

EVALUATION OF ANTIPYRETIC AND ANTIULCER ACTIVITY OF ETHANOLIC EXTRACT OF LEAVES OF *ALSTONIA SCHOLARIS* L. IN ALBINO WISTAR RATS

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ABSTRACT

Objective: The purpose of the present study was aimed at evaluating the antipyretic and antiulcer activity on leaves of *Alstonia scholaris* L. (Family Apocynaceae) on albino Wistar rats. The antipyretic and antiulcer activity of the ethanolic extract of the *A. scholaris* L. leaves in three different concentrations (50, 100, and 200 mg/kg) were compared with standard paracetamol and pantoprazole, which was evaluated by employing brewer's yeast-induced pyrexia and ethanol-induced ulcer model. The biochemical parameters such as the volume of gastric juice secretion, pH, total acidity, ulcer index, percentage protection, and lipid peroxidation (LPO) were also studied.

Methods: *A. scholaris* leaves were extracted with ethanol by Soxhlet extraction method. The dried extract was used for further phytochemical and pharmacological analysis. The antipyretic effect was studied using brewer's yeast-induced pyrexia. The ethanol-induced ulcer model was used to study the antiulcer effect.

Results: The percentage yield of ethanolic extract of *A. scholaris* leaves was 15.81%w/w, respectively. The extract showed significant antipyretic and antiulcer effects when compared with standard paracetamol and pantoprazole.

Conclusion: The ethanolic extract of *A. scholaris* has significant antipyretic and antiulcer activity.

Keywords: *Alstonia scholaris* L., Antipyretic, Antiulcer activity, Ethanol-induced ulcer, ulcer index.

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INTRODUCTION

Peptic ulcers are one of the most common gastrointestinal diseases and widespread global problem in modern era arise due to various factors [1,2]. The pathophysiology of peptic ulcer disease has centered on an imbalance between aggressive and protective factors in the stomach [3]. The peptic ulcer is characterized by an area of the gastrointestinal tract which has been damaged by gastric acid or pepsin [4]. Lifestyle and dietary changes are the most prominent causes of peptic ulcer and related acid peptic disease [5]. The exploding occurrence of peptic ulcer in the first half of 20th century in the medical scene led to recommend it as an epidemiological illness, which was followed by a reducing range of incidence and finally vanished as a surgical medicinal condition. The reason for this decline is due to more effective acid suppression drugs such as H₂ receptor blockers, proton pump inhibitor, and recognition of *Helicobacter pylori* [6].

As a result, more and more drugs, both herbal and synthetic are coming up presenting newer and better options for the treatment of peptic ulcer [7]. *Alstonia scholaris* L., belongs to the family Apocynaceae as shown in Figs. 1 and 2, found to be widely distributed throughout tropical regions of sub-Himalayan belt, West Bengal, Bihar, peninsular India, and Southeast Asia. The shrub is commonly known as "Saptaparni" or the "Devil tree." It is one of the most versatile medicinal plants as well as in pharmacologically as a traditional medicine [8]. It is used in the treatment of antiarthritic [9], anticonvulsant [10], antibacterial [11], antidiabetic [12], anti-inflammatory [13], antioxidant [14,15], antimicrobial [16], ameliorative [17], bronchodilatory [18], and hepatoprotective [19].

METHODS**Animals**

Male albino Wistar rats (180–220 g) were used for the study. The animals were obtained from CPCSEA approved institute Bharat Serums and

Vaccines Limited, Thane West, Maharashtra 400604. The use of these animals and the study protocols were approved by CPCSEA recognized Institutional Animal Ethics Committee of Oriental College of Pharmacy under protocol no. OCP/IAEC/2018-19/04 titled "to evaluate antipyretic, and antiulcer activity of *A. scholaris* L. in albino Wistar rats." Thesis entitled "evaluation of anti-ulcer activity of selected herbal plant." Rats were kept at the animal house of Oriental College of Pharmacy, Sanpada, Navi Mumbai; in polypropylene cages, at 22±2°C, with 12:12 h dark: light cycle. They were provided with commercial rat feed and water given *ad libitum*.

Drugs and chemicals

Paracetamol and pantoprazole were obtained from Cipla Ltd., and ethanol was obtained from Thomas Baker Chemicals, Brewer's yeast powder (Now Foods). All other chemicals used in this study were obtained commercially and were of analytical grade.

