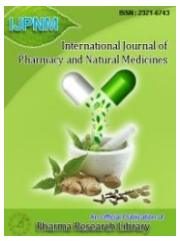

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Evaluation of Anti-ulcer activity of Andrographis paniculate in-vivo using albino Wistar rats

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A B S T R A C T
Andrographis paniculata (Acanthaceae) is given from ancient times in Indian traditional medicine like Ayurveda and Unani for the treatment of gastrointestinal tract disorders, bronchial diseases, fever, inflammatory diseases, liver disorders, parasitic diseases and snake poisoning. Aim of the study was Investigation of ethanolic and aqueous extracts of Andrographis paniculata in the treatment of ulcer by pylorus ligation induced gastric ulcer in rats. The antiulcer activity of ethanolic and aqueous extracts of Andrographis paniculata (APE) was investigated using 25 rats. The first group was subjected as control, the second group was subjected to pylorus ligation on 6th day under ether anesthesia, and the third group was subjected to ranitidine (50 mg/kg) for 5 days + pylorus ligation on 6th day under ether anesthesia. The fourth and fifth groups were administered with the ethanolic and aqueous extracts of Andrographis paniculata (100 and 100 mg/kg/day, respectively). All animals were deprived of food (but not water) for 24 hours prior to being subjected to ulcerogenic challenge. At the end of study, the stomach tissue was cut, washed with ice cold saline. The tissue was fixed in 10% buffered neutral formalin solution for histopathological examination. Ulcer Index, pH, titrable acidity, gastric mucus, antioxidant activity, and gastric pepsin activity was evaluated by using tissue and gastric juice. Results: APE showed dose-dependent ulcer protective effect in ranitidine plus pylorus ligation induced gastric ulcer. The % protection was found in group IV (59.8 %), group V (60.08%) when compared to PL group II and Ranitidine+PL group III, respectively. The APE showed highly significant enhancement of gastric wall mucus at the dose of 100 mg/kg. The results of our study revealed that the extracts of Andrographis paniculata possess significant dose dependent gastroprotective and antisecretory effects by strengthening the gastric mucosa, decreasing the acidity of gastric juice and pepsin activity as well as restore the imbalance antioxidant activity. Further studies on other factors like H. pylori, PGs and cAMP, which play important role in ulcerogenisis may provide more insights on the antiulcerogenic activity of Andrographis paniculata.

Keywords: *Andrographis paniculata, Pylorus ligation, Ulcer index, Gastric output, Ranitidine.*

A R T I C L E I N F O

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C o n t e n t s

1. Introduction

Plants have been used as a source of medicine by man from ancient times. Initially, these formed the bulk of folk or ethno-medicines, practiced in India and some other parts of the world like China, Africa and South America. Later a considerable part of this indigenous knowledge was formulated, documented and eventually passed into the organized system of medicine such as Ayurveda, Unani,

Siddha and some other outside India. Plants have played a significant role in maintaining human health and improving the quality of human life for thousands of years and have served human well as valuable components of medicines, seasonings, beverages, cosmetics, and dyes.

India is one of the world's oldest civilizations, and it is well-known for having a vast collection of medicinal plants. Approximately 8000 herbal medicines have been codified in Ayurveda, which is considered the bible of Indian medicinal science and is used for a variety of therapeutic purposes. Peptic ulcers are any ulcers that have been exposed to the digestive enzyme pepsin. Peptic ulcers are a type of ulcer that develops in the lining of the stomach or duodenum. Pepsin and hydrochloric acid are generally found in the stomach lining, along with other digestive enzymes.

Plant Description:

In wet, shady conditions, the plant grows as an erect herb to a height of 30–110 cm (12–43 in), with a spread of 30–110 cm (12–43 in). The slender stem is dark green in color, square in cross-section, and has longitudinal furrows and wings along the angles of the leaves. Approximately 8 cm (3.1 in) long by 2.5 cm (1.1 in) wide, the lance-shaped leaves have hairless blades (0.98 in). The little blooms are pink and solitary, and they are clustered in racemes orpanicles that are laxly spreading. The fruitis acapsule that measures approximately 2 cm (0.79 in) in length and a few millimeters in width. It contains a large number of yellow-brown seeds. The seeds are subquadrate in shape, rugose in texture, and glabrous in appearance. From September until December, the flowers are in bloom.

