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Gastroprotective activity of methanol leaves extract of *Barleria prionitis* Linn. on ethanol and indomethacin induced ulcer in rats

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ABSTRACT (ARIAL, BOLD, 11 FONT, LEFT ALIGNED, CAPS)

Aims: *Barleria prionitis* L. (Family Acanthaceae) is a medicinal plant found road side in India and whole plant or its various parts like leaves, root, bark, stem and flowers are used traditionally for various treatments like toothache, inflammation, boils, glandular swellings and ulcer. Leaf juice is useful in gastric ulcer. Here, we attempt to prove the use of this plant as gastroprotective agent.
Study Design: This study was conducted to evaluate the antiulcer activity of methanol extract obtained from the leaves of *Barleria prionitis* Linn.
Mention the design of the study here.
Place and Dration of Study: The experiments were conducted at Pharmacology lab of Institute of Pharmaceutical Sciences, Kurukshetra University during the period of July 2012 to December 2012.
Material and methods: Antiulcer activity was performed using the protocols of ulcer induced by ethanol and indomethacin at two different doses (250 and 500mg/kg). Parameters like volume of gastric juice, pH, free acidity, total acidity, aspartate amino transferase (AST) and alanine amino transferase (ALT) were also determined in ethanol induced ulcer model.

Results: The reduction in ulcer index in *Barleria prionitis* treated animals was found to be statistically significant (P=.05), when compared with control groups in both the models. Significant changes were observed in total acidity at dose 500mg/kg only and changes were significant in AST, ALT levels at both the doses. Other parameters showed non-significant results.

Conclusion: The results of the present study show that the methanolic extract of *Barleria prionitis* L. possess antiulcer activity. This work supports the traditional use of this plant in treating gastric ulcer.

*Keywords: Barleria prionitis, G*astroprotective activity, Ulcer index, Methanol extract, Ethanol

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1. INTRODUCTION

Gastric hyperacidity is a very common global problem that affects millions of people worldwide [1,2]. In hyperacidity stomach acid levels are high in the g.i.t, on some occasions this excess acid secretion can lead to inflammation, irritation or erosion of stomach mucosa which is known as gastritis that can be acute (brief and sudden) and chronic (longer lasting). It may provoke peptic ulcer if untreated [3,4]. An ulcer is the disruption in the skin or mucus membrane lining alimentary canal. Ulceration occurs when there is imbalance between aggressive (acid-pepsin secretions) and protective factors (such as mucus secretion, mucosal barrier, cell regeneration, blood flow and prostaglandins) [5,6]. About 95% of ulcers are duodenal, while gastric ulcers are less common. The gastric mucosa is continuously exposed to various noxious agents like acid, pepsin, bile acids, bacterial products and drugs. These agents have been contributed in the pathogenesis of gastric ulcers by increasing gastric acid and pepsin secretion, inhibiting prostaglandin synthesis and by decreasing gastric blood flow and gastric motility [7]. The current treatment of peptic ulcer is mainly done with H_2 receptor antagonists, proton pump inhibitors, and antimuscarinics. But, most of these treatments produce adverse reaction like, hypersensitivity, arrhythmia, impotence, gynecomastia and hematopoietic disorders [8-11]. Therefore, there is requirement for new and safer treatment, with fewer side effects. Plants extracts are among the suitable treatments for the prevention of gastric ulcer [12].

Barleria (Acanthaceae) ia a large genus with about 230 species of herbs and shrubs distributed chiefly in the tropical and subtropical parts of the world. About 30 species occur in India, many of which are known for their ornamental and/or medicinal value. Some of the important species of this genus are *B. prionitis*, *B. greenii*, *B. albostellata*. *B. cristata*, *B. gibsoni*, *B. strigosa*, *B. tomentosa* etc. In some *Barleria* species biological activities such as anti-inflammatory, analgesic, antileukemic and hypoglycemic have been reported [13,14].

