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Research Article

GASTRO PROTECTIVE EFFECTS OF *FICUS DALHOUSIAE MIQ* ROOTS ETHANOLIC EXTRACT IN INDOMETHACIN AND COLD RESTRAINT STRESS INDUCED ULCERS

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ABSTRACT
The aim of the present study was to evaluate the gastro protective effects of FDREE in Indomethacin and cold restraint stress induced ulcer models. Wistar albino rats were employed in the study. The preliminary phytochemical screening of the ethanolic extract of root showed the presence of various phytoconstituents namely, tannins, alkaloids flavonoids, glycosides. The acute toxicity of the extract revealed that 2000 mg/kg was safe as no mortality was seen at this dose. Three doses 100, 200 and 400 mg /kg were chosen for the study. The extract elicited significant gastro protective effect in both the ulcer models which was evident by the results of gastric parameters and biochemical assays of Glutathione and Malondialdehyde. The extract significantly lowered the elevated levels of free acidity, total acidity, volume of gastric juice and malondialdehyde when compared with the negative control group. The levels of Glutathione were increased in the test groups. The decrease in gastric volume, total acidity, free acidity and reduction in the levels of Malondialdehyde and increase in the levels of Glutathione in the test groups suggests the gastro protective effect of the plant.
Keywords: Glutathione, Malondialdehyde, *Ficus dalhousiae* root ethanolic extract, Indomethacin.

INTRODUCTION

Natural products are source for bioactive compounds and have potential of developing into novel therapeutic agents. Over the last decade there has been a growing interest in drugs of plant origin and such drugs formed an important class for disease control. According to world health organisation more than 80 % people in the developing countries rely on traditional medicine for their primary health needs and a recent survey has shown that more than 60 % of the patients use phytomedicine in some part of their therapy[1-4]. Herbal medicine is based on the fact that plants contain natural substances that can promote health and alleviate illness Plants have played a significant role in maintaining human health and improving the quality of human life for thousands of years and have served humans as valuable components of medicines, seasonings, beverages, cosmetics and dyes[5]. Inspite of extensive scientific studies carried out on a large number of Indian botanicals, only a small number of phytochemical entities have entered the evidence-based therapeutics[6-9]. In recent years, a large advancement in chemical and pharmacological studies has contributed to the knowledge about new therapeutically active compounds obtained from the natural products. These compounds can be used directly as leads for the development of new medicines or as pharmacological tools to discover new active compounds. So they can be life-saving or determine the quality of life in long-lasting diseases. However, the incorrect use of the natural products offers danger to society. Hence it is important to identify the active compounds, linking its structure with the biological activity and report the correct manner to use them with regards to dose, route of administration and frequency of use. The naturally active classes of compounds or secondary metabolites as alkaloids, flavonoids, terpenoids, tannins and others have attracted researchers to investigate their chemical, toxicological and pharmacological features[10,11]. For over a century, peptic ulcer disease has been one of the leading causes of gastrointestinal surgery, with high morbidity and mortality rates. The prevalence of gastrointestinal ulcers differs around the world. Duodenal ulcers are dominant in the Western countries and gastric ulcers are more frequent in Asia, especially in Japan[12]. As the prevalence of this disease increases over time, one would expect peptic ulcers to continue to have a significant global impact in the basic health and economic systems and in patient's quality of life. Peptic ulcers are deep gastrointestinal disorders that involve erosion of the entire mucosal thickness, penetrating the muscular mucosa. Fora decade it was believed that gastrointestinal ulcerations were caused by the excessive secretion of gastric acid, but many patients presenting such ulcerations had normal acid secretion rates. Then, researchers reported that peptic ulcers were caused by an imbalance between the aggressive factors and a number of known defence mechanisms. Peptic ulcer and gastritis have been associated with multi pathogenic factors and could be due to disturbances in natural balances between the aggressive factors (acid, bicarbonate, pepsin) and maintenance of themucosal integrity through the endogenous defence mechanism like defensive mechanism of mucus and mucosal blood supply (mucosal barrier)[13]. Ulcer is asymptomatic gastrointestinal disorder defined as a breach in the mucosa of the alimentary tract, which extends through the muscularis mucosa into the sub mucosa or deeper. Peptic ulcer disease (PUD) commonly occurs when the linings of stomach (gastric ulcer (GU)) or proximal duodenum duodenal ulcer (DU) corrode by the acid-peptic juices which are secreted by the stomach cells. Gastric ulcer and Duodenal ulcer may thus have quite different causes. PUD is caused by *Helicobacter pylori* (*H. pylori*) infection, long term and high dose use of drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs), diseases like Zollinger-

