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Study of Antigastric Ulcer Activity of Millettiapeguensis Leave Extract and its Comparison with Rabeprazole in Shay Rats

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ABSTRACT:
In Indian traditional system of medicine, the leaves of Millettiapeguensisare recommended for the management of peptic ulcer. In light of this, the antiulcer activity of alcoholic extract of Millettiapeguensis leaves was evaluated in rats employing the HCl-ethanol, acute stress and pylorus ligation models to find the experimental gastric ulcers. Pretreatment with Millettiapeguensisextract provided significant ulcer protective effect in all the experimental models along with significant increase in gastric pH and decrease in gastric fluid volume.Methanolic extract 800mg/kg Millettiapeguensisafforded complete inhibition of ulceration in shay rat which is nearly equal to the antiulcer activity shown by 2mg/kg of Rabeprazole in shay rat. Thus, it can be concluded that alcoholic extract of Millettiapeguensisleaves possesses antiulcer activity which can be attributed to its putative mechanism of action.

I. INTRODUCTION:

Peptic ulcer is a lesion of gastric or duodenal mucosa occurring at a site where the mucosal epithelium is exposed to aggressive factors. It is one of the major gastro-intestinal disorders, which mainly occur due to an imbalance between the offensive (gastric acid secretion) and defensive (gastric mucosal integrity) factors. Potentially injurious agents such as acid, pepsin, bile acids, food ingredients, bacterial products and drugs have been implicated in the pathogenesis of gastric ulcer, including increased gastric acid and pepsin secretion, decreased gastric blood flow, the suppression of endogenous generation of prostaglandins, inhibition of mucosal growth and alteration of gastric mobility.Reduction of gastric acid production as well as re-enforcement of gastric mucosal production has been the major approaches for current therapy of peptic ulcer disease. Various synthetic antiulcer drugs presently available in market includes antacids, proton pump inhibitors, anticholinergics, H_2-receptor antagonists and cytoprotective agents, used to prevent and treat various types of ulcers. The high recurrence rate which in turn increases financial burden and mental stress to the patient is major hurdle of aforementioned therapy. In addition, these drugs confer simpler to severe side effects ranging from diarrahoea, itching and dizziness to arrhythmia, impotence and gynaecomastia. These conditions may be more worsen when they exhibit certain drug-drug interactions, which may reduce the overall outcome of the therapy. In recent years, there has been growing interest in alternative therapies and the use of natural products, especially those derived from plants since, medicinal plants are among the most attractive sources of new drugs and have been shown to produce promising results for treatment of various diseases and disorders including gastric ulcer. Also, many texa of medicinal plants have been assessed worldwide for their antiulcerogenic effects.

The Millettiapeguensis is found widely growing in the tropical humid climate of North East Odisha,.In Indian traditional system of medicine, leaves of Millettiapeguensisare also claimed to possess antiulcer activity, though it has not been scientifically documented. On the other hand, there is evidence concerning the participation of reactive oxygen species in the etiology and pathologenesis of digestive system disorders such as gastrointestinal inflammation and gastric ulcer. Various studies have shown alterations in the antioxidant status following ulceration, indicating that free radicals seems to be associated with pylorus ligation induced and ethanol induced ulcerations in rats. The aim of the present work was to evaluate the antiulcer activity of alcoholic extract of Millettiapeguensisin stress, drugs and pylorus ligation induced ulcers model.

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II. MATERIALS AND METHODS:

Preparation of extract:

The leaves of Millettiapeguensiswere collected in winter and are shaded dried.About 1kg of dried plant was extracted with methanol in soxhelt apparatus. The extraction procedure was carried out untilthe solvent system becomes clear. The extract was collected and concentrated by evaporating the solvent completely. This extract was dried and stored in refrigerator for our pharmalogical evaluations.

Preparation of drug solution:

Accurately weighed quantity of powdered extract was dissolved in the distilled water to prepare the appropriate stock solution of the drug i.e. 200 mg/ml, 400 mg/ml and 800 mg/ml respectively. The doses were administered orally by selecting the appropriate concentration of the stock solution. Rabeparazolewas dissolved in distilled water to prepare the solution of 1 mg/ml, 2mg/ml and 5 mg/ml respectively.

