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RESEARCH ARTICLE

Anti-ulcer activity of leaves and bark of *ficus racemosa* linn in ethanol & aspirin induced ulcer in rats

Divyash Singh[1*], Shobha Singh[2], G.Amresh[3], Ravindra Pal Singh[4]

[1]*Faculty of Pharmacy, Sherwood College of Pharmacy, BBK*
[2] *Phytochemistry Division CSIR-National Botanical Research Institute Lucknow (Uttar Pradesh), India*
[3]*Faculty of Pharmacy, (Uttar Pradesh University of Medical Sciences, Saifai, U.P, India*
[4]*Faculty of Pharmacy, Suresh Gyan Vihar University, Mahal Jagatpura, Jaipur, Rajasthan.*

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ABSTRACT

Aim- The main of aim of study was to evaluate the Anti-ulcer activity of various extracts of leaves & bark of *Ficus racemosa* in Animals. **Material & Methods-**The crude drugs were extracted out by using various non polar and polar solvents and preliminary phytochemical screening were performed for the presence of different phytocompounds. Ethanol & Aspirin induced ulcer model was used for the experiment & treatment of different Polar & Non Polar extracts of Leaves & barks of *Ficus racemosa* in animals were given. **Results-** On the comparisons from results, it was found that methanolic extract (200 & 400 mg/kg) of bark of *Ficus racemosa* showed highly significant activity (p<0.001) on % protection against ulcer formation in ethanol and aspirin induced models.

Keywords- *Ficus racemosa*, Anti-ulcer activity, Acidity, Ethanol Induced model, Aspirin Induced model

INTRODUCTION

Peptic ulcer disease (PUD) broadly refers to a group of disorders characterized by the presence of ulcers in any portion of the Gl tract exposed to acid for sufficient duration and concentration. PUD encompassing gastric and duodenal ulcer is the most prevalent gastrointestinal disorder (Valle *et al*., 2005). It particularly affects the working years of patient's life and its social implications are therefore considerable. Approximately 500,000 new case and 4 million recurrences of PUD are reported each year, contributing to approximately 10 % of Americans who will develop PUD during their life time (Elta *et al*., 2003; Munnangi *et al*., 1997; Sonnenberg *et al*., 1997).

Several plant species like *Glycyrrhiza glabra* (De B *et al*.,1997), *Allophylus serrates* (Dharmani *et al*., 2005a), *Desmodium gangeticum* (Dharmani *et al*.,2005b), *Ocimum sanctum* (Dharmani *et al*., 2004), *Hemidesmus indicus* (Anoop *et al*., 2003), *Emblica officianalis* (Sairam *et al*., 2002), *Convovulus pluricaulis* (Sairam *et al*.,2001a) have shown encouraging findings in treatment of PUD.

As per the literature review, it has been observed that *Ficus racemosa* Linn. (Leaves & Bark) is listed among the various medicinal plants widely been used as a antibacterial, demulcent, bitter tonic, laxative, carminative, refrigerant, and febrifuge, diuretic, useful in chronic cystitis, gonorrhea and cadiotonic, acute-chronic inflammatory conditions and in treatment of diabetes mellitus, liver diseases and as a antiulcer.

In the absence of any scientific evidence for their anti-ulcer activity in animals, so there is a need in scientifically establishing the anti-ulcer activity so that we are able to come up with a more effective and potent bioactive phytoconstituents with less side effects in comparison with existing synthetic drugs.

MATERIALS & METHODS

Glass wares: Borosil and ASGI make glass wares were used.

Chemicals: All chemicals used were of analytical grade.

Drugs: Free sample of Glibenclamide was procured from Nicholas Piramal, Mumbai.

Animals: Wistar Albino rats of either sex (150 to 200 g) were purchased from the CPCSEA approved vendors for in-vivo antiulcer activity.

Collection and authentication of the plant leaves & barks: The leaves and barks of *Ficus racemosa* Linn. were collected from outfield and also purchased from local markets during the month of July that shows the green color with rough surface. Plant was identified by the Botanist, Research Officer; Botany (Scientist C) at Central Council for Research in Ayurveda, Govt. of India and herbarium specimen was submitted in Department of Pharmacognosy.