Plant material

The fresh leaves of *A. scholaris* L. were collected from near Seawoods station, Seawoods West, Mumbai, in October 2017 and were submitted to Dr. Rajendra D. Shinde, Director, Blatter Herbarium of St. Xavier's College, Mumbai. The leaves were compared and authenticated by comparison with the Blatter Herbarium Specimen No. NI-1417 of N.A. Irani.

Qualitative phytochemical screening

Preliminary chemical tests were carried out on the ethanolic extract of *A. scholaris* L. for determination of the presence of different phytoconstituents. All tests were performed by the procedures given in "Practical Pharmacognosy" by Dr. K. R. Khandelwal [20]. The result was shown in Tables 1 and 2.

Selection of doses

In literature survey, it was found that the ethanolic extract of *A. scholaris* L. was safe. LD₅₀ of the ethanolic extract is reported to be 2000 mg/kg [21]. The plant is often eaten by animals, which is also an indicator to prove

it is less toxic. After thorough survey of various research papers, it is concluded that the final doses for the study are 50, 100, and 200 mg/kg.

Antipyretic study

Brewer’s yeast induced pyrexia model in one of the common models for induction of pyrexia. This model was used by various researchers such as Gupta *et al.* 2011, Akapa *et al.* 2014, and Dewan *et al.* 2000 [22-24]. Yeast is able to produce the pyrogens in the body, causing generation of immune response, thus ultimately leading to the synthesis and release of prostaglandins, which is the final fever mediator in the brain, particularly in the preoptic area of the anterior hypothalamus.

The animals were divided into five groups (six animals in each group) for antipyretic studies.

Groups	Test substance	Total no. of animal
Group I (negative)	20% yeast suspension	6
Group II (standard)	Paracetamol 150 mg/kg	6
Group III (test 1)	EEAS 150 mg/kg	6
Group IV (test 2)	EEAS 100 mg/kg	6
Group V (test 3)	EEAS 200 mg/kg	6

Procedure [25-28]

The normal body temperature of each rat was measured rectally and recorded. Pyrexia was induced by injecting 10 ml/kg body weight of 20% brewer’s yeast suspension in saline solution into the subcutaneous route. Hick’s digital thermometer coated with the lubricant was inserted 3–4 cm deep into the rectum and the basal temperature was recorded. After 18 h of yeast injection, each group receives the respective oral dosage of control/standard/test drug.

The temperature was recorded at 30, 60, 90, 120,150, and 300 min after yeast injection. The result was shown in Table 3 and Fig. 3. Rectal temperature before and after treatment was compared and the percentage change in rectal temperature was calculated by the following formula:

$$\text{Percent inhibition of rectal temperature} = \left(\frac{\text{Temperature at time "t"} - \text{Initial temperature}}{\text{Initial temperature}} \right) \times 100$$

Behavioral changes before and after injection of yeast suspension were also monitored.

Anti ulcer study

Ethanol-induced gastric ulcer model

Ethanol-induced gastric ulcer model is used on rats and is one of the widely used models due to its principle involving the cytoprotective action. Ethanol causes damage to the superficial epithelial layers, as well as is known to inhibit the prostaglandin release. It also increases the concentration of blood neutrophils, causing microcirculatory abnormality and generation of reactive oxygen species, leading to activation of H⁺/K⁺ ATPase, i.e. proton pump, which leads to acid hypersecretion causing damage to GI mucosa [29].

Pantoprazole is widely used, one of the most commonly used drugs to treat gastric ulcers. It belongs to the class of proton pump inhibitors, which is the end step in the secretion of gastric acid. Proton pump inhibitors are prodrugs, which underwent sulfonamide cation form and irreversibly binds to the sulfhydryl group of H⁺/K⁺ ATPase, causing complete inhibition of the acid secretion [30]. It also provides this activity on nocturnal acid secretion [31]. Any chemical agent that prevents the ethanol-induced ulcers might have the cytoprotective activity and may exert its action by stimulating the release of

endogenous prostaglandins, as well as mucin. Similarly, this model can be used to screen possible anti-secretory activity effectively.

