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Investigation on Anti-Ulcer Activity of *Momordica dioica* Fruits in Wistar Rat

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ABSTRACT

To present study was carried out to investigate antiulcer activity of Ethanolic extract of *Momordica dioica* fruits in pylorus ligatated and Cold stress induced ulceration in the wistar rats. Pylorus ligation induced ulcer is one of the most widely used methods for studying the effect of drug on gastric secretion. Effect of distilled water in pylorus ligation has caused the accumulation of gastric sectretion and decreased the pH. Ranitidine and Ethanolic extracts of *Momordica dioica* significantly decreased the gastric volume, total acidity, free acidity, ulcer score, number of ulcer and ulcer index and raise the pH (shown in graph. 1, 2, 3, 4, 5, 6,).Similar studies support our results. Ethanolic extract of *Momordica dioica* at a dose of (400mg/kg. p.o) showed significant inhibition of ulcerative lesion by 46.33% and 54.66%, respectively, as compared to the control value The Ethanol extract of *Momordica dioica* fruits possess significant antiulcer properties in a dose dependent manner.

Keywords- Pylorus ligatated, Ethanolic extracts, *Momordica dioica*, Ulcerative, Cold stress.

I. INTRODUCTION

Peptic ulcer disease represents a serious medical problem. Approximately 500,000 new cases are reported each year, with 5 million people affected in the United States alone. Interestingly, those at the highest risk of contracting peptic ulcer disease are those generations born around the middle of the 20th century. Peptic ulcers are sores that develop in the lining of the stomach, lower esophagus, or small intestine. They're usually formed as a result of inflammation caused by the bacteria *H. pylori*, as well as from erosion from stomach acids. Peptic ulcers are a fairly common health problem.[1] There are three types of peptic ulcers:

- **gastric ulcers:** ulcers that develop inside the stomach
- **esophageal ulcers:** ulcers that develop inside the esophagus
- **duodenal ulcers:** ulcers that develop in the upper section of the small intestines, called the duodenum