***Corresponding Author:** Divyash Singh**, Email:** singh.nir2@gmail.com

Successive Solvent Extraction Methods

Coarsely powdered drugs were extracted by using petroleum ether, chloroform, ethyl acetate, ethanolic, methanol and finally water. Then after extraction, solvents were removed by evaporation and solid mass of extracts were procured.

Phytochemical Screening

Preliminary screening was done for the presence of different phytoconstituents i.e. fatty acids, terpenoids, steroids, alkaloids, flavonoids, carbohydrates etc **(**Kokate, C.K., 1996**).**

Experimental Animals

Wistar Albino rats of either sex (150 to 200 g) were purchased from the CPCSEA approved vendor New Delhi. They were maintained under standard laboratory conditions at 25 ± 2°C, relative humidity (50 ± 15%) and normal photoperiod (12-hour light-dark cycle) were used for the experiment. Commercial pellet diet (MFD, by Nav Maharashtra Chakan Oil Mills ltd., New Delhi, India) and water were provided ad libitum throughout the course of study.

Selection of Dose

Acute oral toxicity test was carried out according to the OECD guideline No. 423. For the studies we selected 1/10 and 1/5th dose i.e. 200 and 400 mg/kg dose.

Preparation of Doses

Doses equivalent to 200 mg and 400 mg of the crude drug per kilogram body weight were calculated, and suspended in 1% w/v tween 80 solutions for the experiment.

Antiulcer Activity of *Ficus racemosa* Linn.

Ethanol Induced Ulcer

The animals were fasted for 24 hours with free access of water. The animals were treated with test extracts or standard or control according to the various groups had been designed. 1 hour later 80% alcohol was administered p.o. to each animal. Animals were sacrificed 1 hour after alcohol administration, stomachs were isolated, cut and opened along the greater curvature and pinned on a soft board (Umamaheshwari *et al*., 2007; Kulkarni, 1999).

0 = Normal colored stomach
0.5 = Red coloration
1 = Spot ulcer
1.5 = Hemorrhagic streaks
2 = Ulcers > 3 but < 5
3 = Ulcers > 5

The percentage ulcer inhibition was calculated by the following formula and the results were tabulated.

$$\% \text{ Ulcer protection} = \frac{\text{Ulcer Index in Control} - \text{Ulcer index in Test}}{\text{Ulcer Index in Control}} \times 100$$

Experimental design for Leaves of *Ficus racemosa* Linn.

Albino Wistar rats of either sex weighing between (150-200 gms) were divided into various groups of six animals in each group.

Group 1: Normal control, 0.9% NaCl-treated animals
Group 2: Disease control, Etahnol treated rats (1 ml/200 gm, p.o.)
Group 3: Standard, Omeprazole (20 mg/kg, p.o.)
Group 4: Treated with Pet. Ether extract of leaves of *FR* (200 mg/kg body weight)
Group 5: Treated with Pet. Ether extract of leaves of *FR* (400 mg/kg body weight)
Group 6: Treated with chloroform extract of leaves of *FR* (200 mg/kg body weight)
Group 7: Treated with chloroform extract of leaves of *FR* (400 mg/kg body weight)
Group 8: Treated with ethyl acetate extract of leaves of *FR* (200 mg/kg body weight)
Group 9: Treated with ethyl acetate extract of leaves of *FR* (400 mg/kg body weight)
Group 10: Treated with ethanolic extract of leaves of *FR* (200 mg/kg body weight)
Group 11: Treated with ethanolic extract of leaves of *FR* (400 mg/kg body weight)
Group 12: Treated with methanolic extract of leaves of *FR* (200 mg/kg body weight)
Group 13: Treated with methanolic extract of leaves of *FR* (400 mg/kg body weight)
Group 14: Treated with aqueous extract of leaves of *FR* (200 mg/kg body weight)
Group 15: Treated with aqueous extract of leaves of *FR* (400 mg/kg body weight)

Experimental design for Barks of *Ficus racemosa* Linn.

