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GASTROPROTECTIVE ACTIVITY OF *FICUS DALHOUSIAE* MIQ. ROOTS ETHANOLIC EXTRACT ON INDOMETHACIN AND COLD RESTRAINT STRESS INDUCED ULCERS IN WISTAR ALBINO RATS

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ABSTRACT: *Ficus dalhousiae* Miq. is a plant found in Andhra Pradesh and Tamil Nadu on rocky hill top of dry deciduous forests. As it possesses antioxidant property wherein it reduces the elevated levels of ROS, the intent of the present study was to evaluate the Gastro protective effect of *Ficus dalhousiae* Miq Root ethanolic extract (FDREE) by means of Indomethacin and Cold Restrain stress induced Ulcers in Albino rats. Indomethacin 5mg/kg body weight p.o; for five days and Cold restraint stress models, were used for inducing gastric ulcers in rats. Biochemical parameters such as Glutathione, Malondialdehyde, acidity, Gastric volume, gastric pH and Ulcer index were determined in order to assess the gastro protective activity of FDREE in both the models. Treatment of rats with Indomethacin and subjecting them to Cold restraint stress (CRS) elevated the levels of Gastric volume, acidity, Glutathione, Malondialdehyde and gastric pH in negative control group in comparison with normal group. The elevated levels were significantly reversed when treated with standard drug Ranitidine 50 mg/kg body weight p.o; and *Ficus dalhousiae* root ethanolic extracts (FDREE). Histopathology of stomach was in support of above mentioned results. In conclusion it can be stated that *Ficus dalhousiae* Miq root ethanolic extracts showed a significant reversal of ulcerative parameters. It could be conceived that it exerts its activity due to the presence of flavonoids which have been reported to protect the mucosa by formation of a protective layer.

INTRODUCTION: Herbal medicines have recently attracted much attention as alternative medicine useful for treatment and prevention of life-style related disorder [1]. However, relatively very little knowledge is available about their mode of action and safety. The earliest recorded use of herbal remedies comes from Hippocrates, who advocated use of simple plants, such as garlic, neem [2].

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Researchers reported that peptic ulcers were caused by an imbalance between the aggressive factors (increase in gastric secretion) and a number of known defense mechanisms (mucus production) [3].

Peptic ulcer disease (PUD) occurs when the stomach lining or the proximal duodenum is corroded which is caused by *Helicobacter pylori* (*H. pylori*) infection, long term and high doses use of drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs), diseases like Zollinger- Ellison syndrome and many of the psychosocial factors including emotional stress, excess alcohol consumption and smoking is considered to be an enhancing factor for ulcers [4]. Gastrointestinal surgery for over a century has been considered as

front line treatment for peptic ulcer disease. Peptic ulcers are deep gastrointestinal disorders that involve erosion of the entire mucosal thickness, penetrating the muscular mucosa. For decade it was believed that gastrointestinal ulcerations were believed to be caused by an increased secretion of gastric acid, but the secretion rates were found to be normal in the majority of the patients suffering with the said type of ulcers.

Pharmacological treatment for ulcers such as proton pump inhibitors (PPI), H2-receptor antagonist, antacids and antibiotics for *H. pylori* are available commercially to ease the patient's discomfort[4]. Owing to the fact that these medications have many untoward effects their use by the patient is declining. As a result many people are turning to traditional system of medicine which comparatively has fewer side effects in accordance with its counterpart.

Ficus dalhousiae is rich in flavonoids and saponins which are reported to have antioxidant property[5] and lowering the levels of reactive oxygen species released due to the oxidation process. The present study incorporates *Ficus dalhousiae* root ethanolic extract, to evaluate its gastro protective effect by using Indomethacin and Cold restraint stress model in albino rats.

MATERIAL & METHODS:

Collection and Authentication of the plant material:

Leaves of *Ficus dalhousiae* commonly known as Somavalkhom (Sanskrit), Kallaal (Tamil), Dalhousiae's Ficus (English) [6]. The plant was checked for data in www.plantlist.org with the following statement (This name is accepted name of a species in the genus Ficus (family Moraceae). The record derives from WCSP (in review) which reports it as an accepted name with original publication details*: Ann. Mus. Bot. Lugduno-Batavi* 3:285 1867.