Barleria prionitis L. common name: Vajradanti known as Sahachara in Ayurveda is a medicinal plant found throughout South Africa, India, Sri-Lanka, and tropical Asia [15,16]. Its leaves juice is used in stomach problems, ulcer, fever and urinary infections in indigenous system of medicine of India [17]. Some Indian tribes use leaves to reduce irritation and for treatment of piles [18,19]. The aerial parts are used in the fever, toothache, inflammation and gastrointestinal disorder; bark in whooping cough as an expectorant. Whole plant especially roots are used as tonic and diuretic [20,21]. Leaves stem and roots of plant possess anti-inflammatory and antibacterial activities [22,13]. It is also used in jaundice, hepatic obstruction and dropsy [23]. Iridoid rich fraction of aerial parts has been reported for hepatoprotective activity [24].

Phytochemical studies on hydro-methanolic extract of *B. prionitis* showed the presence of glycosides, steroids, tannins and flavonoids [25]. Iridoid glycosides, shanzhiside methyl ester, 6-O-trans-p-coumaroyl-8-O-acetylshanzhiside methyl ester, barlerin, acetylbarlerin, 7-methoxydiderroside and lupulinoside have been isolated from aerial parts [26]. The structures of some major phytoconstituents are given in Figure 1. No study was conducted scientifically to prove the gastroprotective effect of *B. prionitis* leaves. Hence the present study was conducted to evaluate the antiulcer properties of methanolic extract of *B. prionitis* Linn.

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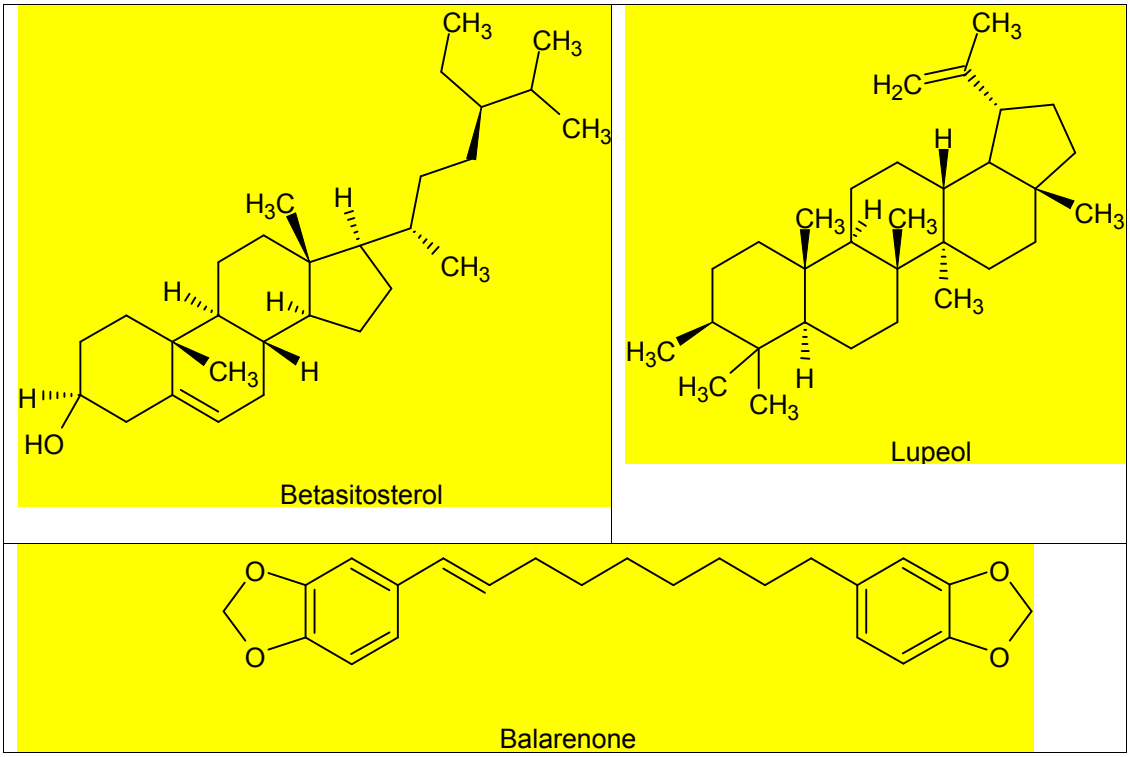