Procedure [32-34]

Ethanol-induced gastric ulcer method was done by the mechanism given by Oates and Hakkinen 1988 [32]. The ulcer was induced by ethanol 95% (absolute ethanol). Male albino Wistar rats were divided into six groups. Six rats in each group, all groups were under a fasting state for 24 h, but they were allowed to drink water. The purpose of fasting was to inhibit the cross-reaction of gastric content with administered treatments. All rats were orally given particular pre-treatment based on their groups and their weight. After 24 h, test groups 1, 2, and 3 were administered with ethanolic extract of *Trema orientalis* L. leaves (100, 200, and 3000 mg/kg, p.o.) and the standard group received pantoprazole (20 mg/kg, p.o.). The control group received vehicle (distilled water). Two hours after drug treatment, the animals were sacrificed in the CO₂ chamber and dissected to extract their stomach. Stomachs are cut open along the greater curvature and content of the stomachs was collected in test tubes for evaluation of gastric volume, total acidity, LPO, and pH. Then, stomachs were gently rinsed with 0.9% saline solution and mounted on the wax plate. The result of ulcer index and percent protection was shown in Table 4 and Fig. 4.

Determination volume of gastric content, total acidity, and pH [35,36]

Gastric contents of each rat were collected in the test tubes, and their volume was determined. To determine the pH, 1 ml of distilled water is added to the 1 ml aliquot of gastric juice. With the help of pH meter, the pH of the resultant solution was measured. To determine the total acidity, 1 ml gastric juice was diluted by addition of 1 ml distilled water.



Fig. 1: Leaves of *Alstonia scholaris*



Fig. 2: Flower of *Alstonia scholaris*

The resultant solution was transferred to the conical flask and titrated against the 0.01 N NaOH with few drops of phenolphthalein solution as an indicator. The result was shown in Table 5 and Fig. 5. The total acidity was determined by the following formula:

$$\text{Total acidity} = \left(\frac{\text{Vol. of NaOH} \times 0.01}{0.1} \right) \times 100$$

Evaluation of antiulcer activity

For determination of protection from the ulcer, ulcer index (UI) given by Ganguly and Bhatnagar (1973) was used, which is as follows [37,38]:

Normal colored stomach - (0), red coloration - (0.5), spot ulcer - (1), hemorrhagic streak - (1.5), deep ulcers - (2), perforation - (3)

UI was measured using following formula:

$$\text{UI} = (\text{UN} + \text{US} + \text{UP}) \times 10^{-1}$$

Where UI;

UN = Average number of ulcers per animal;

US = Average number of severity score;

UP = Percentage of animals with ulcers.

Similarly, from the data obtained after using the above equation, percent protection was determined using the following formula:

$$\text{Percent protection} = \left(\frac{\text{UIa} - \text{UIt}}{\text{UIa}} \right) \times 100$$

Where, UIa: UI of ulcer control group,

UIt: UI of test groups.

Furthermore, another method to determine the area of stomach affected by ulcer was suggested by Rathod *et al.* 2014, which requires the use of ImageJ Software [39]. Using this software, the total area of the antrum and the total ulcerated area was determined, and from this, percent protection was calculated with the following formula:

$$\text{Percent protection} = \left(\frac{\text{UAa} - \text{UAt}}{\text{UAa}} \right) \times 100$$

Where, UAa: Ulcerated area of ulcer control group,

UAt: Ulcerated area of test groups.

Biochemical estimation of lipid peroxidation (LPO) from post mitochondrial supernatant (PMS) [40,41]

Procedure

Stomach was homogenized in chilled phosphate buffer (pH 7.4) using a homogenizer. The homogenates were centrifuged at 800 rpm for 5 min at 4°C to separate the molecular debris. The supernatant so obtained was centrifuged at 10,000 rpm for 20 min at 4°C to get the PMS.

0.5 ml of PMS was taken and it was added 0.5 ml of tris hydrogen chloride buffer and incubated at 37°C for 2 h, and then 1 ml of ice-cold trichloroacetic acid was added and centrifuged at 1000 rpm for 10 min. From the above, 1 ml of supernatant was taken and added 1 ml of thiobarbituric acid and the tubes were kept in boiling water bath for 10 min. The tubes were removed and brought up to room temperature and 1 ml of distilled water was added. Absorbance was measured at 532 nm using an ultraviolet-visible-spectrophotometer. The result was shown in Table 6 and Fig. 6.

Blank

It was prepared without tissue homogenate.

$$3 \times \frac{\text{Absorbance of sample}}{50.156 \times (\text{mg of tissue taken})} = \mu\text{m/mg tissue}$$

Statistical analysis

The data were analyzed with InStat Software by GraphPad (version 3.10). The results are expressed as the mean±SEM for each group. Statistical differences were evaluated using a one-way analysis of variance followed by Dunnett's t-test.