The plant parts like fruit is used in heart diseases while liver and bark are used in liver and skin ailments [6]. It was collected from Tirupati A.P, during the month of December 2012. The authentication of plant material was done by Department of Botany, Osmania University, Hyderabad -500 007, India. The plant was given Voucher number 0949.

Experimental Animals:

Healthy Wistar Albino Rats weighing about (120-160gm) of either sex were obtained from animal house. The animals were maintain under standard condition i.e., housed in polypropylene cages and maintained at a temperature 27 ± 2^0 C, relative humidity 65 ± 10% under 12 hour light and dark cycle. The animals were acclimatized for 10 days under laboratory condition before carrying out the experiments. The animals house approved by the Committee for the Purpose of Control and Supervision on Experimental Animals (CPCSEA)-Registration number – 1534/PO/A/11/CPCSEA. The study was carried out after the approval by the institutional animal ethical committee (IACE), Anwar-ul-Uloom College of Pharmacy. [7]

Chemicals:

All the chemicals were Analytical grade.

Ulcer inducing agent: Indomethacin (PubChem CID: 3715), 5mg/kg body weight, p.o.

Standard Drug: Ranitidine at a dose (PubChem CID: 3001055) of 50 mg/kg body weight administered by oral route.

Method of Preparation of Extract:

The collected roots were washed thoroughly under running water, cut into smaller pieces and air dried for eight days. Then the dried leaves were coarsely powdered using grinder and were continuous extracted in a soxhlet apparatus at 30^0C with 2500 ml ethanol. The extract was filtered through a fine muslin cloth and evaporated under reduced pressure by the rotary evaporator. The obtained extracts were stored in amber colored glass bottle for further processing [8].

Preliminary Phytochemical Screening:

The solution of the methanolic extract was prepared using distilled water and subjected to preliminary phytochemical screening. Test for common phytochemicals were carried out by standard methods described in practical pharmacognosy by Kokate, Khandelwal and Trease and Evans [9-11].

Determination of Acute toxicity (OECD guideline 423):

The acute toxicity for ethanolic extract of leaves of *Ficus dalhousiae* (FDEE) was determined in albino rats following OECD guideline 423, maintained under standard conditions [7].

TABLE 1: EVALUATION OF GASTRO PROTECTIVE ACTIVITY INDOMETHACIN-INDUCED GASTRIC ULCERS [12]

Group no.	Treatment and Label	Dose (b.w. p.o.)
Group 1	Normal control.	Distill water 5 ml/kg orally.
Group 2	Negative control (untreated group)	Indomethacin (5 mg/kg, p.o) for 5 days
Group 3	Positive control	Indomethacin (5 mg/kg, p.o) for 5 days + Ranitidine 50 mg/kg body weight, p.o.
Group 4	Test dose 1	Indomethacin (5 mg/kg, p.o) for 5 days + FDREE 100 mg/kg b.w; p.o.
Group 5	Test dose 2	Indomethacin (5 mg/kg, p.o) for 5 days + FDREE 200 mg/kg b.w; p.o.
Group 6	Test dose 3	Indomethacin (5 mg/kg, p.o) for 5 days + FDREE 400 mg/kg b.w; p.o.

After the completion of the test period the stomach was removed by humanely sacrificing of the rats, ulcer index was then measured. Acidity, volume of gastric juice, pH of gastric acid, endogenous antioxidant like glutathione (GSH) and Malondialdehyde was measured.

TABLE 2: COLD RESTRAINT STRESS - INDUCED ULCERS [13]

Group no.	Treatment and Label	Dose (b.w. p.o.)
Group 1	Normal control.	Distill water 5 ml/kg orally.
Group 2	Negative control (untreated group)	Cold restraint at 4^{o}C for 1 hour daily for 7 days.
Group 3	Positive control	Cold restraint at 4^{o}C for 1 hour daily for 7 days + Ranitidine 50 mg/kg b.w; p.o
Group 4	Test dose 1	Cold restraint at 4^{o}C for 1 hour daily for 7 days + FDREE 100 mg/kg b.w; p.o.
Group 5	Test dose 2	Cold restraint at 4^{o}C for 1 hour daily for 7 days + FDREE 200 mg/kg b.w; p.o.
Group 6	Test dose 3	Cold restraint at 4^{o}C for 1 hour daily for 7 days + FDREE 400 mg/kg b.w; p.o.

