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Full Length Research Paper

Anti-ulcer activity of *Ficus religiosa* stem bark ethanolic extract in rats

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***Ficus religiosa* is being used in Ayurvedic and Malay traditional medicine for the treatment of various diseases including gastric ulcer. Considering the above claims, the present work was undertaken to validate the anti-ulcer potential of the ethanol extract of stem bark of *F. religiosa* against *in vivo* indomethacin- and cold restrained stress-induced gastric ulcer, and pylorus ligation assays. The extract (100, 200 and 400 mg/kg) significantly ($P<0.05$) reduced the ulcer index in all assays used. The extract also significantly ($P<0.05$) and increased the pH of gastric acid while at the same time reduced the volume of gastric juice and, free and total acidities. In conclusion, the present study provide preliminary data on the antiulcer potential of *F. religiosa* stem bark and support the traditional uses of the plant for the treatment of gastric ulcer.**

Key words: *Ficus religiosa*, stem bark, ethanol extract, gastric ulcer, pylorus ligation, indomethacin, cold stress induced gastric ulcers, ulcer index.

INTRODUCTION

Gastric ulcer (GC) resulted from persistent erosions and damage of the stomach wall that might become perforated and developed into peritonitis and massive haemorrhage as a result of inhibition in the synthesis of mucus, bicarbonate and prostaglandins (Wallace, 2008). Various factors can contribute to the formation of gastric ulcer such as the infection of stomach by *Helicobacter pylori* (Phillipson et al., 2002, 2005), the frequent use of nonsteroidal anti-inflammatory drugs (NSAIDs) (Bighetti et al., 2005) and consumption of alcohol (Bandyopadhyay et al., 2002). The success of commercially available antiulcer drugs in the treatment of gastric ulcer is usually overshadowed by various side effects. For examples, H_2-receptor antagonists (e.g. cimetidine) may cause gynecomasia in men and galactorrhea in women (Feldman and Burton, 1990) while proton-pump inhibitors (e.g. omeprazole and lansoprazol) can cause nausea, abdominal pain, constipation and diarrhea (Reilly, 1999; Franco and Richter, 1998). Due to those side effects, there is a need to find new antiulcerogenic compound(s) with potentially less or no side effects and medicinal plants have always been the main sources of new drugs candidates for the treatment of gastric ulcer (Rates, 2001; Borreli and Izzo, 2000).

One of the plants that have been traditionally used in the Indian and Malays folklore medicine to treat gastric ulcer is *Ficus religiosa* L., which belongs to the family Moraceae. It is known to the Malays and Indian as '*Pokok ara suci*' and '*Peepal* tree', respectively. *F. religiosa*, often planted in the vicinity of the temples, is common throughout India and is a large deciduous tree with few or no aerial roots. It is traditionally used to treat gonorrhoea, diarrhea, dysentery, leucorrhea, menorrhagia, for vaginal

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and other urogential disorders haemorrhoids, ulcers and gastrohelcosis (Ravishankar and Shukla, 2007; Uma et al., 2009). A paste of the powdered bark is a good absorbent for inflammatory swellings and can be used to treat burns (Joy et al., 1998; Madhava et al., 2008). Scientifically, the methanol bark extract of *F. religiosa*, which contained carbohydrates, flavonoids, aminoacids, steroids, saponins and tannins (Uma et al., 2009), was reported to show some anthelmintic activity against *Haemonchus contortus* (Iqbal et al., 2001). In addition, the aqueous bark extract of *F. religiosa*, which contained carbohydrates, tannins, flavonoids and polyphenolic compounds (Kirana et al., 2009), exhibited anti-diabetic activity that is associated with its high antioxidant potential (Kirana et al., 2009; Pandit et al., 2010). Moreover, the ethanol bark extract of *F. religiosa* was reported to possess wound healing (Choudhary, 2006), anti-inflammatory, analgesic and anti-lipid peroxidation (Sreelekshmi et al., 2007), and antibacterial activity against *Bacillus cereus* (Nair and Chanda, 2007) whereas the methanol-, followed by chloroform- and aqueous-, extract, at the concentration of 200 mg/ml, were effective against the enterotoxigenic *Escherichia coli* (Uma et al., 2009). On the other hand, the leaf of *F. religiosa* 70% hydroalcoholic extract, which contained glycosides and tannins, when prepared as ointment form exhibited wound healing activity in rats (Roy et al., 2009). Recent study has also revealed that the methanol leaf extract of *F. religiosa*, which contained high total phenolic and total flavonoids contents, exhibited high antioxidant activity (Krishanti et al., 2010). Earlier study on the same methanol extract demonstrated that the extract inhibited the production of nitric oxide and proinflammatory cytokines in LPS-stimulated microglia via the MAPK pathway (Jung et al., 2008). The high content of total flavonoids reported earlier is concurred another findings by Taskeen et al. (2009) who reported that *F. religiosa* is rich in flavonoids, mainly quercitin and myricetin. The methanol extract of figs of *F. religiosa* was also reported to exhibit a dose-dependent anticonvulsant activity against maximum electroshock- and picrotoxin-induced convulsions through serotonergic pathways modulation (Singh and Goel, 2009) and anti-amnesic activity against scopolamine–induced anterograde and retrograde amnesia (Kaur et al., 2010). Despite the pharmacological activities described above, no attempt has been made to determine the antiulcer activity of the stem bark of *F. religiosa*. Thus, the present study was initiated to evaluate anti-ulcer activity of ethanol extract of stem bark of *F. religiosa* extract (EBFR).