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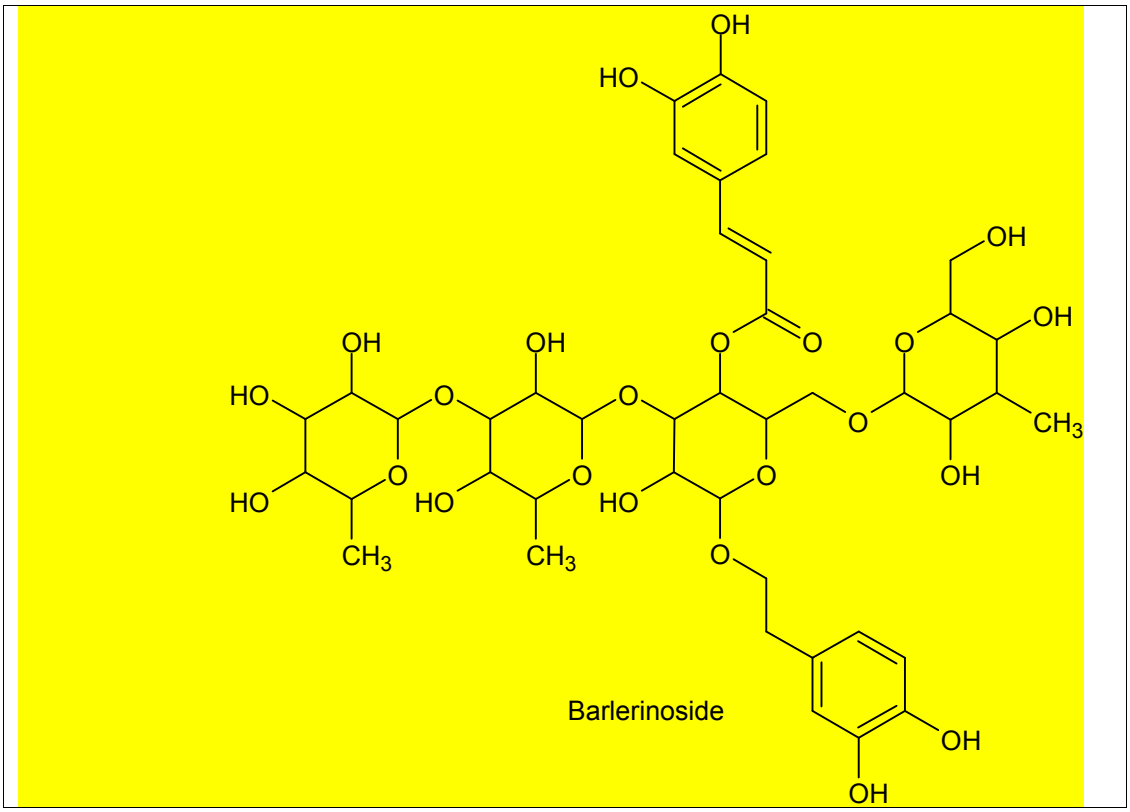

2. MATERIAL AND METHODS

2.1 Plant material

The leaves of *Barleria prionitis* were collected from Ashoka nursery Gharunda, Karnal, Haryana, India in the month of March, 2011. Then, collected leaves were positively identified by Dr. H.B. Singh, Head, Raw Materials Herbarium and Museum (RHMD), New Delhi. A voucher specimen of the plant (Ref. No. NISCAIR/RHMD/CONSULT/-2010-11/1497/95) has been preserved there for future references.

2.2 Extraction

The leaves were thoroughly washed under running tap water so as to remove any type of contamination. Then washed leaves were air dried in shade, powdered in grinder and passed through sieve of mesh size no-40. The dried powder was first defatted by petroleum ether and then successive extraction was done with chloroform and methanol by hot Soxhlet extraction method. The methanol extract was concentrated in a rotary evaporator under reduced pressure. The dried crude extract was collected and preserved in airtight glass container at 4°C - 8°C.