Animals were humanely sacrificed on 7th day using ether and the stomachs were excised. Magnifying glass was used for observation of ulcers for measuring the ulcer area and subsequently ulcer index. Stomachs that were excised from control and treated groups were placed in chilled ice cold saline solution after the evaluation of ulcer index. A 10% stomach homogenate in 1.15% KCl was prepared for estimation of GSH, Malondialdehyde, Acidity, Volume and pH of Gastric acid.

Measurement of Ulcerative properties:

Ulcer Assessment, Mean Score and Ulcer Index: [14-15]

The stomachs were opened along the greater curvature and were exposed for macroscopic evaluation. The ulcer index (UI, mm^2) was assessed and the ulcerated area was calculated as the arithmetic mean for each treatment.

Mean scoring:
00: Normal coloration
0.5: Red coloration
1: Spot ulcers
1.5: Haemorrhagic streaks
2: Ulcers >3mm but <5mm
3: Perforation

$$\text{Mean Ulcer Score} = \frac{\text{Total ulcer indices in a group}}{\text{Total number of animals in that group.}}$$

Ulcer Index = 10/x where x = Total ulcer area.

Statistical Analysis:

Results were expressed as Mean ± SEM. Statistical analysis were performed with Graph pad prism software using one way Analysis of Variance followed by Dunnett's *t*-test.

p values were considered significant when *p<0.05, **p<0.01, ***p<0.001 when the test and standard were compared with the untreated groups.[7]

RESULTS:

Preliminary Phytochemical Analysis:

The phytochemical screening of ethanolic extract of *Ficus dalhousiae* leaves showed the presence of Alkaloids, Tannins, Saponins, Flavonoids and Sterols. Tests were negative for Glycosides, Anthraquinones, and Reducing Sugars.

Acute toxicity studies:

The acute toxicity studies of *Ficus dalhousiae* ethanolic leaves extract was carried out as per OECD guideline no. 423. There was no gross evidence of any abnormality observed up to a period of 4-6 hrs or mortality up to a period of 24hrs at the maximum tolerated dose level of 2000 mg/kg body weight p.o. Further pharmacological screening were carried out with three dose ranges i.e. 100 mg/kg b.w. p.o., 200 mg/kg b.w. p.o. and 400 mg/kg b.w. p.o.

Effect of *Ficus dalhousiae* root ethanolic extract on Indomethacin and Cold Restraint Stress (CRS) induced gastric ulcers:

Administration of Indomethacin (5 mg/kg) and subjecting of rats to CRS produced superficial and deep erosions which lead to the formation of ulcers. However, treatment with FDREE reduced the severity of gastric ulcer. Marked elevated levels of Acidity, volume, pH, GSH and Malondialdehyde was observed when treated with Indomethacin and also when subjected to CRS in comparison with the normal group. Ranitidine (50 mg/kg) showed a marked reversal of the elevated parameters. FDREE 400 mg/kg showed the maximum level of reversal ($p < 0.001$) of the elevated parameters in comparison to normal group.

A dose dependent inhibition of ulcer area and ulcer index was seen with FDRE extracts. FDREE 400 mg/kg produced a significant ($p<0.001$) low ulcer area and ulcer index when compared with negative control group. Ranitidine treated group exhibited a maximum inhibition of ulcer area and ulcer index.

TABLE 3: EFFECT OF FDREE ON BIOCHEMICAL PARAMETER IN INDOMETHACIN-INDUCED GASTRIC ULCERS

Groups	Free Acidity	Total acidity	Volume of Gastric juice	P^H of Gastric acid	GSH (min/mg protein)	MDA (nmol/mg tissue)
Group-I Control(Distilled water)	95.00±0.037	125± 0.26	5.5± 0.025	3 ±0.034	6.16 ± 0.06	56.65± 0.47
Group-II –ve control (Indomethacin 5mg/kg)	126.00±0.66[a]	155.25±0.56[a]	8.52± 0.045[a]	5.5±0.046[a]	8.16± 0.065[a]	116.39± 0.49[a]
Group-III Standard (Ranitidine 50mg/kg)	92.23 ±0.36***	119.25 ±0.69***	5.3±0.054***	3.2± 0.036***	6.21 ± 0.25***	57.08 ± 0.23***
Group-IV test 100mg/kg FDREE	120.35 ± 0.56*	150.50± 0.35*	7.82± 0.26**	5.3± 0.45	8.05 ± 0.52*	100.49± 0.26
Group-V test 200mg/kg FDREE	115.78± 0.85**	142.25±0.56* *	6.94 ±0.35**	4.8±0.39*	7.95 ±0.54**	89.14 ±0.54*
Group-VI test 400mg/kg FDREE	112.59 ± 0.69**	135.58±0.36* *	6.24 ±0.58**	3.8±0.48**	7.01 ±0.24**	75.16±0.634**

