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ANTIULCER ACTIVITY OF ETHANOLIC EXTRACT OF ARCTOCARPUS HIRSUTUS LAM. LEAVES IN ALBINO WISTAR RATS

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ABSTRACT
Peptic ulcers, a prevalent gastrointestinal disorder, remain a significant health concern. *Artocarpus hirsutus Lam.*, a plant deeply rooted in traditional medicine, has been historically employed to address various health issues. Each component of this plant showcases diverse therapeutic activities, offering a holistic approach to health concerns. This study aimed to explore the gastroprotective and antiulcerogenic potential of the ethanol-based extract derived from *Artocarpus hirsutus Lam leaves*. Administered orally in 100, 200, and 400mg/kg doses, the extract's effects were compared with established medications - omeprazole (30mg/kg) and sucralfate (100mg/kg). Parameters such as gastric acid volume, gastric pH, ulcer index, total acidity, and free acidity were evaluated. The ethanol-based extract derived from *Artocarpus hirsutus Lam.* leaves demonstrated activity at doses of 200mg/kg and 400mg/kg, resulting in a marked decrease in free acidity, total acidity, gastric volume, ulcer index, and an increase in gastric pH compared to the ulcer control group. Notably, the ethanol-based extract of leaves of *Artocarpus hirsutus Lam*. exhibited significant gastroprotective and ant-ulcerogenic effects in both ethanol induced ulcer and pylorus ligated ulcer models. These findings underscore the potential therapeutic value of *Artocarpus hirsutus Lam.* as an effective agent against peptic ulcers, supporting its traditional use in holistic health practices.

INTRODUCTION

Peptic ulcer disease (PUD) encompasses a collection of ulcerative conditions affecting the upper gastrointestinal tract (GIT). These conditions are characterized by the development of sores or lesions that require the presence of pepsin and acid [1,2]. The occurrence of these ulcers can take place in any part of the GIT exposed to a sufficient concentration of gastric acid over a specific duration, including the oesophagus, stomach, and duodenum. An ulcer forming in the oesophagus is referred to as an oesophageal ulcer, in the duodenum as a duodenal ulcer, and in the stomach as a gastric ulcer. A gastric ulcer is also

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commonly known as a peptic ulcer. The term "peptic" is derived from pepsin, an enzyme found in the stomach responsible for protein degradation. Peptic ulcer formation is correlated with an imbalance between factors that contribute to aggression, including hydrochloric acid, pepsin, and *H. pylori*, and protective factors such as mucin, bicarbonates, and prostaglandins [2,3]. The gastroduodenal mucosa employs several defense mechanisms against aggressive factors such as HCl and pepsin. Epithelial cells in the duodenum and stomach secrete bicarbonate, which interacts with the surface mucosal layer, constituting the initial line of mucosal defense.

Additionally, mucus neck cells in the stomach release mucins that create a protective coating on the gastric epithelium, safeguarding the stomach by neutralizing the released HCl. Increased blood flow enhances mucus secretion. Mucosal prostaglandins contribute to protection through various mechanisms. Given that pepsin possesses mucolytic properties, it can digest the gastric mucosal layer. The primary cause of peptic ulcers is H. pylori infection, with other factors including hypersecretion of gastric acid in Zollinger-Ellison syndrome, psychological stress, genetic predisposition, cigarette smoking, alcoholic cirrhosis, and the use of non-steroidal anti-inflammatory drugs [2-4].

Presently, the treatment approach for ulcers involves the use of antiulcer drugs that offer ulcer protection, along with H2 blockers and proton pump inhibitors, albeit accompanied by various side effects [5]. *Artocarpus hirsutus Lam*, an evergreen tree predominantly found in the Western Ghats of South peninsular India and commonly known as Wild Jack [6,7], has been chemically investigated, revealing the presence of alkaloids, glycosides, flavonoids, steroids, proteins, and tannins. Previous reports have provided information on its antiulcer activity. This study seeks to scientifically validate the antiulcer properties of *Artocarpus hirsutus Lam.* leaves and aims to explore its gastroprotective effects against ethanol induced ulcers in Albino Wistar rats and the pylorus ligation ulcer model.