Fig.1(a) Andrographis paniculata flower (Closeup View)

Fig.1(b) Andrographis Paniculata Leaves (Normal View)

Plant Description:

In wet, shady conditions, the plant grows as an erect herb to a height of 30–110 cm (12–43in), with a spread of 30–110 cm (12–43in). The slender stem is dark green in color, square in cross-section, and has longitudinal furrows and wings along the angles of the leaves. Approximately 8 cm (3.1in) long by 2.5 cm (1.1in) wide, the lance-shaped leaves have hairless blades (0.98 in). The little blooms are pink and solitary, and they are clustered in racemes orpanicles that are laxly spreading. The fruitis acapsule that measures approximately 2cm (0.79in) in length and a few millimeters in width. It contains a large number of yellow-brown seeds. The seeds are subquadrate in shape, rugose in texture, and glabrous in appearance. From September until December, the flowers are in bloom[40].

2. Materials & Methods

In vivo Anti-ulcer Activity

Animal care and handling as per CPCSEA guidelines:

Wistar albino strain rats of weight 150-250 grams were selected. The animals were acclimatized to the standard laboratory conditions in well cross ventilated animal house at temperature 25+ 20C relative humidity 44-56% and light and dark cycles of 12 and 12 hours respectively for 1week before and during the experiments. The animals were fed with standard diet ad water ad libitum. The experiments were approved by CPCSEA and the institutional ethics committee. Food was withdrawn18hours before the start of the activity.

Acute oral toxicity study and selection of doses:

A safe oral dose of EEAP and AEAP was determined through the acute oral toxic test in rats as described by the Organization of Economic Co-Operation and Development (OECD) as per423 guidelines (OECD Guidelines for the Testing of Chemicals). The EEAP & AEAP at different doses up to 2000mg/kg, was prepared by dissolving the extract in distilled water and the concentration was adjusted in such a way that it did not exceed 1ml/100g of the rat. The extract was then administered (p.o.) and animals were observed for behavioral changes, any toxicity and mortality up to 48 h. The doses (250 mg/kg, p.o.) of EEAP and AEAP were later chosen for this study based on the acute toxicity testing.

Experimental Design

Pylorus Ligation Induced Ulcer Model48

Wistar albino strain rats weighing 150-20g were selected for pyloric ligation ulcer model. Rats were divided into five groups, each group consisting of six animals. Animals were fasted for 48 hours.

Group-I: Normal
Group-II: Control (Saline2ml/kg)
Group-III: Treated with Ranitidine 50mg/kg
Group-IV: Treated with AEAP (100mg/kg)
Group-V: Treated with EEAP (100mg/kg)

The oral treatment was carried out 1hour before pyloric ligation, respectively. After 48 hours of Fasting, ulcer induction was undertaken according to Shayetal. The rats were given a brief anesthetic with Anesthetic Ether before having their abdomens split open with a midline incision. To maintain the pylorus in place, silk sutures were sewn around it, after which the incision was closed, and the animals were allowed to recover from anesthesia. Drinking water was avoided for 18 hours after pylorus ligation in this trial, and stomach checks were performed18hours after the pylorus wastied. The animals were sacrificed with an excess of anesthetic Isoflurane. As indicated, the stomachs

were opened along the larger curvature of the stomach and cleaned with saline to remove gastric contents and blood clots before being viewed under a magnifier lens (10x) to assess the formation of ulcers.

