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Research Article

EVALUATION OF ANTI-ULCER ACTIVITY OF THE ETHANOLIC EXTRACT OF *PHYLLANTHUS URINARIA* IN EXPERIMENTAL ANIMALS

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ABSTRACT

Objective: The objective of this study is to investigate the antiulcer activity of the ethanolic extract of *Phyllanthus urinaria* (EEPU).

Methods: *In vivo* anti-ulcer activity of EEPU was evaluated in the present study at 500 mg/kg body weight by pyloric ligation, ethanol-induced ulcer, aspirin-induced ulcer, and cold restraint-induced ulcer model. The anti-ulcer activity was assessed by determining and comparing the gastric volume, pH, free and total acidity, ulcer number and its inhibition, and ulcer severity.

Result: EEPU at 500 mg/kg body weight dose showed significant antiulcer activity by decreasing ulcer index, gastric volume, pH, and free and total acidity. Gastroprotective effect of EEPU was substantiated by histopathological studies of the stomach in ulcer and treated groups.

Conclusion: It can be concluded from the results that EEPU has potential antiulcer activity.

Keywords: *Phyllanthus urinaria,* Pylorus ligation, Aspirin, Cold restrain, Antiulcer, Antisecretory, Gastroprotective.

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INTRODUCTION

The major population of the world is prone to peptic ulcers, which has become a most prevalent gastrointestinal disorder due to sedentary lifestyle, habituation to junk food, increasing stress, and indiscriminate use of NSAIDS [1]. Peptic ulcer disease occurs due to the alteration of balance between damaging (aggressive) factors such as high acid-pepsin secretion and protective factors (defensive) such as gastromucosal integrity, bicarbonate, and prostaglandin secretion [2]. *Helicobacter pylori* infection is another major cause of peptic ulcer disease [3].

Many synthetic antiulcer and gastroprotective drugs such as proton-pump inhibitors and H_2 receptor antagonists are available in the market, but long-term chronic use of which has led to several serious adverse effects such as osteoporosis [4], cardiac arrhythmias, gynecomastia, and impotence [5]. In addition to the side effects, main problem with the synthetic drug therapy is a recurrence of ulcer after 1 year of the end of treatment [6]. Herbal medicines, due to cheaper accessibility, fewer or no side effects, and perceived effectiveness, are unfolding as substitute treatments to available synthetic drugs [7].

Phyllanthus urinaria belonging to genus *Phyllanthus* (family - Euphorbiaceae) [8] has traditionally being used for jaundice, hepatitis, diarrhea, enteritis, nephritis, edema, and ulcers [9]. Pharmacological studies previously reported are anticancer activity [10], antiviral activity [11], and hypoglycemic activity [12].

The purpose of this investigation was to scientifically reinforce the traditional claim of antiulcer activity of *P. urinaria* plant using different antiulcer models such as ethanol-induced, aspirin-induced, cold restraint stress, and pylorus ligated ulcer model in rats.

METHODS

Plant material

Fresh plants of *P. urinaria* were collected from the Western Ghats of Sahyadri region (Anmod-Mollem). The plant was identified and authenticated by Dr. Sangram Keshari Das, MD (Ayu.) PhD., Professor and Head, Department of Drayaguna Vijna, Gomantak Ayurveda Mahavidyalaya and Research Centre, Shiroda, Ponda, Goa.

Plants were carefully washed with water and were dried in the shade. After drying, the whole plant was powdered using an electrical mixer to obtain fine powder and kept in an airtight container.

Chemicals

Petroleum ether, ethanol, mercuric chloride, potassium iodide, iodine, hydrochloric acid, sodium hydroxide, ferric chloride, acetic anhydride, sulfuric acid, chloroform, glacial acetic acid, Fehling's solution, Benedict's reagent, methanol, and omeprazole were used for this study. All the chemicals used were of high quality and analytical grade.

Preparation of extract

250 g powder of *P. urinaria* plant was packed in a Soxhlet apparatus and was extracted using 95% ethanol (2L) at the temperature of 70°C after pre-treatment with petroleum ether.

