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Gastric acid anti-secretory activity of aqueous leaf extract of *Hypoestes rosea* in ulcer-induced rats

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ABSTRACT

Background: *Hypoestes rosea*, an evergreen shrub belonging to the Acanthaceae family possess anti-ulcer potential amongst its several other medicinal properties, including usefulness as anti-diabetic and anti-inflammatory agents. **Objective:** In this study, we investigated the anti-secretory effect of aqueous leaf extract of *H. rosea* as the possible mechanism for its antiulcer activity in gastric ulcer induced rats. **Methods:** 40 rats were divided into 2 experimental phases of 20 rats each. They were further separated into 5 groups as follows: Group 1 (Normal control: rat chow and water only). Group 2 Ulcer control: Indomethacin-induced (40mg/kg bw). Group 3: Low dose (100mg/kg bw). Group 4: Medium dose (200mg/kg bw). Group 5: High dose (300mg/kg bw). Phase 1 involved determination of ulcer lesion index and % inhibition. Phase 2 involved estimation of gastric acid secretion using the method of continuous perfusion with 10minutes aliquots titrated against 0.01N NaOH. **Results:** Aqueous extract of *Hypoestes rosea* produced a significant ($P<0.05$) dose-dependent decrease in ulcer lesion score with an accompanying increase in percentage inhibition at the various doses used in the study (100, 200 and 300 mg/kg bw). Also, there was a significant decrease in basal and histamine-induced acid secretion at all doses with the greatest effect observed at the high dose (300mg/kg bw). **Conclusion:** Results obtained showed that aqueous extract of *H. rosea* decreased gastric acid secretion possibly due to inhibition of Histamine receptors and may thus be the mechanism for its anti-ulcer activity.

Keywords: Acanthaceae, gastric acid secretion, Histamine, *Hypoestes rosea*, Phytochemical evaluation.

INTRODUCTION

The gastric mucosa is a highly acidic environment created from the release of Hydrochloric acid (HCl) by the gastric parietal cells stimulated by the combined action of acetylcholine and histamine. The HCl secreted is essential for digestion as it degrades food constituents, it also promotes absorption of iron and elimination of harmful micro-organisms present in ingested food [1]. However, elevated acid secretion is detrimental to the integrity of the gastric mucosa [2]. Hyper-acid secretion was so named a mucosal aggressive factor that contributes to gastric ulceration, together with increased pepsin activity [3]. Increased secretion of gastric acid by the stomach has been implicated as a major contributing factor in the aetiology of gastric ulcers and other peptic ulcers. [4] Gastric ulcer is the most common disease of the upper gastro-intestinal tract. Annually, it affects about 4 million people globally with its highest reported prevalence in Africa [5].

The secretion of HCl by the parietal cells is controlled tightly by neurohormonal regulation and stimulating mediators such as acetylcholine, histamine receptors, gastrin receptors, ghrelin amongst others thus hyper acid secretion is prevented in normal physiological conditions [2]. On the basis of this, Anti-ulcer medications developed in recent years have focused on inhibiting acid secretion either by neutralizing secreted acids using antacids like aluminum hydroxide, inhibition of gastrin activity by gastrin-receptor antagonists, inhibition of histamine activity by Histamine-2 Receptor Antagonists (H₂RA) like cimetidine or inhibition of the proton pump by Proton Pump Inhibitors (PPIs) such as omeprazole. [1] Although these drugs are readily accessible, many people still resort to the use of herbal medications formulated from natural medicinal plant parts as they provide a cheaper alternative to orthodox medicines [6]. Medicinal plants such as *Spondias mombin*, *Ficus esperata* and *Gonglonema latifolium*, amongst others have been experimentally proven to possess substantial anti-ulcer activity [7, 8]. Another of such medicinal plant is *Hypoestes rosea*. It is used in traditional medicine formulations by the as remedy for gastrointestinal disturbances amongst other purposes.

Hypoestes rosea, belonging to the Acanthaceae family is a perennial shrub indigenous to the rainforest regions of Nigeria [9]. It grows predominantly in southern Nigeria and other West African countries [10]. *H. rosea* contains some biochemical compounds namely: hypoestoxide, roseadione and lupeol amongst others [11-15]. These compounds possess antioxidant, anti-fungal, anti-inflammatory and anti-ulcer properties as reported by several studies [10, 11, 16]. Findings of a previous research indicated that aqueous extract of *H. rosea* exhibited a dose-dependent anti-ulcer activity in indomethacin-ulcerated rats [17].

