Gastroprotective effect of *Musa acuminata* leaves extract on gastric ulceration and secretion induced by various ulcerogenic agents

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ABSTRACT:

Objective: The goal of this study was to see how effective a 50% ethanolic extract of *Musa acuminata* leaves on peptic ulcer induced by pylorus ligation, ethanol and aspirin in animal models.

Methods: The coarsely powdered of leaves of *Musa acuminata* were thoroughly extracted with 50% ethanol for 3 days (3 X 3L) and centrifuged at 10,000 revolutions per minute which was then concentrated on rotavapour. The acute toxicity study was carried out in male mice at the dose of 1000, 2000, 3000 and 4000 mg/kg b.w. individually by oral route administration for any changes in general behaviour or other physiological activity as per OECD Guideline 425. Gastroprotective effect of prepared extracts (100, 200 and 400 mg/kg) was evaluated on peptic ulcer induced by pylorus ligation, ethanol and aspirin using ranitidine (50 mg/kg) as standard drug.

Result: The extract is nontoxic up to a dose of 4000 mg/kg b.w. over the first 24 hours and for the next 14 days as per OECD Guideline 425, indicating that the extract is considered relatively safe. The oral administration of prepared extract at a dose of 400 mg/kg b.w. to rats significantly ($^{c}p < 0.001$) healed gastric ulcers and produced percentage protection up to 73.62% induced by pylorus ligation, aspirin, and ethanol, indicating its ulcer-protective and antisecretory properties.

Conclusion: The purpose of this investigation is to prove scientifically the use of 50% ethanolic extract of leaves of *Musa acuminata* exhibited a protective effect on a pylorus ligated, aspirin, and ethanol induced gastric ulcer in a dose dependent manner. As a result, the 50% ethanolic extract of *Musa acuminata* leaves could be used as the main source of antiulcer medicines.

KEYWORDS: Antiulcer activity, *Musa acuminate,*extraction,standard drug, ulcer index, percentage protection.

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INTRODUCTION:

The gastric ulcer disease is the most prevalent gastrointestinal problem that requires a potential therapeutic therapy.The imbalance between offensive factors like acid, pepsin, Helicobactor pylori, and defensive ones like mucin, prostaglandin, bicarbonate, nitric oxide, and growth factors can cause gastric ulcer disease[1,2]. Gastric ulcers, the most prevalent type of ulcer in nations like India, are caused by severe illness, shocks, stress, burns, emotional disturbance, and postsurgical problems. Because there are a plethora of synthetic antiulcer medications available to cure ulcers while also minimising numerous long-term side effects, herbal medicine is a viable alternative. *Musa acuminata*of Musaceae family is a famous plant that is commonly known as banana. It is a tropical plant that is grown as a source of food and revenue for farmers all over the world[3]. Bananas come in a variety of hues when ripe, including yellow, red, green, and purple, as well as varying sizes, and they can be farmed year around[4]. *Musa acuminata* may be a wild species of banana that's local to Southeast Asia. In folk medicine, many portions of the Musa plants have been used orally or topically as treatments, and some investigations have confirmed this medicinal potential. In America, Asia, Oceania, India, and Africa, all parts of the plant, including the roots, stem, pseudostems, leaves, fruits, and flowers, have long been utilised in local and traditional medicine[5]. Therefore, the goal of this study was to see how effective a 50% ethanolic extract of *Musa acuminata* leaves on peptic ulcer induced by pylorus ligation, ethanol, and aspirin in animal models.

METHODS:

Collection and extraction of plant materials:

The leaves of *Musa acuminata* collected from local garden of Kanpur, Uttar Pradesh, India were washed with tap and distilled water and air-dried at 30 ± 2°C. To eliminate fatty substances, the coarsely powdered plant materials were macerated with petroleum ether, the marc was then thoroughly extracted with 50% ethanol for 3 days (3 X 3L) and centrifuged at 10,000 revolutions per minute. Filtration was used to separate the extract, which was then concentrated on rotavapour and then dried by using lyophilizer under reduced pressure get 85.0 g of solid residue (yield 8.5% w/w) and stored at 4°C for later use.