MATERIALS AND METHODS

Collection, identification of plant

The leaves of *Artocarpus hirsutus Lam*. were gathered from the Western Ghats of Karnataka in August and verified by a botanical expert. Subsequently, the leaves were subjected to a drying process in the shade and further processed into a powder for successive extraction.

Preparation of leaf extracts

The botanical material was soaked in ethanol solvent for seven days with intermittent stirring. Afterwards, the mixture was filtered, and the resulting filtrate was subjected to distillation under reduced pressure to eliminate the ethanolic fractions. The resultant slurry was subsequently dried and then preserved in a desiccator.

Preliminary qualitative phytochemical investigation [8]

Standard methods, including Dragendroff's, Hager's, and Wagner's tests for alkaloids; Molisch, Benedict's, Fehling's, and Tollen's tests for reducing sugars; the Shinoda test for flavonoids; assessments for saponins and tannins; Libermann-Burchard's and Salkowski tests for steroids; Libermann-Burchard's test for triterpenoids, as well as Biuret and Millon's tests for proteins, were employed for phytochemical investigations and screening.

Selection of animals

Albino Wistar rats, with an age range of 4 to 6 weeks and a weight of approximately 180-250g, were obtained from the Central Animal House at NUCARE, Deralakatte, Mangaluru. The animals were randomly allocated to groups and placed in individual cages within a controlled temperature environment ranging from 20–25°C, with alternating cycles of 12 hours of darkness and light. Standard food and water were made available to the animals ad libitum. The research procedures followed the guidelines established by the CPCSEA (Committee for Purpose of Control and Supervision of Experiments on Animals), New Delhi, India and approval for the research work was obtained from the Institutional Animal Ethics Committee (IAEC) and the protocol number assigned is NGSMIPS/IAEC/MAY-2017/59.

Acute oral toxicity studies [2,9]

To ascertain the lethal dose, LD50, of the ethanol based suspension of *Artocarpus hirsutus Lam* leaves in female albino Wistar rats weighing between 150-200g, acute oral toxicity studies were conducted. The "Up and Down Method" recommended by OECD 425 guidelines was employed for the study, aiming to minimize the number of animals required for estimating acute oral toxicity. Rats that had undergone overnight fasting were orally administered the leaf extract suspension

(2000mg/kg). The animals were continuously observed at 30 minute intervals over 4 hours, with further monitoring for mortality up to 24 hours post-administration with special attention given during the first 4 hours for any changes in their neurological (spontaneous activity, reactivity, touch response, pain response, gait), general behaviour (alertness, irritability, fearfulness, restlessness), autonomic profiles (defecation and urination, physical states (lacrimation, loss of appetite, tremors, hair erection, salivation, diarrhoea) and finally for death after 14 days.

Evaluation of antiulcer activity

Selection of doses

To assess the antiulcer potential of *Artocarpus hirsutus Lam.* leaves, three distinct dose levels were chosen: a lower dose, a medium dose, and a high dose. The moderate dose was equivalent to 200 mg/kg of rat body weight, constituting 1/10th of the highest dose administered in the acute oral toxicity studies (2000mg/kg). Consequently, the higher dose was set at twice the 1/10th dose, amounting to 400mg/kg of rat body weight. The lower dosage was established at 50% of the 1/10th dose, equivalent to 100mg/kg of rat body weight.

***Ethanol induced ulcer model* [2,10]**

Albino Wistar rats, weighing approximately 180-200g, were randomly assigned to six groups, each consisting of six rats. The groups were categorized as follows: Group I - normal control, Group II - ulcer control (administered absolute alcohol at 1ml/kg orally), Group III - standard (sucralfate at 100mg/kg intraperitoneally), Group IV - *Artocarpus hirsutus Lam*. leaf extract (100mg/kg orally), Group V - *Artocarpus hirsutus Lam.* leaf extract (200mg/kg orally), and Group VI - *Artocarpus hirsutus Lam*. leaf extract (400mg/kg orally).