Transparent surgical tapes were utilized to determine the extent of the ulcer. The ulcer area was marked out on a bright and transparent sheet, and the ulcer area was measured independently for each stomach in the experiment. In order to establish the number of erosionsthat had occurred on the glandular region of the stomach, a severity rating was assigned to each one on a scale from one to three. In order tore move any leftover germs, the stomach contents were collected and centrifuged for 10 minutes at 1000RPM to remove any remaining bacteria. One millilitre of the supernatant liquid was pipette out and diluted with distilled water to a concentration of ten millilitres. The result was a concentration of ten millilitres. With Topfer's reagent serving as an indicator, the solution was titrated against 0.01N NaOH until the endpoint was reached, at which point the solution changed colour to an orange. On the basis of the amount of free acidity present, the amount of NaOH that was necessary was estimated. Once the solution had restored its pink tint, the titration procedure was repeated several times more. This information was used to calculate the volume of NaOH required, which was found to be in accordance with the overall acidity of the solution.

Ulcer index will be then calculated by adding the total number of ulcers per stomach and the total severity of ulcers per stomach. Rating/Grading/Scoring of ulcers was be made as per the following criteria

No ulcer (0)
Superficialulcers (1)
Deepulcers (2)
Perforations (3)

Mean ulcer score for each animal will be expressed as ulcer index- U1= (UN+ Us+ UP)10-1
Where,
U1= Average of number of ulcers per animal Us= Average of severity of score
Up=Percentage of animals with ulcers
The percentage of ulcer protection will be determined as follows

$$\% \text{ Protective} = \frac{\text{Control Mean ulcer index} - \text{Test mean ulcer index}}{\text{Control Mean ulcer index}} \text{ X100}$$

Reagents for biochemical estimations of free and total acidity: Reagents for estimation of free and total acidity:

a. Freshly prepared 0.01N oxalic acid solution was used to standardize sodium hydroxide.
b. Freshly prepared 0.01N Sodium Hydroxide
c. Topfer's reagent. It is dimethyl amino azo benzene 0.5% in absolute ethanol available in 100ml package.
d. Freshly prepared1% phenolphthalein solution prepared in 50% absolute ethanol.

Methods for biochemical estimation of free and total acidity.

Collection of gastric juice:

The gastric contents of rats with their pylorus ligated were centrifuged and the volumes of gastric juice extracted were measured. The gastric juice was subjected to the following biochemical analysis to determine its composition:

Determination of free and total acidity

Pipette 1ml of gastric juice into a 100ml conical flask, followed by 2 or 3 drops of Topfer's reagent, which was then titrated with 0.01N Sodium hydroxide until all traces of red colour were gone and the solution turned yellowish orange in hue. The amount of alkali that was used was recorded. This volume relates to the amount of free acidity present. A phenolphthalein solution was then added, and the titration was continued until a distinct red tint was seen on the surface of the solution. The whole volume of alkali added was recorded once more, and this time the volume corresponded to the total acidity. Acidity was calculated by using the formula

$$\text{Acidity} = \frac{\text{Volume of NaoH x Normality of NaoH}}{\text{meq/lt/100g}} \text{ x100}$$

3. Results and Discussion

Extraction:

The extraction value of EEAP:
Total Amount of crude drug used = 250gm
Amount obtained as Ethanolic Extract = 23gm
%Yield=23/250x100 =9.2%W/W
The extraction value of AEAP:
Total Amount of crude drug used = 230gm
Amount obtained as Aqueous Extract = 21gm
%Yield=21/230x100 =9.1%W/W