Having established that increased gastric acid secretion is critical to ulcer formation and *H. rosea* possesses anti-ulcer activity, this study therefore investigates the possible mechanism by which *H. rosea* produces this anti-ulcer activity in ulcerated rats.

MATERIALS AND METHODS

Collection and authentication of plant material

Leaves of *Hypoestes rosea* were freshly obtained from a farm in Calabar, Crossriver state, Nigeria in April 2022. They were identified and subsequently authenticated at the Herbarium unit, Department of Botany, University of Calabar and given an identification number: HERB/BOT/UCC/035.

Preparation of aqueous extract of *H. rosea*

The leaves were shade dried for fourteen (14) days and subsequently pulverized into a fine powder using a blender. Seven hundred and twenty-four grams (724g) of the fine powder was macerated for 48 hours in three liters of distilled water. The resulting mixture was filtered twice using chess cloth and Whatmann filter paper (Size No.1) and a clear homogenous extract was obtained. The extract obtained after filtration was then concentrated and dried using an evaporator and microwave oven respectively [10]. The weight of the resulting crude extract was 63g. It was labelled 'H. rosea (aq. extract)' and preserved in a refrigerator with temperature set at 2-6°C.

Drugs and chemicals

Indomethacin and ranitidine (Embassy Pharmaceuticals and Chemicals Ltd Reagents, Lagos, Nigeria). Urethane, histamine and Ketamine (Sigma Chemical Co. Ltd, St. Louis, Missouri, USA). Sodium hydroxide (NaOH) (AnalaR BDH Chemicals Ltd, UK), Phenolphthalein indicator solution (Biopharm Inc, USA). The Department of Physiology, University of Calabar provided distilled water for the experiment. All the drugs and chemicals used in this study were of analytical standard.

Phytochemical analysis

Qualitative phytochemical analysis was carried out on the crude extract to identify the bioactive chemical compounds present. Test for phenols was done using the method of Sofowora *et al.* [18]. 2ml of ferric chloride was added to equal volume of the crude extract. Formation of a blue-green coloration indicated the presence of phenols.

Test for carbohydrates (reducing sugars) was done using Benedict's test. 5ml of benedict solution was added to 1ml of the aqueous extract and boiled for 5minutes. Formation of a red precipitate indicated the presence of reducing sugars [19].

Salkowski test was used to determine the presence of terpenes. 5ml of the aqueous extract was mixed in 2ml of chloroform. Few drops of concentrated sulphuric acid was added to form a layer. Formation of a red-brown color indicated the presence of terpenes [20].

Presence of flavonoids was determined by addition of 1ml of 2N sodium hydroxide to 2ml of the aqueous extract. Formation of a yellow coloration of the mixture indicated the presence of flavonoids [19].

To test for presence of saponins, a volume of the extract was mixed in equal volume of water in a graduated cylinder and shaken for 15 minutes. A foam layer above the mixture indicated the presence of saponins [19].

Test for tannins was done by adding equal volume of 10% ferric chloride solution into the aqueous extract. Formation of a dark blue coloration indicated the presence of tannins [21].

Hager's test was used to determine the presence of alkaloids. Equal volume of the aqueous extract of *H. rosea* and Hager's reagent (saturated picric acid solution_{aq}) were mixed together. Formation of a yellow precipitate indicated the presence of alkaloids [19].

Experimental animals

Adult Sprague-dawley rats (n=40, 120 ± 20 g) were acclimatized for two weeks. They were freely fed with standard rat chow and had free access to water. This research complies with all the relevant national regulations and institutional ethical standards for animal use as Ethical approval was obtained from the Ethical Committee, Faculty of Basic Medical Sciences, University of Calabar (FAREC) with ethical number: FAREC/PA/UC/049.