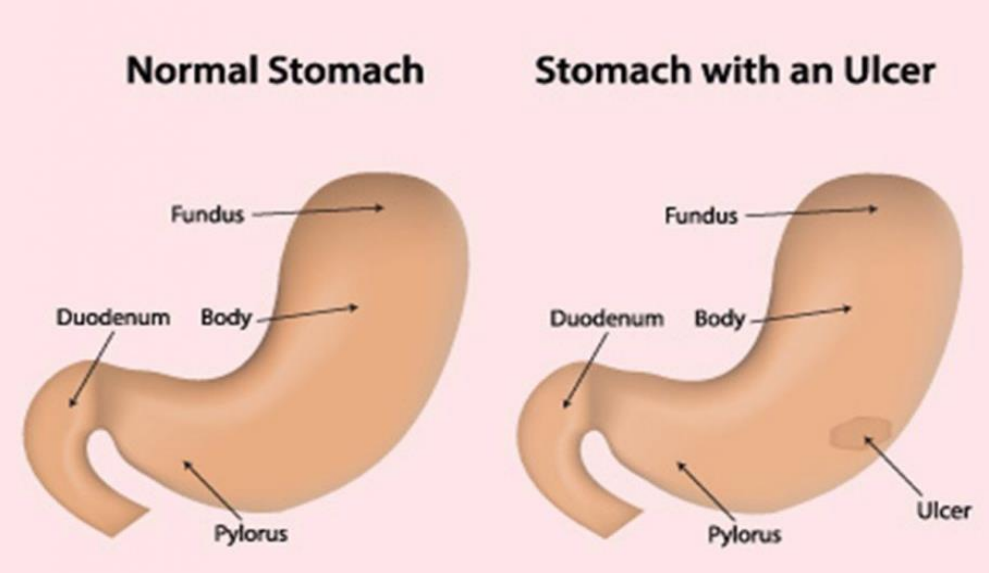

Figure 1: Comparasion between normal stomach and ulcer stomach

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Momordica dioica Roxb Wild is a perennial, dioceous climbing creeper belonging to family Cucurbitaceae. Its common name is Parora, kakora. Flowering occurs during June to July and fruiting during September to November. Leaves of plant are simple membranous, broadly ovate in outline, variable in length 3.8-10 cm by 3.2-8 cm, cordate at the base, deeply lobed in 3-5 triangular lobes, punctated, entire but distantly denticulate, petiole 1.3-4.5 cm. long channelled above, pubescent and glandular .Male flower is solitary, up to 2.8 cm long and yellow coloured.[2] Petals are 1.3- 2.5 cm long, oblong lanceolate. Calyx are five lobed, linear lanceolate. Phytoconstituents of *Momordica dioica* are traces of alkaloids, steroids, triterpenoids, flavonoids, glycosides, saponins, triterpenes of urisolic acid dark brown semidrying oil and saturated fatty acids ,ascorbic acids, vitamin A , thiamine, ribnoflavins, niacin, protein carbohydrates, lectins, ascorbic acids, carotenes, bitter principles, oleanoic acid, stearic acid, gypsogenin, alpha-spiranosterol hederagenin, momordicaursenol.The alkaloid present in seed called momordicin and present in root called momordicafoetida.Cucurbitacins and cucurbitane glycosides: structures. [3]Sadyojatha et al examined the chemical constituents of the rhizome of *Momordica dioica* revealed the presence of β-sitosterol saponin glycosides and alkaloids.The isolated principles of rhizome was tested against bacteria & concluded that the compound exhibits a moderate antibacterial activity. *Momordica dioica* also possess many essential nutrients compound which are essential for proper functioning of the body. It contains Calcium -0.5 mg/g, Sodium -1.5 mg/g, Potassium -8.3 mg/g, Iron -0.14 mg/g, Zinc -1.34 mg/g, Protein -19.38%, Fat -4.7%, Total phenolic compound 3.7 mg/g, Phytic acid -2.8 mg/g , 4.1calories and ash value was 6.7. (Bawara Bhavana; et al 2010).[4]

Figure 2: *Momordica Dioica* Fruits

II. MATERIAL AND METHODS

Reagents and instruments- All the drugs, chemicals and instruments were provided by National Botanical Research Institute (Lucknow).

Collection and authentification of the plant

The fruits of *Momordica dioica* (Family-Cucurbitaceae) were collected from Garden of National Botanical Research Institute, Lucknow, India in month of July 2006. The plant material was authenticated by Dr. Sayeeda Khatoon, chemo taxonomist and the voucher specimens (NAB 180023) were deposited in the departmental herbarium for future reference.

Preparation of crude drug for extraction

The authenticated fruits were used for the preparation of the extract. The fruits were collected and dried under shade and then coarsely powdered with the help of mechanical grinder. The powdered was passed through sieve no. 40 and stored in an airtight container for extraction.

Preparation of Ethanolic extract of Momordica dioica

The marc left was dried and then further exhaustively extracted with of ethanol for 3 days (3 X 5L). The extract was separated by filtration and concentrated on Rotavapour (Buchi, USA) and then dried in lyophilizes (Labconco, USA) under reduced pressure and low temperature to obtain 35.52 g of solid residue (yield 7.75 % w/w). The extract obtained was further subjected to toxicological and pharmacological investigations. The results were shown in Table.2.

Preliminary phytochemical screening-Phytochemical studied was done by well-established method and perform various test such as Tritrerpenes, Steroids, Carbohydrates, Tanins, Fixed oils & fats, Mucilage, Alkaloids, Proteins, glycosides etc.