Chemicals and drugs:

Rabeprazole was used as standard drug.The other reagents used were Toffler's reagent 0.01N sodium hydroxide Tyrosine,Folin's Phenol reagent etc.Formalin, ethanol, sodium hydroxide (NaOH), hydrochloric acid (HCl), Di-ethyl ether etc.

Animals:

Adult wistar Albino rats (150-170gm) were used for this experiment obtained from M/S Chakravorty Enterprises, Kolkata were housed in standard polypropylene cage at room temperature of 27-30ºC and 60-65 relative humidity and had free access to food and water adlibilum. The rats were used for the experiment after an acclimization period of one week. All procedures described were approved by the Animal ethical committee of UDPS registration no (990/C/06/CPCSEA).All experiments were carried out between 12:00-16:00 hours.

Acute toxicity test:

Acute toxicity study was performed in healthy adult male albino mice (18-22 g) as per guidelines (AOT 425) suggested by the Organization for Economical Co-operation and Development (OECD). Dose of the extract were administered orally. Rats were observed individually after administration of extract during the first 30 minutes, and periodically for 24 hours with special attention given during the first 4 hours and daily thereafter for a total of 14 days for toxic symptoms and mortality. All observations were systematically recorded with individual records being maintained for each animal observed continuously for two hour for behavioral and autonomic profiles and for any other sign of toxicity or mortality The study was performed in a step wise manner was found that the extract was not toxic up to 4000 mg/kg dose level. One-tenth dose of the maximum dose used in the acute toxicity study was considered as therapeutic dose for further pharmacological study.

Total Acidity:

A volume of 5ml diluted gastric juice was titrated with 0.01N sodium hydroxide run from a micro burette using phenolphthalein as an indicator and the acidity was expressed as mg.HCL/00gm body weight of rat.

Free acidity:

It is determined by using Toffer's reagent as an indicator and titrating with sodium hydroxide which was run until canary yellow colour was observed.

Peptic Activity:

The method as followed by the lowereyetal 1951 was followed to estimate peptic activity and was expressed as µ mol Tyrosine/100gm body weight.

Ulcer Index:

Anderson and Soman have given the score as shown below:

1. A few small ulcers upto 4
2. Several small ulcers 5 to 8
3. Many small ulcers
4. Large area of ulceration with confluence or more small ulcer or inpending perforations.

In addition to this we have given a score 5+ for more than 30 small ulcer or large areas of ulcer with confluence or impending perforation. Then the average of the score in a group was calculated..

III. EXPERIMENTAL PROCEDURES:

Pylorus ligation induced ulcers:

Rats of either sex were divided into five groups with six rats in each group. Group 1 received vehicle (distilled water, 1 ml/kg, p.o.), group 2-4 received MEMP at doses of 200, 400 and 800 mg/kg body weight and group 5 received 2

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mg/kg Rabeprazole as 10 days pretreatment. Rats were deprived of food, but not water, for 36 hours prior to the experiment. On 10th day, 1 hour after the respective treatments, pylorus ligature was performed under ketamine anesthesia. Four hours later, animals were sacrificed by cervical dislocation and their stomachs were dissected out and cut open along the greater curvature, inspected internally for gastric juice volume, Free Acidity, Total Acidity, Peptic Activity and ulcer index were recorded.

Statistical analysis:

The results are expressed as mean ±SEM. The statistical analysis of all the results was carried out using one way ANOVA followed by Dunnet's t- test using graph pad instat.

Table-1: Effect of methanol extract of Millettiapeguensison Volume Gastric Juice, Free Acidity, Total Acidity, Peptic Activity, Ulcer Index and % reduction in shay rats and its comparison with Rabeprazole.