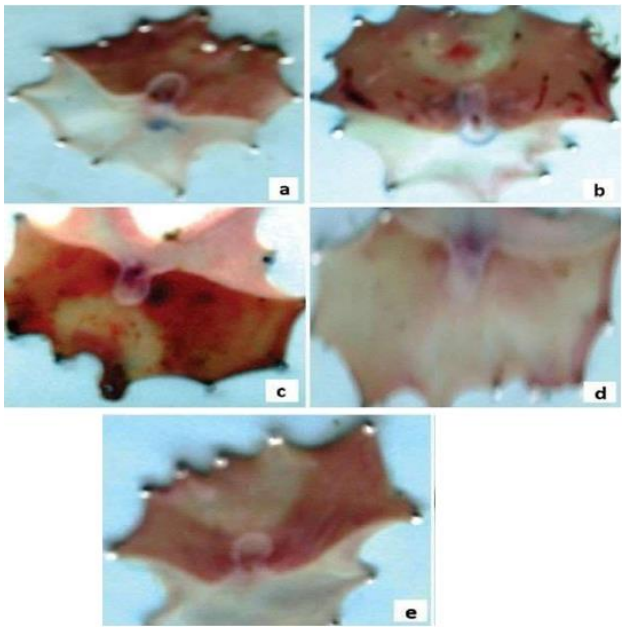

Fig.2. Macroscopical view of puylorus ligation induced ulcer a. Normal b. Control c. Standard d. Ethanolic extract of e. Andrographis paniculata f. Aqueous extract of Andrographis paniculata

