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Research Article

A Pharmacological Study of Gastric Antiulcer Activity of the Leaf Extracts of *Moringa oleifera* Linn

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Abstract

Moringa oleifera Linn., a fast growing, drought resistant tree, is widely grown in Indian subcontinent and South Asia. The leaves of this tree have immense nutritional value. It is conventionally used by the people of the region as a traditional cure of many ailments including gastric ulcer. Diverge groups of Wistar rats belonging to different sexes were treated with pyloric ligation and by cold and restraint stress for induction of ulcer experimentally. The induced animals were treated with aqueous extracts of fresh leaves of *Moringa oleifera* (MOL) in the doses of 200 mg and 400 mg per kg as anti-ulcer cure and were compared with standard anti-ulcer drug Ranitidine. The study revealed the antiulcer activity of aqueous extract of leaves of MOL in animal models of pyloric ligation and cold restraint induced gastric ulcers. The ulcer protection in ranitidine group was 64.12% against the groups treated with MOL in doses of 200 and 400 mg/kg was 45.2% and 50.07%, respectively. The acute toxicity study by the administration of doses of MOL up to 2000 mg/kg in the above for a period of 14 days did not show any acute toxicity. The satisfactory evidence of antiulcer activity of MOL extract suggests the necessity of further advanced scientific study for testing its usefulness in human.

Keywords: *Moringa oleifera* Linn.; Gastric Ulcer; Antiulcer Activity

Introduction

Peptic ulcer is associated with acute or chronic inflammation and is the most common gastrointestinal disorder in clinical practice around the world and is caused mostly by damage to mucosal lining of stomach or duodenum. Imbalance between the protective factors and acid secretion may substantially contribute its causation [1]. The incidence of peptic ulcer disease in the world is 1 to 1.9 per 1000 and the prevalence based on physician diagnosis is 0.12-1.50% [2]. Though several antiulcer drugs are available which reduce acid secretion, enhance gastric protection, prevent apoptosis or incite epithelial cell proliferation for healing, multiple adverse reactions and high rate of relapses are known with the use of such conventional drugs [3]. The potential natural drugs may cause lesser adverse reactions or to a minimum extent.

The earlier reports revealed that nature of food consumed like spicy food, food containing caffeine etc. incite gastric acid secretion in the stomach [4] and makes vulnerable to ulcer. Surprisingly, the people of south Asian countries suffer less due to duodenal ulcer and it was revealed that they frequently consume leaves of *Moringa oleifera* Linn. (*Moringaceae*) as a preventive measure which is speculated to protect against ulcers [5]. *Moringa oleifera,* a drought-resistant tree belonging to the family *Moringaceae,* subclass Dilleniidae and family *Moringaceae*, is native to the Indian subcontinent. The common names of the plant include moringa,

drumstick tree, horseradish tree, and ben oil tree or benzolive tree. Several reports [6,7] [8] stated that origin of the tree is from the northern India. More specifically, wild habitat of *Moringa oleifera* stands only in hilly lowlands of north western India and thus is the actual centre of origin [9]. This is one of the fast growing, evergreen, deciduous medium sized perennial tree of about 10 m to 12 m height. *Moringa oleifera* is rich in fairly unique group of phytochemicals, glucosinolates and isothiocyanates [10,11]. *Moringa oleifera* leaves contain high quantity of vitamin A, calcium, iron, vitamin C and potassium and protein which are of better quality than milk and eggs [11-13]. Different parts of this plant have been used as foods as well as medicinal purposes. Traditionally, *M. oleifera* leaves are used to treat many ailments, such as nervous debility, paralysis, asthma, diabetes, blood pressure, diarrhoea, infection and ulcer [14,15] and anti-ulcer properties [16,17]. Moringa has been reported to possess all powerful anti-oxidants that help in the detoxification of harmful compounds in the body. The flower bud of *Moringa pteygosperma* Linn., a synonym of *Moringa oleifera* Linn., widely consumed in Pakistan, was reported to possess antiulcer activity against aspirin-induced gastric ulcers in rats [18].

Materials and Methods

The study was carried out in the Department of Pharmacology, Gauhati Medical College and Hospital, Guwahati after getting necessary approval from the Institutional Animal Ethics Committee of Gauhati Medical College and Hospital, Guwahati with CPCSEA Registration No. 351: 03/01/2001 and study protocol approval No. MC/05/2015/88).