Extract was concentrated, and the solvent was recovered using a rotary evaporator. The concentrated extract was further air dried until blackish semisolid mass was obtained (Fig. 1).

Phytochemical screening

The ethanolic extract of *P. urinaria* (EEPU) was subjected to preliminary phytochemical screening for the qualitative detection of phytoconstituents such as carbohydrates, proteins, amino acids, steroids, glycosides, flavonoids, and alkaloids [13].

Animals

Male Wistar albino rats weighing 150–200g were procured from Adita Biosys Pvt. Ltd., Tumkur (1868/PO/Bt/S/16/CPCSEA), and housed in an animal house of PES's Rajaram and Tarabai Bandekar College of Pharmacy, Farmagudi, Goa (RTBCOP), and were acclimatized to the standard condition having room temperature 24±2°C with relative

Fig. 1: Ethanolic extract of *Phyllanthus urinaria*

humidity of 50–60% and 12 h light and 12 h dark cycle. Animals were maintained on synthetic pellet feed and clean water *ad libitum*. The Institutional Animal Ethics Committee (IAEC) of RTBCOP under the guidance of committee for the purpose of control and supervision of experiments on animals (CPCSEA) approved animal activity of this study with resolution number PESRTBCOP/IAEC;clear/2015-16/R-15.

Acute toxicity studies
The acute toxicity studies of EEPU were carried on Swiss albino mice (25–30g) with "up and down" acute toxicity as per the method described by the OECD guideline 425 [14]. Group of 5 mice was divided into two groups (male and female) and was deprived of feed for 12 h with excess to water *ad libitum*. Treated group received EEPU at the increasing dose of 100 mg, 500 mg, 1000 mg, 2000 mg, and 4000 mg/kg orally and control group received vehicle distilled water 10 ml/kg. Mortality and behavioral changes were observed periodically up to 72 h.

Antiulcer activity of EEPU

Pylorus ligation-induced ulcer [15]

In pylorus ligation-induced ulcer model, Wistar albino rats were divided into three groups containing six animals each. Group I received normal saline at the dose of 2 ml/kg. Group II received standard drug omeprazole at 20 mg/kg. Group III received EEPU at the dose of 500mg/kg. For all three groups, drugs were administered orally 1 h before pylorus ligation. Pylorus ligation was done under ether anesthesia at 35 mg/kg body weight without causing damage to stomach blood supply. Ligated rats were allowed to recover and were maintained in individual cages. In the post-operative period, animals were deprived of water. 4 h after pyloric ligation, animals were sacrificed by overdose of ether and the stomach was cut open along the greater curvature to do ulcer scoring. Gastric content was collected to determine gastric juice volume, gastric pH, free acidity, and total acidity [16].

Ethanol induced ulcer
In ethanol-induced ulcer model, Wistar albino rats were divided into three groups containing six animals each. Group I received normal saline 2 ml/kg orally. Group II received standard drug omeprazole 2 mg/kg by oral route, and Group III received EEPU orally at the dose of 500 mg/kg. After 45 min of the drug treatment (omeprazole and EEPU in Groups II and III, respectively), gastric ulcer was induced in rats by administering absolute ethanol at 1 ml/200 g. Animals of all three groups were sacrificed post 1 h of ethanol administration [17]. The stomach was opened along the greater curvature, and ulcer scoring was done [18].

Aspirin-induced ulcer

In aspirin-induced ulcer model, Wistar albino rats were divided into three groups of six animals. Animals were fasted 36 h before administration of aspirin. Group I received normal saline at 2 ml/kg, Group II received ranitidine 20 mg/kg, and Group III received EEPU 500 mg/kg orally. All treatments were administered 1 h before administration of aspirin. Ulcers were induced by the administration of aspirin orally at the dose of 200 mg/kg. Animals were sacrificed by cervical dislocation after 6 h of administration of aspirin, and ulcer scoring was done counting the gastric lesion after opening the stomach along the greater curvature [19].