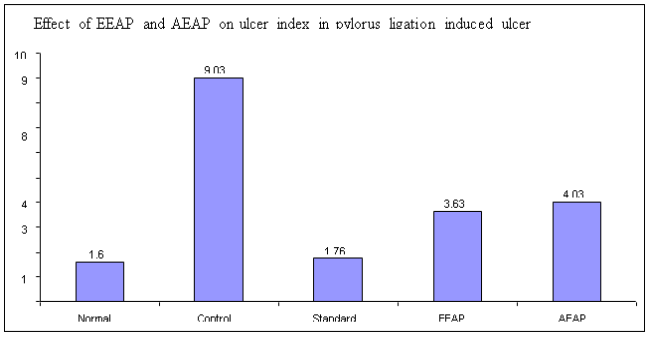

Fig.3: Effect of EEAP and AEAP on ulcer index in pylorus ligation induced ulcer

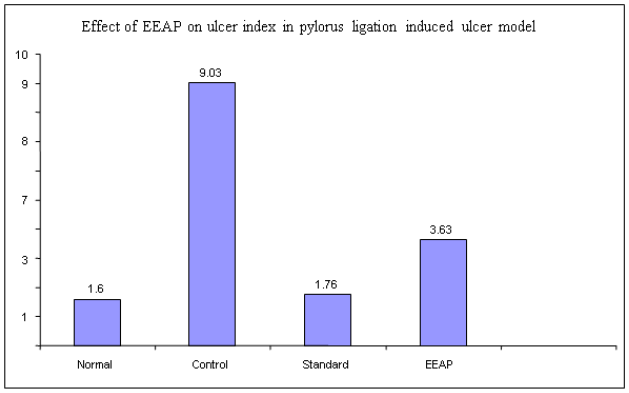

Fig:4. Effect of EEA Pon ulcer index in pylorus ligation induced ulcer model

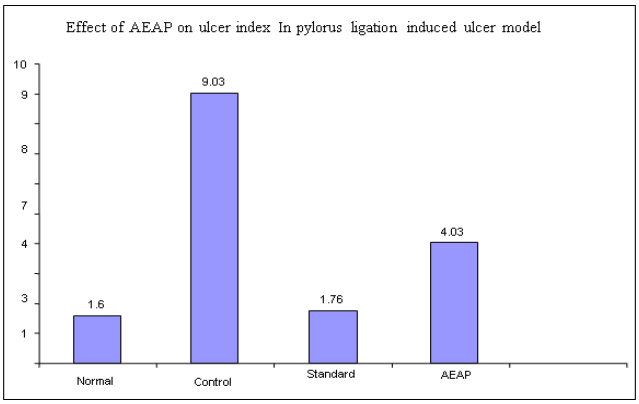

Fig:5. Effect of AEAP on ulcer index in pylorus ligation induced ulcer model

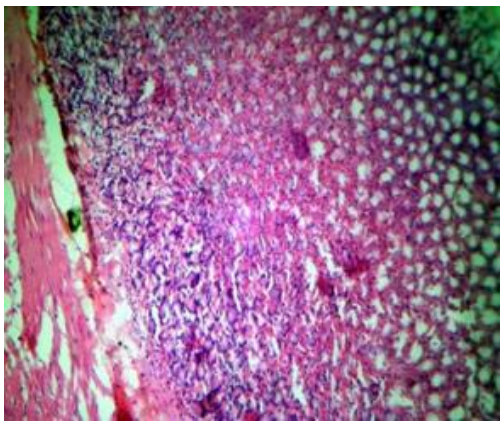

Fig: 6. Stomach of a rat which is normal

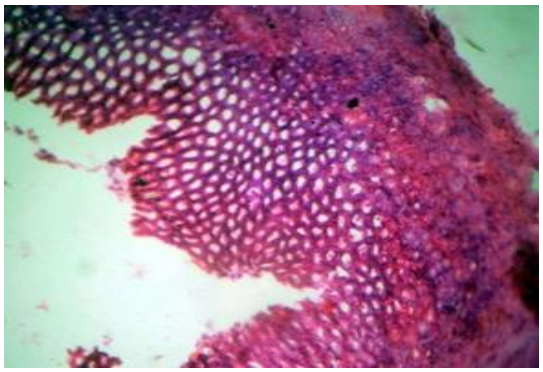

Fig.7. Stomach of a control rat showing erosion in the upper part of epithelium with RBCs in Eroded portion

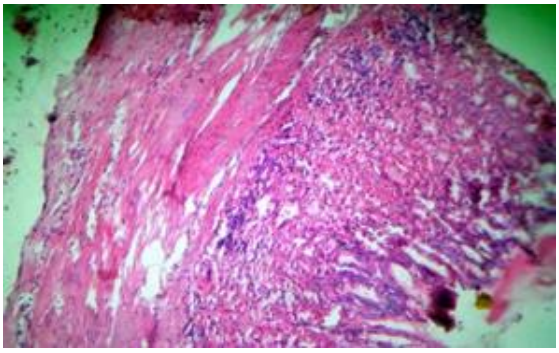

Fig: 8. Stomach of a rat treated with ranitidine

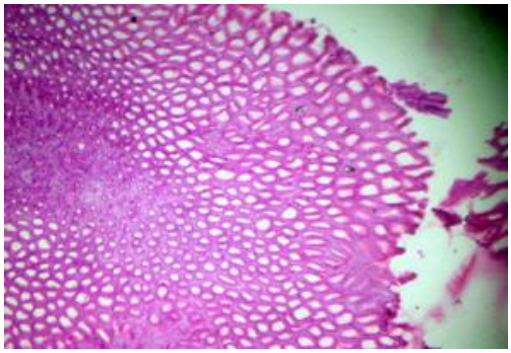

Fig 9: Stomachs of EEAP treated rats showing small erosions with minimum small superficial erosion with minimum deviation from normal morphology from normal morphology

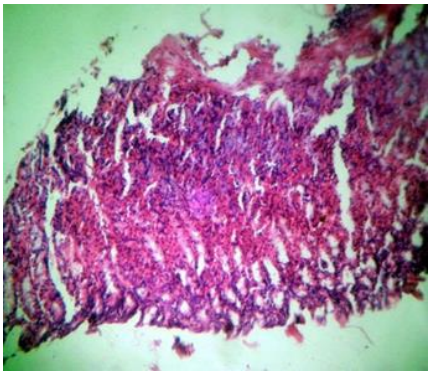

Fig.10. Stomachs of AEAP treated rats showing small superficial erosion with minimum deviation from normal morphology

Discussion

In addition to being associated with a variety of pathogenic factors, it is possible that these conditions are caused by disruptions in the natural balances between aggressive factors (e.g.,acid, bicarbonate, pepsin) and the preservation of mucosal integrity through the endogenous defense mechanism of peptic ulcer and gastritis (gastric inflammation). The use of a range of general techniques to rectify these imbalances is widespread practice in the industry. Some of these include eating on a regular schedule, getting adequate sleep, and avoiding ulcerogenic substances, among other things (e.g., tobacco, alcohol and coffee). Their goals are to decrease, if not completely eliminate, stomach acid output while at the same time strengthening mucosal defense systems. The latter can be done, among other things, by increasing mucus production, stabilizing the surface epithelial cells, or interfering with the production of prostaglandins. Treatment for ulcers includes the use of medications such as pump inhibitors, histamine (H2) receptor antagonists, anti-cholinergic, and antacids, among other things.