The experiment was conducted with 54 Wistar rats of either sex having the weight in the range of 150-250 grams. All the animals were kept in the Animal House of our Institute, in a clean area. The temperature was maintained at 24 ± 2°C, with relative humidity of 30 - 70%, with alternate light and dark cycle of 12 hours. Six rats were kept in a polypropylene cage during the study. Cages had a stainless-steel top grill having facilities for food and drinking water in polypropylene bottles with stainless steel sipper tube. Standard rat pellet feed and pure drinking water were provided *ad libitum*. Maintenance of the study animals was done strictly following the CPCSEA guidelines.

Materials

Drugs and chemicals: (1) Ranitidine (2) Aqueous extract of *Moringa oleifera* (3) Normal Saline (0.9% NaCl) (4) Topfer Reagent (5) 0.1 N NaOH solution (6) Phenolphthalein solution

Plant material

Fresh leaves of MOL were collected from botanical garden in the month of September, 2016. Authentication and verification of the plants were done by Dr. Gajendra Sharma, Department of Botany, Gauhati university.

Preparation of aqueous extract

The leaves were thoroughly washed and shade dried, grinded into fine powders and were kept in air tight containers. The soxhlet apparatus was used for extraction. The resultant extracts were filtered using Whatman filter paper no. 1, concentrated by evaporation and collected in petri dishes. The final yield of MOL leaf extracts were 66.3 grams (26.5%), stored in a refrigerator at 4°C in air tight containers.

Acute toxicity tests [19]

This was carried out as per OECD guidelines. The rats were randomly selected, marked for identification, and kept in their cages for seven days prior to dosing. Animals were fasted prior to dosing (food was withheld for 3 - 4 hours). The dose was calculated according to the fasted body weight. Post fasting, the first animal was dosed at 175 mg/kg body weight with aqueous extract of study drug by gavage. Food was withheld for a further 1 - 2 hours. The animal was observed for mortality for 48 hours. Then a second animal was dosed at 550 mg/kg body weight by the same process. Again after 48 hours a third animal was dosed at 2000 mg/kg and observed for the next 48 hours for mortality. All the above animals were observed for a period of 14 days and were found to be alive at 2000 mg/kg. Two doses of the study drug were selected i.e. 200 mg/kg, and 400 mg/kg.

Study groups

The study had 2 experimental models.

- Ulcer induction by pyloric ligation [20]
- Ulcer induction by cold and restraint stress [21].

For each model, 5 groups of 6 animals each were selected. Group I (Normal control) served as a common for both models. Thus, for both models, a total of 54 animals were taken, detailed as follows [22,23].

Groups	Group code	Treatment given
Normal Control	NC	No induction or intervention given
Disease Control	DC	Normal saline 1 ml/kg
Standard	R20	Ranitidine 20 mg/kg
Moringa oleifera aqueous extract low dose	AEMK200	*Moringa oleifera* aqueous extract 200 mg/kg
Moringa oleifera aqueous extract high dose	AEMK400	*Moringa oleifera* aqueous extract 400 mg/kg

Table 1

Duration and route of drug administration: All study drugs were administered orally for 7 days, using an oral feeding tube for rats.

Study procedure

- **Ulcer induction by pylorus ligation by Shay's method:** Under proper aseptic and antiseptic conditions, ulcer induction was done by pylorus ligation as per the standard procedure [20].
- **Ulcer induction by cold and restraint stress by Vincent., *et al*:** Under proper aseptic and antiseptic conditions, the animals were starved and on 7th day, ulcers were induced by cold while putting the animal in restraint [21].

Variables assessed in the study [25]

Following variables were measured in both models in the study:

- Ulcer index
- Percentage of ulcer protection. Additionally, following variables were studied in pyloric ligation model:
  - Gastric content volume
  - Free acidity
  - Total acidity
  - pH

Estimation of variables

The ulcers were evaluated quantitatively using ulcer index and scoring number [26]. Percentage ulcer protection was also calculated. Volume, pH, free and total acidities of gastric content was determined. Titration was done with 0.01N NaOH, till total acidity was achieved.

Histopathological examination

Stomach tissues were fixed in 10% formalin for 24 hrs, and then embedded in paraffin. Small sections were made (3 - 5 µm) and stained with H&E dye and examined under light microscopy.

Statistical analysis:

- Analysis done using the Graph pad prism 5.01software.
- Between the groups, the data was compared using one way ANOVA test followed by post hoc Tukey's test [31]
- The level of significance for each comparison in the analysis was calculated at 0.05.