RESULTS AND DISCUSSION

Physicochemical analysis of powdered leaves

Table 1: Result of quantitative physicochemical analysis of powdered leaves of *Alstonia scholaris* L.

S. No.	Test	Result (%)
1.	Water-soluble extractive value	4
2.	Ethanol soluble extractive value	8
3.	Chloroform soluble extractive value	7
4.	n-Hexane soluble extractive value	2
5.	Petroleum ether soluble extractive value	2
6.	Ethyl acetate	4%

Qualitative phytochemical screening

Table 2: Result of quantitative phytochemical analysis of powdered leaves of *A. scholaris* L.

S. No.	Phytoconstituents	Ethanol extract of the leaves <i>A. scholaris</i> L.
1.	Alkaloids	+
2.	Flavonoids	+
3.	Cardiac glycosides	--
4.	Saponins	+
5.	Steroids	+
6.	Terpenoids	+
7.	Tannins and phenolic compounds	+

+: Presence; --: Absence. *A. scholaris*: *Alstonia scholaris*

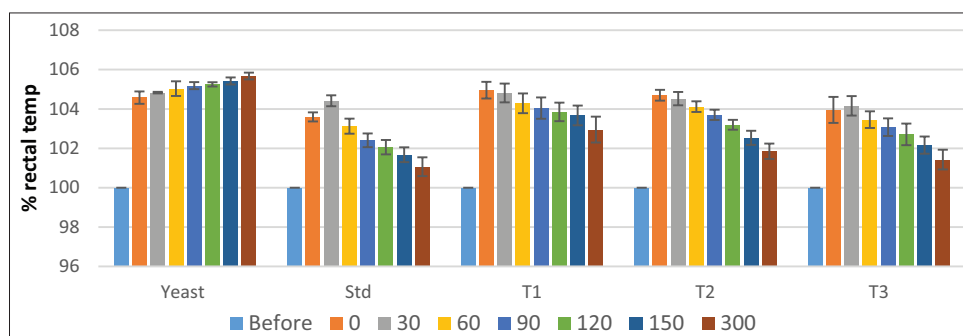


Fig. 3: Effect of ethanolic extract of *Alstonia scholaris* L. leaves on percent change in rectal temperature yeast-induced pyrexia in albino Wistar rats

Table 3: Effect of ethanolic extract of *Alstonia scholaris* L. leaves on percent change in rectal temperature in yeast-induced pyrexia in albino wistar rats

Group	0 min	30 min	60 min	90 min	120 min	150 min	300 min
Yeast control	104.579±0.314	104.831±0.040	105.033±0.37 ^{##}	105.1852±0.18 ^{##}	105.2526±0.107 ^{##}	105.4209±0.180 ^{##}	105.673±0.170 ^{##}
Standard	103.597±0.23	104.417±0.28	103.126±0.38 ^{**}	102.4097±0.35 ^{**}	102.0612±0.364 ^{**}	101.6776±0.375 ^{**}	101.067±0.477 ^{**}
Test 1 (EEAS 50 mg/kg)	104.952±0.42	104.813±0.48	104.287±0.50	104.0419±0.54 [#]	103.8483±0.47 ^{###}	103.6731±0.502 ^{###}	102.955±0.656 ^{###}
Test 2 (EEAS 100 mg/kg)	104.697±0.28	104.523±0.34	104.121±0.27	103.7027±0.26 [*]	103.1965±0.251 ^{**}	102.534±0.358 ^{**}	101.853±0.387 ^{**}
Test 3 (EEAS 200 mg/kg)	103.954±0.66	104.160±0.49	103.458±0.42 [*]	103.0738±0.45 ^{**}	102.7081±0.547 ^{**}	102.1629±0.437 ^{**}	101.428±0.503 ^{**}

Values are the mean±SEM of n=6 rats/treatment. ^{**}Indicates p<0.01, ^{*}indicates p<0 when compared with negative control. ^{##}Indicates p<0.01, [#]indicates p<0 when compared with standard control

Table 4: Effect of ethanolic extract of *Alstonia scholaris* L. leaves on UI and percent ulcer in albino wistar rats