Animals

Albino-Wistar rats (150-200g) and Swiss albino mice (20-25 gm) of either sex and of approximately the same age were procured from the animal house of Central Drug Research Institute, Lucknow. They were kept in the departmental animal house at 26 ± 2 °C and relative humidity 44 – 56 % in polypropylene cages. The animals were exposed to alternate 12 hrs of darkness and light each. Animals were provided with standard rodent pellet diet (Dayal, India) and the food was withdrawn 18-24 h before the experiment though water was allowed *ad libitum*. All experiments were performed in the morning according to current guidelines for investigation of experimental pain in conscious animals. The standard or gastric cannula was used for oral drug administration in experimental animals.

Acute toxicity studies (OECD Guideline 423)

Acute Toxic Category Method is a method for assessing acute oral toxicity that involves the identification of a dose level that causes mortality.This test involves the administration of a simple bolus dose of test substances to faster healthy young adult rodents by oral gavages, observation for up to 15days after dosing

and recording of body weight and the necropsy of all the animals. In this method pre-specified fixed doses of the test substances were used i.e., 5mg/Kg, 50mg/Kg, 300mg/Kg, 2000mg/Kg and the mortality due to these doses were observed. Generally female animals were used for this study and each dose group should consist of 3 animals.

III. EXPERIMENTAL DESIGN

Albino Wistar rats of either sex weighing 150-250 g were divided into four groups each containing 6 animals, for each model.[5]

1-Pyloric ligation model

The ulcer protective effect of alcohol extract of *Momordica dioica* was studied as per the method of Shay (Shay,H.et al 1945). In pyloric ligation induced ulcers, ulcers are caused by accumulation of acidic gastric juice in stomach.

Group I: Control (2% v/v Tween 80, 5 ml/kg), p.o
Group II: Ranitidine 50 mg/kg body weight, p.o
Group III: EEMD 200 mg/kg body weight, p.o
Group IV: EEMD 400 mg/kg body weigh, p.o

Albino rats were fasted for 24 h with free access to water prior to the tests. Under light ether anesthesia, the abdomen was opened by a small midline incision below the xiphoid process; the pyloric portion of the stomach was slightly lifted out and ligated, avoiding traction to the pylorus or damage to its blood supply. The stomach was replaced carefully and the abdominal wall closed by interrupted sutures. Control vehicle, alcohol and aqueous extracts of *Momordica dioica* and standard drug (ranitidine 50 mg/kg) were administered orally immediately after pyloric ligation. After 4h of pyloric ligation, the animals were sacrificed with excess of anesthetic ether and stomach was dissected out; the gastric contents were drained into graduated tubes and its volume, pH, total acidity were determined. Glandular portion of stomach was cut open along the greater curvature and inner surface examined for ulceration. Stomach was rinsed under a stream of water and pinned flat on a corkboard. The mucosa was flushed with saline and stomach was pinned on frog board. The lesion in glandular portion was examined under a 10x magnifying glass and length was measured using a divider and scale and gastric ulcer was scored. Ulcer index of each animal was calculated by adding the values and their mean values were determined (Malairanjan, P. et al. 2007).[6,7]

- 0 – Normal coloured stomach
- 0.5 – Red colouration
- 1 – Spot ulceration
- 1.5 – Haemorrhagic streak
- 2 – ulcers

Perforations Ulcer index was measured by using following formula (Vogel, H.G., 2002).

$$U_I = U_N + U_S + U_P \times 10^{-1}$$

Where-
U_I = Ulcer index
U_N = Average number of Ulcer per animal
U_S = Average number of severity score
U_P = Percentage of animal with Ulcer

Percentage inhibition of Ulceration was calculated as below:

$$\% \text{ Inhibition of Ulceration} = (\text{Ulcer index}_{Control} - \text{Ulcer index}_{Test}) \times 100 / \text{Ulcer index}_{Control}$$

The gastric content was centrifuged at 2000 rpm for 10 minutes and volume supernatant was measured.An aliquot of 1ml of gastric juice was diluted with the 1ml of distilled water and pH of the solution was measured using digital pH meter. For total acidity an aliquot of 1ml of gastric juice was diluted with the 1ml of distilled water contained in to 50 ml of conical flask, two drops of phenolphthalein indicator were added to it and titrated with 0.01 N NaOH until a permanent pink color was observed.[8,9]

The volume of 0.01 N NaOH consumed was noted. The total acidity is expressed as meq/l by the following formula-

$$\text{Total acidity} = n \times 36.45 \times 1000$$

Where n is volume of NaOH consumed, 36.45 is molecular weight of NaOH, and 1000 is the factor (to be represented in litre).

