has potent antisecretory and antiulcer effects in animal models and has no significant adverse effect (Bandyopadhyay et al., Life Sciences, 71, 2845-2865, 2002). The objective of the present study was to investigate whether Neem bark extract had similar antisecretory and antiulcer effects in human subjects. For this purpose, a group of patients suffering from acid-related problems and gastroduodenal ulcers were orally treated with the aqueous extract of Neem bark. The lyophilised powder of the extract when administered for 10 days at the dose of 30 mg twice daily caused a significant ($p < 0.002$) decrease (77%) in gastric acid secretion. The volume of gastric secretion and its pepsin activity were also inhibited by 63% and 50%, respectively. Some important blood parameters for organ toxicity such as sugar, urea, creatinine, serum glutamate oxaloacetate transaminase, serum glutamate pyruvate transaminase, albumin, globulin, hemoglobin levels and erythrocyte sedimentation rate remained close to the control values. The bark extract when taken at the dose of 30-60 mg twice daily for 10 weeks almost completely healed the duodenal ulcers monitored by barium meal X-ray or by endoscopy. One case of esophageal ulcer (gastroesophageal reflux disease) and one case of gastric ulcer also healed completely when treated at the dose of 30 mg twice daily for 6 weeks. The levels of various blood parameters for organ toxicity after Neem treatment at the doses mentioned above remained more or less close to the normal values suggesting no significant adverse effects. Neem bark extract thus has therapeutic potential for controlling gastric hypersecretion and gastroesophageal and gastroduodenal ulcers.
PMID: 15454339 [PubMed - indexed for MEDLINE]

Indian J Exp Biol. 2004 Apr;42(4):389-97.

Effect of Bacopa monniera and Azadirachta indica on gastric ulceration and healing in experimental NIDDM rats.

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http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15088689&query_hl=18&itool=pubmed_docsum

Gastric ulcers were induced in normal/NIDDM rats by various physical (2 hr cold restraint stress and 4 hr pylorus ligation) and chemical agents (ethanol, 1 ml/200 g, oral, 1 hr before; aspirin, 200 mg/kg, oral, 4 hr) and duodenal ulcers were induced by cysteamine (40 mg/200 g). Ulcer healing activity was studied in gastric ulcers induced by acetic acid (50%) and HCI (0.6 M). The result indicated that in both, normal and NIDDM rats, B. monniera extract (BME, 20-100 mg/kg) did not show any significant effect on blood glucose level, while A. indica (AIE, 250-1000 mg/kg) significantly decreased it. However, both BME (50 mg/kg) and AIE (500 mg/kg) showed significant anti-ulcer and ulcer-healing activities in normal and NIDDM rats. Further, the present results also indicated that the ulcer protective effects of BME was more pronounced in non-diabetic, while that of AIE was more in NIDDM rats. The anti-ulcer and ulcer-healing activities of BME and AIE may be due to their effects on various mucosal offensive and defensive factors, and correction of blood sugar level by AIE may help to have more ulcer protective effect in NIDDM rats.
PMID: 15088689 [PubMed - indexed for MEDLINE]

J Ethnopharmacol. 2004 Jan;90(1):167-70.

Effects of Azadirachta indica extract on gastric ulceration and acid secretion in rats.

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The effect of Azadirachta indica extract on gastric ulceration was studied in albino rats. Azadirachta indica extract (100-800 mg/kg p.o., 100-25 mg/kg i.p.) significantly inhibited gastric ulceration induced by indomethacin (40 mg/kg). Administration of 800 mg/kg p.o. and 250 mg/kg i.p. caused 100% cytoprotection against indomethacin (40mg/kg, i.p.)-induced gastric ulceration. This action was accompanied by a dose-dependent decrease in total gastric acidity. In order to investigate the probable mechanism of Azadirachta indica antiulcer activity, the effect of the extract alone and in combination with histamine (1mg/kg) and cimetidine (0.12 mg/kg) on gastric acid secretion in situ was studied. Azadirachta indica (250 mg/kg) significantly inhibited the basal and histamine-induced gastric acid secretion. Cimetidine seemed to augment Azadirachta indica inhibition of gastric acid secretion.The results suggest that the stem bark extract of Azadirachta indica possesses antiulcer agents, which probably act via histamine H(2) receptor.
PMID: 14698526 [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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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]

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

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The antisecretory and antiulcer effects of aqueous extract of Neem (Azadirachta indica) bark have been studied along with its mechanism of action, standardisation and safety evaluation. The extract can dose dependently inhibit pylorus-ligation and drug (mercaptomethylimidazole)-induced acid secretion with ED(50) value of 2.7 and 2 mg Kg(-1) b.w. respectively. It is highly potent in dose-dependently blocking gastric ulcer induced by restraint-cold stress and indomethacin with ED(50) value of 1.5 and 1.25 mg Kg(-1) b.w. respectively. When compared, bark extract is equipotent to ranitidine but more potent than omeprazole in inhibiting pylorus-ligation induced acid secretion. In a stress ulcer model, it is more effective than ranitidine but almost equipotent to omeprazole. Bark extract inhibits H(+)-K(+)-ATPase activity in vitro in a concentration dependent manner similar to omeprazole. It offers gastroprotection against stress ulcer by significantly preventing adhered mucus and endogenous glutathione depletion. It prevents oxidative damage of the gastric mucosa by significantly blocking lipid peroxidation and by scavenging the endogenous hydroxyl radical ((z.rad;)OH)-the major causative factor for ulcer. The (z.rad;)OH-mediated oxidative damage of human gastric mucosal DNA is also protected by the extract in vitro. Bark extract is more effective than melatonin, vitamin E, desferrioxamine and alpha-phenyl N-tert butylnitrone, the known antioxidants having antiulcer effect. Standardisation of the bioactive extract by high pressure liquid chromatography indicates that peak 1 of the chromatogram coincides with the major bioactive compound, a phenolic glycoside, isolated from the extract. The pharmacological effects of the bark extract are attributed to a phenolic glycoside which is apparently homogeneous by HPLC and which represents 10% of the raw bark extract. A single dose of 1g of raw extract per kg b.w. (mice) given in one day and application of 0.6g raw

extract per kg b.w. per day by oral route over 15 days to a cumulative dose of 9g per kg was well tolerated and was below the LD(50). It is also well tolerated by rats with no significant adverse effect. It is concluded that Neem bark extract has therapeutic potential for the control of gastric hyperacidity and ulcer.
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Planta Med. 1993 Jun;59(3):215-7.

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

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http://www.ncbi.nlm.nih.gov/pubmed/8316589?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

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]