Group	UI (Ganguly and Bhatnagar 1973)	Percent protection	Percent Ulcer (ImageJ Software)	Percent protection
Normal control	0.00±0.000	-	-	-
Ulcer control	14.50±0.67	-	18.48±3.26 ^{##}	-
Standard (pantoprazole)	4.83±0.60	66.33	0.41±0.12 ^{**}	99.59
Test 1 (50 mg/kg EEAS)	9.24±0.34	35.97	2.45±1.38 ^{**}	97.55
Test 2 (100 mg/kg EEAS)	7.47±0.27	48.21	1.10±0.99 ^{**}	98.90
Test 3 (200 mg/kg EEAS)	5.87±0.19	59.32	0.69±0.32 ^{**}	99.31

Values are the mean±SEM of n=6 rats/treatment. ^{**}Indicates p<0.01, ^{*}indicates p<0.01, when compared with negative control. ^{##}Indicates p<0.01 when compared with standard control. UI: Ulcer index

Table 5: Effect of ethanolic extract of *Alstonia scholaris* L. leaves on gastric volume, total acidity and pH of gastric juice in albino wistar rats

Group	Gastric volume (ml/100 g)	Total acidity (mEq/L)	Ph
Normal control	2.10±0.19 ^{**}	14.53±0.63 ^{###}	2.30±0.15 ^{###}
Alcohol control	3.93±0.25 [#]	20.04±0.56 ^{##}	1.01±0.01 ^{##}
Standard (pantoprazole)	2.43±0.40 [*]	7.82±0.30 ^{**}	6.81±0.89 ^{**}
Test 1 (50 mg/kg EEAS)	2.04±0.62 ^{**}	12.82±0.30 ^{###}	3.02±0.31 ^{###}
Test 2 (100 mg/kg EEAS)	2.35±0.14 [*]	10.00±0.14 ^{###}	3.91±0.28 ^{###}
Test 3 (200 mg/kg EEAS)	2.18±0.23 ^{**}	8.14±0.92 ^{**}	6.15±0.64 ^{**}

Values are the mean ± SEM of n=6 rats/treatment. ^{**}Indicates p<0.01, ^{*}indicates p<0, when compared with negative control. ^{##}Indicates p<0.01, [#]indicates p<0 when compared with standard control

Antipyretic study

All three test groups of the ethanolic extract of leaves of *Alstonia scholaris* L. showed dose-dependent decrease in body temperature when compared against control as well as against paracetamol (standard).

Antiulcer studies

All the three test doses of the ethanolic extract of leaves of *A. scholaris* L. showed dose-dependent decrease in UI when it was compared against control as well as against pantoprazole which was used as a standard.

LPO

Table 6: Effect of ethanolic extract of *Alstonia scholaris* L. leaves on LPO in albino wistar rats

S. No.	Treatment	Lipid peroxidation
1.	Normal control	2.30±0.38
2.	Alcohol control	2.64±0.14 [#]
3.	Standard (pantoprazole)	1.83±0.13 [*]
4.	Test 1 (50 mg/kg EEAS)	1.72±0.07 ^{**}
5.	Test 2 (100 mg/kg EEAS)	1.32±0.09 ^{**}
6.	Test 3 (200 mg/kg EEAS)	0.77±0.17 ^{###}

Values are the mean±SEM of n=6 rats/treatment. ^{**}Indicates p<0.01, ^{*}indicates p<0 when compared with negative control when compared with standard. Significance ^{##}p<0.01, [#]p<0.05

DISCUSSION

A. scholaris showed the inhibition of the increase in paw volume, as well as rectal temperature in albino Wistar rats in dose-dependent manner, it can be due to inhibition of inflammatory mediators such as cyclooxygenase, interleukins, or prostaglandins.

Ethanol produces massive intracellular accumulation of calcium, which represents a major step in the pathogenesis of gastric mucosal injury. This leads to cell death and exfoliation in the surface epithelium. Ethanol also acts on mitogen-activated protein kinase-II to release inflammatory mediators, which ultimately causes the mucosal injury. The antiulcer property of *A. scholaris* in ethanol-induced ulcer model is evident from its significant reduction in total acidity, gastric volume, pH, LPO, number of ulcers, and UI.