For free acidity, instead of phenolphthalein indicator, the Topfer's reagents are used. An aliquot of 1ml of gastric juice was titrated with 0.01 N NaOH until a canary yellow colour was observed. The volume of 0.01 N NaOH consumed was noted. The free acidity was calculated by the same formula used for total acidity (Archana, R.J.et. al. 2009).

2-Cold restrait stress induced gastric ulcer model

Group I: Control (2% v/v Tween 80, 5 ml/kg)
Group II: Ranitidine 50 mg/kg body weight, p.o
Group III: EEMD 200 mg/kg body weight, p.o
Group IV: EEMD 400 mg/kg body weigh, p.o

Animals were deprived of food for 12 h with free access to water prior to the tests. The test drug extracts, control (2% Tween 80) and standard drug ranitidine were administered 30 mins prior to immobilizing the animals. For stress induced ulcers, 30 mins after administration of drugs, each animal was individually immobilized in a stress cage and kept for 3 h in a refrigerator, maintained at 4-6^{0}C. The animals were sacrificed by a blow on the head, stomach isolated and gastric juice was collected, volume, pH and total acidity of gastric juice were determined. The stomach was opened along the greater curvature, rinsed under a stream of water and pinned flat on a corkboard. Erosions formed on the glandular portion of the stomach were counted and each given a severity rating on 1-3 scale based on diameter of ulcers. The overall total diameter

of ulcers in one stomach divided by factor 10 was designated as ulcer index (UI).[10, 11]

Histophathology

From each group small pieces of stomach were embedded in paraffin wax. Section of 5µm thick were cut in a microtome and mounted on glass slides using standards techniques (Sairam pathology, Meerut). After staining the tissue with hematoxylin-eosin stain, the slides were viewed under a light microscope equipped for pathology.

Statistical Analysis

All the values are expressed as mean ± S.E.M for groups of six animals each. Analyzed by one way ANOVA and compared by using Newman-Keuls Multiple Comparison Test. The values are statistically significant at three levels, ***p<0.001. **p<0.01. *p<0.05. But ns if p > 0.05.

IV. RESULT

Table 1: Preliminary phytochemical screening of the EEMD.

Type of constituents	Results
Tritrerpenes	-
Steroids	-
Carbohydrates	+
Tanins	+
Flavanoids	+
Fixed oils &fats	-
Mucilage	-
Proteins	-
Alkaloids	+
Saponins	+
Glycosides	+

Acute Oral Toxicity Studies

Table 2: LD50 Value of EEMD, LD 50=2000mg/kg, ED 50=200mg/kg.

NO. OF ANIMALS	DOSE	OBSERVATION
3 Mices	5mg/kg BODY WEIGHT	NO DEATH
3 Mices	50mg/kg BODY WEIGHT	NO DEATH
3 Mices	300mg/kg BODY WEIGHT	NO DEATH
3 Mices	2000mg/kg BODY WEIGHT	2 DEATH

Effect of distilled water in pylorus ligation induced ulcer

The distilled water at a dose (5 ml/kg, p.o), was administered one hour before ligation of pylorus end of rat stomach in control group. The pyloric ligation has caused the accumulation of gastric secretion 4.22±0.064 with pH 2.86±0.049 in control group. The total acidity and free acidity of gastric secretions were found to be 3.68±0.047 and 1.91±0.060 meq./l.The ulcer index was found to be 3.18±0.47 shown in fig.3(a).