Prior to the experiment, the animals underwent overnight fasting. During this period the rats were housed in single cages with raised bottoms of wide wire mesh in order to avoid coprophagy and cannibalism. Access to drinking water ad libitum was provided. Absolute alcohol was orally administered at a dose of 1ml/animal, regardless of the animal's weight, one hour after drug administration through the oral route. Following the ethanol administration, the animals were euthanized after one hour, and their stomachs were dissected along the greater curvature before being affixed to a thermocol board. The isolated stomachs were then exposed and examined for ulcerations, and the ulcer index was subsequently computed.

***Pylorus ligation induced ulcer model* [2]**

Albino Wistar rats weighing between 180-200 g were randomly distributed into six groups, each comprising six animals, with the following designations: Group I - normal control, Group II - ulcer control (administered 0.25% w/v CMC at 5ml/kg orally), Group III - standard (Omeprazole at 30mg/kg intraperitoneally), Group IV - *Artocarpus hirsutus Lam.* leaf extract (100mg/kg orally), Group V - *Artocarpus hirsutus Lam.* leaf extract (200mg/kg orally), and Group VI - *Artocarpus hirsutus Lam.* leaf extract (400mg/kg orally).

The albino Wistar rats underwent an overnight fasting period and were individually housed in cages with elevated bottoms constructed from broad wire mesh to prevent coprophagy and cannibalism. Unrestricted access to drinking water was granted. After one hour of drug administration, the animals were anaesthetized. A 1cm-long midline incision was performed below the sternum in the abdomen. The stomach was located, and the pyloric sphincter was securely tied with a sterile thread without compromising the blood supply to the stomach. The abdominal wall was sutured, and the animals were allowed to recover in individual cages, during which they were deprived of water for the post-operative period.

Animals in Group I were designated as the normal control. These animals were euthanized using the cervical decapitation method six hours following pylorus ligation. The stomachs were dissected, cut along the greater curvature, pinned to a cork plate and inspected for ulcerations. Gastric juice was collected from the stomach, and measurements of its volume, pH, free acidity, and total acidity were conducted. The severity of ulcer scores was macroscopically observed using a hand lens (10x) and compared with the standard drug. Subsequently, the ulcer index was determined.

Biochemical estimations

Estimation of ulcer index (UI) [2,11]

The standard scoring system for ulcers is outlined as follows: Normal stomach – 0, Red colouration – 0.5, Spot ulcer – 1.0, Haemorrhagic streaks – 1.5, Ulcers – 2.0, Perforations – 3.0.

The ulcer index was computed using the formula: $UI = UN + US + UP \times 10^{-1}$

where UI represents the ulcer index, UN denotes the average number of ulcers per animal, US signifies the average severity scores, and UP represents the percentage of animals with ulcers. The percentage of ulcer protection was calculated as follows:

$$\%protection = \frac{control\ mean\ ulcer\ index - test\ mean\ ulcer\ index}{control\ mean\ ulcer\ index} \times 100$$

***Estimation of free acidity and total acidity* [2]**

The procedure included the extraction of the stomach, slicing it along the greater curvature, and gathering the gastric fluid in a test tube. Subsequently, the collected juice was centrifuged at 3000 rpm for approximately 10 minutes. From the resulting supernatant, 1 ml was transferred into a 100 ml conical flask and diluted with 10ml of distilled water. The pH of the solution was documented, and 2-3 drops of Topfer's reagent (dimethyl-amino-azo-benzene with phenolphthalein) were introduced. The solution was titrated against 0.01N NaOH until it reached an orange endpoint, with the quantity of alkali added noted, indicating free acidity. The titration was then continued to obtain total acidity, and the solution reverted to its pink colour. The total volume of NaOH used was recorded, corresponding to the total acidity.

Gastric acidity is expressed using the formula:

$$Acidity = \frac{volume\ of\ NaOH \times normality\ of\ NaOH}{0.1} \times 100 mEq/L$$
$$/100g\ 0.1$$

Statistical analysis

The data obtained was statistically analyzed using One-way ANOVA, followed by post hoc Scheffe's test utilizing SPSS software version 10. A p-value <0.05 was deemed statistically significant.