Values are mean ± SEM; $N = 6$ in each group

P values: a < 0.001 Negative Control group VS Normal Control group

* < 0.05, ** < 0.01, *** < 0.001 Test Groups VS Negative Control Group

TABLE 4: EFFECT OF FDREE ON BIOCHEMICAL PARAMETER IN COLD RESTRAINT STRESS-INDUCED ULCERS

Groups	Free Acidity	Total acidity	Volume of Gastric juice	P^H of Gastric acid	GSH (min/mg protein)	MDA (nmol/mg tissue)
Group-I Control(Distilled water)	98.00 ±0.065	129 ± 0.24	5.9 ± 0.028	3.6± 0.037	6.69± 0.025	59.12 ±0.49
Group-II –ve control cold restraint stress	128 ±0.025[a]	156 ±0.26[a]	8.9 ±0.41[a]	7.5 ±0.78[a]	9.19± 0.65[a]	99.10 ±0.69[a]

Group-III Standard (Ranitidine 50mg/kg)	95.00± 0.32***	126 ± 0.36***	5.5± 0.25***	3.00±0.34***	6.18 ±0.35***	57.19± 0.23***
Group-IV test 100mg/kg FDREE	124.00± 0.025	150 ±0.32*	8.1±0.36	7.1± 0.71	9.07± 0.5*	91.99±0.62
Group-V test 200mg/kg FDREE	120±0.45*	145± 0.36**	7.95±0.3*	6.2± 0.65**	8.95± 0.56**	89.05± 0.35*
Group-VI test 400mg/kg FDREE	115.00± 0.58**	135.00 ± 0.59*	6.900±0.4*	5.9 ± 0.5**	8.10 ± 0.25**	80.95 ±0.33**

Values are mean ± SEM; *N* = 6 in each group
P values: a < 0.001 when Negative Control group VS Normal Control group
* < 0.05, ** < 0.01, *** < 0.001 Test Groups VS Negative Control Group

Ulcers with damage to mucosal area were seen in the groups subjected to toxicant like Indomethacin and when subjected to CRS. Ranitidine and FDREE treated groups showed signs of recovery from stress and ulcers. FDREE 400 mg/kg and Ranitidine 50 mg/kg showed a significant reduction of ulcers in contrast with the negative control group.

