

# ANTI-ULCER AGENTS USED IN ETHNOMEDICINE

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## INTRODUCTION

In the recent times, focus on plant research has increased all over the world and a large body of evidence has been collected to show the immense potential of medicinal plants used in various traditional systems. In the recent years, there has been an upsurge in the clinical use of indigenous drugs. Such herbal plants, originally used in the traditional system of medicine are now being effectively tried in a variety of pathophysiological states. Non-specific mechanisms like restoration of normal physiological milieu and generalized increase in resistance against infections are proposed and the role of immune system in these drug effects is suggested.

Peptic ulcer therapy has undergone many strides over the past few years and a number of drugs are now available for treatment. These drugs are broadly classified into two, those that decrease or counter acid-pepsin secretion and those that afford cytoprotection by virtue of their effects on mucosal defensive factors. Although these drugs have brought about remarkable changes in ulcer therapy, the efficacy of these drugs is still debatable. Reports on clinical evaluation of these drugs show that there are evidences of relapses and adverse effects and danger of drug interactions during ulcer therapy. Hence, the search for an ideal anti-ulcer drug continues and has also been extended into herbal drugs in search for new and novel molecules, which afford better protection and decrease the incidence of relapse. The present review is an attempt to summarize some of the plant products with anti-ulcerogenic potential and their proposed mechanism of action.

- I. Agents that reduce the aggressive factors (gastric acid secretion and pepsin activity)  
The commonly used drugs that reduce gastric acid secretion are:

- a).  $H_2$  (Histamine<sub>2</sub> receptor) antagonists like Ranitidine, Famotidine, Loxatidine. These drugs act by competitive blockade of gastric  $H_2$  receptors. The most prominent action is on the acid output, but its volume, pepsin content and intrinsic factor secretion are also reduced.

*Side effects:* CNS effects, bradycardia, arrhythmias can occur. Also interfere with hepatic metabolism of several drugs by inhibiting cytochrome.P450.

- b). Proton pump inhibitors like Omeprazole, Lansoprazole, Pantoprazole. These substituted benzimidazole agents inhibit the final common step in the gastric acid secretion. They react covalently with the sulphydryl groups of  $H^+K^+$ ATPase enzyme (commonly known as proton pump) and inactivate it irreversibly. Acid secretion resumes only when new  $H^+K^+$ ATPase molecules are synthesized.

*Side effects:* GI disturbances, drowsiness. Marked hypergastrinemia (due to prolonged achlorhydria) may lead to carcinoid-like lesions in stomach.

- c). Anticholinergics like Pirenzepine, Trimipramine, Doxepin. These drugs are used mainly for their antimuscarinic effect on the gastric acid and pepsin secretion and the gastric motility.

- d). Prostaglandin analogues like Misoprostol and Enprostol. The prostaglandins ( $PGE_2$  and  $PGI_2$ ) are produced in the gastric mucosa and serve a protective role by inhibiting acid secretion and promoting mucus and bicarbonate secretion.

*Side effects:* Diarrhoea, abdominal cramps, uterine bleeding and abortion. It is contraindicated in pregnancy. Some of the herbal agents which produce similar effects have been identified.

### Zingiber officinale (Ginger)

The powdered rhizome of ginger root has been used as a traditional remedy for gastrointestinal complaints including in treating peptic ulceration despite the fact

that ginger promotes gastric secretions. Several anti-ulcer compounds have been isolated from ginger, including 6-gingesulphonic acid, 6-shogaol and ar-curcumene. The anti-ulcer activity of ginger may also be due to the potent thromboxane synthetase inhibitor.

#### **Ocimum basilicum**

The gastric anti-ulcer activity of the fixed oil of *O. basilicum* against various ulcerogens in different animal models were studied and it was found to significantly suppress the development of ulcers in a dose-dependent manner. Hence it was concluded that the fixed oil of *O. basilicum* possessed significant anti-ulcer activity which may be due to lipoxigenase inhibitory, (H<sub>2</sub>) antagonistic and antisecretory effects of the oil.

#### **Fenugreek**

The gastroprotective effects of Fenugreek seeds compared to Omeprazole were studied on ethanol induced gastric ulcers. The near normal levels of mucosal glycoproteins indicated the cytoprotective effects of the seed. The significantly lower levels of pepsin activity, protein content and the volume of gastric juice confirmed the anti-secretory activity, which is important in protecting gastric mucosa.

#### **Emblica officinalis**

The ulcer protective potential of methanolic extract of *Emblica officinalis* was assessed in different acute gastric ulcer models, and the healing effect was assessed in chronic gastric ulcers induced by acetic acid in rats. The extract was found to significantly reduce the offensive factors like the volume and concentration of acid as well as pepsin activity.

#### **Ocimum sanctum**

Studies were conducted to investigate the anti-ulcer effect of *Ocimum sanctum* in different ulcer models like cold restraint stress, aspirin, alcohol, pylorus ligation induced gastric ulcer and histamine induced duodenal ulcer and the ulcer healing effect in chronic acetic acid induced ulcer model in comparison to the standard anti-ulcer drug, Omeprazole. The extract was found to reduce the free and total acidity supporting the fact that anti-secretory effect may be responsible for the anti-ulcer efficacy of *O. sanctum*.