Results

Pyloric ligation induced ulcer model

- **Ulcer index:** On comparison using one-way ANOVA, the mean ulcer index between the groups was significantly different ($P < 0.001$) (Table 2). On post hoc analysis, it was higher in all pyloric ligated groups than the normal control group. In all treatment groups, the mean ulcer index was significantly lower than the disease control group ($P < 0.001$). On comparison with ranitidine treated group, it was significantly higher in aqueous extract *Moringa oleifera* 200 mg/kg ($p = 0.002$) and 400 mg/kg ($p = 0.041$). The mean ulcer index in the groups treated with both doses of MOL were comparable ($p = 0.92$) as shown in table 3.
- **Percentage of ulcer protection:** Compared to the disease control group, the ulcer protection in ranitidine group was 64.12%; in groups treated MOL in doses of 200 and 400 mg/kg, it was 45.2% and 50.07%, respectively (Table 4).
- **Volume of gastric juice:** On comparison using one-way ANOVA, the mean volume of gastric juice between the groups was significantly different ($P < 0.001$) (Table 2). On post hoc analysis, volume was significantly higher ($P < 0.001$) in induced groups than the normal control group. It was significantly lower in the ranitidine ($P < 0.001$), *Moringa oleifera* 400 mg/kg ($p = 0.042$) treated groups than the disease control group. Compared to ranitidine treated group, the mean volume in MOL 200 mg/kg ($P < 0.001$) and 400 mg/kg ($p = 0.001$) was significantly higher (Table 3).
- **pH of gastric juice:** On comparison using one-way ANOVA, the mean pH of gastric juice between the groups was significantly different ($P < 0.001$) (Table 2). On post hoc analysis, the mean pH was significantly lower in the disease control ($P < 0.001$)

and AEMK200 (P < 0.001) groups than normal control. The mean pH was significantly higher in the all treatment groups than the disease control group (P < 0.001). On comparison with ranitidine treated group, the mean pH of gastric juice in MOL 200 mg/kg (P < 0.001) treated groups was significantly lower. The mean pH in the group treated with MOL 400 mg/kg (P < 0.001) was significantly higher than the 200 mg/kg treated group (Table 3).

- **Free acidity of gastric contents:** On comparison using one-way ANOVA, it was observed that the mean free acidity of gastric juice between the groups was significantly different (P < 0.001) (Table 2). On post hoc analysis, it was observed that the mean free acidity of gastric juice was significantly higher (P < 0.001) in all induced groups than the normal control group. The mean free acidity of gastric juice was significantly lower in the all treatment groups than the disease control group (P < 0.001). On comparison with ranitidine treated group, the mean free acidity of gastric juice in aqueous extract MOL 200 mg/kg (P < 0.001) and 400 mg/kg (P < 0.001) treated groups was significantly higher. The mean free acidity of gastric juice in the group treated with aqueous extract MOL 400 mg/kg (P < 0.001) was significantly lower than the 200 mg/kg treated group (Table 3).
- **Total acidity of gastric contents:** On comparison using one-way ANOVA, it was observed that the mean total acidity of gastric juice between the groups was significantly different (P < 0.001) (Table 2). On post hoc analysis, it was observed that the mean total acidity of gastric juice was significantly higher (P < 0.001) in all induced groups than the normal control group. The mean total acidity of gastric juice was lower in the all treatment groups than the disease control group (P < 0.001). On comparison with ranitidine treated group, the mean total acidity of gastric juice in aqueous extract MOL 200 mg/kg (P < 0.001) and 400 mg/kg (P < 0.001) treated groups was significantly higher. The mean total acidity of gastric juice in the group treated with aqueous extract MOL 400 mg/kg (P < 0.001) was significantly lower than the 200 mg/kg treated group (Table 3).

Groups	Ulcer index	Volume of gastric juice (ml)	Ph of gastric juice	Free acidity of gastric contents	Total acidity	Statistical	P value	Interpretation
NC	0	1.14 ± 0.13	3.08 ± 0.11	10.02 ± 0.24	18.47 ± 0.38	One way ANOVA	P < 0.001	The mean ulcer index, volume of gastric juice, ph of gastric juice, free acidity and total acidity of gastric juice between the groups was significantly different
DC	4.38 ± 0.43	3.31 ± 0.34	1.81 ± 0.09	30.94 ± 1.56	42.86 ± 0.58			
R20	1.57 ± 0.32	2.45 ± 0.27	3.26 ± 0.11	11.48 ± 0.4	24.34 ± 1.09			
AEMK200	2.4 ± 0.44	3.23 ± 0.14	2.54 ± 0.22	19.35 ± 0.64	32.6 ± 0.58			
AEMK400	2.19 ± 0.37	2.96±0.11	3.12 ± 0.09	16.28 ± 0.39	28.14 ± 0.88			

Table 2: Pyloric ligation model.