The preliminary phytochemical analysis of *A. scholaris* extract showed the presence of alkaloids, flavonoids, triterpenoids, carbohydrates, and glycosides. The significant increase in the antiulcer activity of *A. scholaris* could be attributed to the presence of flavonoids, alkaloids, tannins, saponins, glycosides, and phenolic compounds. Flavonoids are among the cytoprotective materials for which antiulcerogenic efficacy has been extensively confirmed. The leaves and flowers of *A. scholaris* were reported ursolic acid. Ursolic acid was found to be having reducing the effect of ulcer. It is suggested that, these active compounds would

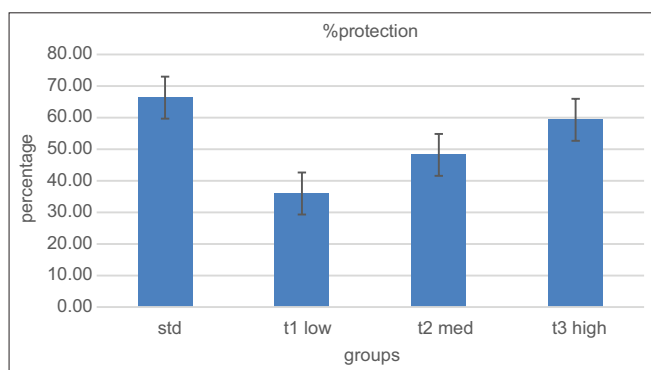


Fig. 4: Effect of ethanolic extract of *Alstonia scholaris* L. leaves on ulcer index and percent ulcer in albino Wistar rats

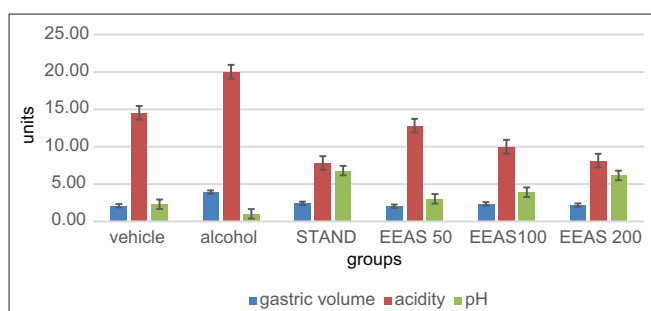


Fig. 5: Effect of ethanolic extract of *Alstonia scholaris* L. leaves on gastric volume, total acidity, and pH in albino Wistar rats. Significance ** $p \leq 0.01$, *indicates $p \leq 0.05$ when compared with negative control

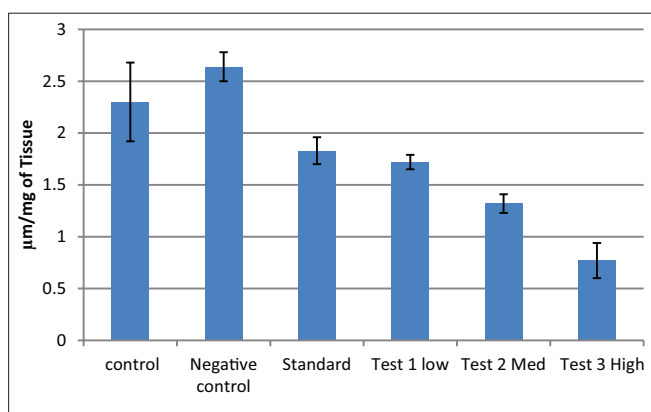


Fig. 6: Effect of ethanolic extract of *Alstonia scholaris* L. leaves on lipid peroxidation parameter in albino Wistar rats

be able to stimulate mucus, bicarbonate, and prostaglandin secretion and counteract with the deteriorating effects of reactive oxidants in gastrointestinal lumen. Hence, the antiulcer activity of *A. scholaris* may be attributed to its flavonoids content.

The results of the present study suggest that the methanol extract of *A. scholaris* leaves may be beneficial in the treatment of gastric ulcer induced by aggressive factors. Further studies to identify the active moieties and elucidation of the mechanism of action are recommended.

CONCLUSION

The present study does confirm that the ethanolic extract of *A. scholaris* does exhibit significant dose-dependent antipyretic and anti-ulcer activity. The bioactivity-guided phytochemical screening of ethanolic extract of *A. scholaris* revealed the presence of flavonoids, tannins, and

triterpenoids, which may be responsible for the anti-ulcer effect and can be further fractionated and investigated for their role and utility in any of the anti-ulcer mechanisms.

AUTHORS' CONTRIBUTIONS

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Miss Deepali Mane collected the data and analyzed the data Dr. (Mrs.) Vanita Kanase proofread the whole manuscript, and suggested the necessary changes, and helps in designing manuscript.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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