Ellison syndrome and psychosocial factors such as smoking, emotional stress and excessive alcohol consumption. Ulcers can be treated by pharmacological treatment such as by proton pump inhibitors (PPI), H_2-receptor inhibitors, antacids and antibiotics for *H. pylori*[14]. However, many side effects that may occur due to actions of these drugs forced people to find alternative medications. Many researchers found that the plants have properties to treat the peptic ulcer. *Ficus dalhousiae* is an umbrageous tree 9-12 metres having young branches at first softly pubescent and afterwards glabrous. It is mainly found in Kerala and Tamil Nadu states, India (Coimbatore, Dundigal, Namkkal, Niligiri, Salem, Theni, Tirunaveli and Vellore districts) the leaves and bark of *Ficus dalhousiae* Miq are recommended for liver complaints. Fruit is used as cardiotonic[15]. From the literature survey it was seen that *Ficus dalhousiae* Miq has not been evaluated for any pharmacological activity. The allied species of this genus ficus like *Ficus religiosa* etc have shown gastro protective activity. In the present study the ethanolic extract of roots of *Ficus dalhousiae* Miq was selected to determine the gastro protective effect.

MATERIAL AND METHODS

Plant Material

Plant material was collected from Tirupati A.P, India during the month of Dec. 2013. Authentication of plant material was previously done in Department of Botany, Osmania University, Hyderabad -500 007. India, S. No. 112, Voucher No. 0949. Freshly collected plant material was used for the study.

Experimental Animals

Healthy Wistar Albino Rats weighing about (120-160 g) of either sex was obtained from animal house. The animals were maintained under standard conditions 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 werehoused in the house approved by the Committee for the Purpose of Control and Supervision on Experimental Animals (CPCSEA)- Registration number – 1534/PO/A/11/ CPCSEA.

Chemicals

Mayers reagent, Dragendroffs reagent, ferric chloride, Ammonia solution, chloroform and distilled water were procured from the drug store, Anwarul Uloom College of Pharmacy, New Mallepally, Hyderabad, India. The solvents used for extraction were of analytical grade and were obtained from SD fine chemicals. Standard drug misoprostol was procured from Mercury medicare Chennai, India and ranitidine was from Allied Chemicals and Pharmaceuticals New Delhi, India.

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 roots were coarsely powdered using grinder and were continuously extracted in a soxhlet apparatus (Borosil,Mumbai, India) by different solvents in the increasing order of polarity. The extracts were filtered through a filter paper (Whatman No. 1) and evaporated under reduced pressure in a rotary evaporator (Roteva-Equitron, Medical instruments, Mumbai, India). The obtained extracts were stored in amber coloured glass bottles for further processing[16].

Method of Phytochemical Screening

The percentage yield of the different extracts was as follows, n-hexane-6.4 %; Ethylacetate-6.7 %; Chloroform-5.6 %; Ethanol-7.5 %; Distilled water-6.2 %. Phytochemical screening of the extracts was performed by simple qualitative methods[17].

Method of Determination of Acute Toxicity

Acute oral toxicity study was performed as per OECD-423 guidelines category IV (acute toxic class method,). Albino rats (n = 3) of either sex selected by random sampling technique were employed in this study. The animals were kept fasting for 4 h with free access to water only. The plant extract was administered orally with maximum dose of 2000 mg /kg body weight by gastric intubation. The mortality was observed for three days. If mortality was observed in 2 out of 3 animals or 3 out of 3 animals then the dose administered was assigned as toxic dose. If mortality was observed in 1 animal, then the same dose was repeated again to confirm the toxic dose. If mortality was not observed, the procedure was repeated for further higher dose such as 3000 mg/kg of body weight[18].