2.3 Preliminary phytochemical studies

To determine the chemical constituents, the methanol extract obtained was thus subjected to phytochemical analysis [27].

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2.4 Antiulcer activity

2.4.1 Experimental animals

Healthy Wistar rats of either sex were obtained from a disease free animal house of Chaudhary Charan Singh, Haryana Agriculture University, Hisar, Haryana (India). The animals were housed in the animal house, Institute of Pharmaceutical Sciences, Kurukshetra University, Kurukshetra, Haryana (India). Rats were fed with commercially available feed and were maintained under standard conditions of temperature (25°C ± 5°C), relative humidity (55 ± 10%), and 12/12 h light/dark cycle. They were housed in standard polycarbonate cages with wire mesh top and husk bedding.

2.4.2 Experimental design

Wistar rats weighing between 175-250 g of either sex were used for antiulcer study. All animals were divided into 4 groups of 6 animals. Before the experiments, animals were deprived of food but allowed free access to water.

2.4.3 Dose and route of administration

For experimentation 250mg/kg and 500mg/kg doses of *Barleria prionitis* methanolic (BPM) extract were used. Fresh drug solutions were prepared in sterile distilled water at the time of administration and were administered Per Oral (p.o.) so as to avoid any additional stress to the animals.

2.4.4 Group designing for ethanol and indomethacin induced ulcer models

Group I (Control): Animals received only distilled water; Group II (BPM 250): Animals received *B. prionitis* (250mg/kg, *p.o.*) I hr before the ulcerogenic procedure; Group III (BPM 500): Animals received *B. prionitis* (500mg/kg, *p.o.*) I hr before the ulcerogenic procedure; Group IV (Standard): Animals received ranitidine (50mg/kg, *p.o.*) I hr before the ulcerogenic procedure.

2.4.5 Ethanol induced gastric mucosal lesions

This is a widely used model that seems to cause gastric ulcer. The activity was performed according to the slightly modified method of Mizui and Dotuchi [28]. Rats were fasted for 36 h before administration of absolute ethanol (1.0mL). The group I was given only distilled water. The extract (250 mg/kg, 500mg/kg, *p.o.*) and ranitidine (50mg/kg, *p.o.*) as standard drug, were given to Group II, III and IV respectively. One hour after treatment, all the rats received ethanol to induce gastric ulcer. Another one hour later, animals were sacrificed by cervical dislocation. The stomachs were removed, cut and opened along the greater curvature, washed with normal saline to remove the gastric contents and observed for the severity of the ulcers. The pH and volume of gastric juice was measured after centrifugation at 2000rpm for 10 min. From the supernatant, aliquots were taken for the determination of total and free acidity. The percentage protection was calculated using the following formula:-

% I = (UI of control- UI of test) ×100/UI of the control

Where I = Inhibition, UI= Ulcer index

2.4.6 Ulcer indexing

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The mucosal layer of the stomach was observed under a magnifying lens and ulcers were checked. The area (mm^2) of all lesions was measured using digital callipers' to give a gastric damage score. The ulcer index was determined using the following formula [29].

UI =10/X

Where X= total mucosal area/total ulcerated area

2.4.7 Total acidity and free acidity determination

1.00mL of centrifuged and filtered gastric juice was taken in a conical flask. Two drops of 1% phenolphthalein indicator for total acidity and Topfer´s reagent for free acidity was added to it. It was titrated against 0.1mol/L sodium hydroxide until a permanent pink color (total acidity) or canary yellow colour (free acidity) was observed. The total/free acidity is expressed as meq./L by the following formula:-

Total/free acidity=n×0.01×36.45×1000

Where, n is the volume of NaoH consumed, 0.01 is normality of NaoH, 36.45 is molecular weight of NaoH, 1000 is the factor (to be represented in litre).