Experimental design

Animal grouping

Forty Sprague-dawley rats were divided into 2 batches of 20 rats each. The batches were further separated into 5 groups of 4 rats each. The first batch was used for determination of ulcer lesion index and percentage inhibition, while the second batch was used for Acid secretion analysis. The groups are given as follows: Group 1 (Normal control: rat chow and water only). Group 2 (Ulcer control: Gastric ulcer induced with 40mg/kg indomethacin). Group 3: *H.rosea* 100mg/kg bw (Low dose). Group 4: *H.rosea* 200mg/kg bw (Medium dose). Group 5: *H.rosea* 300mg/kg bw (High dose).

Determination of ulcer lesion index and calculation of percentage inhibition

Using a previously described method, the rats were treated for 21 days with different doses of extract according to their various groupings [22]. The animals were then fasted for 24 hours and water withdrawn 1 hour before ulcer was induced by oral administration of indomethacin (40mg/kg bw). They were then anaesthetized with 1ml i.p. injection of ketamine and sacrificed using the method of cervical dislocation. The stomachs of the rats were excised and dissected along the greater curvature. Stomach debris was cleaned off using normal saline and they were pinned onto a white corkboard for examination. The degree of ulceration was evaluated using a hand lens and Vernier caliper to determine the ulcer lesion index [23]. Ulcer lesion index was calculated as the mean ulcer scores for the various groups. The ulcer lesions were graded according to a previously described method. Ulcer inhibition percentage was calculated using the formula:

$$\% \text{inhibition} = \frac{\text{Ulcer lesion index}_{\text{control}} - \text{Ulcer lesion index}_{\text{test}}}{\text{Ulcer lesion index}_{\text{control}}} \times 100$$

Ulcer lesion index_{control}

Acid secretion analysis

Animal preparation for gastric acid collection

The continuous perfusion acid secretion method of Ghosh and Schild was used [26]. This method measures total acid secretion within a given time interval. A total number of 20 rats weighing between 100 and 130g pretreated with the extract for 21 days were divided into 5 groups of 4 animals each. Groups 1 and 2 were the negative and positive controls respectively. The rats were fasted overnight and anaesthetized with 25% solution of Urethane administered via intraperitoneal injection. An incision was made on the trachea, it was cannulated and ligated to prevent obstruction of the airways. A feeding tube was passed through the mouth and oesophagus into the animal's stomach. The feeding tube was affixed to a syringe carried by a pump, in the neck region, around the oesophagus, a ligation was made to stop backward flow of fluid. The abdomen was exposed along the *Linea alba*, a fistula was passed into the stomach through a small incision made before the pylorus. The gastric content was collected into a container from this point. The animals were warmed

with a light bulb set up above them to maintain the temperature at 37°C.

Collection of perfusate and measurement of acid secretion

The rats were first perfused with 0.9% Normal saline (pH 7.0). Aliquots of gastric secretions were collected after every 10 minutes of infusion. The first 2 aliquots were discarded to avoid erroneous readings. After basal secretions were obtained, histamine and ranitidine were administered successively and the acid secretion was determined.

The gastric secretion aliquots were titrated against 0.01 mol/L NaOH solution with phenolphthalein used as indicator (2 drops/aliquot). Titrimetric calculation was done to determine the gastric acid output using the given formula: $Conc_{acid} \times Vol_{acid} = Conc_{base} \times Vol_{base}$

Statistical analysis

Data obtained were presented as Mean ± Standard deviation (SD). One-way ANOVA was done using SPSS software package for windows (IBM SPSS Statistics 25.0) to determine differences between means, followed by post-hoc with Turkey HSD. Values of $P < 0.05$ were considered statistically significant. Ulcer inhibition values were expressed as percentages (%).

RESULTS

Phytochemical analysis

The result of the qualitative phytochemical screening of aqueous extract of *H. rosea* is shown in Table 1. There was presence of terpenes, flavonoids together with saponins, carbohydrates (reducing sugars) and tannins.

Ulcer lesion score and % ulcer inhibition

The effects of aqueous leaf extract of *H. rosea* on the ulcer lesion index is shown in Figure 1. Administration of 40mg/kg Indomethacin produced a significant ($p < 0.05$) increase in the ulcer lesion score to a value of 13.5 ± 0.8 as seen in group 2 (ulcer control). A dose dependent decrease in the ulcer lesion score was observed in the groups administered with aqueous extract of *H. rosea* with the values of 6.4 ± 0.7 , 4.1 ± 0.7 and 1.5 ± 0.4 representing low dose, medium dose and high dose respectively. Furthermore, there was a dose dependent increase in the percentage ulcer inhibition values, with the highest inhibition value of 88.9% observed at 300mg/kg. The individual inhibition values for the various groups as shown in Table 2.