Experimental animals:

Albino Wistar rats of either gender weighted 150-200g were used for the study. Animals were maintained in polypropylene cages under standard environmental conditions (26 ± 2°C and relative humidity 30-35%) in 12 hours light and 12 hours dark cycle respectively for 1 week before and during the experiments. The animals were fed with standard pellet diet and fresh water ad libitum. The animals were exposed to the environment for two weeks before being used in the experiment. They were fasted for the night before the experiment, but have free access for water ad libitum. The experiments were carried out after the approval of Institutional Animal Ethical Committee (Approval No: CPCSEA No.1275/PO/Re/S/09/CPCSEA).

Toxicity studies:

Swiss albino male mice were divided into five groups, each with six animals: one control group and four treatment groups. The control group got saline water, while the four treated groups received oral administration of a 50% ethanolic extract of *Musa acuminata* leaves at doses of 1000, 2000, 3000, and 4000 mg/kg b.w., respectively. The animals were monitored for 72 hours in accordance with OECD guidelines to look for any changes in general behaviour or other physiological activity[6].

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Phytochemical Screening:

50% ethanolic extract was examined for its phytoconstituents such as alkaloids, carbohydrate, glycoside, saponins, phyto steroids, polyphenol, tannins, flavonoids, proteins and amino acids[7,8].

Exprimental protocol: Antiulcer activity:

Evaluation of peptic ulcer protective and preventive activities was made as set forth by Shay et al. (1945)[9]using albino rats. The animals were divided into five groups, each with six animals and were treated as below:

Group I: Control group (distilled water 10 mL/kg/day, p.o.) + pylorus ligation

Group II: 50% ethanolic extract of leaves of *Musa acuminata*(100 mg/ kg b.w.)

Group III: 50% ethanolic extract of leaves of *Musa acuminata* (200 mg/ kg b.w.)

Group IV: 50% ethanolic extract of leaves of *Musa acuminata* (400 mg/ kg b.w.)

Group V: The standard, Ranitidine (50 mg/kg b.w.)

The experimental groups II, III and IV which received 50% ethanolicextracts and the group V received only ranitidine were given in distilled water, orally before subjecting them to ulcerogen.

Pyloric ligated induced ulcer in rats:

The experimental groups II, III, and IV were administered 50 percent ethanolic extracts orally for 5 days before being exposed to ulcerogen, while group V was given just ranitidine in distilled water. On the fifth day, a pyloric ligation was performed under light diethyl ether anaesthesia by ligating the pyloric end of the rat's stomach, the stomach was carefully repositioned, and the abdominal wall was closed with sutures. During the post-operative phase, the animals were kept in isolated cages to recover and stabilize, and they were denied access to drink. Rats were sacrificed with chloroform four hours after surgery, and their stomachs were dissected out and cut open along the larger curvature, gastric juice was collected for a gastric secretion research, and each rat's stomach was assessed for ulcer index[10, 11].

Ethanol induced ulcers in rats:

The rats were divided into five groups according to the experimental protocol on day 5, following 30 min of extract and ranitidine therapy, stomach ulcers were generated in rats by administrating 100% ethanol (1 ml/200g)[12]and after one hour, the rats were sacrificed by cervical dislocation, and the stomachs were sliced along the greater curvature and gastric juice was collected for a gastric secretion research, as well as the ulcer index of each rat's stomach[13].

Aspirin induced ulcers:

The animals were given aspirin at a dose of 200 mg/kg (20 mg/ml) on the day of the experiment, and ulcers were scored after 4 hours[14]. The stomach was removed and cut open along the greater curvature, and gastric juice was collected for a gastric secretion research, as well as the ulcer index of each rat's stomach. The total number of ulcers per stomach and the total severity of ulcers per stomach were combined to create the ulcer index[15].