Cold stress restraint ulcer

Three groups of Wistar albino rats (150–200 g), with each group containing six animals, were used. The first group served as a control (normal saline at 2 ml/kg orally), second group served as standard (omeprazole at 20 mg/kg), and third group served as the test group (EEPU at 500 mg/kg). All treatments were administered 1 h before stress in restraint cages that were kept at 3°C±1°C in a refrigerator for 4 h treatment. After 4 h, the animals were sacrificed by cervical dislocation and gastric lesions were enumerated after opening the stomach along the greater curvature, and ulcer scoring was done [20].

Statistical analysis
All values are expressed as a mean ± standard error of the mean, n=6, the minimum value of *p<0.05, **p<0.01, ***p<0.001 as compared to control group (one-way analysis of variance followed by multiple comparison Dunnett's test) [21].

Ulcer score [22]
Scoring of ulcers was made as follows:
- Normal-colored stomach - 0
- Red coloration - 0.5
- Spot - 1
- Hemorrhagic streak - 1.5
- Ulcers - 2
- Perforations - 3.

Mean ulcer score for each animal is indicated as ulcer index.

Histopathology studies
Sections of tissue from the stomach were examined histopathologically to study the effect of EEPU. Slides were prepared at Ashwini Patholabs, Panjim, Goa.

The examination of slides was done microscopically for any pharmacological changes such as hemorrhage, congestion, edema, and erosions using an arbitrary scale for the assessment of the severity of these changes [23].

RESULTS AND DISCUSSION

Phytochemical screening
Preliminary phytochemical screening of EEPU showed the presence of flavonoids, glycosides, tannins, and triterpenoids.

Acute toxicity studies
EEPU did not demonstrate any sign and symptoms of evident toxicity, with no behavioral alteration or changes, and it did not cause animal deaths within 72 h. EEPU was safe until the maximum dose of 4000 mg/kg of body weight.

Pylorus ligation-induced ulcer
In this ulcer-induced model, EEPU at the dose of 500 mg/kg body weight showed significant ulcer reduction as in comparison to control and standard omeprazole. EEPU showed remarkable lowering in ulcer index, gastric volume, gastric pH, total acidity, and free acidity. In the control group, mean ulcer index was 2.033±0. 0296, the mean ulcer index of standard group was 0.7933±0.007, whereas the ulcer

Table 1: Effect of EEPU on various parameters in pylorus ligated-induced ulcer

Treatment groups	Dose	Mean ulcer index	Gastric volume	Gastric pH	Free acidity (mEq/l/100 g)	Total acidity (mEq/l/100 g)
Control (normal saline)	2 ml/kg	2.033±0.0296	3.050±0.1335	3.633±0.1892	35.54±0.99	55.62±1.04
Standard (omeprazole)	20 mg/kg	0.7933±0.0071***	1.7170±0.1922***	5.733±0.0918***	14.06±0.61**	24.14±0.81**
EEPU	500 mg/kg	0.92±0.045**	2.383±0.1887*	4.5500±0.02473**	22.25±0.52**	34.68±0.79**

*p<0.05, **p<0.01, ***p<0.001 standard group as compared to control group. EEPU: Ethanolic extract of *Phyllanthus urinaria*

Table 2: Effect of EEPU on various parameter in cold restrain, ethanol-induced, and aspirin-induced ulcer model

Treatment groups	Cold stress restraint ulcer	Ethanol-induced ulcer	Aspirin-induced ulcer
Control	5.267±0.3333	2.360±0.06439	2.3750±0.0853
Standard omeprazole 20 mg/kg	2.500±0.1807***	0.5700±0.0459***	0.5750±0.03354***
EEPU 500 mg/kg	3.867±0.1563**	1.517±0.041***	1.350±0.2078***