Group 1: Normal control, 0.9% NaCl-treated animals
Group 2: Disease control, Etahnol treated rats (1 ml/200 gm, p.o.)
Group 3: Standard, Omeprazole (20 mg/kg, p.o.)
Group 4: Treated with Pet. Ether extract of bark of *FR* (200 mg/kg body weight)
Group 5: Treated with Pet. Ether extract of bark of *FR* (400 mg/kg body weight)
Group 6: Treated with chloroform extract of bark of *FR* (200 mg/kg body weight)
Group 7: Treated with chloroform extract of bark of *FR* (400 mg/kg body weight)
Group 8: Treated with ethyl acetate extract of bark of *FR* (200 mg/kg body weight)
Group 9: Treated with ethyl acetate extract of bark of *FR* (400 mg/kg body weight)
Group 10: Treated with ethanolic extract of bark of *FR* (200 mg/kg body weight)
Group 11: Treated with ethanolic extract of bark of *FR* (400 mg/kg body weight)
Group 12: Treated with methanolic extract of bark of *FR* (200 mg/kg body weight)

Group 13: Treated with methanolic extract of bark of *FR* (400 mg/kg body weight)
Group 14: Treated with aqueous extract of bark of *FR* (200 mg/kg body weight)
Group 15: Treated with aqueous extract of bark of *FR* (400 mg/kg body weight)

Aspirin Induced Ulcer

The test drugs were administered orally to each animal 30 mins prior to the administration of Aspirin (250mg/kg). Six hours later the animals were sacrificed by using anesthetic ether and their stomachs were dissected for the determination of gastric lesions. The ulcer scoring was counted and calculated as per Kulkarni SK. (Rajagopalan *et al*., 2004; Yamamota *et al*., 1989)

The mean ulcer score for each animal was expressed as ulcer index. The percentage ulcer inhibition was calculated by the following formula and the results were tabulated.

$$\% \text{ Ulcer protection} = \frac{\text{Ulcer Index in Control} - \text{Ulcer index in Test}}{\text{Ulcer Index in Control}} \times 100$$

In this model, disease control group treated with Aspirin (250 mg/kg, p.o.) and remaining grouping and treatment schedules were same as described in above models.

RESULT

Ethanol induced ulcer

Antiulcer activity of Leaves of *Ficus racemosa* Linn.

The gastric mucosa of ethanol (1ml/200 gm b.w.) administration induced ulceration in rats of the control group characterized by hemorrhagic gastric lesions. The methanolic extract of leaves caused a reduction in the severity of these lesions induced by ethanol which was evident by a moderately significant ($p<0.01$) reduction in the ulcer index and an increase in the percentage protection of ulcers when compared with the control group.

Rats treated by omeprazole caused a reduction in the severity of these lesions induced by ethanol which was evident by a significant ($p<0.001$) reduction in the ulcer index and an increase in the percentage protection of ulcers when compared with the control group.

Table No.1: Effect of various extracts on % Protection of Leaves of *Ficus racemosa* Linn.

S. No.	Treatments	Mean Ulcer Index±SEM	% Protection
1	Normal Control	0±0	0
2	Disease Control (Ethanol Treated)	4.5±0.341***	0%
3	Omeprazole Treated (20 mg/kg)	0.58±0.08***	87.11%
4	Pet. Ether extract (200 mg/kg)	3.25± 0.33*	27.77%
5	Pet. Ether extract (400 mg/kg)	3.16±0.21*	29.77%
6	Chloroform extract (200 mg/kg)	3.51±0.22*	22%
7	Chloroform extract (400 mg/kg)	3.18±0.07*	29.33%
8	Ethyl acetate extract (200 mg/kg)	3.15± 0.31*	30%
9	Ethyl acetate extract (400 mg/kg)	2.16±0.23*	52%
10	Ethanolic extract (200 mg/kg)	3.57±0.21*	20.66%
11	Ethanolic extract (400 mg/kg)	3.11±0.01*	30.88%
12	Methanolic extract (200 mg/kg)	2.15± 0.23**	52.22%
13	Methanolic extract (400 mg/kg)	2.09±0.31**	53.55%
14	Aqueous extract (200 mg/kg)	3.22±0.42*	28.44%
15	Aqueous extract (400 mg/kg)	3.10±0.03*	31.11%

Values are expressed as mean ± SEM (n=6) in each group.*P < 0.05, **P< 0.01compared with the control (ANOVA test)

Antiulcer activity of bark of *Ficus racemosa* Linn.