Effect of ranitidine (standard drug) in pylorus ligation induced ulcer

The Ranitidine at a dose (50 mg/kg, p.o), was adin)istered one hour before ligation of pylorus end of rat stomach in standard group. The pyloric ligation has caused the accumulation of gastric secretion 1.565±0.041 with pH 5.2±0.057 in standard group. The total acidity and free acidity of gastric secretions were found to be 0.916±0.070and 0.389±0.047meq./l.The ulcer index was found to be 0.716±0.047 shown in fig.3(b).

Effect of EEMD at a dose (200 & 400 mg/kg p.o) in pylorus ligation induced ulcer

The fruits extract of *Momordica dioica* at a dose (200 and 400mg/kg, p.o) were administered one hour before ligation of pylorus end of rat stomach in treated group. The pretreatment with the *Momordica dioica* reduced the volume of gastric secretion shown in fig 1. pH of the gastric fluid was elevated 3.41±0.047, 4.455±0.041 at a dose 200 and 400mg/kg of the extract shown in fig 2. The total acidity of gastric secretions was found to be 2.88±0.040**,** 1.983±0.47 at a dose of 200 and 400mg/kg of the extract shown in fig 3. The free acidity of gastric secretions was found to be1.20±0.031, 0.725±0.030 at a dose of 200 and 400mg/kg of the extract. Animals treated with the extract of *Momordica dioica* at 200 and400mg/kg, p.o doses shows significant (p<0.05) reduction in the ulcer index shown in fig.3(c).

Effect of distilled water in cold restrait stress induced ulcer

The distilled water (5 ml/kg, p.o), was administered 30 mint before immobilizing the animal in control group.The ulcer index was found to be 2.4±0.031 shown in fig.4(d).

Effect of ranitidine (std.drug) in cold restrait stress induced ulcer

The Ranitidine (50 mg/kg, p.o), was administered 30 mint before immobilizing the animal in standard group. The ulcer index was found to be 0.44±0.034 shown in fig.4(e).

Effect of eemd at a dose (200 & 400 mg/kg p.o) in cold restrait stress induced ulcer

The **f**ruits extract of *Momordica dioica* at a dose (200&400mg/kg/p.o) was administered 30 mint

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before immobilizing the animal in treated group. The effect of fruit extract of *Momordica dioica* at a dose on ulcer index were shown in fig.4(f).

Effect of distilled water, ranitidine and eemd at a dose (400mg/kg p.o) on histopathalogical sections of stomach mucosa of wister rats using in pylorus ligation induced ulceration

The sections of stomach of control animals show hemorrhage and discontinuity in the lining epithelium hyperplastic mucosal glands. The treated animal Ethanolic *Momordica dioica f*ruits extract (400 mg/kg, p.o) show no ulcer formation, small atrophic glands, thick muscularis, and edematous sub-mucosa with inflammatory infiltrate. But Ranitidine has great effect with no ulcer formation, mild hyperplastic mucosa without any edema formation. (Fig.-4)

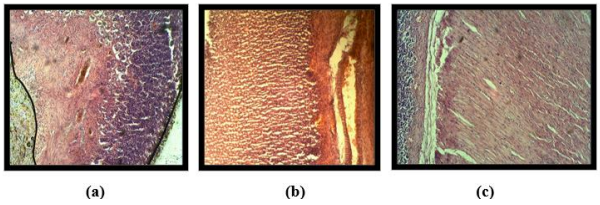


Figure 3: Histopathological section of stomach mucosa in wistar rat using pylorus ligation induced ulcer.