2.4.8 Indomethacin induced gastric ulcers

In this model, the gastric lesions are induced by the inhibition of prostaglandin synthesis. Activity was performed according to method of Djahanguiri [30] and 24 h fasted rats were used for study. Group I animals were treated orally with distilled water. The extract (250 mg/kg, 500mg/kg, *p.o.*) and ranitidine (50mg/kg, *p.o.*) as standard drug, were given to Group II, III and IV respectively. One hr. after the treatment, 20mg/kg of indomethacin (dissolved in 2% sodium bicarbonate) was administered orally. After 4 h, all animals were sacrificed by cervical dislocation. The stomachs were isolated, washed with normal saline and various parameters like ulcer index, free acidity and total acidity were measured as discussed above [31].

2.4.9 Serum biochemical parameters

Blood samples were analysed for AST and ALT level estimation in ethanol induced gastric lesions.

2.5 Statistical analysis

All the values were expressed as mean±standard error of mean. The statistical significance of difference among groups was analysed using one-way ANOVA. A value of $P<0.05$ was considered significant.

3. RESULTS

3.1 Preliminary phytochemical screening

The percentage yield of petroleum ether, chloroform and methanol leaf extracts were found to be 4.9, 6.9 and16.7% (in weight). Preliminary phytochemical screening of methanol extract showed the presence of steroids, alkaloids, saponins, glycosides and flavonoids.

3.2 Antiulcer activity

3.2.1. Ethanol induced gastric ulcer

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In this study, BPM was screened for gastroprotective activity against ethanol induced gastric ulcer in rats. The absolute ethanol administration (*p.o.*) induced severe ulceration. BPM and ranitidine groups showed the significant reduction in incidence and severity of ulceration. BPM and ranitidine showed a significant change in ulcer index when compared with the control group $P<0.01$ (Table 1). BPM and ranitidine showed slight changes in pH, volume of gastric juice, free acidity and total acidity but changes were not significant when compared with control group except total acidity in BPM (500mg/kg) treated group, $P<0.01$(Table 2).

Table 1. Ulcer index of ethanol and indomethacin induced gastric ulcers

Model	Group	Dose(mg/kg body weight)	Ulcer index	% Inhibition
Ethanol	Ethanol	--	0.90±0.01	-
	BPM	250	0.43±0.02**	52.2%
	BPM	500	0.29±0.04**	67.7%
	Ranitidine	50	0.22±0.02**	75.5%
Indomethacin	Indomethacin	20	1.35±0.15	-
	BPM	250	0.51±0.03**	62.2%
	BPM	500	0.40±0.02**	70.3%
	Ranitidine	50	0.51±0.03**	62.2%

*Results as mean±S.E.M. for six rats. Statistical comparison was performed using ANOVA followed by the Dunnett's test. **P<0.01 when compared with control group.*

Table 2. Volume of gastric juice, pH, free acidity and total acidity in ethanol induced gastric ulcer

Group	Dose(mg/kg)	Volume of gastric juice(ml)	pH	Free acidity(mmol/h)	Total acidity(mmol/h)
Ethanol	--	2.08±0.01	4.42±0.06	0.53±0.008	1.22±0.008
BPM	250	2.55±0.18	4.51±0.06	0.48±0.02	1.23±0.02
BPM	500	2.22±0.18	4.40±0.05	0.46±0.02	0.81±0.01**
Ranitidine	50	2.72±0.27	4.51±0.03	0.51±0.03	1.26±0.02

*Results as mean±S.E.M. for six rats. Statistical comparison was performed using ANOVA followed by the Dunnett's test. **P<0.01 when compared with control group.*

3.2.2 Biochemical parameters

Ethanolic group induced ulcer showed a increase in liver enzymes (ALT and AST) as shown in (Table 3). When rats were pretreated with BPM (250mg/kg and 500mg/kg) and ranitidine, there were significant reductions in serum concentration of these markers, $P<0.01$, $P<0.05$.