RESULTS

Preparation of extract

The percentage yield of the ethanolic extract is provided below: (Table 1)

Table 1: Percentage yield of ethanolic extract of *Artocarpus hirsutus Lam.* leaves:

Extracts	Colours	Consistency;	Percentage yield
Ethanolic	Green	Semisolid	18%

Preliminary phytochemical analysis of leaf extract

The initial phytochemical examination of the ethanolic extract from *Artocarpus hirsutus Lam.* leaves indicated the existence of alkaloids, carbohydrates, flavonoids, tannins, proteins, and saponins, as revealed by the outcomes of diverse chemical tests (refer to Table 2).

Table 2: Qualitative analysis of *Artocarpus hirsutus Lam.* leaf extract

Tests	Ethanolic extract
Alkaloids: a) Dragendroff's test b) Hager's test c) Wagner's test d) Mayer's test	Positive
Reducing sugars: a) Molisch's test b) Benedict's test c) Fehling's test d) Tollen's test	Positive
Flavonoids: Shonda test	Positive
Steroids: a) Liebermann Burchard's test b) Salkowski test	Positive
Triterpenoids: a) Liebermann Burchard's test	Positive
Proteins a) Biuret test b) Millon's test	Positive
Saponins	Positive
Tannins	Positive

Acute oral toxicity studies

The leaf extract of *Artocarpus hirsutus Lam.* was determined to be non-toxic when administered orally up to a dosage of 2000mg/kg body weight. The animals demonstrated stability 24 hours post drug administration, with no observed mortality or indications of toxicity. Consequently, the leaf extract was deemed safe, leading to the selection of three dosage levels for the study: 100mg/kg, 200mg/kg, and 400mg/kg body weight.

Evaluation of anti-ulcer activity

Ethanol induced ulcer model

Table 3 displays the results of gastric ulcers induced by ethanol. The ethanolic leaf extract of *Artocarpus hirsutus Lam.* exhibited significant activity in a dose-dependent manner at doses of 100, 200, and 400mg/kg, with maximum inhibition percentages of 21.3%, 42.9%, and 69.7%, respectively, compared to the normal control group. A notable and dose-dependent decrease in the ulcer index (8.37, 6.07 and 3.22) was observed at doses of 100,

200, and 400mg/kg, respectively, in comparison to the normal control group. Sucralfate (100mg/kg), chosen as a reference standard, demonstrated potent antiulcer activity significantly across all parameters.

Table 3: Effect of ethanol based leaf extract of *Artocarpus hirsutus Lam*. on ethanol induced ulcer model

Groups	Treatment	Ulcer Index	% Protection
Group I	Normal control	0^{bc}	-
Group II	Ulcer control	10.64 ± 0.15^{ac}	-
Group III	Sucralfate (100mg/kg)	1.23 ± 0.10^{ab}	88.4
Group IV	Extract (100mg/kg)	8.37 ± 0.39^{abc}	21.3
Group V	Extract (200mg/kg)	6.07 ± 0.45^{abc}	42.9
Group VI	Extract (400mg/kg)	3.22 ± 0.06^{abc}	69.7

The values are reported as Mean ± SEM, with a sample size of n=6. Concerning statistical significance, "a" signifies $p<0.05$ in contrast to the Normal Control group, "b" indicates $p<0.05$ compared to the ulcer control group, and "c" denotes $p<0.05$ compared to the standard group.

