Peptic ulcer therapy: Useful effects of non toxic herbal preparations

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ABSTRACT
Peptic ulcer disease (PUD) is a common problem and about 4 million people suffer from this disease per year in the US. The most common causes of PUD are *H. pylori* infection, over use of NSAIDS, stress, alcohol and tobacco consumption. The anti ulcer drugs are unaffordable and have limitations in their use though are effective. Thus a search for herbal preparations is increasing. *Azadirachta indica* popularly known as neem has been claimed to be of great medicinal importance. The anti ulcer effects of nimbidin a neem compound have been shown to posses anti ulcer and anti secretory activity in experimentally induced acute and chronic duodenal ulcers and in a clinical trial. The anti ulcer effect of aqueous extract of neem leaves were shown on ethanol induced ulcers in rats. Similarly the gastroprotective effect of neem bark extract has been shown to inhibit 94% of gastric secretion. In pyloric ligation induced gastric ulceration an 85% inhibition was shown. Bark extract was found to be equipotent to ranitidine and more potent to Omeperazol. Bark extract was provided gastroprotection by inhibition of acid secretion by H⁺-K⁺-ATPase and prevention of oxidative damage by OH⁻. The bark extract was more effective than nimbidin. *Azadirachta indica* have been shown to inhibit basal and histamine induced gastric acid secretion. Neem bark extract has also been shown to have anti ulcer activity in a clinical trial. Thus in this study the anti ulcer effect of methanolic neem leaves extract (NLE) and an isolated compound of neem nimolicine (NC) has been studied and shown to have anti ulcer effects. The anti ulcer effect of NLE was found to be better than NC.

KEY WORDS:
*Azadirachta indica*, nimbidine, endoscopy, anti oxidant, Neem leaf Extract, nimolicine

INTRODUCTION
Peptic ulcer (PU), also known as *ulcus pepticum*, is a mucosal erosion equal to or greater than 0.5 cm of an area in the stomach or duodenum. Duodenal ulcers are usually but about 4% of gastric ulcers can change to gastric cancers.

As many as 80% of peptic ulcers are associated with *Helicobacter pylori*. *H. pylori* was responsible for PU and not stress as was commonly believed¹,². They won Nobel Prize in 2005 on this discovery in Stockholm.

The other common cause of PUD is NSAIDS which are mostly used all around the world. In the US over 100 million prescriptions are sold yearly. Thus the drug related complications due to NSAIDS are most common. The toxicity of NSAIDS is due to inhibition of COX-1 isoform resulting in ulceration. Aspirin, by reducing Prostaglandins (PG), are responsible for peptic ulcers. These drugs used in a short period of time are not typically dangerous but regular use can lead to gastritis³. Other risk factors include cigarette smoking and alcohol consumption.

Tobacco smoking leads to atherosclerosis and vascular spasms, causing vascular insufficiency and promoting the development of ulcers. Nicotine increases the secretion of histamine and gastrin by stimulating the entochromaffin and G cells. Spicy foods also play a minor role in the development of peptic ulcers. O-blood groups are also prone to ulcers.

Alcohol consumption erode the mucosal lining of the stomach. Low doses of alcohol stimulate hydrochloric acid secretion but high doses of alcohol do not stimulate secretion of acid⁴.
Stress is a possible cause of ulcers. The Academy of Behavioral Medicine Research concluded that psychological factors play a significant role. Stress might promote *H. pylori* infection by increase in gastric acidic secretion. Chronic stress was strongly associated with an increased risk of peptic ulcer.

The prevalence of *H. Pylori* infection in Western countries roughly matches according to age (20% at 20 years of age, 30% at 30 and 80% at 80 years). Prevalence is higher in the third world. The life time risk of developing PU is 10%. About 3000 deaths/year are due to PUD in the USA.

Most of the synthetic preparations used in the treatment of ulcers have limitations. Thus a search for herbal products has been increased specially in the last decade. There are many herbal preparations under study amongst which neem is also included.

Aspirin is the most widely used drug to reduce pain and inflammation, is strongly associated with peptic ulcers even if used in low doses (100 mg daily orally) for prevention of myocardial infarctions. It is therefore suggested that a lower dose of aspirin will inhibit synthesis of gastric prostaglandins to reduce the incidence of gastric mucosal injury. A controlled study to reduce the chances of mucosal damage is recommended. The inhibitory role of Nitric Oxide-releasing derivatives of aspirin causing adhesion of neutrophils to the vascular endothelium reduces the susceptibility of shock-induced damage of stomach. A comparison of NO-releasing aspirin derivatives with plain aspirin showed that adding nitroxybutylerol to acetyl salicylic acid greatly reduces the ulcerogenic effects without altering anti inflammatory property. In spite of all these efforts the problems of PUD still persisted.