The gastric mucosa of ethanol (1ml/200 gm b.w.) administration induced ulceration in rats of the control group characterized by hemorrhagic gastric lesions. The methanolic extract of bark caused a reduction in the severity of these lesions induced by ethanol which was evident by a highly significant ($p<0.001$) reduction in the ulcer index and an increase in the percentage protection of ulcers when compared with the control group.

Rats treated by omeprazole caused a reduction in the severity of these lesions induced by ethanol which was evident by a significant ($p<0.001$) reduction in the ulcer index and an increase in the percentage protection of ulcers when compared with the control group.

Table No.2: Effect of various extracts on % Protection of Barks of *Ficus racemosa* Linn.

S. No.	Treatments	Mean Ulcer Index±SEM	% Protection
1	Normal Control	0±0	0
2	Disease Control (Ethanol Treated)	4.5±0.341***	0
3	Omeprazole Treated (20 mg/kg)	0.58±0.08***	87.11%
4	Pet. Ether extract (200 mg/kg)	4.25± 0.23*	5.55%
5	Pet. Ether extract (400 mg/kg)	3.11±0.11*	30.88%
6	Chloroform extract (200 mg/kg)	3.21±0.22*	28.66%
7	Chloroform extract (400 mg/kg)	3.14±0.17*	30.22%
8	Ethyl acetate extract (200 mg/kg)	3.29± 0.31*	26.88%
9	Ethyl acetate extract (400 mg/kg)	2.16±0.23*	52%
10	Ethanolic extract (200 mg/kg)	3.87±0.21*	14%
11	Ethanolic extract (400 mg/kg)	3.21±0.01*	28.66%
12	Methanolic extract (200 mg/kg)	2.21± 0.33***	50.88%
13	Methanolic extract (400 mg/kg)	1.09±0.41***	75.77%
14	Aqueous extract (200 mg/kg)	3.32±0.32*	26.22%
15	Aqueous extract (400 mg/kg)	3.16±0.22*	29.77%

Values are expressed as mean ± SEM (n=6) in each group.*P < 0.05, **P< 0.01compared with the control (ANOVA test)

Aspirin Induced Ulcer

Antiulcer activity of methanolic extract of *Ficus racemosa* Linn.

NSAIDs like aspirin because gastric mucosal damage by decreasing prostaglandin levels through inhibition of prostaglandin synthesis. Thus Anti ulcer activity of methanolic (Bark) extract of *Ficus racemosa* Linn. was studied at two dose levels (200 & 400 mg/kg) in aspirin induced ulcer in rats to find out the potency of the extracts.

At 200 mg/kg b.w. the methanolic extract showed a protection ulcer index of 59.28% and 73.11% respectively and at 400 mg/kg b.w. respectively.

Table No.3: Effect of methanolic extracts on % Protection of Barks of *Ficus racemosa* Linn.

S. No.	Treatments	Mean Ulcer Index±SEM	% Protection
1	Normal Control	0±0	0
2	Disease Control (Ethanol Treated)	7.81±0.083***	0%
3	Omeprazole Treated (20 mg/kg)	0.68±0.170***	91.29%
4	Methanolic extract (200 mg/kg) of FR	3.18± 0.73***	59.28%
5	Methanolic extract (400 mg/kg) of FR	2.10±0.51***	73.11%

Values are expressed as mean ± SEM (n=6) in each group.*$P < 0.05$, **$P < 0.01$compared with the control (ANOVA test)

DISCUSSION

Prolonged exposure to free radicals is a pivotal cause of tissue stress and injury. The free radical permanent damage to tissue structures results from a permanent alteration in the molecular pattern of carbohydrates, lipids, proteins and even nucleic acid bases. In diabetes, the level of free radicals was reported to increase in alloxan and streptozocin treated rats an elevated level of free radicals was detected in several tissues including the kidneys (Shabeer *et al*., 2009).