EEPU: Ethanolic extract of *Phyllanthus urinaria*

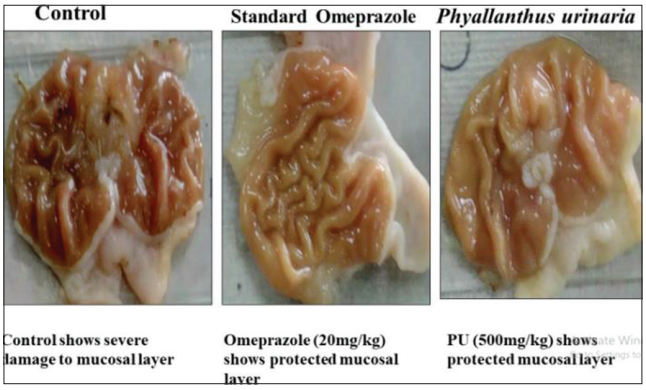

Fig. 2: Ethanolic extract of *Phyllanthus urinaria* showing significant gastric mucosal layer protection as compared to control and significant with standard

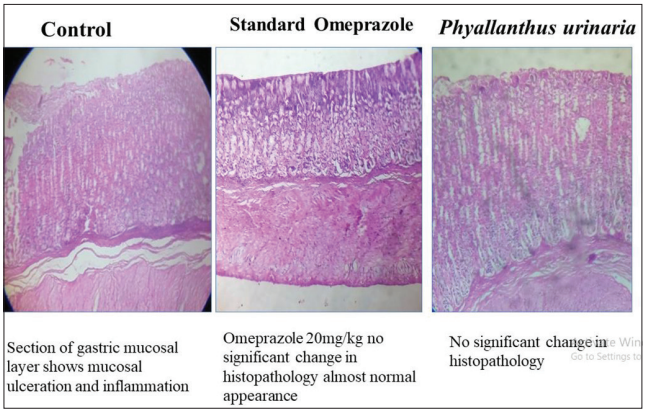

Fig. 3: Histopathology of rat stomach layer in pylorus-ligated ulcer model

index of EEPU was 0.92±0.045 (Table 1). It is clearly evident from the macroscopic photograph that there is damage to the mucosal layer of the control, whereas EEPU shows significant protection of gastric mucosal layer relevant to standard (Fig. 2). Histopathological slides reinforce the above observations (Fig. 3).

Ethanol-induced ulcer

In ethanol-induced ulcer model, there was significant damage to the gastric mucosal layer in control group, and EEPU-treated group showed comparatively good prevention of gastric mucosa in which results are compared to standard omeprazole-treated group (Figs. 4 and 5). Mean ulcer index of EEPU-treated group was 1.517±0.041*** which showed better results as compared to control group which had mean ulcer index 2.360±0.06439 (Table 2).