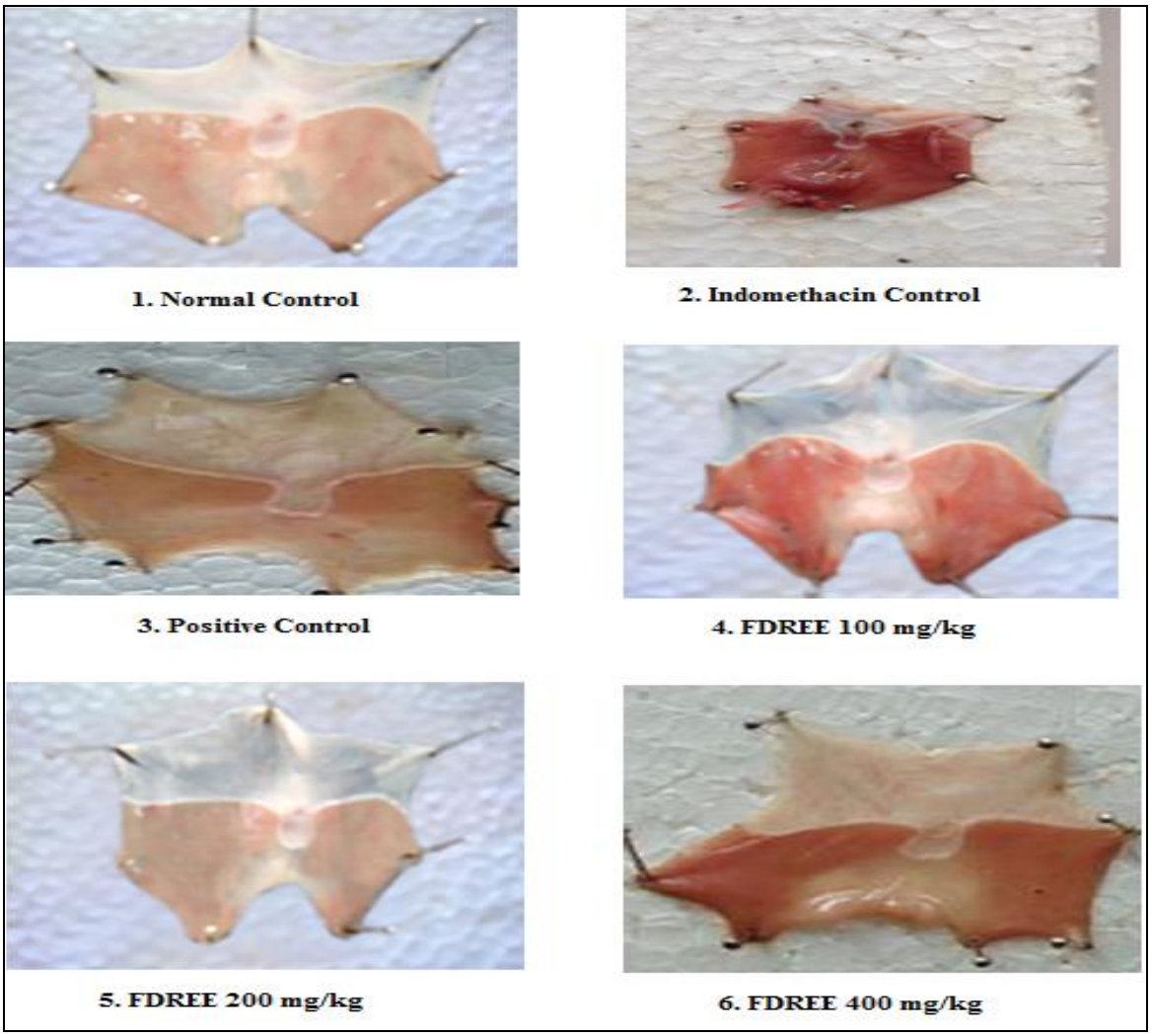

FIG. 1: OBSERVATIONS OF ULCERS IN INDOMETHACIN-INDUCED ULCERS

Effect of FDREE on ulcer index and percentage inhibition

Treatment with *Ficus dalhousiae* root ethanolic extract illustrated a significant reduction of ulcer index. FDREE 200 mg/kg was moderate in its action ($p<0.05$), whereas FDREE 400 mg/kg and Ranitidine 50 mg/kg b.w produce a significant effect ($p<0.001$) in contrast with negative control group in Indomethacin and CRS induced ulcers. FDREE 400 mg/kg and Ranitidine 50 mg/kg showed an inhibition of 58.81% and 66.94%

respectively in Indomethacin model whereas the percentage inhibition was at 63.88% and 76.16% respectively in Cold restraint stress model.