Statistical analysis

The data was expressed as mean ± SEM analyzed statistically using one way ANOVA procedures followed by Dunnet 't'test. P value < 0.01 regarded as less significant and P-value < 0.001 as highly significant.

Evaluation of gastro protective activity

The gastro protective activity was determined by two experimental models namely Indomethacin-induced Gastric Ulcer and Cold Restraint Stress-Induced Ulcer.

Indomethacin-induced Gastric Ulcer Model

The gastric ulcers were induced by administering indomethacin (IND; 20 mg/kg. p.o) for five days in all the experimental groups[19-23]. The animals of standard group were then treated with misoprostol (100 µg/kg p.o). The test groups were administered FDREE100, 200 and 400 mg/kg once daily for another five days after the induction of ulcers. The control group received only vehicle. On the fifth day after the test dose administration the gastric content was collected from all the groups and the gastric volume, total acidity, pH was determined. The rats were sacrificed and the ulcer index was determined. The homogenate of stomach was used for determination Malondialdehyde and Glutathione[24].

Cold Restraint Stress-Induced Ulcers

The ulcers were induced by subjecting the animals to cold restraint stress. The standard group received Ranitidine (50 mg/kgpo) and to the test groups FDREE100, 200 and 400 mg/kg was administered orally 30 minutes 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, the gastric contents were collected and the gastric volume, pH, free acidity and total acidity were determined. The stomachs were excised, chilled and the ulcer count was done. Later the homogenate was used for estimation of GSH and MDA[25].

Determination of Free and Total Acidity

One ml of gastric juice was pipetted into a 100 ml conical flask, 2 or 3 drops of Topfer's reagent was added and titrated with 0.01 N Sodium hydroxide until all traces of red colour disappears till the colour of the solution turns yellowish orange. The volume of alkali added was noted. This volume corresponds to free acidity. Then 2 or 3 drops of phenolphthalein solution was added and the titration was continued until a definite red tinge appears. Again the total volume of alkali added was noted. This volume corresponds to total acidity. Acidity was calculated by using the formula[26-32].

$$\text{Acidity} = \frac{\text{Volume of NaOH} \times \text{Normality of NaOH} \times 100}{0.1} \text{ meq/ l /100g}$$

Estimation of Gastric Volume and pH

The gastric content that was transferred into centrifuge tubes was used for estimation of gastric volume and pH. The tubes were centrifuged at 1000 rpm for 10 minutes and the gastric volume was directly read from the graduations on the tubes. The supernatant was then collected and pH was determined by using a digital pH meter.

Estimation Glutathione

Glutathione (GSH) was determined by the method of moron *et al*. Aliquots of the homogenate were mixed with equal volume of ice cold 5 % TCA and the precipitated proteins were removed by centrifugation. The supernatant was added to equal volume of 0.2 M phosphate buffer, pH 8.0 and measured at 412 nm. GSH was used as a reference standard[33].

Estimation of Tissue Malondialdehyde

The concentrations of MDA were determined by estimating MDA using the thiobarbituric acid test. The rat stomach was promptly excised and rinsed with cold saline. To minimize the possibility of interference of haemoglobin with free radicals, any blood adhering to the mucosa was carefully removed. The corpus mucosa was scraped, weighed and homogenized in 10 ml of 100 g/L KCl. The homogenate (0.5 ml)was added to a solution containing 0.2 ML of 80 g/L sodium lauryl sulphate, 1.5 ml of 200 g/L acetic acid, 1.5 ml of 8 g/L 2-thiobarbiturate and 0.3 mL distilled water. The mixture was incubated at 98^0C for 1 hour. Upon cooling, 5 ml of n-butanol: pyridine (15:1) was added. The mixture was vortexed for 1 minute and centrifuged for 30 minutes at 4000 rpm. The absorbance of the supernatant was measured at 532 mn. A standard curve was generated using 1, 1, 3, 3-tetramethoxypropane. The recovery was over 90 %. The results were expressed as nanomoles MDA per gram wet tissue (nmol/mg tissue)[34,35].