Effect on ulcer index, volume of gastric juice, Ph of gastric juice, free acidity of gastric juice and total acidity.

Group 1	Group 2	Ulcer index		Volume of gastric juice		Ph of gastric juice		Free acidity		Total acidity	
		P value	Interpretation	P value	Interpretation	P value	interpretation	P value	Interpretation	P value	Interpretation
NC	DC	<0.001	The mean ulcer index in the other groups was significantly higher than the NC group	<0.001	The mean gastric juice volume in the other groups was significantly higher than the NC group	<0.001	The mean pH was significantly lower in the DC, AEMK200 group than NC, while it was comparable with NC group in R20, and AEMK400 groups	<0.001	The mean free acidity in DC, R20, AEMK200, AEMK400 groups was significantly higher than the NC group	<0.001	The mean total acidity in DC, R20, AEMK200, AEMK400 groups was significantly higher than the NC group
	R20	<0.001		<0.001		0.309		0.019		<0.001	
	AEMK 200	<0.001		<0.001		<0.001		<0.001		<0.001	
	AEMK 400	<0.001		<0.001		0.998		<0.001		<0.001	

DC	R20	<0.001	The mean ulcer index in R20, AEMK200, AEMK400 groups was significantly lower than the DC group	<0.001	The mean gastric juice volume was significantly lower in the R20, AEMK400 group than DC group, while it was comparable with DC group in AEMK200 groups	<0.001	The mean pH in R20, AEMK200, AEMK400 groups was significantly higher than the DC group	<0.001	The mean free acidity in R20, AEMK200, AEMK400 groups was significantly lower than the DC group	<0.001	The mean total acidity in R20, AEMK200, AEMK400 groups was significantly lower than the DC group
	AEMK 200	<0.001		0.990		<0.001		<0.001		<0.001	
	AEMK 400	<0.001		0.042		<0.001		<0.001		<0.001	
R20	AEMK 200	0.002	The mean ulcer index in AEMK200 groups was significantly higher than the R20 group, while it was comparable with R20 group in AEMK-400groups	<0.001	The mean gastric juice volume was significantly higher in the AEMK200, AEMK400 than R20 group	<0.001	The mean pH in R20, AEMK200 groups was significantly lower than the R20 group, while it was comparable with R20 group in AEMK400	<0.001	The mean free acidity in AEMK200, AEMK400 groups was significantly higher than the R20 group	<0.001	The mean total acidity in AEMK200, AEMK400 groups was significantly higher than the R20 group
	AEMK 400	0.041		0.001		0.638		<0.001		<0.001	
AEMK 200	AEMK 400	0.920	Mean ulcer index was comparable between AEMK200 and AEMK400 groups	0.200	Mean gastric juice volume was comparable between AEMK200 and AEMK400 groups	<0.001	Mean pH was significantly higher in AEMK400 group than AEMK200 group	<0.001	Mean free acidity was significantly lower in AEMK400 group than AEMK200 group	<0.001	Mean total acidity was significantly lower in AEMK400 group than AEMK200 group

Table 3: Post hoc analysis using Tukey's test.

Groups	Percentage of ulcer protection compared to disease control	
	Pyloric ligation method	Cold restraint method
NC	-	-
DC	-	-
R20	64.12%	67.9%
AEMK200	45.2%	47.49%
AEMK400	50.07%	54.82%

Table 4: Percentage of ulcer protection.

Cold Restraint stress induced ulcer model

- **Ulcer index:** On comparison using one-way ANOVA, it was observed that the mean ulcer index between the groups was significantly different ($P < 0.001$) (Table 5). On post hoc analysis, it was observed that in all induced groups, the mean ulcer index was significantly higher ($P < 0.001$) than the normal control group. The mean ulcer index in all treatment groups, the mean ulcer index was significantly lower than the disease control group ($P < 0.001$). On comparison with ranitidine

treated group, the mean ulcer index in aqueous extract MOL 200 mg/kg (P < 0.001) and 400 mg/kg (p = 0.013) treated groups was significantly higher. The mean ulcer index in the groups treated with both doses of MOL were comparable (p = 0.4) (Table 6).

- **Percentage of ulcer protection:** Compared to the disease control group, the ulcer protection in ranitidine group was 67.9%; in groups treated with aqueous extract of MKL in doses of 200 and 400 mg/kg, it was 47.49% and 54.82%, respectively (Table 4).