Table 1: Qualitative phytochemical analysis of the aqueous extract of *H. rosea*

Phytochemical compound	Result
Phenols	Absent
Carbohydrates (reducing sugars)	Present
Terpenes	Highly present
Flavonoids	Present
Saponins	Present
Tannins	Present
Alkaloids	Mildly present

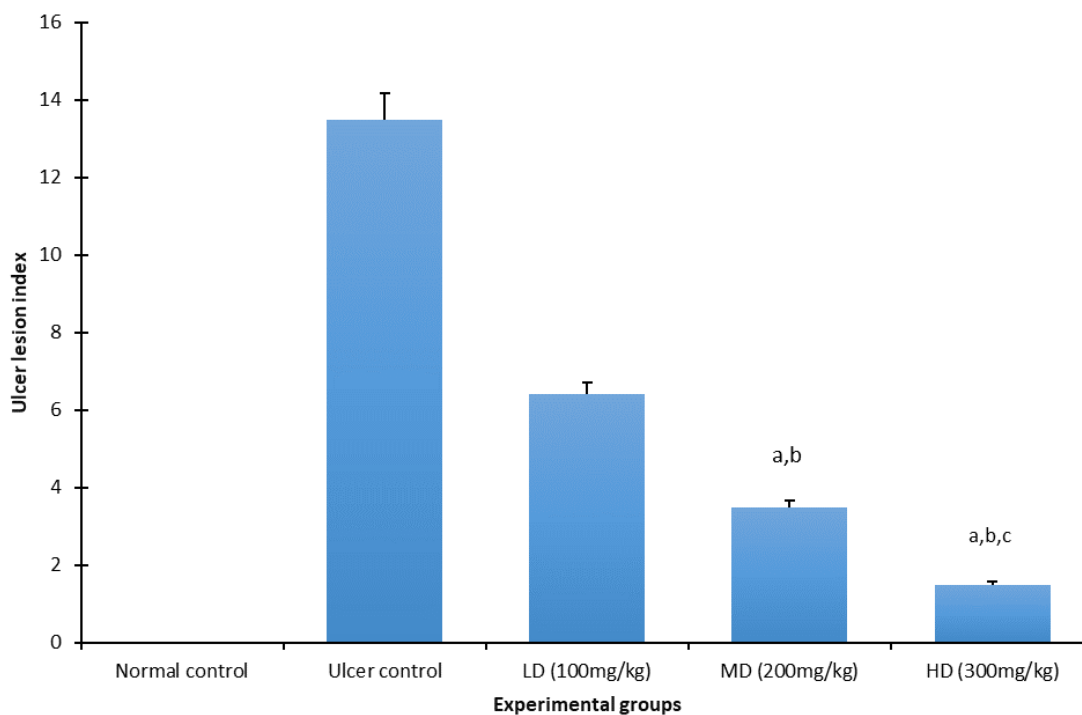


Figure 1: Ulcer lesion score of the various experimental groups. Superscripts ^{a,b,c} represent mean pairs with significantly different values as indicated by Turkey HSD (post-hoc). (a) indicates significant difference in comparison to mean of Ulcer control; (b) indicates significant difference in comparison to mean of Low dose; (c) indicates significant difference in comparison to mean of Medium dose.

Table 2: Ulcer inhibition values

Group	Treatment	Ulcer lesion index (mean ± SD)	% Ulcer inhibition
1 (Normal control)	Normal control	-	-
2 (Ulcer control)	Indomethacin (40mg/kg)	13.5 ± 0.8	-
3 (Low dose)	100mg/kg bw <i>H. rosea</i>	6.4 ± 0.7 ^a	52.6%
4 (Medium dose)	200mg/kg bw <i>H. rosea</i>	4.1 ± 0.7 ^{a,b}	74.1%
5 (High dose)	300mg/kg bw <i>H. rosea</i>	1.5 ± 0.4 ^{a,b,c}	88.9%

Superscripts ^{a,b,c} represent mean pairs with significantly different values as indicated by Turkey HSD (*post-hoc*). (a) indicates significant difference in comparison to mean of Ulcer control; (b) indicates significant difference in comparison to mean of Low dose; (c) indicates significant difference in comparison to mean of Medium dose.