MATERIALS AND METHODS

Collection of plant material

The plant material was collected from local area of Peerancheru in November 2009 and was authenticated at the Department of Botany, Osmania University. A voucher specimen number 0606 (OUH) has been deposited in the herbarium.

Preparation of the extract

The preparation of extract was carried out according to the method of Oktay et al. (2003). Briefly, the stem bark of *F. religiosa* was shade dried after collection for 15 days and was powdered. Approximately 0.95 kg of powdered drug material was extracted using 99% pure ethanol in the ratio of 1:2 (w/v) in a Soxhlet apparatus (Borosil, Mumbai, India). The extract obtained (EBFR) was dried in a rotavapor (Roteva-Equitron, Medica Instruments, Mumbai, India) and the dried mass was weighed and recorded. The percentage of yield was calculated. The weight of dried crude extract obtained was approximately 0.16 g which commemorated with the percentage yield of 17.16%.

Experimental animals

Male albino Wistar rats weighing 150 to 200 g were used in the present study. The experimental animals were maintained under standard laboratory conditions in an animal house approved by the committee for the purpose of control and supervision on experiments on animals (CPCSEA) under 12 h light/dark cycle and controlled temperature (24 ± 2°C) and fed with commercial pellet diet and water *ad libitum*. All animals were acclimatized to the laboratory environment for at least one week before the commencement of experiment. The experimental protocol was approved by the Institutional Animal Ethical Committee, Shadan College of Pharmacy, Peerancheru, Hyderabad, Andhra Pradesh, India.

Acute oral toxicity study and selection of doses

A safe oral dose of EBFR was determined through the acute oral toxic test in rats as described by the Organization of Economic Co-Operation and Development (OECD) as per 423 guidelines (OECD Guidelines for the Testing of Chemicals, 2010). The EBFR, at different doses up to 2000 mg/kg, was prepared by dissolving the extract in distilled water and the concentration was adjusted in such a way that it did not exceed 1 ml/100 g of the rat. The extract was then administered (p.o.) and animals were observed for behavioral changes, any toxicity and mortality up to 48 h. Three different doses (100, 200 and 400 mg/kg, p.o) of EBFR were later chosen for this study based on the acute toxicity testing.

Anti-ulcer assays

Indomethacin-induced gastric ulcers

The gastric ulcers were induced by administering indomethacin (IND; 5 mg/kg. p.o) for five days (Khare et al., 2008). The animals were then treated either with misoprostol (100 µg/kg p.o) or EBFR (100, 200 and 400 mg/kg) once daily for another five days, after the induction of ulcer, while the control group received only vehicle. The rats were sacrificed on the fifth day after the test solutions administration and the ulcer index was determined (Gülcin et al., 2004).

Briefly, the animals were divided into six groups (n = 5) and treated with the respective test solutions as given below:

(i) Group 1 (normal control group) – vehicle + vehicle.
(ii) Group 2 (negative control group) – 5 mg/kg IND + vehicle.
(iii) Group 3 - 5 mg/kg IND + 100 mg/kg misoprostol.
(iv) Group 4 - 5 mg/kg IND + 100 mg/kg EBFR.