The H2receptor is a G protein coupled receptor (GPCR) that activates the Gs- adenyl cyclase-cyclic AMP-PKA pathway. The H2 Receptor antagonists inhibit acid production by reversibly competing with histamine for binding to H2 receptors on the basolateral membrane of parietal cells. Four different H2–receptor antagonists, which differ mainly in their pharmacokinetics and propensity to cause drug interactions, are available in the United States: cimetidine (TAGAMET), Ranitidine (ZANTAC), famotidine (PEPCID), and nizatidine (AXID). These drugs are less potent than proton pump inhibitors but still suppress 24-hour gastric acid secretion by about 70%. We evaluated effects of ethanolic, and aqueous extracts obtained from *Andrographis paniculata* leaves in animals using the different standard experimental models of induced gastric ulcers. In case of Pylorus ligation model, the total acidity was decreased. Circular and linear lesions were frequently observed in the stomach of all the control animals.

Administration of *Andrographis paniculata* extracts resulted in a significant reduction in ulcer index in dose dependent manner when compared to control, despite the availability of many pharmaceutical products for the treatment of gastric ulcers in the market as mentioned bove, their successes were limited by presence of several adverse effects (e.g., anaphylaxis reactions, gynecomastia, hematopoietic changes, thrombocytopenia, acute interstitial nephritis, nephrotoxicity and hepatotoxicity). Due to the reported side effects of available antiulcer drugs, focused have been shifted towards natural products as the new sources of antiulcer agents.

Andrographis paniculata has been reported to exert several pharmacological properties such as, anti-inflammatory, antiviral, antioxidant, antidiabetic, hepatoprotective, activities. Despite claim of its potential in the treatment of gastric ulcer, this plant so for not been screened for anti-ulcer potential activity. Thus, we take this opportunity to report the preliminary findingson anti-ulcer potential of *Andrographis paniculata* leaf extracts for the first time.

The present study demonstrated the potential of EEAP and AEAP to significantly reduced gastric ulceration as indicated by the reduction in ulcer index in the pylorus induced assays. Based on further findings using the PL assay, the extracts were suggested to act by reducing the volume of gastric juice secreted, gastric free and total acidities. These results suggested that EEAP and AEAP possess anti-secretory potency as well as acid neutralizing effect. It is also possible to suggest that the observed antiulcer activity associated with *A.paniculata*is the ability to exhibit antioxidant activity cited above. Oxidative stress, resulting from the increase production of oxygen derived free radicals (e.g., superoxide anion, hydrogen peroxide and hydroxyl radicals), has been known to take part in the pathogenesis of various diseases including gastric ulcer and antioxidants help to protect cells from damage elicited by oxidative stress while enhancing the body's defense systems against degenerative diseases.

A.paniculata leaf extract had been reported to possess antioxidant activity and to contain various types of compounds such as alkaloids, phenols, flavonoids, tannins, terpenoids and saponins. The anti-ulcer activity is probably due to the presence of bioactive compound like flavonoids and sterols. Statistical analysis revealed that ethanolic and aqueous extracts of *Andrographis paniculata contains* antiulcer activity due to the presence of Flavanoids and Sterols. In the histopathological examination, stomachs of control rat show erosion in the upper part of epithelium and RBCs are seen in the eroded portion (Fig 2), stomachs of rats treated with standard drug (ranitidine) showed small erosions with a minimal deviation from nor- mal morphology,(Fig3).Stomachs of rats treated with EEAP extract showed small superficial erosion with minimal deviation from normal morphology, (Fig 4) and stomachs of rats AEAP extract showed superficial erosions with minimum deviations from normal morphology (Fig 5).