Acid secretion analysis

The mean basal output in the various groups are given as follows: 0.35 ± 0.04 μmol/10min and 0.56 ± 0.04 μmol/10min for normal control and ulcer control. *H. rosea* Low dose, medium dose and high dose basal output values are respectively given as 0.34 ± 0.04 μmol/10min, 0.32 ± 0.02 μmol/10min and 0.29 ± 0.02 μmol/10min. From these values, we observed that *H. rosea* caused a decrease in the basal acid secretion in comparison to the control. As shown in Figure 2, administration of histamine caused a significant increase (p < 0.05) in the gastric acid secretion across all the groups. The increase was greatest in the ulcer control group (group 2) where the mean acid secretion rose from 0.56 ± 0.04 μmol/10min to 1.95 ± 0.1 μmol/10min. The least increase in mean acid secretion was observed in the high dose extract group (300mg/kg bw) where there was a rise

from 0.29 ± 0.02 μmol/10min to 0.71 ± 0.06 μmol/10min. Ranitidine administration diminished the effect of histamine in all the groups. In the normal control group, the mean acid secretion value decreased from 1.53 ± 0.03 to 0.38 ± 0.06 μmol/10min. In the ulcer control group, it decreased from 1.95 ± 0.1 to 0.7 ± 0.14 μmol/10min. There was a concomitant decrease in the acid secretion values among the *H. rosea* treatment groups with the greatest decrease observed in the high dose group where the acid secretion decreased from 0.71 ± 0.06 to 0.26 ± 0.03 μmol/10min. Figure 3 shows the effects of histamine and ranitidine on the various experimental groups. In all the groups, when compared to the basal secretion, there was a significant difference (p < 0.05) in the mean acid secretions after histamine administration. Figure 4 shows the effects of various treatments on basal, histamine and ranitidine gastric acid secretion.