Collection of gastric secretion study:

Gastric content was collected 4 hours after pyloric ligation and centrifuged for 10 minutes at 3000 rpm. The volume of the supernatant was calculated as the amount of gastric juice (mL/kg b.w.). A pH metre was used to determine the pH of the gastric juice, which was then exposed to many biochemical parameters such as volume, acid and pepsin content, and output [16].

Estimation protocols:

Ulcer index:

The stomachs of the rats were dissected and gently washed with normal saline water along the greater curvature. With the use of a magnifying glass, the ulcer lesions were counted and the ulcer diameter was measured. Ulcer index was assayed according to the method described by Suzuki et al. (1998)[17].The sum of the length (mm) of all lesions in each stomach was used to determine the Ulcer Index (UI), and the protection % against ulcer was calculated using the formula below:

Percent protection against ulcer= [(UI control - UI treated) / UI control] x 100

Determination of Total and free acidity[18]:

One millilitre of centrifuged stomach secretion, together with a few drops of Topfer's reagent, was pipetted out and titrated with NaOH until all traces of the red colour vanished and the colour changed to yellowish orange. The amount of free acidity added is proportional to the volume of alkali utilised. A few drops of phenolphthalein solution (1%) were added and titrated until a clear red color emerged. Total alkali volume was measured as mEq/ l/100 g20, which corresponds to total acidity.[20].

pH:

By dipping the electrode of a pH metre in a beaker containing gastric contents, the pH of stomach was determined.

Volume of gastric content:

The volume of gastric contents was determined by gently pouring the contents into a graduated cylinder.

Estimation of pepsin[20]:

The reaction mixture was incubated for 15 minutes with 5 mL of substrate (1% BSA in HCl at pH 2.1) and 1 mL of gastric juice sample (equal amount of gastric juice with HCl at pH 2.1, warmed to 37 ^{o}C.The reaction was stopped by the addition of 10 mLTCA. The blank, which comprised a mixture of 10 mL TCA and 1 mL gastric juice sample, was incubated for 15 minutes before 5 mL of substrate was added.The reaction mixture and the blank were filtered separately after 30 minutes. The absorbance was measured at 680 nm after adding 10 mL of 0.5 M NaOH and 1 mL of Folin-phenol reagent to the filtrate. Different tyrosine concentrations were prepared on a graph.Pepsin activity was measured in micrograms of tyrosine equivalents released per minute per mL of stomach juice.

Statistical analysis:

All the experimental results were presented as mean ± SEM (Standard Error Mean) (n = 6) using. To determine the difference between multiple groups, one-way analysis of variance (ANOVA) was used to statistically process the data (Graph pad prism 4.0 software).p-Value of 0.001 was considered extremely significant.

RESULTS:

Toxicity studies:

The acute toxicity study indicated that the 50% ethanolic extract of leaves of *Musa acuminata*possessed high safety profile up to 4000 mg/kg b.w. According to the OECD (Organization for Economic Co-operation and Development) Guideline 425, all animals appeared to be in good health and there was no mortality up to 4000 mg/kg over the first 24 hours and for the next 14 days[21, 22].The experimental animals' physical and behavioural observations indicated no evident symptoms of acute toxicity, such as lacrimation, loss of appetite, tremors, hair erection, salivation, or diarrhoea, indicating high safety margins. Dose selected for antiulcer studies was 100, 200 and 400 mg/kg respectively.

Preliminary phytochemical screening:

The qualitative phytochemical test for 50% ethanolic extract of leaves of *Musa acuminata* confirmed the presencealkaloids, glycosides, flavonoids, steroid, carbohydrates, protein, amino acid, tannins, fats and oils and phenolic compounds. (Table 1)

Table 1.Phytochemical Screening of 50% ethanolic extract of leaves of *Musa acuminata*:

Phytochemical Constituents	**50% Ethanolic extract of leaves of *Musa acuminata***
Alkaloids	+ve
Flavanoids	+ve
Carbohydrates	+ve
Saponins	-ve
Triterpenes	+ve
Sterols	-ve
Tannins	+ve

+ve = Present, -ve = absent

Antiulcer activity:

Pyloric ligated induced ulcer in rats:

Ulcer index and percent protection:

The50% ethanolic extract of leaves of *Musa acuminata*was administered to various groups, orally, daily for five days in 100, 200, 400 mg/Kg twice a day and the experiment were carried out on overnight fasted rats on 6th day. The result showed that the 50% ethanolic extract of leaves of *Musa acuminata*prevented the acute gastric ulcers in a dose related manner. In a pylorus ligation caused ulcer model, oral treatment of *Musa acuminata* reduced the index of gastric lesion compared to a control group. (Table 2)

Table 2. Effect of 50% ethanolic extract of leaves of *Musa acuminata* (twice daily for five days) on Pylorus ligation-induced gastric ulcers.

Group	**Treatment**	**Dose (mg/kg)**	**Ulcer index (mm^2/rat)**	**Percent protection**
I	Pylorus ligation	-	16.3 ± 2.8	-
II	*Musa acuminata*extract	100	13.2 ± 2.1^a	19.02
III	*Musa acuminata*extract	200	9.2 ± 2.0^b	43.56
IV	*Musa acuminata*extract	400	3.8 ± 0.92^c	76.68
V	Ranitidine	50	2.5 ± 1.2^c	84.66

Values are expressed as Mean $\pm$ SEM of 6 rats in each group. $^aP < 0.05$ compared to respective pylorus ligated group. ^{b} $P < 0.01$ compared to respective pylorus ligated group. $^cP < 0.001$ compared to respective pylorus ligated group.

Gastric secretion study (Effect on volume, acid and pepsin secretion):

The effect of 50% ethanolic extract of leaves of *Musa acuminata*(400 mg/Kg) when administered orally, twice daily for 5 days was studied for their effect on volume, acid and pepsin secretion in 4 hours pylorus ligated rats. The effect of 50% ethanolic extract of *Musa acuminata* leaves indicated a propensity for volume, acid-pepsin concentration, and output to decrease. However, the standard drug Ranitidine, a well-known cytoprotective agent, had little or no effect on volume, acid and pepsin concentrations, or acid output, but it did demonstrate a considerable reduction in peptic output. (Table 3)

Table 3.Effect of 50% ethanolic extract of leaves of *Musa acuminata* on gastric secretion in 4 h pylorousligaed rats: effect on volume, pH acid and pepsin.

Treatment	Dose (mg/kg)	Volume (ml/100g)	pH	Acid		Pepsin	
				Concentration (μEq/ml)	Output (μEq/4 h)	Concentration (μmol/ml)	Output (μmol/4 h)
Positive Control	-	1.96 ± 0.18	2.740 ± 0299	92.86 ± 12.65	268.4 ± 29.49	286.82 ± 28.24	746.20 ± 86.86
*Musa acuminata*e xtract	400	1.72 ± 0.22	6.452 ± 0.247[a]	66.84 ± 10.86	136.68 ± 31.46	272.76 ± 29.98	412.56 ± 83.64
Ranitidine	50	1.76 ± 0.16	6.628 ± 0.245[a]	84.45 ± 7.91	164.56 ± 27.83	198.78 ± 25.86	493.23 ± 66.72[a]

Values are mean ± SEM of 6 rats in each group. [a]P<0.05 compared to respective control group.

Effect of 50% ethanolic extract of leaves of *Musa acuminata*on ethanol induced gastric ulcers in rats:

The 50% ethanolic extract of leaves of *Musa acuminata*was administered to various groups, orally, daily for five days in 100, 200, 400 mg/kg b.w. twice a day and the experiment were carried out on overnight fasted rats on 6th day. The result showed that the 50% EtOH extract of *Musa acuminata*prevented the acute gastric ulcers in a dose related manner. The oral administration of *Musa acuminata*inethanol (EtOH) induced ulcer model decreased the index of gastric lesion in comparison to control. (Table 4)

Table 4. Effect of 50% ethanolic extract of leaves of *Musa acuminata* (twice daily for five days) on Ethanol-induced gastric ulcers.