Table 3. Effect of BPM extract on liver functions tests in ethanol induced gastric ulcers

Group	Dose(mg/kg)	ALT(IU/L)	AST(IU/L)
Ethanol	--	65.98±2.5	353±2.1
BPM	250	56.08±2.1*	325±7.1**
BPM	500	45.44±2.0**	305±4.8**
Rantidine	50	55.18±3.5*	331±3.07*

*Results as mean±S.E.M. for six rats. Statistical comparison was performed using ANOVA followed by the Dunnett's test. **P<0.01,*P<0.05 when compared with control group.*

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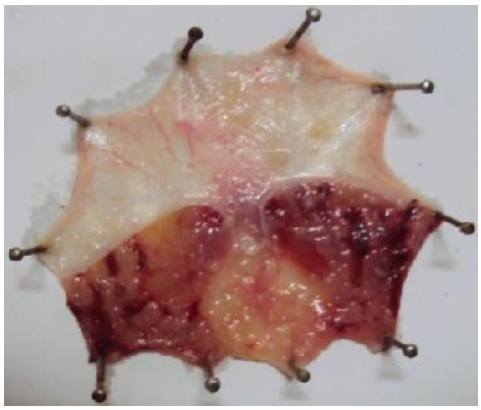
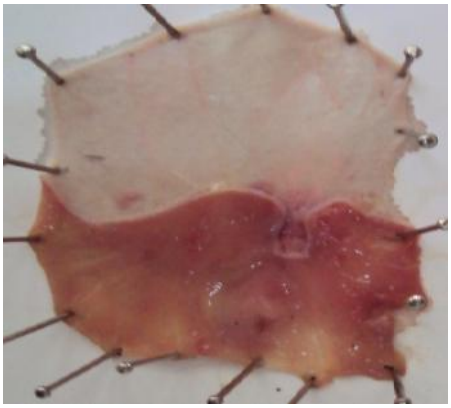
3.3.3. Indomethacin induced mucosal lesions

Indomethacin (20mg/kg, *p.o.*) administration induced severe gastric mucosal damage. BMP, at tested doses 250 and 500mg/kg, showed significant gastroprotective effect against gastric lesions, $P<0.01$. Standard drug ranitidine (50mg/kg, *p.o.*) included in the study as positive control also exhibited significant protection, $P<0.01$ (Table1 and Figure 2& 3).

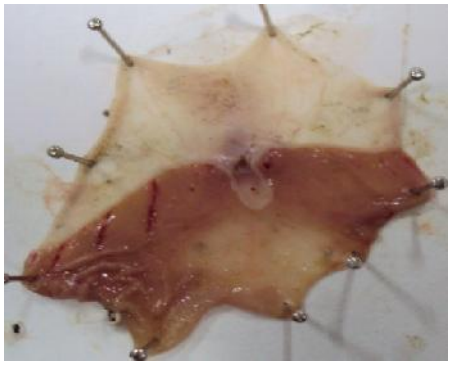
Figure 2. Macroscopic view of rat stomach in indomethacin induced gastric ulcer



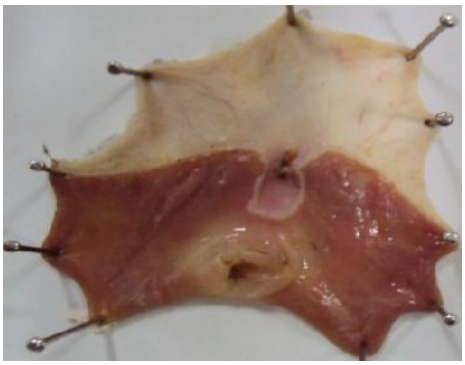
Indomethacin Group



Ranitidine Group



BPM (250mg/kg)



BPM (500mg/kg)

Figure 2. Histopathology of rat stomach in indomethacin induced gastric ulcer model