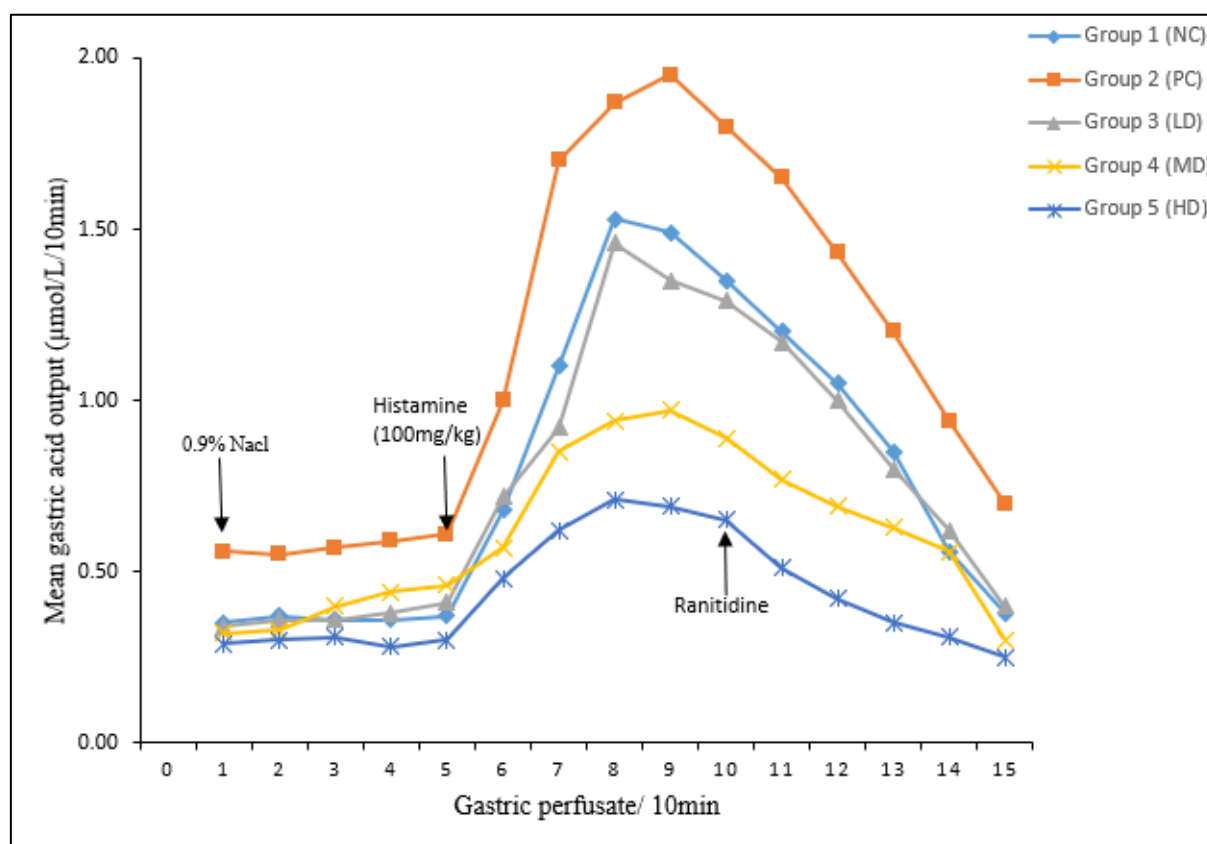


Figure 2: Comparison of basal, histamine and ranitidine induced gastric acid secretions of the experimental groups. Group 1(NC: normal control), Group 2(UC: ulcer control), Group 3(LD: 100mg/kg bw *H. rosea*), Group 4(MD: 200mg/kg bw *H. rosea*), Group 5(HD: 300mg/kg bw *H. rosea*).