Table 1. Effect of EBFR on ulcer index in the three models of gastric ulcers.

Treatment group	Dose (mg/kg)	PL-induced gastric ulcer[1]	IND-induced gastric ulcer[1]	CRS-induced gastric ulcer[1]
Control	-	10.32	10.4	10.32
Standard drugs		4.08[*A]	6.14[*B]	4.08[*A]
EBFR	100	8.22	8.20	8.22
	200	6.16[*]	6.18[*]	4.12[*]
	400	4.10[*]	4.08[**]	2.06[**]

[1]Each value represent s the mean (Standard deviation for each of the test solution was less than 10% of the mean value), [*] Data differs significantly (P<0.05) when compared to the control of respective column, [**] Data differs significantly (P<0.05) when compared to the control of respective column, [A] The standard drugs used was 50 mg/kg ranitidine, [B] The standard drugs used was 100 µg/kg misoprostol.

(v) Group 5 - 5 mg/kg IND + 200 mg/kg EBFR.
(vi) Group 6 - 5 mg/kg IND + 400 mg/kg EBFR.

Cold restraint stress-induced ulcers

The ulcer was induced by subjecting the animals to cold restraint stress (CRS). Ranitidine (50 mg/kg.) or EBFR (100, 200 and 400 mg/kg) were administered orally 30 min prior to subjecting the animals to cold stress. The animals were placed in a restraint cage and the cage was placed at a temperature of 2°C for 3 h (Khare et al., 2008). The animals were sacrificed after three hours and the ulcer index was determined. Briefly, the animals were divided into six groups (n = 5) and treated with the respective test solutions as given below:

(i) Group 1 (normal control group) – vehicle + vehicle.
(ii) Group 2 (negative control group) – CRS + vehicle.
(iii) Group 3 - CRS + 50 mg/kg ranitidine.
(iv) Group 4 - CRS + 100 mg/kg EBFR.
(v) Group 5 - CRS + 200 mg/kg EBFR.
(vi) Group 6 - CRS + 400 mg/kg EBFR.

Pylorus ligation-induced ulcers in rats

Animals were fasted for 48 h before pylorus ligation (PL) but allowed to have free access to water *ad libitum*. Animals were housed singly in cages to prevent cannibalism and coprophagy. Under anesthesia, a one-inch midline abdominal incision was given below the xiphoid process. The pylorus was carefully lifted out with minimal handling and traction and ligated without damaging its blood supply. The stomach was replaced and the abdominal wall was closed with sutures. The test solutions were administered orally and the animals were placed in plastic cylinders. Approximately 18 h after pyloric ligation, the animals were sacrificed and the stomachs were dissected out. The contents of stomach were drained into a graduated centrifuge tube and the volume of gastric content, pH of gastric acid, after centrifugation its acidity was determined by titration with 0.1 N NaOH (Gupta, 2005). Total and free acidity were determined as previously described (Kulkarni, 2005).

The stomach was opened along its greater curvature pinned on a cork plate and inner surface was examined for ulceration with binocular microscope. The ulcer index was calculated and the ulcer severity was graded as previously described (Gupta, 2005). Ulcer severity is graded as:

0-No ulcer, 1-Superficial ulcer, 2-Deep ulcer and 3-Perforation

The ulcer index (UI) was calculated by the following equation:

$UI = UN + US + UP \times 10^{-1}$

where, UN = Average number of ulcers/ animal, US = Average severity scores, UP = Percentage of animals with ulcers. Ulcer index and acidity of the gastric content of the treated animals were compared with the control.

Statistical analysis

Data is expressed as mean ± SEM. Data was analyzed by one way ANOVA followed by Dunnett's multiple comparison test. The significance of difference was accepted at P< 0.01.

RESULTS

Acute toxicity study carried out on EBFR up to the dose of 2000 mg/kg demonstrated that the extract did not show any sign of toxicity and mortality. However, there was a decrease in physical activity, which was observed only at the dose of 2000 mg/kg. Thus, the present doses regime (100, 200 and 400 mg/kg) was chosen for further studies. Based on the gross examination of the rats' stomach, the control animals had ulcers and confirmed by the presence of haemorrhagic streaks. However, there was significant (P<0.05) reduction in ulcer development in IND- and CRS-induced gastric ulcer groups treated with 200 and 400 mg/kg EBFR as indicated by reduction in ulcer index (Table 1).