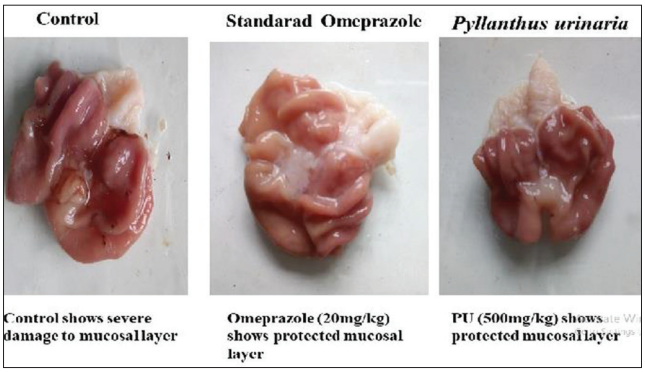

Fig. 4: Rat stomach of ethanol-induced ulcer model

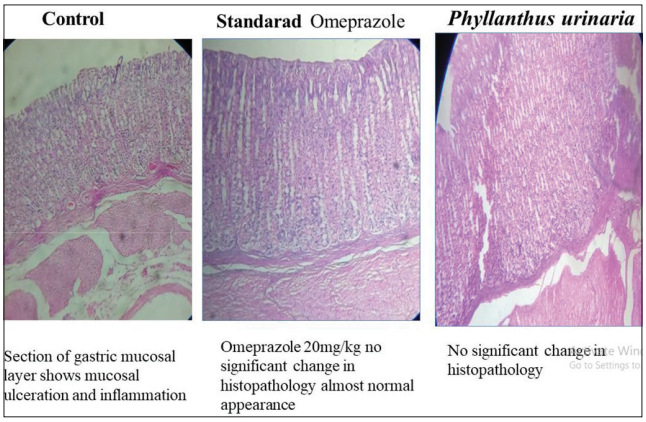

Fig. 5: Histopathology of rat stomach layer in ethanol-induced ulcer model

Aspirin-induced ulcer

In aspirin-induced ulcer model, EEPU showed ulcer protective activity with mean ulcer index 1.350±0.2078*** which is near to standard group treated with omeprazole which showed protection of gastric layer with mean ulcer index 0.5750±0.03354*** (Figs. 6 and 7). Control group showed significant damage to the mucosal layer with mean ulcer index 2.3750±0.0853 (Table 2).

Cold stress-restraint ulcer

It is evident that ulcer index of EEPU-treated group was less than the control group in cold stress-restraint ulcer model. From a macroscopic photograph and histological slides, it is clear that EEPU at a dose of 500 mg/kg showed better gastric mucosal protection (Figs. 8 and 9). Ulcer index of EEPU was 3.867±0.1563**, whereas of standard omeprazole, was 2.500±0.1807*** which was better than control group 5.267±0.3333 (Table 2).