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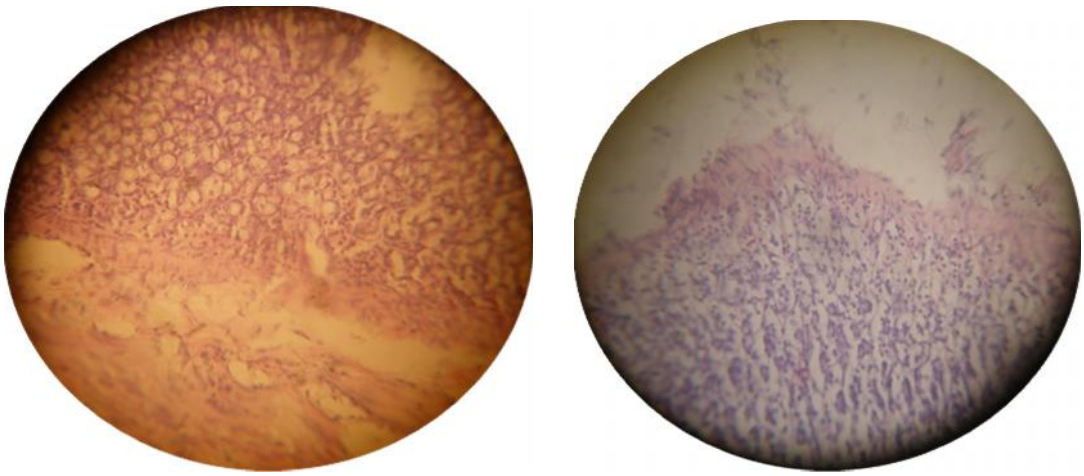
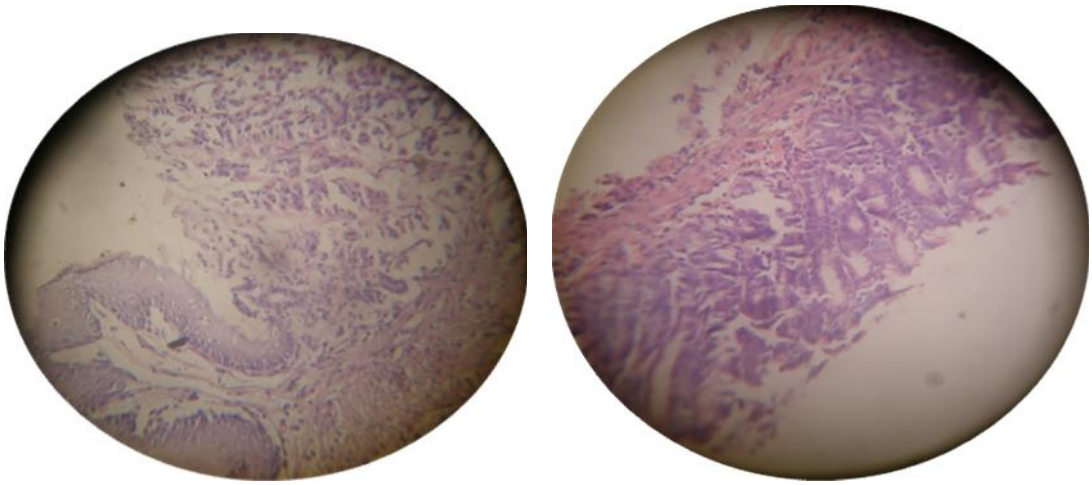


Indomethacin group Ranitidine Group



BPM (250mg/kg) BPM (500mg/kg)

Results showed that rats pretreated with BPM at doses of 250 and 500mg/kg and ranitidine improved the histopathology of rat stomach compared to indomethacin (control) group. Ulcer induced group showed severe disruption to the epithelium and deep mucosa.

4. DISCUSSION

Various noxious stimuli of endogenous (acid and pepsin) and exogenous (drugs and alcohol) origin, constantly comes in contact with gastric mucosa. Gastric mucosal defensive mechanism, like mucosal blood flow, bicarbonate and mucus secretion protect the gastric mucosa from damage. It is generally believed that it results from an imbalance between aggressive factor (acid, pepsin) and defensive factors (mucous secretions, prostaglandins) [32]. Therapeutic agents including different plant extracts are used to regain the balance by inhibiting the gastric acid secretion or by increasing the mucous production, stabilizing the surface epithelial cells. Herbs are one of the most promising sources of new drugs as these are free of or having very less side effects and adverse reactions.