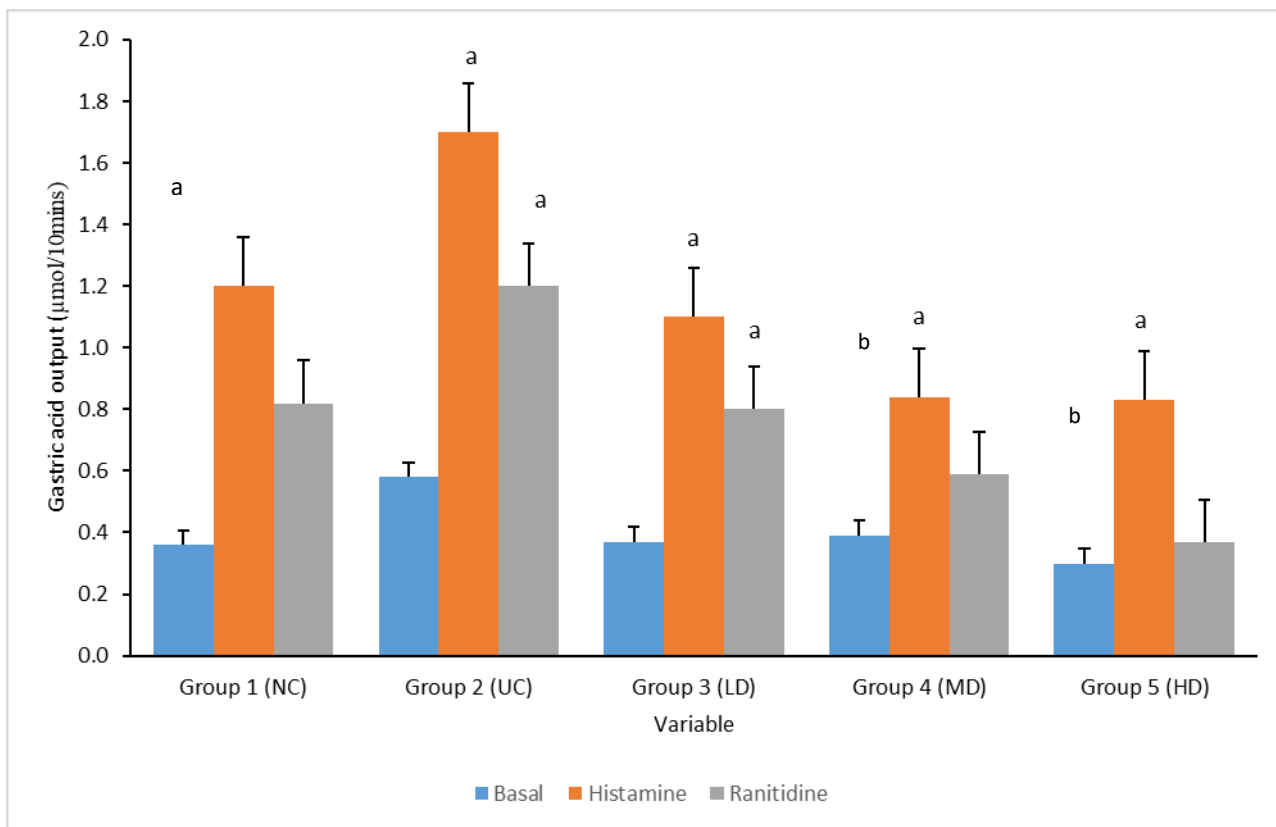


Figure 3. Effect of histamine and ranitidine on basal gastric acid outputs in the different experimental groups.

Values are expressed as mean ± SD.

- (a) indicates significantly different values ($p < 0.5$) in comparison to Basal acid secretion
- (b) indicates significantly different values ($p < 0.5$) in comparison to Histamine-induced acid secretion

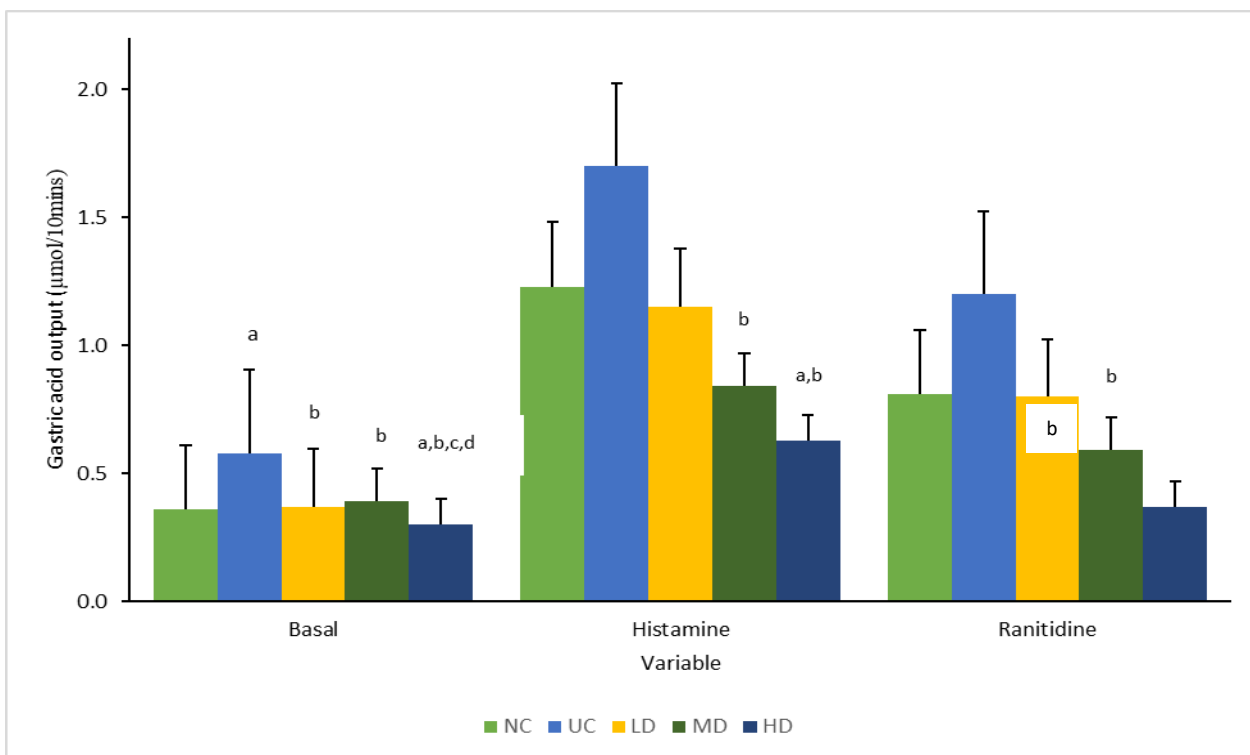


Figure 4. Effect of different treatments on basal, histamine and ranitidine induced gastric acid secretion in rats. (NC: Normal control, UC: Ulcer control, LD: low dose(100mg/kg), MD: mid dose (200mg/kg), HD: High dose (300mg/kg)

Values are expressed as mean ± SD.