In group underwent PL-induced gastric ulceration, the same doses of EBFR (200 and 400 mg/kg) were significantly (P<0.05) effective in reducing the ulcer index (Table 1).

To determine the mechanisms of action of EBFR, the extract antiulcer potency was tested against PL-induced gastric ulcer. The macromorphological data obtained when ulceration of the gastric mucosa was provoked using PL are shown in Table 2. EBFR, at doses of 200 and 400 mg/kg, significantly (P<0.05) reduced the volume of gastric juice and free acidity while at the three doses used (100 to 400 mg/kg) significantly (P<0.05) reduced total acidity. However, at all doses tested, EBFR failed to affect the pH of gastric juice.

The extract ability to influence the volume of gastric juice, free acidity and total acidity was similar to the effect of 50 mg/kg ranitidine.

Table 2. Effect of EBFR on pylorus ligation induced gastric ulcers model.

Parameters	Control	Ranitidine	EBFR		
	-	50	100	200	400
Volume of gastric juice	3.36 ± 0.45	1.54 ± 0.17**	2.8 ± 0.34	1.86 ± 0.10**	1.7 ± 0.30**
pH	2.14 ± 0.49	1.54 ± 0.17	1.88 ± 0.08	2.6 ± 0.40	3.0 ± 0.45
Free acidity	42.8 ± 10.15	4 ± 0.71**	26.2 ± 4.10	11.8 ± 2.48**	3.2 ± 0.58**
Total acidity	94.8 ± 17.59	10.2 ± 1.28**	56.4 ± 8.84*	24.8 ± 4.38**	6 ± 0.71**

Note: Data in each column is represented as Mean ± SEM; ** indicates $P < 0.01$ and * P indicates < 0.05 when compared to the control group.

DISCUSSION

Peptic ulcer and gastritis have been associated with multipathogenic factors and could be due to disturbances in natural balances between the aggressive factors (e.g. of acid, bicarbonate, pepsin) and maintenance of the mucosal integrity through the endogenous defense mechanism (e.g. of defensive mechanisms of mucus, mucosal turnover and blood supply (mucosal barrier) (Shetty et al., 2008, Abdulla et al., 2010). Generally various non-specific methods are used to restore these imbalances including regular food intake, adequate rest and avoidance of ulcerogenic agents (e.g. tobacco, alcohol and coffee). Their aims are to attenuate and possibly block the gastric acid secretion or to enhance the mucosal defense mechanisms (Muralidharan and Srikanth, 2009). The latter can be achieved through increasing mucus production, stabilizing the surface epithelial cells, or interfering with the prostaglandin synthesis. In addition, there are also drugs, such as pump inhibitors, histamine ($H_{2)}$-antagonists, anticholinergics and antacids, used in the treatment of ulcer (Gregory et al., 2009). Despite the availability of many pharmaceutical products for the treatment of gastric ulcers in the market as mentioned above, their successes were limited by presence of several adverse effects (e.g. anaphylaxis reactions, gynecomastia, hematopoietic changes, thrombocytopenia, acute interstitial nephritis, nephrotoxicity and hepatotoxicity) (Anoop and Jegadeesan, 2003; Dharmani et al., 2005; Muralidharan and Srikanth, 2009).