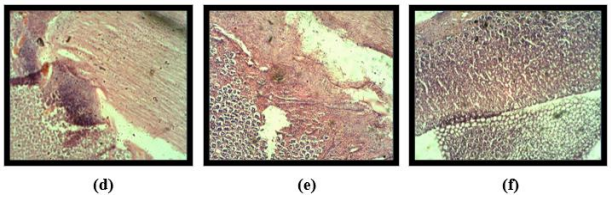


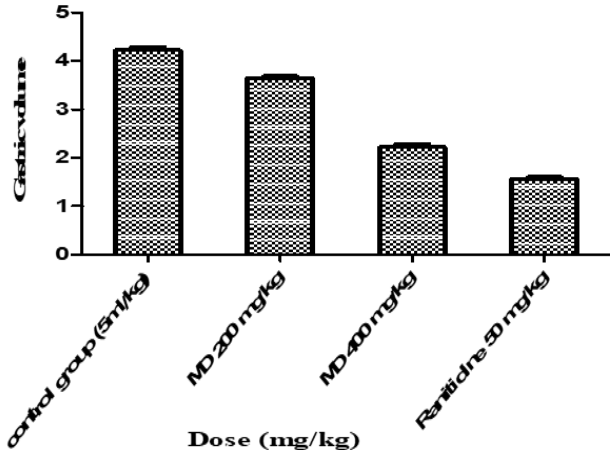
Figure 4: Histopathological section of stomach mucosa in wistar rat using Cold restrait stress induced ulcer.

(a) and **(d)** Distilled water (5ml/kg,p.o) – Shows hemorrhage and discontinuity in the lining epithelium hyperplastic mucosal glands.

(b) and **(e)** Ranitidine(50mg/kg)– No ulcer formation, mild hyperplastic mucosa without any edema formation.

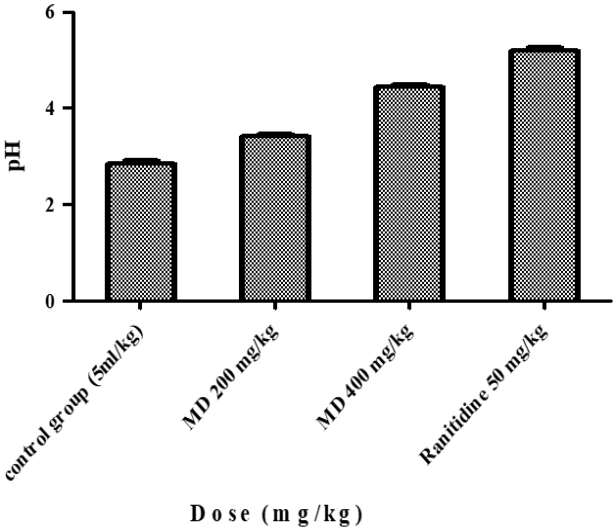
(c) and **(f)** EEMD 400 mg/kg,p.o – No ulcer formation, small atrophic glands, thick muscularis, and edematous sub-mucosa with inflammatory infiltrate.

- The distilled water at a dose (5 ml/kg, p.o), Ranitidine, a standard drug (50mg/kg, p.o) and EEMD (200 and 400mg/kg, p.o) were respectively administered one hour before ligation of pylorus end of rat stomach in control, standard and extract treated groups. P
- <0.05(MD 200mg/kg), p<0.01(MD 400 mg/kg) and p≤0.001(Ranitidine 50 mg/kg) were considered.
- significantly different in comparison with control group.



Graph 1: Effect of Ranitidine and EEMD on gastric volume in pylorus ligation induced ulcer

- The distilled water at a dose (5 ml/kg, p.o), Ranitidine, a standard drug (50mg/kg, p.o) and EEMD (200 and 400mg/kg, p.o) were respectively administered one hour before ligation of pylorus end of rat stomach in control, standard and extract treated groups.p<0.001(Ranitidine 50mg/kg), p<0.05(MD 400 mg/kg)was considered significantly different in comparison with control group.



Graph 2: Effect of Ranitidine and EEMD on pH in pylorus ligation induced ulcer.