- (a) Indicates significantly different values ($p < 0.5$) in comparison to group 1 (normal control)
- (b) Indicates significantly different values ($p < 0.5$) in comparison to group 2 (ulcer control)
- (c) Indicates significantly different values ($p < 0.5$) in comparison to group 3 (low dose)
- (d) Indicates significantly different values ($p < 0.5$) in comparison to group 4 (mid dose)

DISCUSSION

This study was carried out to evaluate the anti-acid secretory potential of *Hypoestes rosea* against gastric ulcers induced by indomethacin administration in rats. Preliminary qualitative phytochemical analysis of the aqueous leaf extract of *H. rosea* revealed the presence of some secondary metabolites such as terpenes, flavonoids, saponins and reducing sugars. Also, there was minimal presence of alkaloids. This result is in consonance with the findings obtained after the phytochemical analysis of the ethanolic extract [15] and the aqueous extract of the same plant [12]. Other chemical compounds such as roseanolone and hypoextoxide have been isolated from *H. rosea* [25, 9]. Roseanolone is a diterpene that functions as an anti-inflammatory agent [11]. It has also been reported to possess anti-tumor activity [28]. Generally, the biochemical compounds in *H. rosea* have been researched to be effective in the management of several ailments. Flavonoids and phenols are effective anti-oxidant and anti-inflammatory agents [10, 16]. Terpenes have been reported to function as anti-ulcer agents [27].

Indomethacin is a non-steroidal anti-inflammatory drug (NSAID) used in clinical practice as an anti-pyretic, anti-inflammatory agent and as pain relief medication. Despite its medical utility, indomethacin has been adjudged to be majorly involved in the pathogenesis of gastric ulcer and other peptic ulcers. It inhibits the synthesis of prostaglandins by inhibiting the cyclo-oxygenase enzymes (COX 1 and 2). Also, it causes marked inflammation and free radical accumulation that may cause damage to the gastric mucosa by oxidation [7, 28]. As observed in this study, indomethacin administration caused a marked elevation of the ulcer lesion index. Administration of aqueous extract of *H. rosea* produced a significant lowering of the ulcer index. Also, a dose dependent ulcer inhibitory effect was observed hence *H. rosea* exhibits a remarkable antiulcer activity. This effect may be due to the actions of certain biochemical compounds such as terpenoids and flavonoids that have been identified in the plant. Findings from a number of researches have determined that these compounds possess significant anti-ulcer and anti-oxidative potentials [27, 29].

Acid secretion is moderated majorly by the activities of acetylcholine, gastrin and histamine. Histamine is released by Enterochromafin-like (ECL) cells in the stomach after stimulation by acetylcholine and gastrin. It then binds to Histamine-2 (H_2) receptors on parietal cells and stimulates gastric acid production. Presence of histamine thus elevates acid secretion [3, 30]. Histamine release is one of the most important regulatory pathways in gastric acid secretion. Histamine-2 Receptor Antagonists (H_2RA) are a class of drugs that competitively inhibit binding and activation of the histamine receptor on the parietal cells [5]. As observed in this study, *H. rosea* produced a dose-dependent suppression of basal and histamine induced acid secretion. This seems to suggest that aqueous extract of *H. rosea* possibly acts by inhibiting H_2 receptors in a way similar to Histamine-2 Receptor Antagonists. This study is not without limitations, as only the histamine pathway for acid secretion was examined. However, further studies are underway to investigate the possible involvement of other mediators and receptors in producing this anti-secretory effect.

CONCLUSION

This study indicates that administration of aqueous leaf extract of *H. rosea* produced a beneficial effect on indomethacin-induced gastric ulcer in rats as it reduced the ulcer index and produced a dose-dependent suppression of gastric acid secretion.

Conflict of Interest

None declared.

Financial Support

None declared.

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