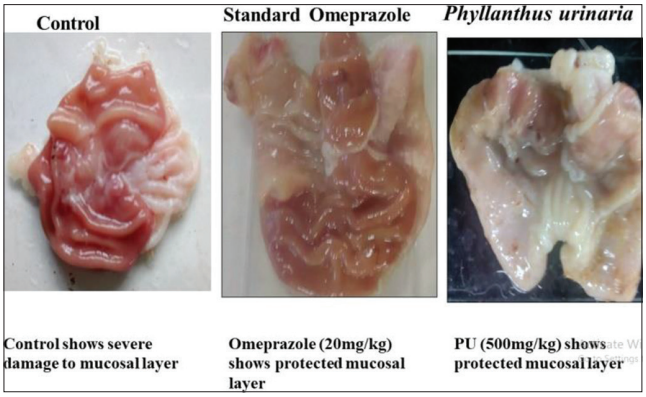

Fig. 6: Rat stomach of aspirin-induced ulcer model

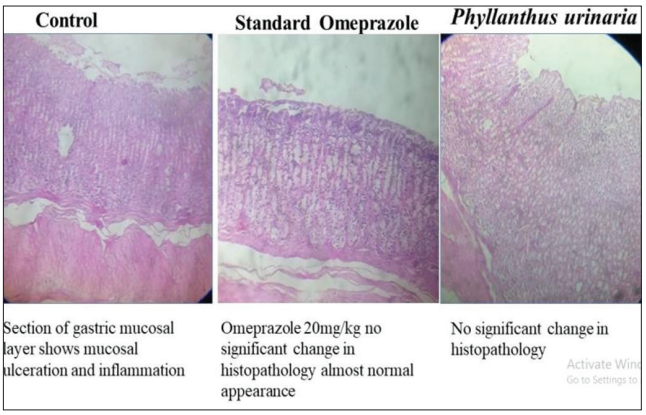

Fig. 7: Histopathology of rat stomach layer in aspirin-induced ulcer model

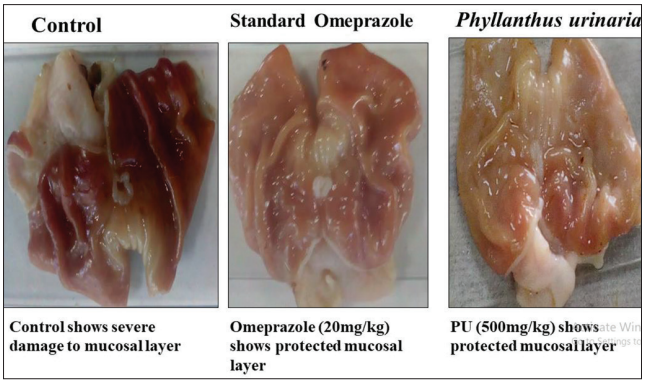

Fig. 8: Rat stomach of cold stress restraint ulcer model

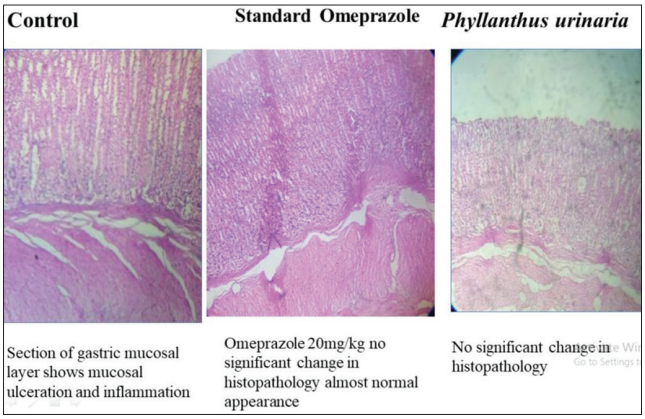

Fig. 9: Histopathology of rat stomach layer in cold stress-restraint ulcer model

The plants of genus *Phyllanthus* have been used traditionally to treat cough and bronchitis and for the treatment of fever and skin disease [24]. *P. urinaria* is a herbal plant belonging to genus *Phyllanthus* and family Euphorbiaceae which is being traditionally used in Ayurvedic system of medicines for various ailments including liver disease [25].

Peptic ulcer disease occurs due to the alteration of balance between damaging (aggressive) factors such as high acid-pepsin secretion and protective factors (defensive) such as gastromucosal integrity, bicarbonate, and prostaglandin secretion [26]. *H. pylori* infection is another major cause of peptic ulcer disease [27].

Literature survey revealed that *in vitro* studies have shown that *P. urinaria* inhibits *H. pylori* [28], so in the present work, *in vivo* antiulcer activity of EEPU was studied using different ulcer models such as pylorus ligation-induced ulcers, aspirin-induced ulcer, ethanol-induced ulcer, and cold restraint-induced ulcer. Some of the most probable causes of ulcers which occur in humans are represented by these models [29].

EEPU at the oral dose of 500 mg/kg has shown a potential antiulcer activity in pylorus ligation-induced ulcer model which is representative of ulcers formed due to the buildup of acid in the stomach which by interfering with gastric blood circulation causes gastric ulceration [30,31]. EEPU is effective in reducing total acidity, free acidity, gastric volume, and increase in pH.

In ethanol-induced ulcer model, EEPU at an oral dose of 500 mg/kg has significantly provided gastric mucosal protection from ulcers which are produced by peripheral damage to the gastric cells which occurs due to injury associated with the significant production of oxygen free radicals causing increase lipid peroxidation [32,33].

EEPU was significantly effective in ulcers caused due to mucosal damage due to a decrease in prostaglandin levels because of the inhibition of prostaglandin synthesis as represented by aspirin-induced ulcer model [34].

In cold-restraint stress model, stress leads to gastric hypermotility and mucosal over friction which are prime causes of ulcer production [35]. EEPU may be effective in stress-related ulcers.

Natural products contain various important biologically active constituents such as tannins, flavonoids, alkaloids, amino acids, and terpenes which have been reported having an antiulcer effect [36]. EEPU have revealed the presence of bioactive compounds such as flavonoids, glycosides, and tannins which might be responsible for the anti-ulcer activity of *P. urinaria*.

CONCLUSION

It can be concluded on the basis of the results that EEPU possesses anti-ulcer activity which supports its traditional use.

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AUTHORS' CONTRIBUTION

Mangirish Deshpande author for this publication, research scholar RK University, and working as Assistant Professor has carried out all the above research work in Pharmacology Laboratory of PES's Rajaram and

Tarabai Bandekar College of Pharmacy under the guidance of Dr. Neelam Balekar, Principal College of Pharmacy, IPS Academy, Indore, MP.

CONFLICTS OF INTEREST

The authors have none to declare.

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