Morphological evaluation

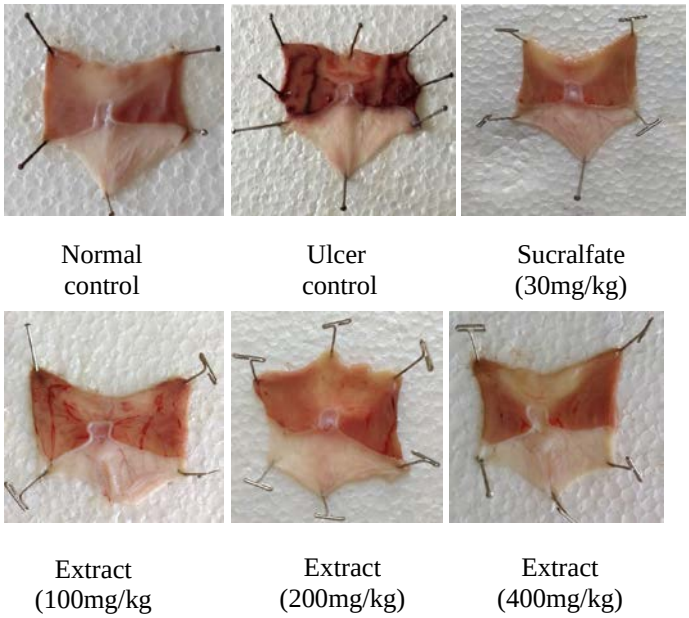
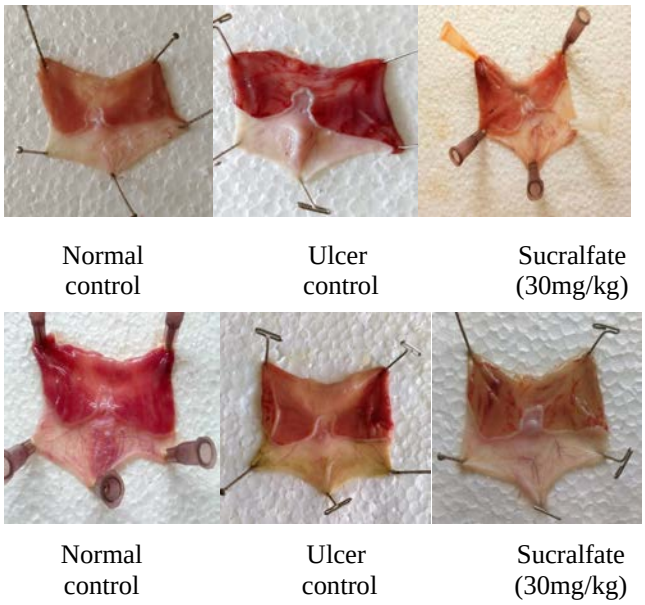


Figure 1: Images of ethanol induced gastric ulcer model

Pylorus ligation induced ulcer model

Table 4 illustrates the results of gastric ulcerations induced by pylorus ligation. The ethanol based leaf extract of *Artocarpus hirsutus Lam.* demonstrated a substantial, dose-dependent reduction in gastric volume (1.55ml, 2.46ml and 2.90ml), with maximum inhibition percentages of 72.1%, 57.9% and 36.2% at doses of 400, 200, and 100mg/kg, respectively, compared to the ulcer control group. At the doses of 400, 200, and 100mg/kg, the extract significantly and dose-dependently elevated pH, ulcer index (2.40, 3.65, and 5.54), free acidity, and total acidity when compared to the ulcer control group. Chosen as a reference standard, Omeprazole (30mg/kg) demonstrated notably potent gastroprotective activity, significantly affecting all parameters.



DISCUSSION

Peptic ulcers persist as a prevalent ailment in the modern era, representing the most widespread gastrointestinal disorder affecting diverse populations globally and leading to the erosion of the stomach's inner lining. Ongoing research focuses on developing drugs from natural sources to address peptic ulcer disease (PUD). *Artocarpus hirsutus Lam.* plant is known for its medicinal value and significance in the food industry, with various plant parts utilized for treating various ailments. This study assessed the gastroprotective potential of the *Artocarpus hirsutus Lam.* ethanolic leaf extract through experiments involving ethanol-induced gastric ulcers and pylorus ligation-induced ulcers in rats. The results indicated that the ethanolic leaf extract demonstrated substantial gastroprotective activity in a manner dependent on the dosage.

The ethanol-induced gastric ulcer model serves as a straightforward and expeditious method for evaluating the anti-ulcer activity of plant extracts and their cytoprotective effects.