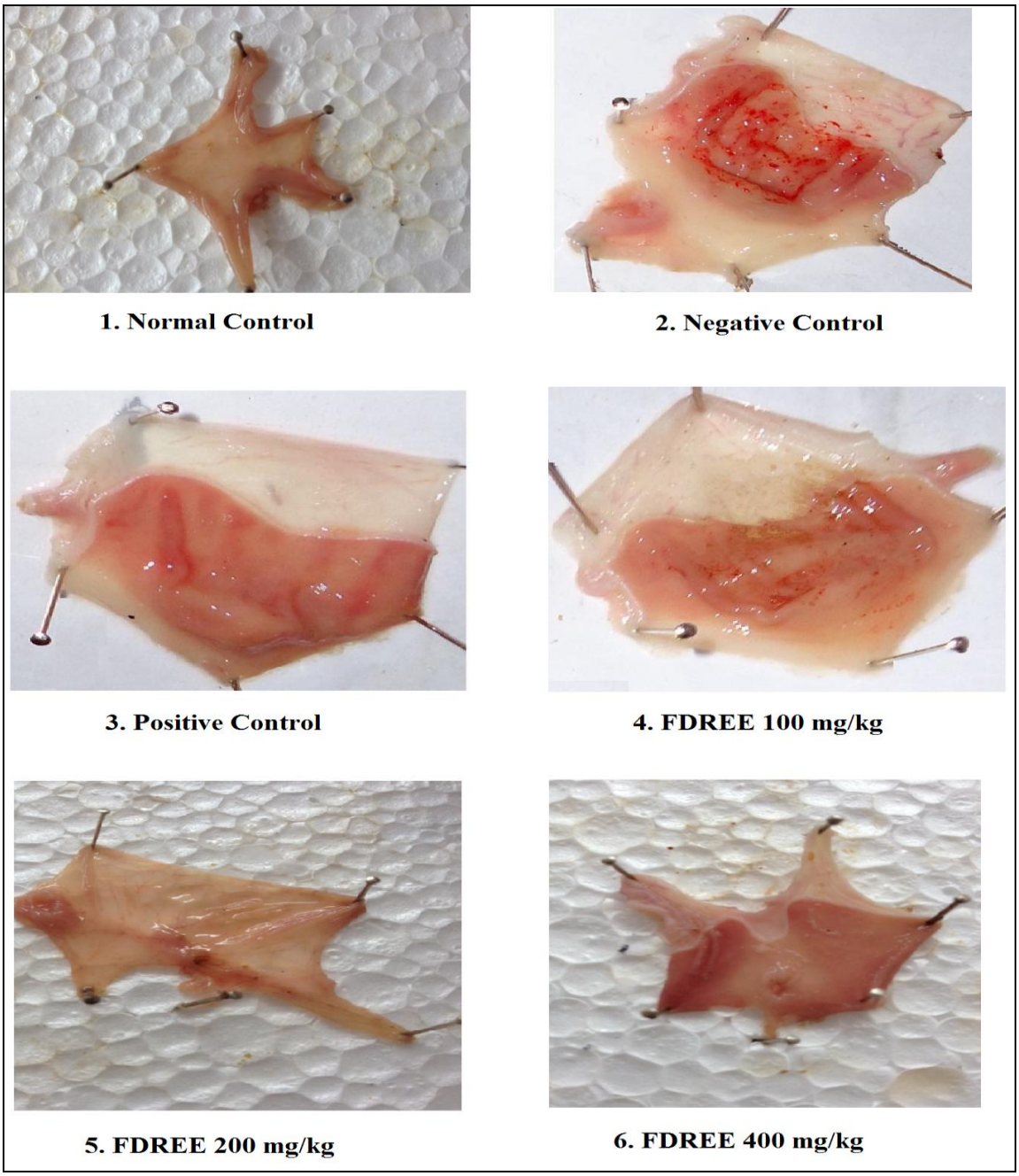

FIGURE 2: OBSERVATIONS OF ULCERS IN COLD RESTRAINT STRESS-INDUCED ULCERS

TABLE 5: EFFECT OF FDREE ON ULCER PARAMETERS IN INDOMETHACIN-INDUCED ULCERS

Groups	Mean Ulcer Score	Ulcer Index	Percentage Inhibition
Negative Control Group (Indomethacin)	3.361± 0.332	0.947 ± 0.08	---
Ranitidine 50 mg/kg	1.275± 0.279	0.313 ± 0.10	66.94***
FDREE 100 mg/kg	2.541± 0.33	0.68 ± 0.12	28.1*
FDREE 200 mg/kg	1.93 ± 0.45	0.47 ± 0.08	50.36**
FDREE 400 mg/kg	1.45 ± 0.22	0.39 ± 0.13	58.81***

Values are mean ± SEM; $N = 6$ in each group

p values: *** < 0.001 Negative Control group VS Positive Control group (Ranitidine).

* < 0.05, ** < 0.01, Test Groups VS Negative Control Group

TABLE 6: EFFECT OF FDREE ON ULCER PARAMETERS IN COLD RESTRAINT STRESS-INDUCED ULCERS

Groups	Mean Ulcer Score	Ulcer Index	Percentage Inhibition
Negative Control Group (CRS)	2.9166 ± 0.045	4.07 ± 0.23	------
Ranitidine 50 mg/kg	0.971 ± 0.057	0.97 ± 0.12	76.16***
FDREE 100 mg/kg	2.22 ± 0.039	3.11 ± 0.17	23.58*
FDREE 200 mg/kg	1.875 ± 0.023	2.23 ± 0.157	45.20**
FDREE 400 mg/kg	1.31 ± 0.017	1.47 ± 0.09	63.88***

Values are mean ± SEM; $n = 6$ in each group

p values: *** < 0.001 Negative Control group VS Positive Control group (Ranitidine).