H2-receptor antagonist or a proton pump inhibitor for the toxicity of NSAIDS and discontinuation of NSAIDS for the prevention of PUD was proposed. Although H2 receptor blockers (Ranitidine, Famotidine etc.) and proton pump inhibitors (Omeprazole, Lansoprazole etc.) have been used for efficient management of gastric hypersecretion and gastroduodenal ulcers, several adverse effects of these drugs have also been reported. Moreover these antiulcer drugs are usually non affordable. Thus currently, the global view is changing towards the development and therapeutic use of traditional medicinal plants for various diseases.

**Role of Herbal preparations as an anti ulcer agent**

The role of different anti ulcer agents has long been studied to find a solution and provide relief to the suffering patients. These studies have been on plant products and a detailed book "Indusunie" on medicinal uses of neem have been published.

Studies on the antigastric ulcer effects of Nimbidin in rats and guineapigs have been conducted. Nimbidin is the main bitter principle isolated from oil seeds and the trunk bark of *Melia azadirachta* Linn. It is an amorphous cream coloured water insoluble granular powder administered orally. It had significant anti gastric ulcer activity in doses of 20 mg/kg orally in Shay ulcers in rats and histamine induced ulcers in guinea pigs. At 40 mg/kg Nimbidin was found to possess anti secretory effect in Shay rats.

The effects of Nimbidin on acute and chronic duodenal ulcers have shown a significant protective and healing effect in doses of 20-40 mg/kg orally in chemically induced gastric and duodenal ulcers. For the induction of gastric and duodenal ulcers, stress factors, Acetylsalicylic acid, Indomethacin, Steroids, Serotonin and Histamine were used. Nimbidin was given prior to ulcer induction in some experiments and after ulcer induction in others. They showed that nimbidin had antiinflammatory and anti arthritic as well as antiulcer effect which is quite opposite to the other antiinflammatory agents. At higher doses (80 mg/day orally for 10 days) the compound showed significant reduction in ulcer index and a healing rate of 57.8%. They also observed that Nimbidin had antihistaminic (H2 receptor blocking) effect shown in vitro studies. They also showed that even at higher doses up to 2000mg/kg orally and 1000 mg intraperitoneal there were no toxic effects of Nimbidin.

In a clinical trial on 18 diagnosed patients of duodenal ulcers, Nimbidin was given 300 mg/day (60 mg thrice and 120 mg at bed time) for 8 weeks. There was complete healing of ulcers in 16 patients showing that Nimbidin was safe and effective in treatment of duodenal ulcers. There was a significant fall in maximal acid output (MAO). There was no alteration in blood chemistry, urinalysis, haemoglobin and electrocardiogram.
The anti ulcer effects of Chinese Cinnamon in rats by inducing gastric ulcers by cold stress have shown a significant reduction in ulcerogenesis and a reduction in gastric secretion and pepsin output by 46.3% and 44% respectively. These anti ulcer effects were compared to cimetidine. Chinese cinnamon also increased the gastric mucosal blood flow at 30 min. and 60 min. but this effect disappeared at 90 min\textsuperscript{29}.

The anti ulcer effects of aqueous extract of Neem leaves showed a reduction in severity of gastric ulcers induced in rats subjected to stress or by ethanol. The effect was dose dependent against stress induced ulcers and in case of mucosal damage by ethanol the maximum effect can be achieved by smaller doses. The decreased mucosal mast cell degranulation and increased gastric mucus adherence play a role in protection against ulcers induced by stress\textsuperscript{30}.

It has been mentioned that the anti ulcer effect of Neem Leaf extract describing about the potent anti secretory and anti ulcer activity is attributed to a glycoside\textsuperscript{31}.

The gastroprotective effect of Neem bark extract have been reported. The extract can inhibit MMI (Mercaptomethylimidazole) induced acid secretion with 94% inhibition at 20 mg/kg. In pylorus ligated models there was 95% dose dependant inhibition at 30 mg/kg. In ethanol induced gastric damage there was 65% inhibition at 80 mg/kg and 85% inhibition pyloric ligation induced gastric ulceration. In comparison with standard ulcer healing drugs like ranitidine and omeperazole bark extract (ED50 =2.7 mg/kg b. w.) was found to be more potent than Omeperazole (ED50=10 mg/kg b.w.) and equipotent to ranitidine (ED50=2.5 mg/kg b.w.)

b. w.). However in stress ulcer model, the extract (ED50=1.5 mg/kg b. w.) is equipotent to omeperazole (ED50=1 mg/kg b. w.) but much more potent than ranitidine (ED50=36 mg/kg b. w.) in blocking gastric lesions. They have shown that the mechanism of action in gastroprotection is mediated through inhibition of acid secretion by H+-K+-ATPase and prevention of oxidative damage by OH. The antioxidant activity is by directly scavenging the OH and by prevention of OH mediated damage of DNA seen in apoptotic cell death in gastric mucosal injury.