Ethanol is a common potential ulcerogenic agent that induces gastric hemorrhagic erosion on intragastric administration (Shetty *et al*., 2000; Goel & Bhattacharya, 1991). The high concentration of ethanol is immensely employed to damage gastric mucosal of rats. The extracts obtained from plants are employed to check the gastro protective effect in rats. The enzyme 5 lipoxygenase pathway performs essential part in the progression of such ulcer. Authors Mizui and Terano reported the implication of free radicals in alcohol incited gastric ulceration and antioxidant action, and lipid peroxidation, respectively (Mizui & Doteuchi, 1986). Alcohol triggered the origination of LTC-4 and LTD-4 in gastric mucosal, and it leads ulceration in stomach.

Alcohol leads intense devastation to the gastric mucosa when it is dispensed orally. The gastric mucosal barrier damaged by alcohol. This can incite intense micro-vascular alterations with robust vaso-constriction accompanied by arteriolar dilatation. Miller *et al*., (1985) stated that the free radicals produced during lipid peroxidation of cells and the cell membranes produce mucosal mast cell degranulation foremost to the liberation of vasoactive intermediaries embracing histamine. Histamine is responsible for the activation of adenyl cyclase which produces cyclic AMP which in turn activates the gastric proton pump and releases hydrogen ions. The amount of hydrogen ions generated is proportional to the gastric acid formed.

In our study, methanolic extract of bark of *Ficus racemosa* produced a significant percentage protection against ulcer formation. They also changed the production of mucosal layer formation and it may be probable mechanism that both extract by formation of mucosal layer prevents the formation of ulcer.

Aspirin like synthetic NSAIDs leads to gastric mucosal damage and break-up of the mucosal barrier by originating an enlarged secretion of acid and back diffusion of H+ ions. The anti-ulcer activity can be determined by checking the gastric volume reduction and acidity changes (Jafri *et al*., 2001).

In anti-ulcer activity the mucosa of the gastrointestinal protected against aggressive factors, such as hydrochloric acid, bile acid and non steroidal anti-inflammatory drugs. These factors are mainly consists of functional, humoral and neuronal factors. All these factors are noted to furnish to mucosal protection (Jafri *et al*., 2001). The back diffusion of HCl leads to devastation of the cells. The back diffusion of HCl leads to devastation of the cells, capillaries and veins resulting in hemorrhagic ulcers. Moreover, the histamine deliverance increases the acid output, and it leads to destruction of the gastric mucosa. The acid leads to lowering of gastric pH which causes to stimulation of pepsinogen to pepsin. This proteolytic activity expands the size of lesions. Hence the lowering of acid secretion is essential for curative and elimination of esophageal reflux disease (Dorababu *et al*., 2006). The non steroidal anti-inflammatory drugs lead to ulcer is by influencing H+K+ATPase in gastric parietal cells. Hence the gastric acid secretion is increased, and it leads to decreases pH in ulcerated rats. After administration of Omeprazole to rats, it inhibits H+K+ATPase in gastric parietal cells (Dorababu *et al*., 2006), lowering the lesion of ulcer in rats.

The findings of investigation exhibited decrease in ulcer score in *Ficus racemosa* treated animals may be due to inhibiting the HCl secretion and inhibition of H+ ions.

CONCLUSION

In our study, methanolic extract of bark of *Ficus racemosa* showed a significant percentage protection against ulcer formation in pylorus ligation model, ethanol induced model and aspirin induced model in rat at the dose of 200 and 400 mg/kg.

These components could serve as lead molecules for development of prospective antiulcer agents. Further detailed studies are required to elucidate the exact mechanism based on molecular and genetic level responsible for antiulcer activity. The present findings are significant for the development of alternative, inexpensive and perhaps safer strategies for the treatment of diseases.

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