Group	Treatment	Dose (mg/kg)	Ulcer index (mm^2/rat)	Percent protection
I	Ethanol	1 ml/200 gm	18.2 ± 3.5	-
II	*Musa acuminata* extract	100	14.7 ± 2.8 [a]	19.23
III	*Musa acuminata* extract	200	8.1 ± 2.4[b]	55.49
IV	*Musa acuminata* extract	400	4.8 ± 1.6[c]	73.62
V	Ranitidine	50	3.4 ± 1.7[c]	98.13

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Values are expressed as Mean ± SEM of 6 rats in each group. [a]P< 0.05 compared to respective Ethanol group. [b]P< 0.01 compared to respective Ethanol group. [c]P< 0.001 compared to respective Ethanol group.

Effect of 50% ethanolic extract of leaves of *Musa acuminata*on Aspirin (ASP) induced gastric ulcers in rats:

The rats were treated with 50% ethanolic extract of *Musa acuminata* leaves orally twice a day for five days at doses of 100, 200, and 400 mg/kg twice a day, and the experiment was carried out on overnight fasting animals on the 6th day. 1 hour before the incubation of gastric lesion by Aspirin, showed significant activity, and decreased the total ulcer index respectively. Ranitidine decreased the total ulcer index. Results for *Musa acuminata*are comparable to Ranitidine at the dose of 50 mg/Kg. (Table 5)

Table 5. Effect of 50% ethanolic extract of leaves of *Musa acuminata* (twice daily for five days) on Aspirin-induced gastric ulcers.

Group	Treatment	Dose (mg/kg)	Ulcer index (mm^2/rat)	Percent protection
I	Aspirin	200	20.4 ± 3.4	-
II	*Musa acuminata* extract	100	17.1 ± 2.8 [a]	16.17
III	*Musa acuminata* extract	200	9.5 ± 2.1[b]	53.43
IV	*Musa acuminata* extract	400	6.5 ± 2.7[c]	68.13
V	Ranitidine	50	5.2 ± 2.0[c]	74.50

Values are expressed as Mean ± SEM of 6 rats in each group. [a]P < 0.05 compared to respective Aspirin group. [b]P< 0.01 compared to respective Aspirin group. [c]P < 0.001 compared to respective Aspirin group.