#### **Azadirachta indica**

The aqueous leaf extract of *Azadirachta indica* was found to inhibit H<sup>+</sup>K<sup>+</sup>ATPase activity *in vitro* to inhibit acid secretion in different ulcer models.

- II. Agents that augment the gastro duodenal mucosal defensive factors.

The major mucosal defensive mechanisms for physiological defense of ulcer formation are

- a). **Increasing gastric mucus:-** mucus produced by the goblet cells which form a protective layer on the gastric mucosa and prevent diffusion of H<sup>+</sup> ions across this mucus layer. The gastric mucus secretion can be quantified in terms of total carbohydrate: protein ratio; significant decrease in protein content contributed to the increase in TC:P ratio. Decrease in protein content signifies decreased leakage from gastric mucosa indicating increased strengthening of gastric mucosal barrier.
- b). **Increasing bicarbonate ions:-** secreted by surface epithelial cells which protect the gastric mucosa from the effects of the acid gastric luminal contents. The rapid proliferation of gastric mucosa during normal state and following mucosal damage as well as the mucosal blood flow also plays important role in mucosal protection.
- c). **Inhibition of reactive oxygen intermediates:-** Studies have shown that lipid peroxidation and the subsequent generation of oxygen derived free radicals are associated with the pathogenesis of gastric ulcer. Lipid peroxidation involves the formation and propagation of lipid radicals, the uptake of oxygen and rearrangement of double bonds in unsaturated lipids which eventually results in destruction of membrane lipids. Biological membranes are often rich in unsaturated fatty acids and hence these membranes are susceptible to peroxidative attack. Several of the herbal agents are found to augment the production of the cytoprotective mechanism of action. The antioxidant activity of the herbal agents is suggested by their ability to scavenge the peroxide radicals.

There are many plants which are found to possess these effects

1. *Musa sapientum* var. *paradisiaca* (unripe plantain banana)

The anti-ulcerogenic activity of dried powder of banana pulp against ulcers induced by histamine in guinea pigs and, ulcerogenic drugs like aspirin, phenylbutazone and restraint stress in rats have been reported. The effect was mostly ascribed to increase in gastric mucus secretion quantified in terms of total carbohydrate: protein (TC: P) ratio; significant decrease in protein content

contributed to the increase in TC : P ratio. Decrease in protein content signifies decreased leakage from gastric mucosa indicating increased strengthening of gastric mucosal barrier. Hence the anti-ulcer activity was proposed to be due to its predominant effect on mucosal defensive factors and was reported to have no activity on offensive acid-pepsin secretion.

#### ***Asparagus racemosus* (Satavari)**

The anti-ulcerogenic activities of juice of fresh roots of *A. racemosus* have been reported against cold restraint stress and pylorus ligation induced gastric ulcers. The activity was reported to be due to both decrease in offensive acid-pepsin secretion and increase in defensive mucin secretion. Mucin secretion was quantified in terms of TC; P ratio in gastric juice. The strengthening of mucin barrier further led to a decrease in DNA content of gastric juice indicating decrease in cell shedding.

#### ***Phyllanthus emblica***

The *Phyllanthus emblica* extract was found to enhance secretion of the cytoprotective gastric mucus and hexosamine in indomethacin induced ulceration of rats. Its cytoprotective action on the gastric mucosa was also supported by morphological observations. The strong anti-oxidant property was also proposed to be responsible for the cytoprotective action of the drug.

#### ***Amomum subulatum***

The crude methanolic extract of fruits of *Amomum subulatum* (large cardamom) and its fractions inhibited gastric lesions induced by ethanol significantly and the ethyl acetate fraction increased wall mucus in pylorus ligated rats. The results suggested a direct protective effect of the ethyl acetate fraction on gastric mucosal barrier.

#### ***Fenugreek***

Fenugreek seeds were found to prevent the rise in lipid peroxidation presumably by enhancing the anti-oxidant potential of gastric mucosa thereby lowering mucosal injury.

#### ***Emblica officinalis* (Gooseberry)**

The *Emblica officinalis* extract increased the defensive factors like mucin secretion, cellular mucus and life span of mucosal cells. It was also found to have a significant anti-oxidant effect, which contributes to the cytoprotective effect.

#### ***Punica granatum***

The methanolic extract of *Punica granatum* showed significant reduction in gastric mucosal injury induced by aspirin and ethanol. Significant increases in free

radical scavenging enzymes were obtained which revealed the potent anti-oxidant activity of the extract. The histopathological studies also confirmed the cytoprotective activity. The *in vivo* anti-oxidant and anti-ulcer activity of *P.granatum* may be due to the presence of flavanoids and terpenes.