They have also shown that the bark extract was more potent than Nimbidine\textsuperscript{32}.

The protective effect of Polygodial on gastric mucosal lesion induced by ethanol in rats have been studied. Polygodial is an isolate of Tasmania Lanceolata. It significantly inhibits gastric mucosal lesions caused by ethanol and aspirin. It also partly inhibits ulcers caused by pyloric ligation. It had no effect on acid output suggesting a different mechanism of action to Omeperazole. They have suggested a possible mechanism of action of prostaglandins, nitric oxide, sulphhydrils and vanniloid receptors mediated effects are involved in the protective\textsuperscript{33}.

The effect of Azadirachta indica extract on gastric ulceration and acid secretion in rats have shown that Azadirachta indica significantly inhibited gastric ulceration induced by indomethacin at a dose of 40 mg/kg orally and basal and histamine induced gastric acid secretion. Cimetidine seemed to augment the Azadirachta indica inhibition of gastric acid secretion. They also reported that at a high dose of 1000mg/kg intra peritoneal there were no toxic effects or death and suggested that the extract had a wide range of safety and can easily be used in folk medicine\textsuperscript{34}.

Bandyopadhyay et al., (2004) studied the antulcer effect on humans. In a clinical trial on 26 patients, 20 having symptoms of gastric acidity and 6 diagnosed cases of gastroduodenal ulcers were selected. Capsules containing 30 mg of Neem bark was given before lunch and dinner for 10 weeks. The collection of gastric secretion for assay of acid and peptic activity was done by a Ryle's tube after 12 hours of fasting at 8 AM. There was complete healing of the ulcers monitored by barium meal X-ray or endoscopy. The volume of gastric secretion and its pepsin activity were also inhibited by 63% and 50% respectively. Brahmachari (2004) has also reported about the anti gastric ulcer effect of neem in a concise table of biological activities of some active principles of neem.

Dorababu et al., (2004) have studied the effects of Bacopa monniera (BME) and Azadirachta indica (AIE) on gastric ulceration and healing in NIDDM rats and have shown that both of them have significant anti ulcer and ulcer healing effects. They have shown that
nimbidine has hypoglycemic effects and this may have a more protective role in NIDDM rats because Diabetes increases the mucosal susceptibility to ulcerogenic stimuli. As compared to Azadirachta indica, BME did not show any effect on blood glucose level. AIE showed a decrease in blood glucose level of 21.3% in normal rats and 43.5% in NIDDM rats.

Subapriya and Nagini (2005) in a review article on the medicinal properties of Neem leaves has mentioned about the gastric ulcer healing properties of Neem leaves apart from the other uses of Neem.

Alhagi maurorum (AME) belongs to the family of Leguminosea and is used in Iranian folk medicine to treat gastric upsets. Naseri and Mard (2007) have studied the anti ulcer effect on gastric ulcers in rats induced by ethanol. They have suggested that the anti ulcer and anti secretory effect of AME is related to a terpene which is also present in some other plants.

Ofusori et al., (2008) have reported that neem extract administered twelve hours after ethanol induced ulcers for 21 days showed anti ulcer effect and regenerative potential in stomach and ileum in Wistar rats. They have demonstrated a significant increase in the thickness of mucosa and muscularis externa when the treated group was compared with the ulcer induced group.

This study has shown the anti ulcer effects of methanolic extract of neem leaf and neem compound NC on albino rats after induction of gastric ulcers by oral ethanol. The effect was compared to ranitidine and Omeperazole. Peanut oil was used as a control for the treatment of ulcers showed no healing effect. It has been shown that the ulcer inhibition of NLE was better than Omeperazole but lesser than ranitidine. NC had the least ulcer inhibition activity. The antioxidant activity of NLE was 80% compared to 11% of NC. The high antioxidant activity of NLE may explain the mechanism of action of anti ulcer effect. Clinical trials are recommended to support our results.

CONCLUSIONS
Herbal preparations can be used as a safe remedy for treatment of ulcers. It will be cost effective and help the poor patients of developing countries.

REFERENCES