* < 0.05, ** < 0.01, Test Groups VS Negative Control Group.

DISCUSSION: *Ficus dalhousiae* roots ethanolic extract did not show any untoward effect when administered orally up to dose of 2000 mg/kg body weight per oral (p.o). As there was no mortality, $1/5^{th}$, $1/10^{th}$ and $1/20^{th}$ of the maximum tolerated dose was taken i.e. 400 mg/kg, 200 mg/kg and 100 mg/kg. The preliminary phytochemical screening of ethanolic extract of *Ficus dalhousiae* leaves revealed the presence of Alkaloids, Tannins, Saponins, Flavonoids and Sterols. Tests were negative for Glycosides, Anthraquinones, and Reducing Sugars. As flavonoids and saponins possess antioxidant property they might have played a significant role in Gastro protective activity.

The intent of the present study is to evaluate the ulcer inhibition/protection of *Ficus dalhousiae* roots ethanolic extract in albino rats wherein the ulcers were induced by toxicant Indomethacin and Cold stress.

Non-steroidal anti-inflammatory drug (NSAID) like Indomethacin is commonly used as a prescription medicine for fever, pain and swellings. Indomethacin works by inhibiting prostaglandins production by nonselective inhibition of cyclooxygenase (COX) 1 and 2. Prostaglandins are present throughout the body and perform various functions such as causing pain, fever and inflammation [16].

Since Indomethacin inhibits both COX-1 and COX-2, it thereby inhibits the production of prostaglandins in various organs such as stomach and intestine, in stomach prostaglandins play a vital role in stimulating the secretion of bicarbonate and mucus, which maintains the mucosal blood flow, mucosal turnover and repair and mucosal lining of the gastrointestinal tract. Thereby, excess administration of Indomethacin results in ulcers. These ulcers can result in serious bleeding and perforation[17-19].

In the present study, administration of Indomethacin to rats resulted in severe ulcers. However, administration of FDREE 200 mg/kg and FDREE 400 mg/kg produced a significant gastric protection which is evident in parameters like mean score and ulcer index. Reduction in damage to the mucosal lining which was induced by free radicals may seem to be related to the gastro protective activity of FDREE extracts and this may be attributed to the plants antioxidant property. There was an increase in the levels of MDA and reduction in the levels of GSH, which were reversed when treated with Ranitidine 50 mg/kg and FDREE 400 mg/kg.

Stress induced ulcers might probably be triggered by the release of histamine. Histamine results in an increased gastric secretion and also causes disturbances in gastric mucosal microcirculation resulting in abnormal motility and decreases the mucus production in the stomach. Acetylcholine released by the increased stimulation of vagus nerve, interacts with the muscarinic receptors resulting in excess acid secretion in stomach. As these receptors are located on the cell surface of parietal cells and histamine secretory cells, the increased acid secretion is a consequence of acetylcholine action on parietal and histamine cell activity [20].

Subjecting of rats to cold exposure and immobilization individually and collectively is responsible for generation of reactive oxygen species (ROS). The generation of ROS results in

lipid peroxidation in membranes and results in tissue injury. Increased levels of end products produced in lipid peroxidation were observed in rats subjected to cold restraint stress. Increased MDA and reduced GSH levels indicate increased peroxidation finally leading to tissue damage. Treatment with FDREE 400 mg/kg and Ranitidine 50 mg/kg significantly reversed the elevated levels. Hence, it may be interpreted that the likely mechanism of action of *Ficus dalhousiae* root ethanolic extracts is due to its antioxidant potential.

CONCLUSION: In conclusion, the present study indicates that the *Ficus dalhousiae* root ethanolic extracts possess a significant ulcer protective effect. This effect may be attributed to the free radical scavenging activity of the phytochemical constituents found in the plant and its ability to inhibit the process of lipid peroxidation. Based on the results obtained a conclusion can be made that, *Ficus dalhousiae* root extracts may have a significant potential as an alternate to commercially available drugs for the treatment of ulcer or in reducing the severity of the ulcers.

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CONFLICT OF INTEREST:

We declare that we have no conflict of interest.

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