

## Antiulcer effect of *Feronia elephantum* Correa leaf and bark extract in indomethacin induced albino rats

A. Muthulakshmi<sup>1</sup>, R. Jothibai Margret<sup>2</sup> and V.R. Mohan<sup>3\*</sup>

<sup>1</sup>Department of Chemistry, V.O. Chidambaram College, Tuticorin-628002, Tamil Nadu, India.

<sup>2</sup>Department of Chemistry, Pope's College, Sawyerpuram-628251, Tamil Nadu, India.

<sup>3</sup>Ethnopharmacology Unit, Research Department of Botany, V.O. Chidambaram College, Tuticorin-628008, Tamil Nadu, India.

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### ABSTRACT

In the present study, the gastro protective effect of *Feronia elephantum* leaves and bark in a model of NSAID-induced ulcer in rat was analyzed. The lyophilized extract was given by oral gavages (500 mg/kg) three times at 12 hr intervals before administering Indomethacin at 20 mg/kg. Pretreatment with extract significantly decreased the ulcerated area. The volume and acidity of the gastric juice decreased in the pretreated rats. In conclusion, *F. elephantum* was able to decrease the acidity and increase the mucosal defense in the gastric areas, there by justifying its use as an antiulcerogenic agent.

### INTRODUCTION

Ulcer is a common disorder of the gastrointestinal system, which causes much discomfort in patients, disrupting their daily routines and causes mental agony. It is generally more common in those who keep themselves in hurry, become worry and consume curry (David and Peura, 2004). Peptic ulcer disease can be characterized by inflamed lesions or excavations of the mucosa and tissue that protect the gastrointestinal tract. A peptic ulcer is a sore in the lining of stomach or duodenum, the first part of small intestine. If peptic ulcers are found in the stomach, they are called gastric ulcers. If they are found in the duodenum, they are called duodenum ulcers (McGuigan, 1991).

Gastric ulcers are also associated with considerable morbidity related to chronic epigastric pain, nausea, vomiting, and anemia (Shin *et al.*, 2002). Rarely, an ulcer can lead to a gastric or duodenal perforation. This is extremely painful and requires immediate surgery (Brooks, 1996). Recently, *Helicobacter pylori* have been implicated in the antral gastritis, peptic ulcer, gastric malignancy and the non-ulcer dyspepsia (NIHCC 1994). With the increasing use of non steroidal anti inflammatory drugs (NSAIDs)

and the possibility for co-infection with *Helicobacter pylori*, the prevalence of gastric ulcers is estimated to be as high as 4%, with a 10% life time risk (Leung and Sung, 1996).

NSAID-induced ulcers account for approximately 26% of gastric ulcers, and they are believed to be secondary to a decrease in prostaglandin production resulting from the inhibition of cyclooxygenase. The topical effects of NSAIDs are superficial gastric erosions. However, the risk of gastroduodenal ulcer is not diminished with parental or rectal use of NSAIDs indicating injury occurring from the systemic effect of NSAIDs on the gastrointestinal mucosa. The greatest risk of developing ulcer occurs during the first 3 months of NSAID use; thereafter, the risk decreases but continues to be present. Whether, concurrent *H. pylori* infection and NSAID use are synergistic in producing gastric ulcers remains unclear, recent accumulating evidence indicates that, patients with *H. pylori* infection may be twice as likely to get a bleeding peptic ulcer.

Plants with medicinal properties "The gift of mother nature to mankind" are in use for centuries in the traditional system of medicine like Ayurveda, Unani, Siddha etc., in India and other countries for the treatment of diseases including ulcer. They are considered to be effective and non-toxic.

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\* Corresponding Author  
E-mail: [vrmohan\\_2005@yahoo.com](mailto:vrmohan_2005@yahoo.com)

Natural products from plants are a rich resource used for centuries to cure various ailments. The use of natural medicine in the treatment of various diseases like peptic ulcer is an absolute requirement of our time (Sasmal *et al.*, 2007).

The treatment of peptic ulcers with plant products and herbs as used in folk medicine was reported (Adami *et al.*, 1964; Ageel *et al.*, 1987; Best *et al.*, 1984; Satyavati *et al.*, 1987). The protection of induced gastric ulcer in laboratory animals using medicinal plants was reported (Affifi *et al.*, 1997).

*Feronia elephantum* is one of the medicinally important plants belonging to Rutaceae, commonly known as wood apple. Various parts of wood apple have been used against various ailments in ethnomedicine. Juice of young leaves is mixed with milk and sugar candy given as remedy for biliousness and intensive troubles of children.

A powdered gum mixed with honey, is given to overcome dysentery and diarrhea in children. The leaves are used traditionally in Ayurveda as antiemetic, aromatic, expectorant, purgative, useful in anorexia, bronchitis, calculus, cardiac debility, cough, gastropathy, hiccup and in vitiated conditions of vayu (Gill *et al.*, 1998). The bark is occasionally prescribed for biliousness and useful in liver diseases (Priya, 2000). The present study was carried out to provide scientific validation for antiulcer activity of *Feronia elephantum*.