Ethanol, a powerful solvent, digests the gastric mucosa, resulting in the formation of lesions in the mucosal barrier. Additionally, it impedes the release of bicarbonates and the synthesis of mucus. This impact is associated with various biological processes, including lipid peroxidation, depolarization, intracellular oxidative stress and the generation of free radicals. Prominent microvascular changes are provoked within a few minutes after the oral administration of ethanol. The oral intake of alcohol can lead to a necrotizing impact on the gastric mucosa. The development of ethanol-induced gastric ulcers in this context includes mediators such as oxygen-derived free radicals, lipoxygenase, and cytokinins [11]. It has been reported that the administration of antioxidants or cytoprotective agents prevents ethanol induced gastric lesions in rats.

Table 4: Ethanolic based extract of *Artocarpus hirsutus lam.*leaves on pylorus ligated ulcer model

Groups	Treatment	Gastric Volume (ml)	Gastric pH	Free Acidity (mEq/L)	Total Acidity (mEq/L)	Ulcer Index	% Protection
Group I	Normal control	1.32 ± 0.03^{bc}	3.75 ± 0.15^{bc}	48.8 ± 2.05^{bc}	78.8 ± 2.05^{bc}	0^{bc}	-
Group II	Ulcer control	4.56 ± 0.05^{ac}	2.27 ± 0.08^{ac}	92.3 ± 2.43^{ac}	95.6 ± 0.76^{ac}	8.63 ± 0.01^{ac}	-
Group III	Omeprazole (30mg/kg)	2.28 ± 0.05^{ab}	5.34 ± 0.07^{ab}	25.8 ± 0.87^{ab}	46.1 ± 0.83^{ab}	1.58 ± 0.02^{ab}	81.8
Group IV	Extract (100mg/kg)	2.90 ± 0.01^{abc}	3.42 ± 0.06^{bc}	64.5 ± 0.99^{abc}	85.1 ± 0.87^{abc}	5.54 ± 0.09^{abc}	36.2
Group V	Extract (200mg/kg)	2.46 ± 0.04^{ab}	4.41 ± 0.12^{abc}	45.0 ± 0.96^{bc}	65.3 ± 0.88^{abc}	3.65 ± 0.10^{abc}	57.9
Group VI	Extract (400mg/kg)	1.55 ± 0.09^{bc}	5.27 ± 0.03^{ab}	34.6 ± 1.14^{abc}	54.6 ± 1.14^{abc}	2.40 ± 0.04^{abc}	72.1

The data is expressed as Mean ± SEM, based on a sample size of n=6. Regarding statistical significance, "a" denotes $p<0.05$ in comparison to the Normal Control group, "b" signifies $p<0.05$ compared to the ulcer control group, and "c" indicates $p<0.05$ compared to the standard group

The findings of the study indicate notable antiulcer activity associated with the leaf extract, which is ascribed to its flavonoid content (refer to Table 2). Previous research has indicated that flavonoids play a crucial role in shielding the mucosa, acting as free radical scavengers and thereby safeguarding the gastric mucosal barrier from erosive lesions. The *Artocarpus hirsutus Lam.* leaf extract was found to diminish gastric ulcerations in rats. At doses of 200mg/kg and 400mg/kg, the extract resulted in ulcer indices of 3.22 and 6.07, respectively, in contrast to the ulcer control group (10.64). The 200mg/kg and 400mg/kg extracts exhibited percentage protection of 42.9% and 69.7%, respectively. In contrast, the standard sucralfate (30mg/kg) displayed 88.4% protection against ethanol induced ulcers in rats (refer to Table 3).

The pylorus ligation-induced gastric ulcer model is widely acknowledged as the predominant method for assessing gastric ulcers in rats as it resembles most common stomach ulcers in humans. Pylorus ligation induces the accumulation of a significant quantity of gastric acid, causing an elevation in, free acidity, total acidity, gastric volume and a reduction in gastric pH. This augmented gastric juice accumulation contributes to the autodigestion of the gastric mucosa, ultimately resulting in the compromise of the mucosal barrier and the formation of gastric ulcers. The gastric injury after pyloric ligation is also assumed to be because of stress induced rise in release of gastric hydrochloric acid and/or stasis of acid.