- The distilled water at a dose (5 ml/kg, p.o), Ranitidine, a standard drug (50mg/kg, p.o) and EEMD (200 and 400mg/kg, p.o) were respectively administered one hour before ligation of pylorus end of rat stomach in control, standard and extract treated groups.p<0.05(MD 400 mg/kg), p<0.01(Ranitidine 50mg/kg) was considered significantly different in comparison with control group.

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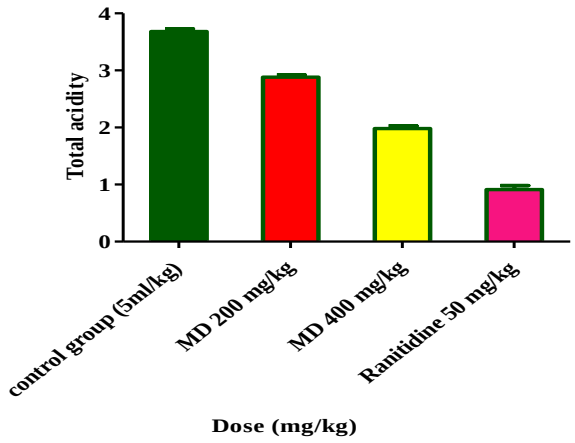
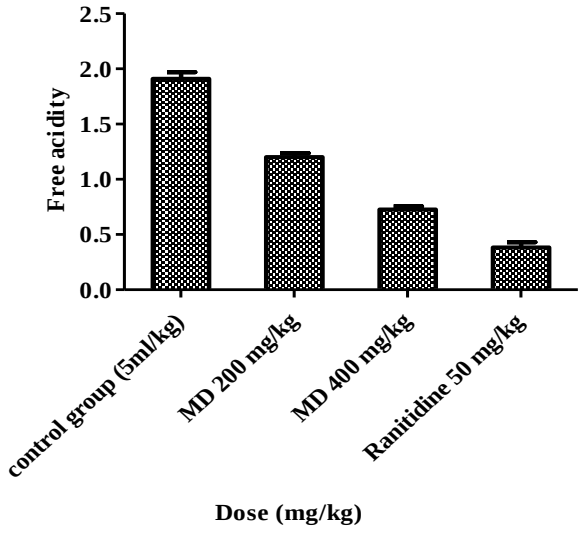


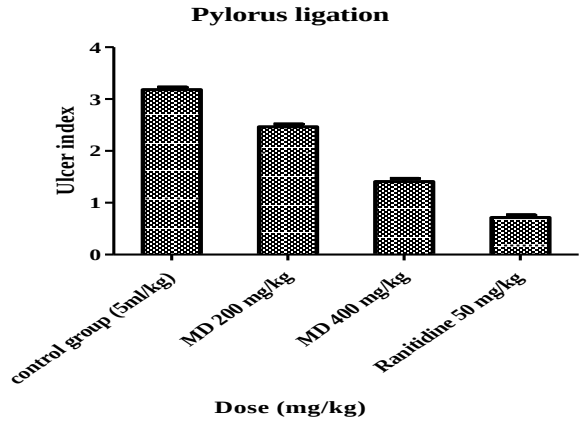
Graph 3: Effect of Ranitidine EEMD on total acidity in pylorus ligation induced ulcer.

- The distilled water at a dose (5 ml/kg, p.o), Ranitidine, a standard drug (50mg/kg. p.o) and EEMD (200 and 400mg/kg, p.o) were respectively administered one hour before ligation of pylorus end of rat stomach in control, standard and extract treated groups. $p<0.01$ (MD 400 mg/kg), $p<0.001$ (Ranitidine 5omg/kg) was considered significantly different in comparison with control group.