Effect of EEAP and AEAP in pylorus ligated rats

Pylorus ligation in ulcerated control group had produced ulcer in all animals and the mean ulcer index was 9.03 indicating the ulcerogenic effect. Mean gastric content volume as 4.2±0.18, free acidity as 4.6±0.05, total acidity as 22.3±0.3 indicating the ulcer production in animal. However, the ulcer index showed significant dose dependent reduction in the animal pretreated with EEAP 100mg/kg (UI; 3.63) and with AEAP 100mg/kg (UI;4.03). It indicated 59.8% gastro protection with EEAP 100mg/kg and 60.8% with AEAP 100mg/kg as compared with ulcerated control. The results indicate that AEAP 100mg/kg was effective in protecting ulcers in pylorus ligated rats. Pylorus ligation had produced ulcers in all animals pretreated with Ranitidine 50mg/kg. However, ulcer index (1.76) showed significant reduction as compared with ulcerated control and showed 80.5% gastro protection.

Table 1: Phytochemical analysis

Group	Treatment	Dose(mg/kg)	Ulcer index (mm2/rat)	%Protection
I.	Normal	2	1.60	--
II.	Control	2	9.03	--
III.	Standard	50	1.76	80.5
IV.	EEAP	100	3.63*	59.8*
V.	AEAP	100	4.03*	60.8*

Table 2: Effect of Andrographis paniculata leaf Ethanolic extract on volume of gastric juice, Total acidity and free acidity in Pylorus ligation induced ulcer.

Group	Treatment	Dose (mg/kg)p.o.	Volume of gastric juice	p^H	Free Acidity (mEq/L)	Total Acidity (mEq/L)
I	Normal	2	3.1±0.23	4.1	5.4±0.08	7.6±0.2
II	Control	2	4.2±0.18	2.8	4.6±0.05	22.3±0.3
III	Standard	50	1.9±0.07	7.5	3.1±0.02	6.8±0.16
IV	EEAP	100	2.4±0.11*	6.9	3.4±0.03*	5.9±0.12*

Table 3: Effect of Andrographis paniculata leaf Aqueous extract on volume of gastric juice, Total Acidity and Free acidity in Pylorus ligation induced ulcer

Group	Treatment	Dose (mg/kg) p.o	Volume of gastric juice	p^H	Free Acidity (mEq/L)	Total Acidity (mEq/L)
I	Normal	2	3.1±0.23	4.1	5.4±0.08	7.6±0.2
II	Control	2	4.2±0.18	2.8	4.6±0.05	22.3±0.3
III	Standard	50	1.9±0.07	7.5	3.1±0.02	6.8±0.16
IV	AEAP	100	1.5±o.28*	6.4	2.1±0.18*	6.3±0.27

4. Conclusion

The findings of this study provide evidence that the leaves of Andrographis paniculata have significant anti-ulcer activity in animal models. It is believed that the addition of bioactive compounds such as flavonoids and sterols is responsible for the anti-ulcer action of the supplement. Furthermore, the observation supports the plant's ethnomedical use as an anti-ulcer agent and an antacid in addition to its nutritional value. Using pylorus ligation models, researchers discovered that the stomach tissue has a normal architecture. Although it is unlikely, it is possible that this protective effect was mediated by a combination of anti-secretory and cytoprotective mechanisms. Comparing the normal dose of Ranitidine and Andrographis paniculata extracts to a placebo, researchers discovered that the regular dose significantly reduced stomach volume, total acidity, free acidity, and ulcer index. AEAP with 100mg/kg is more effective than EEAP with 100mg/kg when it comes to comparing the effectiveness of the different extracts. As a result, I came to the conclusion that my plant, Andrographis paniculata, has anti-ulcer activity based on the data, and that future research work on alternative formulations may be conducted. However, there has been a shortage of clinical investigations and clinical trials to determine its potency and efficacy.

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