## MATERIALS AND METHODS

### Collection of plant material

Fresh and disease free leaf and bark of *Feronia elephantum* Correa were collected in the month of Feb and March-2012 from the Agasthiarmalai Biosphere Reserve, Western Ghats, Tirunelveli.

The plant was identified with the help of local flora and voucher specimen, preserved in Ethnopharmacology unit, Research Department of Botany, V.O.Chidambaram College, Tuticorin-628 008, Tamil Nadu, India.

### Experimental animals

Healthy female albino wistar rat of 110-200g were used throughout the study. Animals were housed under standard environmental conditions at temperature ( $25\pm 2^{\circ}\text{C}$ ) and light and dark (12:12h) Rats were feed standard pellet diet (Goldmohurbrand, Ms. Hindustan Lever Ltd., Mumbai, India) and water *ad libitum*.

### Preparation of plant extract for phytochemical screening

The *F. elephantum* leaf and bark were shade dried separately at room temperature and the dried leaves and bark were powdered in a Wiley mill. Hundred grams of powered *F. elephantum* leaves and bark was packed in a soxhlet apparatus separately and extracted with ethanol. The ethanol extracts were subjected to qualitative test for the identification of various phytochemical constituents as per the standard procedures (Brinda *et al.*, 1988; Anonymous 1990; Lala 1993).

### Preparation of ethanol extracts of *F. elephantum* leaf and bark for antiulcer activities

Leaf and bark of *F. elephantum* were cut separately into small pieces and shade dried for the experimental studies. Dried leaves and bark were powdered separately and then extracted in ethanol by keeping the leaf and bark powder separately (1:50w/v) for 48 hours and then it was filtered with the help of Whatmann paper No.1 filter paper and filtrate was lyophilized. Both the leaf and bark lyophilized samples were stored at dry place.

### Induction of ulcer

The non-steroidal antiinflammatory drug, Indomethacin was used as the ulcerogenic agent at the dose of 20 mg/kg body weight.

### Experimental design

All the animals were grouped into five groups. Each group had 3 animals.

**Group I:** Served as control animals, without any treatment fed with normal water.

**Group II:** Animals were treated with NSAID, Indomethacin at a dose 20 mg/kg., body weight.

**Group III:** Animals co-treated with ethanol leaf extract of *F. elephantum* (500 mg/kg body weight) and Indomethacin (20 mg/kg)

**Group IV:** Animals co-treated with ethanol bark extract of *F. elephantum* (500 mg/kg body weight) and Indomethacin (20 mg/kg).

**Group V:** Animals were pretreated with ranitidine (20mg/kg) and then treated with NSAID following the dose and mode of administration (Berenguer *et al.*, 2006).

Standard antiulcer drug ranitidine are used at the rate of 20 mg/kg of body weight. All the groups of animals were kept overnight fasting, fed only with the tap water. The animals of group III and IV were treated with the sample extract at the doses of 500 mg/kg of body weight. This treatment was given thrice at the 12 hours interval. Animals of Group V were treated with ranitidine simultaneously. After one hour of last administration of sample extract, the NSAID was given by oral gavages to the Group II to Group V animals. After 6 hours of NSAID administration, the animals were sacrificed by cervical dislocation.

The animals were dissected and the stomach was taken out. Finally the ulcers were observed macroscopically. The observation was made for any bulging or inflammation in the stomach. The stomachs were opened along the greater curvature and the mucosa was exposing for evaluation. The ulcer scores (US) were calculated as the arithmetic mean for each treatment. By sacrificing the rat, stomach was removed and opened along the greater curvature and washed it slowly under tap water, but it on the glass slide and observed naked eye.

**Table 1:** Effect of leaf and bark extracts of *F. elephantum* on gastric acidity parameters and ulcer index.

| Parameter | Treatment                | Dose (mg/kg) | pH of gastric contents | Concentration of acid in gastric contents (meq/L) | Gastric ulcer index |
|-----------|--------------------------|--------------|------------------------|---|---------------------|
| Group I   | Normal saline            | -            | 2.50±0.43              | 0.12±0.03   | 0.401±0.031         |
| Group II  | Indomethacin             | 20           | 2.05±0.13              | 0.23±0.09   | 4.672±0.594         |
| Group III | Indomethacin+FEL extract | 500          | 3.89±0.15              | 0.03±0.02   | 1.103±0.221         |
| Group IV  | Indomethacin+FEB extract | 500          | 2.96±0.21              | 0.06±0.01   | 3.829±0.102         |
| Group V   | Indomethacin+ ranitidine | 20           | 3.26±0.11              | 0.17±0.04   | 0.650±0.041         |

### Collection of Gastric Juice

The stomach was carefully keeping the oesophagus closed, opened along the greater curvature and the gastric contents were removed. The gastric contents were collected in plain tubes, centrifuged at 3000rpm for 5 min. The volume of the supernatant was expressed as ml/100g body weight. The mucosa was flushed with saline and observed for gastric lesions using the macroscopic structure.