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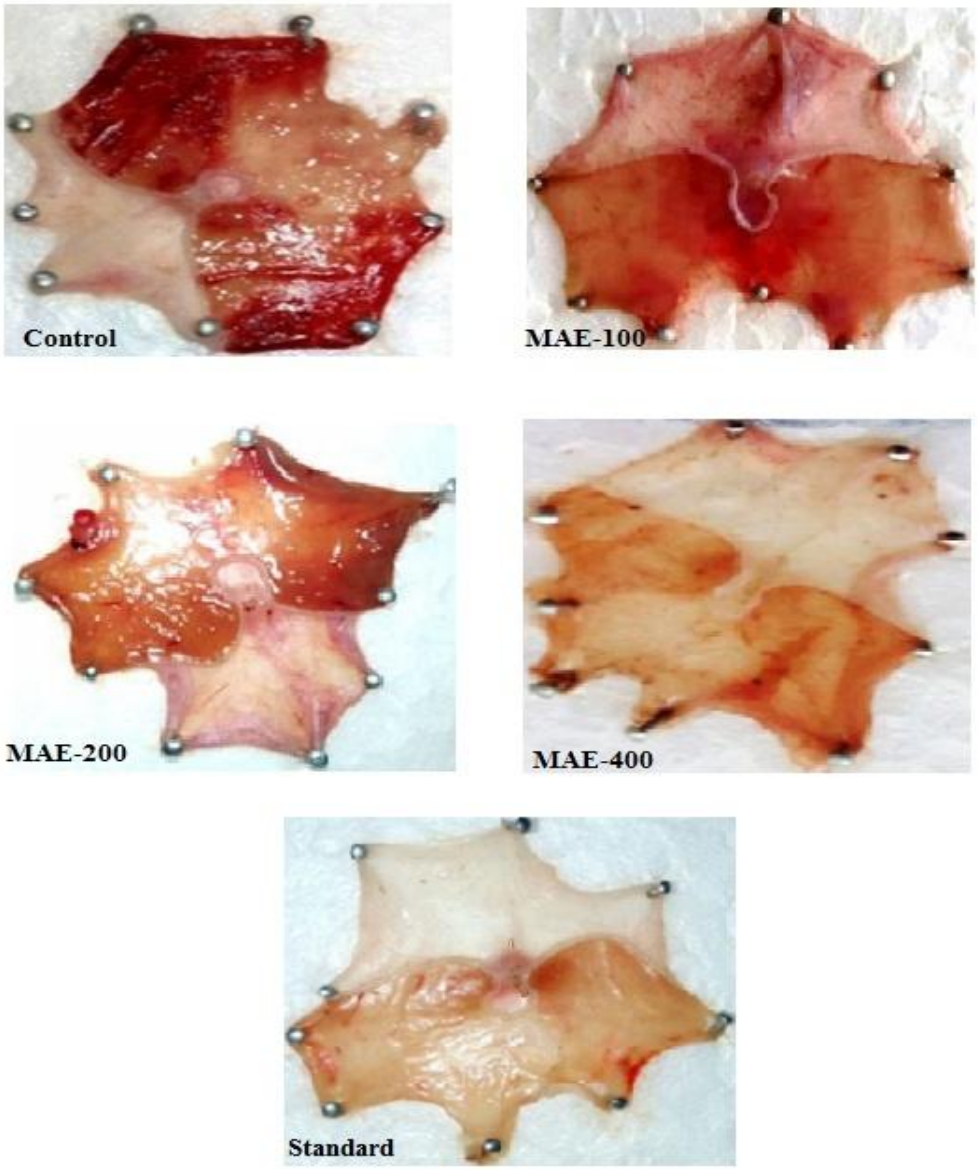
Macroscopic examination:

Macroscopical examination of the stomachs dissected from animals significantly showed a protective effect against ulceration in animals treated with 50% ethanolic extract of leaves of *Musa acuminata*at 100, 200 and 400 mg/kg b.w. and standard drug, ranitidine 50 mg/kg b.w. (Figure1).

Figure.1. Gross appearances of gastric mucosal lesions in rat stomach:

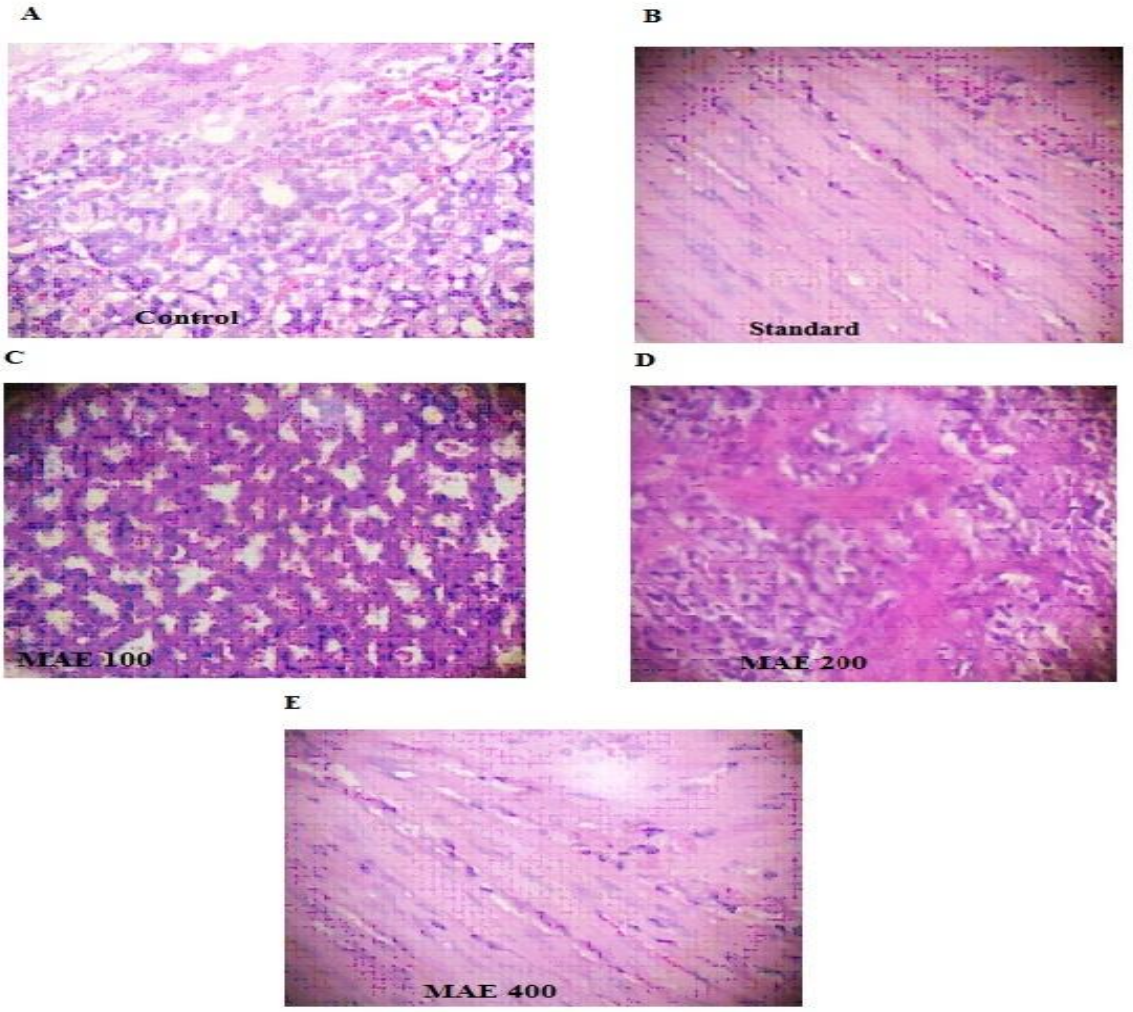


Histopathology:

The size and frequency of ulcers in the pylorous ligation, ethanol, and aspirin groups were greater than in the other treated groups, and according to histological evaluation of stomach tissue sections, extensive necrosis, lesions, and damage occurred in the epithelial mucosa and gland cells. These cells were degenerated epithelial cells with black nuclei and eosinophilic cytoplasm, and they were separated from the underlying layer. In this area, hemorrhages were visible (Figure A). In

treatment groups, ulcers were observed, but they were decreased at doses of 100 mg/kg, 200 mg/kg and 400 mg/kg of *Musa acuminata* extract. The ulcers in the 100 mg/kg group were limited to the upper part of the glands (Figure 2-C). The number of ulcers decreased in the 200 mg/kg group, and the mucosal cells showed necrosis(Figure 2-D). In the treated 400 mg/kg group showed focal mucosal ulceration consisting of degenerated cells and also contain few regenerated epithelial cells. (Figure 2-E)(Figure 2).

Figure.2. Histopathology of Pylorus ligation induced ulcer with treated animals



DISCUSSION:

Acute toxicity studies were carried out in order to determine the proper dosefor ulcer healing activity. It indicated that the extract is nontoxic up to a dose of 4000 mg/kg b.w., indicating that the extract is considered relatively safe[23].The oral treatment of a 50% ethanolic extract of *Musa acuminata* leaves at a dose of 400 mg/kg b.w. to rats significantly ($^{c}p < 0.001$) healed gastric ulcers produced by pylorus ligation,