Flavonoids play a pivotal role in safeguarding the gastric mucosa by inhibiting enzymes such as alkaline phosphatase, cAMP, phosphodiesterases, lipases, hydrolases, and more. Additionally, they reduce histamine secretion from mast cells by inhibiting histidine decarboxylases and stimulate the biosynthesis of prostaglandins, thereby protecting the mucosal barrier. It is hypothesized that these mechanisms of action of flavonoids contribute to the gastroprotective activity of the leaf extract. Chemical constituents like flavone and flavanone are responsible for stimulating the production of PGE2 in the gastric mucosa [12]. Tannins are reported to precipitate microproteins at the location of peptic ulcer, forming a protective pellicle over it. Tannic acid and ellagic acid were also reported to have an inhibitory activity on gastric H+ K+ ATPase, causing an inhibition of acid secretion. And so, as stated, the presence of tannins in *Artocarpus hirsututs Lam.* may be related to the gastroprotective effect.

The ethanolic leaf extract of *Artocarpus hirsutus Lam.* demonstrated notable antiulcerogenic activity in a dose-

dependent manner. Doses of 200mg/kg and 400mg/kg exhibited substantial antiulcer effects, evidenced by reductions in total acidity, free acidity, gastric acid volume and an elevation in gastric pH. At doses of 200mg/kg and 400mg/kg, the ulcer indices were 3.65 and 2.40, respectively, and exhibited an ulcer index of 8.63. The standard group treated with omeprazole showed an ulcer index of 1.58. The extract, administered at doses of 200mg/kg and 400mg/kg, conferred percentage protection of 57.9% and 72.1%, respectively. In comparison, the standard drug omeprazole achieved a percentage protection of 81.8%. These findings suggest that the 400mg/kg dose of the extract demonstrated a more pronounced effect than the 200mg/kg dose, and the 100mg/kg dose of the extract displayed a lower activity (see Table 4).

CONCLUSION

This study aimed to explore the anti-ulcerogenic potential of the ethanolic leaf extract of *Artocarpus hirsutus Lam.* The preliminary phytochemical analysis revealed the presence of flavonoids, alkaloids, reducing sugars, proteins, steroids, saponins, and tannins in the leaf extract. Acute oral toxicity studies affirmed the safety of the extract up to 2000mg/kg. In both the model of ethanol induced gastric ulcers and pylorus ligated gastric ulcerations in rats, the leaf extract exhibited significant dose-dependent activity.

At a dosage of 400mg/kg, the leaf extract exhibited significant effects, encompassing a decrease in total acidity, free acidity, ulcer index and gastric volume along with an elevation in gastric pH in comparison to the standard drug. The observed activity of the leaf extract closely paralleled that of the standard drug, indicating its effectiveness. Thus, the research concludes that the ethanolic leaf extract of *Artocarpus hirsutus Lam.* possesses substantial anti-ulcerogenic and gastroprotective properties.

These findings not only validate the traditional use of *Artocarpus hirsutus Lam.* leaves as an anti-ulcer agent but also provide pharmacological evidence for its efficacy. Future research can expand on this preliminary work by incorporating additional ulcer models to further confirm the antiulcer potency of *Artocarpus hirsutus Lam.* leaves by fully understanding the mechanism of action. Additionally, efforts can be directed towards isolating and characterizing the phytoconstituents responsible for the observed pharmacological activity. Toxicological studies may also provide insights into the safety profile of the drug.

FINANCIAL ASSISTANCE

NIL

CONFLICT OF INTEREST

The authors declare no conflict of interest

AUTHOR CONTRIBUTION

Chaithra B N, Ullas Prakash D'Souza, Prasanna Shama Khandige and Vandana Sadananda have made substantial contributions to the conception and designing of the work, performed the experimental work, analyzed and interpreted the data and observations and approved the submitted version. All authors read and approved the final manuscript.

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