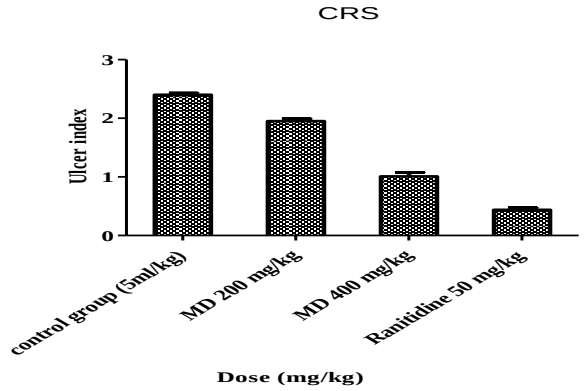
Graph 4: Effect of Ranitidine and EEMD on free acidity in pylorus ligation induced ulcer.

- The distilled water at a dose (5 ml/kg, p.o), Ranitidine, a standard drug (50mg/kg, p.o) and EEMD (200 and 400mg/kg, p.o) were respectively administered one hour before ligation of pylorus end of rat stomach in control, standard and extract treated groups. $p<0.05$(MD 400mg/kg) $p<0.001$(Ranitidine 50 mg/kg) was considered significantly different in comparison with control group.



Graph 5: Effect of Ranitidine and EEMD on Ulcer index in pylorus ligation induced ulcer.

- The distilled water at a dose (5 ml/kg, p.o), Ranitidine, a standard drug (50mg/kg, p.o) and EEMD (200&400mg/kg, p.o) were respectively administered 30mint before immobilizing the animal in control, standard and extract treated group. $p<0.01$(MD 400mg/kg), $p<0.05$(MD200mg/kg) was considered significantly different in comparison with control group.



Graph 6: Effect of Ranitidine and EEMD on ulcer index in Cold restrait stress induced ulcers.

V. CONCLUSION

Ulcer is a major problem today. Therefore, in the present study Pyloric induced, and Cold Restrait stress induced were employed to induce ulcers. The antiulcer activity of ethanolic extract of fruits of *Momordica dioica* against the ulcer was studied. Gastric ulcer is often a chronic disease and it may persist for 10–20 years characterized by repeated episodes of healing and re-exacerbations.cold restrait stress -induced ulcer better resembles clinical ulcers in location, chronicity and severity and servers as the most reliable model to study healing process (Okabe,S.,et,al,1972).MDE significantly healed the penetrating ulcers induced by

cold restrait stress after concluding days treatment. Free radicals affect lipids by initiating peroxidation. Superoxide (O2−), hydrogen peroxide and hydroxyl radical (OH) are important ROS causing tissue damage and lipid peroxide level is an indicator for the generation of ROS in the tissue. The experimental data stated that the cold-restraint stress aggravated the ulcer severity, lipid peroxidation, and plasma corticosterone as compared to unstressed rats. The higher lipid peroxidation and SOD levels indicated increased production of O2− within the tissue as elevated O2− level was thought to increase the concentration of cellular radical level. These radicals functioned in concert to induce cell degeneration via peroxidation of membrane lipids, breaking of DNA strands and denaturing cellular proteins (Halliwell, B.,et,al.1985) This effect was significantly reversed by prior administration of *Momordica dioica* providing a close relationship between free radical scavenging activity and the involvement of endocrinological (plasma corticosterone) responses. The more work is required for the clear understanding of the mechanism of action with chemically identified active principles. However, in the present study the plant shows a potent antiulcer activity, which justifies the ethnomedical claims. The present study states that *Momordica dioica* the data presented above shows that the fruit of Ethanolic extract of *Momordica dioica* exhibits antiulcer effect at different dose levels. Above results also indicates that the use of this extract as an antiulcer agent and analysis of the risk-benefit balance appears to be fruitful. Further investigations are necessary to determine the extent in which the characterization of its active compounds for the best antiulcer activity.

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DECLARATIONS

Conflict of Interest- The authors declare no potential conflicts of interest.
Ethical Approval- Central Drug Research Institute, Lucknow.

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