Group	Treatment	VGJ ml/100gm	FA mg/100gm	TA mg/100gm	PA umol of Tyrosine/100gm	Ulcer index (UI)+
I	Vehicle Control (1% CMC)	5.22±0.01014[b] (0)	2.7±0.0601[a] (0)	12.4±0.0557[a] (0)	2277.85±57.72[c] (0)	5 (0)
VI	MEMP 200mg/kg	3.88±0.047[a] (25.67)	1.23±0.49[b] (54.44)	1.73±0.066[b] (86.04)	1494.17±0.621[c] (34.4)	2.5 (50)
VII	MEMP 400mg/kg	4.15±0.042[a] (32.94)	0.88±0.06[b] (67.4)	1.8±0.057[b] (85.48)	1406.65±1.148[c] (38.24)	1.5 (70)
VIII	MEMP 800mg/kg	3.37±0.042[a] (35.44)	1.0±0.062[a] (72.96)	1.48±0.047[b] (88.06)	1336.9±1.473[c] (41.3)	0.5 (90)
X	Rabeprazole 2mg/kg	1.7±0.036[a] (67.43)	1.0±0.051[a] (62.96)	1.35±0.061[a] (89.11)	1378.55±0.96[c] (39.47)	0 (100)

MEMP-Methanolic extract of Millettiapeguensis
VGJ-Volume of Gastric Juice
FA-Free Acidity
TA-Total Acidity
PA-Peptic Activity
UI-Ulcer Index

Results are ex pressed means+-SEM of six readings, Significance evaluated by one-way analisis of variances (ANOVA) followed by Dennet's test verses control group.
[a]P<0.005,(n=6),[b]P<0.005,(n=6),[c]P<0.05,(n=6)
Value in ( ) represents percentage in reduction.

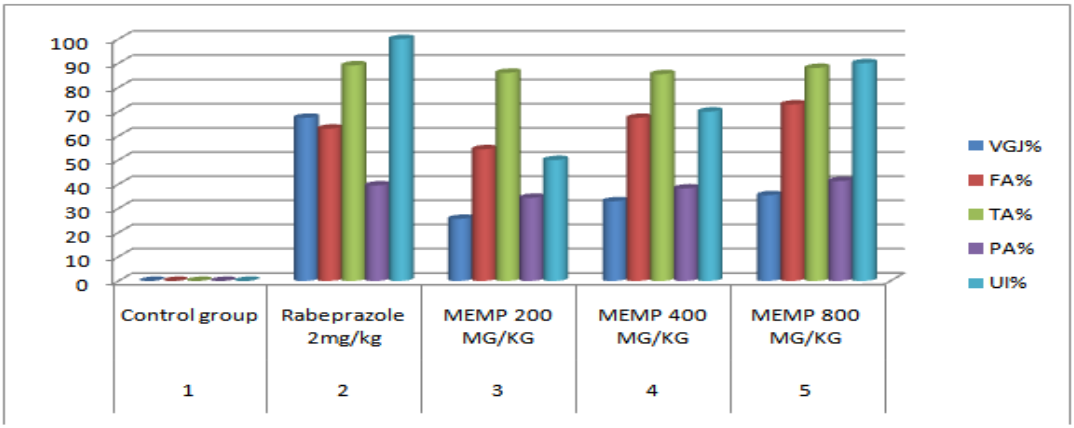

Fig-1:Bar chart of comparison of % reduction of observed activities of different extract of Millettiapeguensiswith Rabeprazole

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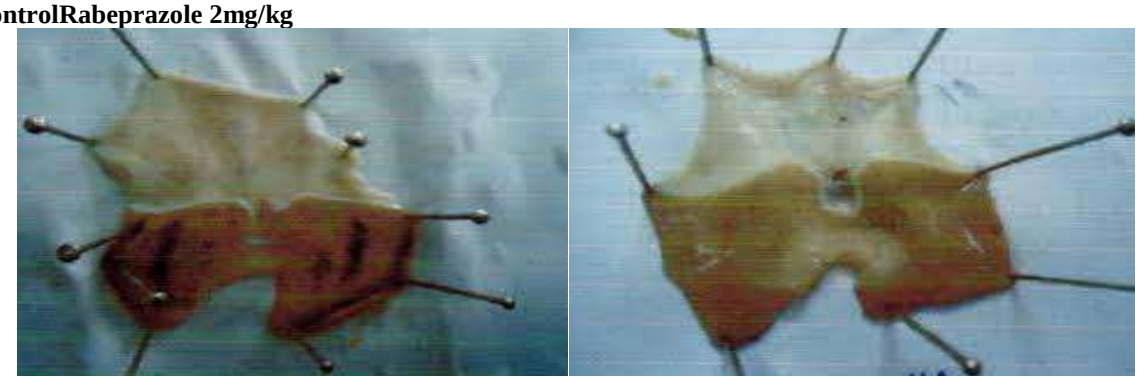
ControlRabeprazole 2mg/kg