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aspirin, and ethanol, indicating its robust ulcer-protective and antisecretory properties. Pylorus ligation-induced ulcers may be caused by autodigestion of the stomach mucosa, decreased mucosal blood flow, and the collapse of the gastric mucosal barrier[24].They are frequently linked to gastrointestinal problems like lesions, ulcers, and potentially fatal perforation and haemorrhage[25]. Due to exposure of the unprotected lumen of the stomach to accumulated acid, the volume of gastric secretion is an important element in the establishment of a gastric ulcer[26, 27].In a pylorus ligation model, the antiulcer efficacy of a 50 %ethanolic extract of *Musa acuminata* leaves offers significant restoration of gastric juice volume, pH, free acidity, and total acidity. As a result, the current data suggest that a 50% ethanolic extract of *Musa acuminata* leaves interfered with the digestion of stored gastric juice. Gastrin secreted by G cells in the pyloric gastric glands, histamine released by enterochromaffin-like cells in the oxyntic glands, and acetylcholine released by postganglionic enteric neurons all enhance stomach acid production[28].As a result, it is logical to assume that the reduction in gastric acidity and secretory volume in 50% ethanolic extract treated experimental rats is due to an antihistamine effect that blocks H2 receptors in the stomach, thereby lowering gastric acidity[29]. These results indicate that high doses of extract (400 mg / kg body weight) are effective in reducing gastric ulcers caused by gastric hyperacidity. Absolute ethanol is commonly used to induce ulcers in experimental rats. Ulcers can cause severe gastric mucosal damage. In rats, ulcer formation produces active species that cause mucosal damage and lipid peroxidation[30,31]. This is a free radical-mediated process that ultimately destroys the lipid membrane. In the gastrointestinal mucosa, microvascular damage that disrupts the vascular endothelium causes increased vascular permeability, edema, and epithelial lifting[32].Additionally, it has a direct toxic effect on the mucosa of the digestive tract, causing necrotic lesions and reducing the production of bicarbonate and mucus[33].The protection offered by 50% ethanolic leaves of *Musa acuminata* suggests its ability to treat ulcers by any of the above mechanisms. In this respect, it is known that oral administration of 100, 200, or 400 mg/kg b.w. of a 50% ethanolic extract of *Musa acuminata* leaves to rats can stop ethanol-induced stomach lesions.The 50% ethanolic extract of *Musa acuminata* leaves leads to anti-irritant property, indicating its preventive impact, while the accompanying large rise in mucus production gives the gastric mucosal strengthening mechanism[34].

As a result, the present investigation clearly shown that this species contains significant levels of numerous secondary metabolites, particularly flavonoids. Many flavonoids and terpenoids have been shown to have anti-secretory and cytoprotective activities in rats with stomach ulcers[35, 36].The antiulcer activity of the flavonoid, rutin has been found to protect the gastric mucosa against oxidative cell damage and hemorrhagic injury[37]. Although the mechanism of ulcer prevention by this extract is unknown, the presence of flavonoids in large quantities in the 50 percent ethanolic extract of *Musa acuminata* leaves may play a key role in the defence mechanism by continuing to increase mucus production, stabilising surface epithelial cells, or interfering with prostaglandin synthesis[38,39].

CONCLUSION:

The purpose of this investigation is to prove scientifically the use of 50% ethanolic extract of leaves of *Musa acuminata* exhibited a protective effect on a pylorus ligated, aspirin, and ethanol induced gastric ulcer in a dose dependent manner.It also caused a reduction in acidity and an increase in the pH of gastric juice. Furthermore, it is also worth noting that no deaths happened after being treated to very high dosages of 50% ethanolic extract of *Musa acuminata* leaves, indicating that the raw material's safety profile can be employed for therapeutic purposes and continued studies in invivo models. As a result, the 50%ethanolic extract of *Musa acuminata* leaves could be used as the main source of antiulcer medicines.

Ethics approval:

The experiments were carried out after the approval of Institutional Animal Ethical Committee (Approval No: CPCSEA No.1275/PO/Re/S/09/CPCSEA) and it is coherent with the experimental guidelines of the CPCSEA-India and IAEC on the care and use of laboratory animals.

Availability of data and material:

The authors assure that the data supporting the findings of the study are available within the article.

Competing interests:

The authors declare that there are no commercial or financial relationships that could constitute as potential conflicts of interest in the conduct of the research.

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