RESULTS

Results of phytochemical screening

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

Results of acute toxicity studies

The ethanolic extract ofthe plant didn't show any mortality up to a dose of 2000 mg/kg. Based on this three doses 100, 200 and 400 mg/kg were used for the gastro protective studies.

Indomethacin-Induced Gastric Ulcer Models

Biochemical Parameters

Treatment with Indomethacin markedly showed elevated levels of Free Acidity, Total Acidity and Volume of Gastric Juice. The Glutathione levels were decreased which were reversed by the test extracts. Malondialdehyde levels were increased which were effectively decreased by the standard drug and test extracts; while the normal readings were recorded in the control group. Treatment with the standard drugs Ranitidine (50 mg/kg) positively affected all the parameters and restored them to the optimum levels as displayed in the (Table 1). The effect of FDREE 400 mg/kg on gastric juice was closer to that of the standard.

Table 1: Biochemical Parameters in Indomethacin-induced Gastric Ulcers

Groups	Free Acidity	Total acidity	Volume of Gastric juice	P^H of Gastric acid	GSH(min/mM)	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 ± 0.0600	** 56.65 ± 0.47
Group-II –ve control (Indomethacin 5mg/kg)	126.00± 0.66	155.25± 0.56	8.52± 0.045	5.5± 0.046	5.16 ± 0.0650	116.39± 0.49
Group-III Standard (Ranitidine 50mg/kg)	** 92.23± 0.36	** 119.25± 0.69	** 5.3± 0.054	** 3.2± 0.036	** 8.21 ± 0.025	** 57.08 ± 0.23
Group-IV test 100mg/kg FDREE	* 120.35± 0.56	* 150.50± 0.35	** 7.82± 0.026	5.3± 0.45	* 7.05 ± 0.0520	* 100.49 ± 0.260
Group-V test 200mg/kg FDREE	** 115.78± 0.85	** 142.25± 0.56	** 6.94± 0.035	** 4.8± 0.039	* 7.95 ± 0.054	* 89.14 ± 0.540

Values are mean ±SEM (n = 6), P < 0.01*, P < 0.001** as compared to negative control

Cold Restraint Stress-Induced Ulcer Model

Biochemical Parameters

Treatment with cold restraint stress markedly showed elevated levels of Free Acidity, Total Acidity, and Vol. of gastric Juice. The Glutathione levels were decreased which were reversed by the test extracts. Malondialdehyde levels were increased which were effectively decreased by the standard drug and test extracts; while the normal readings were recorded in the control group. Treatment with the standard drugs Misoprostol 100 µg/kg, po affected all the parameters and restored them to the optimum levels as displayed in the (Table 2). The effect of *Ficus dalhousiae* root ethanolic extract (FDREE) 400 mg/kg on gastric juice was closer to that of the standard.

Table 2: Biochemical Parameters in Cold Restraint Stress-Induced Ulcers in Experimental Groups

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	156 ± 0.26	8.9 ± 0.041	7.5 ± 0.078	9.19 ± 0.065	99.10 ± 0.069
Group-III Standard (Misoprostol 100µg/kg,po)	** 95.00± 0.032	** 126± 0.36	** 5.5± 0.025	** 3.00± 0.034	** 6.18 ± 0.035	** 57.19 ± 0.023
Group-IV test 100mg/kg FDREE	* 124.00± 0.025	* 150 ± 0.32	8.1 ± 0.036	7.1 ± 0.071	* 9.07 ± 0.05	91.99 ± 0.062
Group-V test 200mg/kg FDREE	* 120 ± 0.045	** 145 ± 0.36	7.95± 0.03	** 6.2± 0.065	** 8.95 ± 0.56	* 89.05± 0. 035
Group-VI test 400mg/kg FDREE	** 115.00± 0.058	** 135.00± 0.59	* 6.900± 0.401	** 5.9 ± 0.05	** 8.10± 0.025	** 80.95 ± 0.025