MEMP 400mg/kg **MEMP 800mg/kg**

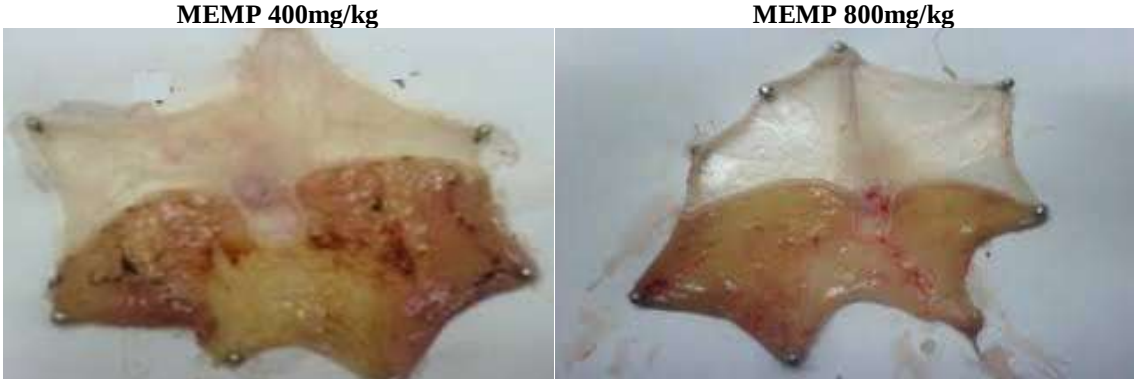


Fig-2: Antiulcer activity of Methanolic extract of Millettiapeguensis and its comparision with control and Rabeprazole

IV. RESULTS:

Acute toxicity test:

All mice were free of any toxicity as per acceptable range given by the OECD guidelines up to the dose of 4000 mg/kg. From these data and pilot study reports; three different doses 200, 400 and 800 mg/kg were selected for further study.

Pylorus ligation induced ulcers:

MEMP at 400 and 800 mg/kg dose significantly reduced ulcer index in pylorus ligated rats. However, 800 mg/kg dose was found to be more significant ($p<0.01$) as compared to 400 mg/kg dose ($p<0.05$). Moreover, MEMP 800 mg/kg significantly ($p<0.05$) reduced the volume and increased the pH of the gastric fluid. The doses 200 mg/kg and 400 mg/kg neither reduced the volume significantly nor increased the pH of gastric fluid. On the other hand, reference standard drug rabeprazole significantly ($p<0.01$) reduced the volume and increased the pH of gastric fluid.

V. DISCUSSION:

This study revealed a significant antiulcer effect of methanolic extract of leaves of Millettiapeguensis in experimental models of gastric ulcers induced by pylorus ligation in rats.Although in most of the cases, the etiology of ulcer is unknown, it is generally accepted that it results from an imbalance between aggressive factors and the maintenance of the mucosal integrity through the endogenous defense mechanism. To regain the balance, different therapeutic agents including herbal preparations are used to inhibit the gastric acid secretion or to boost the mucosal defense mechanism by increasing mucus production.MEMP prevented the mucosal lesions induced by pylorus ligation. It was also found to increase the pH and decreased the volume of gastric fluid. These effects of MEMP treatment on the parameters that influence the initiation and induction of ulceration may be considered as highly desirable property of anti-ulcerogenic agent.

VI. CONCLUSION:

To conclude, the alcoholic extract of Millettiapeguensis showed significant antiulcer activity in this experimental models in rats suggesting its putative mechanism of anti-ulcerogenic effect probably due to numerous phytochemicals present in the extract. However, study needs further investigation in order to know its exact mechanism of action.

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