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The methanol extract of *B. prionitis* was used to evaluate gastro protective activity by using ethanol and indomethacin induced gastric ulcers. Ethanol is one of the most widely used agents in experimental models to evaluate the gastroprotective activity in rats [33,34]. The acute effect of ethanol induced ulcer has been proved to be its rapid penetration into gastric mucosa, which may cause more mucosal permeability and release of vasoactive mediators such as leukotrienes C4 (LTC 4), endothelin-1(ET-1) and histamine. The vasoactive mediators induce blood flow stasis in mucus membrane circulation; which increase the lesions in mucosa [35,36]. In addition, ethanol also induces reduction in mucus production, gastric mucosal blood flow, endogenous glutathione, bicarbonate secretion, prostaglandin (PG) production, tissue level of DNA, RNA and proteins, which leads to tissue injury [37-39]. The other factor responsible may be formation of reactive oxygen species, which cause an imbalance between oxidant and antioxidant process, that results rupture of blood vessels, thus contributes to the haemorrhage, tissue necrosis and disrupting the protective mucosal barrier [40,41]. Indomethacin is an indole derivative act not only as anti-inflammatory but also analgesic and antipyretic. This drug has better ulcerogenic potential than other NSAIDS [42] Indomethacin reduces the PG by inhibiting both COX enzymes, that impares the mucosal barrier thus rendering gastric mucosa more susceptible to injury [43,44]. Further, COX-1 inhibition leads to the release of ET-1 which has been shown to induce mucosal injury and inhibition of PGs activate the neutrophils and the local release of reactive oxygen specie (ROS) and thus starts gastric injury [45]. In the present study, *B. prionitis* leaves were found to possess remarkable gastroprotective activity compared to the control. It is plausible to suggest that antiulcer activity is associated with *B. prionitis* ability to antagonize these aggressive factors while augmenting the defensive mucosal factors that protect the gastric mucosa from injury. To study the side effects of *B. prionitis* on liver, serum AST and ALT were determined in ethanol induced gastric ulcer model. Control group animals showed, increase of serum concentration of these enzymes that indicates hepatic injury since level of these enzymes increases in chemically triggered tissue injury [46]. *B. prionitis* administration decreased the levels of AST and ALT that shows its tissue damage preventing action.

The preliminary phytochemical analysis indicated the presence of flavonoids, sterols, glycosides, saponins. These secondary metabolite classes are related to gastro protective activity. There are many studies related to the antiulcer genic properties of flavonoids [38,39]. Leaves of the plant also contain saponins. Saponins exhibit ulcer protective effect by selective inhibition of prostaglandin $F_{2\alpha}$ and by protection of gastric mucosa [35,40]. In view of this fact it is suggested that gastro protection elucidated by the methanol extract of *B. prionitis* may be related to the presence of these phytoconstituents.

5. CONCLUSION

The results provide support for the traditional use of this plant in the treatment of gastric ulcer. However, the data so far obtained do not indicate the specific mechanism(s) responsible for the antiulcer activity. Further studies are required to isolate the active components and to elucidate their mechanism of action. In conclusion, the results show that methanolic extract of *Barleria prionitis* Linn. possess gastro protective activity.

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COMPETING INTERESTS

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The authors declare that they have no competing interests.

AUTHOR'S CONTRIBUTION

1st author wrote the protocol, performed the study and statistical analysis 2nd author designed the study, managed the analysis, write the first draft of manuscript, 3rd author helped in the literature study and finally all the authors read and approved the final manuscript.

ETHICAL APPROVAL

All authors hereby declare that, Principles of laboratory animal care (NIH publication No.85-23, revised 1985) were followed. All the experimental procedures and protocols used in the study were reviewed by the Institutional Animal Ethics Committee (IAEC) (Register Number: 562/GO/02/a/CPCSEA) and were in accordance with the CPCSEA guidelines, Government of India.

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