Values are mean ±SEM (n = 6).P < 0.01*, P < 0.001** as compared to negative control

DISCUSSION

The results of present study indicated that the Ethanolic extract of *Ficus dalhousiae* roots exhibited significant gastro protective activity against indomethacin and cold stress induced ulcer models. In indomethacin induced ulcer model the ethanolic extract showed a decrease in ulcer score which might be due to imbalance in the mucosal factors. Various methods like regular intake of food, avoidance of ulcerogenic agents like tobacco, alcohol etc are employed to restore the imbalances in the different factors responsible for ulceration of the stomach mucosa. The main aim of these methods is to block the gastric secretions or to enhance the mucosal defence mechanisms[30]. Cytoprotection by drugs has been considered due to generation of prostaglandins by anti-ulcer drugs when used in their non-anti secretory doses[36,37]. In the same ulcer model there was significant decrease in the Malondialdehyde (MDA) in the test extracts when compared to the negative control. The increase in MDA (Malondialdehyde) levels in the stomach suggests enhanced peroxidation leading to tissue damage and failure of the antioxidant defence mechanisms to prevent formation of excessive free radicals. The decrease in the mucosal malondialdihyde production in the test extracts suggests that there could be a close relationship of free radicals with peptic ulcer and gastritis involving lipid peroxidation[38]. This provides the evidence of antioxidant mechanism of the test extracts for gastro protection. In the cold restraint stress model there was also reduction in the gastric parameters. Cold restraint stress in experimental medicine elicits purest form of psychological frustration with vigorous struggling[39]. The stress in the control group clearly produced mucosal damage in the stomach which might be due to severe imbalance in the normal physiological conditions, resulting in a stressful condition leading to ulcer. Stress induced ulcer is probably mediated by the release of histamine[40,41]. Pre treatment with FDREE (*Ficus dalhousiae* root ethanolic extract) significantly reversed these changes. Hence, it is likely to say that the mechanism of gastro protection of FDREE (*Ficus dalhousiae* root ethanolic extract) is due to its antioxidant effect. Reduced glutathione is one of the non enzymatic antioxidant biomolecule present in the tissues[40]. In the stress induced ulcer model, stress enhanced the activities of GSH-related enzymes GPx and GST, thereby decreasing the GSH content whereas treatment with FDREE (*Ficus dalhousiae* root ethanolic extract) reversed these effects. It can be assumed that the effect of FDREE (*Ficus dalhousiae* root ethanolic extract) might be due to increased synthesis of GSH. *Ficus dalhausiae* roots were found to be rich in phytochemical constituents as evident by the preliminary phytochemical screening report. Flavonoids have been reported to possess a significant anti-ulcer activity, in various experimental models of gastric and duodenal ulceration[42]. Some recent reports have indicated that many flavonoids possess anti-ulcerogenic activity. Oral treatment with the extract demonstrated good level of gastric protection. Usually after administration of flavanoids mucous content is increased accompanied by proportionate increase in protein and hexosamines[43]. Quercetin, kaemferol, morin, myricetin and rutin when tested were found to inhibit the mucosal content of platelet activating or (PAF) in a dose dependent manner suggesting that the protective role of these substances may be mediated by endogenous PAF[44]. As the extract contains flavanoid sit can be suggested that *Ficus dalhousie* Roots Extract could be beneficial component of preventing ulcer formation by the above mechanism. However, further studies are required to establish its exact mode of action, isolation and characterization of constituents responsible for this activity.

CONCLUSION

In conclusion it can be said that the gastro protective effect of *Ficus dalhouseae* root ethanolic extract is due to decrease in gastric acid secretion and also by reducing the levels of MDA concentration i.e. increasing antioxidant activity through decrease in free radical formation.

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