Groups	Ulcer index	Statistical test	F distribution and P value	Interpretation
NC	0	One way ANOVA	F (6,35) = 139.8 P < 0.001	The mean ulcer index between the groups was significantly different.
DC	3.76 ± 0.44			
R20	1.21 ± 0.14			
AEMK200	1.97 ± 0.26			
AEMK400	1.7 ± 0.22			

Table 5: Cold restraint model.

Group 1	Group 2	P value	Interpretation
NC	DC R20 AEMK200 AEMK400	<0.001 <0.001 <0.001 <0.001	The mean ulcer index in DC, R20, AEMK200, AEMK400 groups was significantly higher than the NC group
DC	R20 AEMK200 AEMK400	<0.001 <0.001 <0.001	The mean ulcer index in R20, AEMK200, AEMK400 groups was significantly lower than the DC group.
R20	AEMK200 AEMK400	<0.001 0.013	The mean ulcer index in AEMK200, AEMK400 groups was significantly higher than the R20 group
AEMK200	AEMK400	0.4	Mean ulcer index was comparable between AEMK200 and AEMK400 groups

Table 6: Post hoc analysis using Tukey's test.

Discussion

The present study demonstrated the antiulcer activity of aqueous extract of leaves of MOL in animal models of pyloric ligation and cold restraint induced gastric ulcers. MOL leaf extract has demonstrated antiulcer activity in some animal studies. These plants are easily available throughout the country in abundance, thus, giving us the opportunity to develop a cheap and easily available alternative for management of peptic ulcers. Thus, these plants were chosen and their antiulcer efficacy was evaluated in comparison to that with ranitidine.

In the present study, induction of ulcer by pyloric ligation or cold restraint stress was seen in the disease control groups, which was evident from the increase in ulcer index in comparison to the normal control group. Other variables also differed significantly.

Pyloric ligation induced ulcer model findings

With treatment by aqueous extract of MOL, the ulcer index was lower compared to the disease control group, but higher compared to ranitidine. Dose dependent effect was not observed. The ulcer protection was 50% at 400 mg/kg dose and 45.2% at 200 mg/kg dose. The gastric juice volume was lower at 400mg/kg dose compared to disease control group. Compared to ranitidine, at both doses the gastric volume was higher. The gastric pH was increased compared to disease control group. In comparison to ranitidine, only 400 mg/kg dose gave comparable results. pH was higher com-

pared to 200 mg/kg dose, representing a dose dependent effect. The free and total acidity of gastric contents was reduced than disease control group, however, the effect was not comparable to the ranitidine group, and also a dose dependent effect was observed with better response at higher dose. These results revalidate the findings of some other previous studies [26-29].

Cold restraint stress induced ulcer model findings

The ulcer index in the aqueous extract of MOL at both doses was lower than the disease control group, but was higher than ranitidine group, and similar at both doses. The ulcer protection provided was lower than that by ranitidine treatment at both doses.

From the findings of the study, it was evident that the aqueous extracts of leaves of MOL have antiulcer activity. This activity measured in terms of ulcer index and ulcer protection was evident compared to the disease control group. Ulcer protection was found to be more at higher doses compared to the lower doses. The pH, volume, free and total acidity represent secretory activity in the stomach. The effect on these variables demonstrated anti-secretory activity of the aqueous extract of MOL. Antiulcer activity of aqueous extract of *Moringa oleifera* leaves in the dose of 200 mg/kg and 400 mg/kg has been demonstrated in few studies. All the macroscopic and biochemical parameters showed significant antiulcer activity of *Moringa oleifera*. Study by Hamid., *et al*. [30] also showed significant anti-ulcer activity of *Moringa oleifera* aqueous extract like that of Rantidine, the positive control. Thus, the present study findings are in agreement with the previous studies evaluating the antiulcer activity of aqueous extract of leaves of MOL. However, the leaves contain numerous other phytoconstituents which have not yet been evaluated individually for their antiulcer potential.

Conclusion

The present study adds to the evidence of antiulcer efficacy of aqueous extracts of leaves of *Moringa oleifera*. Though not as efficacious as ranitidine, it is a promising agent possessing the potential antiulcer activity. Advanced research methodologies should be encouraged to identify and isolate the active phyto-constituents of the leaves of these native indigenous medicinal plants. The available evidence of antiulcer activity provides satisfactory evidence for further advanced studies with more pure and refined products for testing its efficacy in human. Development of compounds as antiulcer agents may have an additional advantage of being more cost effective.

Conflict of Interest

Nothing to declare.

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