#### ***Piper betle***

The effect of ethanol extract of *Piper betle* leaf on healing of indomethacin induced experimental ulcer was investigated and it was found that the anti-oxidant enzyme activity as well as the gastric mucosal barrier, primarily the hexosamine and mucus content gradually increased indicating significant protective as well as healing action of the drug. In contrast, the oxidized lipids and oxidatively modified proteins were reduced to near normalcy. The results suggested that the anti-oxidant or free radical scavenging activity of the plant extract might be responsible for its healing action.

#### ***Phyllanthus amarus***

The methanolic extract of *Phyllanthus amarus* significantly inhibited gastric lesions, induced by intra gastric administration of absolute ethanol. Mortality, increased stomach weight, ulcer index, and intra luminal bleeding were reduced by *P.amarus*. The reduced glutathione produced by ethanol administration was significantly elevated by treatment with extract. The anti-oxidant activity of the extract as well as the presence of tannins (precipitate protein and so may be considered as ulcer protectant) in the extract may be responsible for the observed activities.

#### ***Ocimum sanctum* (Thulasi)**

*Ocimum sanctum* increase the mucin secretion in comparison to control. It was concluded that a cytoprotective effect substantiated by the increase in mucin content and the free radical scavenging effect contributed to the anti-ulcer efficacy of *O.sanctum*.

#### ***Caesalpinia pulcherrima***

The studies demonstrated that the pretreatment of rats with the extract of *Caesalpinia pulcherrima* prevented the formation of gastric lesions in HCl/ethanol induced ulcer model, revealing a probable cytoprotective effect of the extract. In the aspirin and the pylorus ligation model, the extract was able to significantly reduce ulcer formation and

increase the mucus content, but had no effect on the gastric volume or acid secretion. Thus the results indicated that the anti-ulcerogenic action of the extract could be attributed to augmentation of gastric defensive mechanisms.

#### ***Azadirachta indica* (Neem)**

The oxidative membrane damage by hydroxyl radical as measured by lipid peroxidation in stress ulcer was significantly blocked by the *Azadirachta indica* leaf extract. The aspirin induced ulcer index was reduced, supports their cytoprotective effect, which may be mediated by prostaglandins as aspirin is known to irreversibly inhibit the prostaglandin synthesis.

#### ***Pongamia pinnata***

The extracts of the seeds of *Pongamia pinnata* showed significant anti-ulcerogenic effect in fasting mice. The petroleum ether, benzene and ethanolic extracts of the root of the same plant showed significant anti-ulcerogenic effect in the pylorus ligated rat ulcer model. The extract decreased acid pepsin secretion as well as increased the mucus secretion, thus probably relieving stress induced ulceration.

#### **CONCLUSION**

Ulcers were previously thought to be due to increase in offensive factors namely acid and pepsin, but it

has been found that acid secretion is either normal or below normal in gastric ulcer patients, and that 40-70% cases of duodenal ulcer patients show acidity within normal range, suggesting that other factors are also involved in ulcerogenesis. Hence the interest then shifted to the defensive factors, whose imbalance with the offensive factors are now thought to be the cause of ulcers. Most of the anti-secretory drugs reduce acid secretion, thus giving immediate symptomatic relief, but there are reports of adverse effects and relapses in the long run. On the contrary natural drugs mostly augment the defensive factors and may be slow in activity but are reliable and safe. Hence use of natural drugs alone or with combination with other drugs should be seriously considered.

It is apparent that experimental evaluation of herbal drugs for the treatment of gastric ulcer is rather impressive, but very few have reached clinical trials and still few have been marketed. This shows that the benefits of research are not reaching the people to whom medical research is directed and hence the time, manpower and resources are not efficiently utilized.



## **BIRD FLU STRUCK INDIA AGAIN**

The Department of Animal Husbandry of Government of India on 14th March 2006 confirmed the second outbreak of Avian Influenza in the Indian subcontinent. Samples received by High Security Animal Disease Laboratory (HSADL), Bhopal from Maharashtra towards the end of February were tested positive for Avian Influenza (H5 strain). Outbreak of Avian Influenza is now confirmed in four villages of Jalagaon District of Maharashtra.

These villages are (i) Jalagaon Hated village of Chopada Taluka (ii) Sawada village of Raver Taluka (iii) Salve village of Dharangaon Taluka and (iv) Marul village of Yaval Taluka. Poultry reared in the 10 kilometre zone will be destroyed by Rapid Response Teams of Veterinarians of the State Government of Maharashtra. No human case of Avian Influenza has been detected in India till now.

This has occurred at a time when the control and containment operations in Navapur and Uchchal areas of Maharashtra and Gujarat respectively, where Avian Influenza was notified on 18th February 2006 were nearing completion. More than 4 lakh birds in 57 farms have been killed in Maharashtra and Gujarat. The number of eggs that have been destroyed in control operations are more than 14.75 lacs. Other infected materials such as feed, feed ingredients, egg trays and feathers have also been destroyed. An amount of Rs. 1.34 crores has been spent as compensation to poultry owners for birds killed in operations.