### RESULTS AND DISCUSSION

Peptic ulcer disease (PUD) is one of the common diseases. The causes of PUD are increased gastric acid secretion and / or reduced gastric cycloprotection. Peptic ulcer diseases occur mainly due to consumption of NSAIDs, infection by *Helicobacter pylori*, stress or due to pathological conditions such as Zollinger-ellison syndrome (Crawford 2000).

Cause of PUD due to NSAIDs include factors that increase acid secretion, reduction of gastric mucosal blood flow, inhibition of prostaglandin synthesis, disruption of mucosal barrier, inhibition of mucus and bicarbonate secretion in the gastro intestinal mucosa (Aase 1989; Allen and Leonard 1985). That is an imbalance between increased aggressive factors and decreased protection factors. In the present study, parameters such as ulcer index, gastric pH, and concentration of acid in gastric contents have been analyzed. Indomethacin caused damage on the glandular mucosa (4.672 ±0.594). In contrast to it, the pretreatment with ethanol extracts of leaf bark of *F. elephantum* at the doses of 500 mg/kg body weight, decreases the ulcerated area to 1.103±0.221 and 3.823± 0.102 respectively, which was comparable to the effect exerted by ranitidine 0.650±0.041. Administration of leaves extract of *F. elephantum* decreased the gastric volume, simultaneously the gastric acidity also decreased significantly in comparison with rats treated with ranitidine. The results suggest that, indomethacin altered the parameters to considerable extent, which were restored to near normal with *F. elephantum* leaf extract. Indomethacin produced mucosal injury was confined to glandular stomach which was revealed by increase in ulcer index (Table I). Treatment with *F. elephantum* produced remarkable changes to cure ulcer. The present study showed that, pretreatment with leaf and bark extract of *F. elephantum* caused a beneficial effect on NSAID-induced gastric ulcer in rats as evidenced by the reduction in the ulcer score. Indomethacin induces H<sup>+</sup>/K<sup>+</sup> ATPase in gastric parietal cells. This increases the gastric acid secretion. In the present study, increased gastric acid secretion resulted in decreased pH in indomethacin induced rats (2.05±0.13) (Table 1).

*F. elephantum* leaf extract (3.89±0.15) brought back the altered values to normal.

NSAIDs induced PUD mainly due to inhibition of prostaglandin (Barnett *et al.*, 2000). Prostaglandin has inhibitory effect on hydrochloric acid secretion in the stomach cells. NSAIDs block the synthesis of prostaglandin by inhibiting cyclooxygenase (COX-I and COX-II). Inhibition of both COX-I and COX-II induces gastric ulcer (Chakraborty *et al.*, 1996).

The defense mechanism of the gastrointestinal mucosa against aggressive factors such as HCl, bile acid and NSAIDs, mainly consisting of functional, humoral and neuronal factors, while prostaglandins and nitric oxide act as humoral factors. In recent experiments, it has been found that, heat shock proteins (HSPs), specifically HSP 70 and HSP47 are involved in gastric production. The HSC 70 (a constitutive form of HSP 70) is co-precipitated with COX-I and the neuronal form of nitric oxide synthase after treatment with mild irritants (20% ethanol). A positive relationship between enhanced interaction of HSC 70 with either cyclooxygenase-1 or nitric oxide synthase and mucosal defense mechanisms and ulcer healing, most probably through protecting key enzymes related to cytoprotection (Jasuihiro *et al.*, 2000).

The anti-ulcerogenic activity was proved in the present study of *F. elephantum* leaf and bark extract. These results indicate that, *F. elephantum* has anti-ulcer compounds, which have anti secretory and cytoprotective effects which may be related to the presence of flavonoids, phenolic compounds, tannins detected by phytochemical analysis of ethanol extracts of leaf and bark of *F. elephantum*.

On the other hand, tannins may prevent ulcer development due to their protein precipitating and vasoconstricting effects (Augwa and Nwako, 1988). Their astringent action can help precipitating microproteins on the ulcer site, thereby forming an impervious layer over the lining that hinders gut secretions and protects the underlying mucosa from toxins and other irritants (Nwafor, 2004). This preparatory to bind with proteins also explains the fact that, polyphenols inhibit enzymes tested *in vitro* (AL-Rehailey, 2002).

The results of present study support the traditional use of *F. elephantum* leaf and bark extracts, possessing significant antiulcer activity. This may be due to the presence of phytochemicals such as flavonoids, triterpenoids, saponins and tannins. Of the studied plant parts, leaf of *F. elephantum* showed more antiulcer activity at the dose of 500 mg/kg when compared with standard drug ranitidine. These results indicate that, the *F. elephantum* leaf extract has antisecretory activity.

## CONCLUSION

The present study showed that, pretreatment with leaf and bark extract of *F. elephantum* caused a beneficial effect on NSAID-induced gastric ulcer in rats as evidenced by the reduction in the ulcer score. Further studies are required to establish its exact mode of action and the active principles involved in its antiulcer effect.

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