Due to the reported side effects of available antiulcer drugs, focused have been shifted towards natural products as the new sources of antiulcer agents. With the increasingly growing interest in natural medicine, various plants have been studied based on the traditional knowledge of their pharmacological properties and confirmed to be useful in treating and managing ulcer (Gregory et al., 2009). Furthermore, medicinal plants have been known to be amongst the most attractive sources of new drugs, and have been shown to give promising results in treatment of various diseases including gastric and duodenal ulcers (Borrelli and Izzo, 2000; Dharmani and Palit, 2006). *F. religiosa* has been reported to exert several pharmacological properties such as anthelmintic (Iqbal et al., 2001), antibacterial (Nair and Chanda, 2007; Uma et al., 2009), anti-diabetic and antioxidant (Kirana et al., 2009; Pandit et al., 2010; Krishanti et al., 2010), wound healing (Choudhary, 2006; Roy et al., 2009), anti-inflammatory, analgesic and anti-lipid peroxidation (Sreelekshmi et al., 2007), anticonvulsant (Singh and Goel, 2009), and anti-amnesic (Kaur et al., 2010) activities. Despite claim of its potential in the treatment of gastric ulcer (Kirtikar and Basu, 1984), this plant has so far not been screened for anti-ulcer activity. Thus, we take this opportunity to report the preliminary findings on anti-ulcer potential of *F. religiosa* leaf ethanolic extract for the first time here. The present study demonstrated the potential of EBFR to significantly reduced gastric ulceration as indicated by the reduction in ulcer index in the IND- and CRS-induced assays. Chronic use of anti-inflammatory drugs and stress are some of the main causes of gastric ulcers (Bighetti et al., 2005), and since EBFR exerted significant antiulcer activity under experimental models that mimic those conditions, further study to determine the possible mechanisms are undertaken using the PL assay. Based on further findings using the PL assay, the extract was suggested to act by reducing the volume of gastric juice secreted, gastric free and total acidities. These results suggested that EBFR possesses anti-secretory potency as well as acid neutralizing effect. Furthermore, based on findings by Ubaka et al. (2010) the anti-secretory effect is suggested to be one of the mechanism through which the extract was able to protect the stomach mucosa from NSAIDs (IND)-induded damage. It is well known that inhibition of prostaglandin synthesis, which is essential for mucosal integrity and regeneration, will trigger the mucosal lining damage. It is also believed that the extract exert its antiulcer activity by increasing the synthesis of endogenous prostaglandins, which in turn promote mucus secretion and enhance the mucosal barrier against the actions of various damaging agents (Jain et al., 2002). It is also plausible to suggest that the observed antiulcer activity is associated with *F. religiosa* ability to exhibit antioxidant and anti-inflammatory activities as cited above. Oxidative stress, resulting from the increase production of oxygen derived free radicals (e.g. superoxide anion, hydrogen peroxide and hydroxyl radicals), has been known to take part in the pathogenesis of various diseases including gastric ulcer (Shetty et al., 2008) and antioxidants help to protect cells

from damage elicited by oxidative stress while enhancing the body's defense systems against degenerative diseases (Abdulla et al., 2010). *F. religiosa* bark extracts have been reported to possess antioxidant activity (Kirana et al., 2009; Pandit et al., 2010) and to contain various types of compounds such as flavonoids and polyphenolic compounds, saponins and tannins (Kirana et al., 2009; Uma et al., 2009). The gastroprotective effect exhibited by EBFR is speculated to be attributed to its antioxidant property, which in turn could be linked to the presence of flavonoids and polyphenolic compounds, saponins and tannins (Abdulla et al., 2010; Shokunbi and Odetola, 2008; Borrelli and Izzo, 2000). These compounds most likely inhibit gastric mucosal injury by scavenging the IND- or stress-generated oxygen metabolites (Shetty et al., 2008). Furthermore, the gastroprotective effect seen with EBFR could be attributed to its anti-inflammatory activity (Swarnakar et al., 2005). Extensive damage to the gastric mucosa by IND or stress leads to increase neutrophils infiltration into the ulcerated gastric tissue These neutrophils, which are a major source of inflammatory mediators, inhibit gastric ulcer healing by mediating lipid peroxidation through the release of highly cytotoxic and tissue damaging reactive oxygen species such as superoxide, hydrogen peroxide and myeloperoxidase derived oxidants. Suppression of neutrophil infiltration during inflammation was found to enhance gastric ulcer healing (Cheng and Koo, 2000). Other than that, leukotrienes antagonist and 5-lipoxygenase inhibitors have been demonstrated to inhibit NSAIDs-induced gastric ulceration in rats (Muralidharan and Srikanth, 2009). Hence, the observed antiulcer activity of EBFR could also be suggested to be due to inhibition of 5-lipoxygenase pathway or to leukotriene's antagonistic activity.

In conclusion, the present study provided preliminary data for the first time that the bark of *F. religiosa* possesses significant anti-ulcer activity in animal models. It has a gastric antisecretory and acid neutralizing effect that are comparable to reference drug ranitidine. The anti-ulcer activity is probably due to the presence of bioactive compounds like flavanoids, saponin and tannins. Further studies are required to confirm the exact mechanism underlining the ulcer healing and protecting property of the extract and to identify the chemical constituents responsible for it.

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