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Evaluation Of Anti-Ulcer Activity Of Ethanolic Extract Of *Annona Squamosa Linn* (Root) On Experimental Animals

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Abstract:

This study investigates the anti-ulcer activity of the ethanolic extract of Annona squamosa linn (Root) against Aspirin induced and Pylorus ligated ulcers. Gastric ulcer disease is caused by an imbalance between mucosal defense factors and injurious factors, such as acid and pepsin. Ulcers caused by pylorus ligation result from increased gastric acid and pepsin accumulation, leading to auto digestion of gastric mucosa and breaking down the gastric mucosal barrier. NSAIDs are frequently associated with peptic ulcers.

The anti-ulcer effect is supported by decreased aggressive factors like gastric volume, decreased free and total acidity, and increased resistance factors like pH. The anti-ulcer agent may protect the mucosa from acid effects by selectively increasing prostaglandins, which have a vital protective role. The mucosal defense mechanism may be due to the epithelial cells of the gastric mucosa, which are impermeable to H+ ions and form a physical barrier.

The ethanolic extract of Annona squamosa *linn* (Root) was evaluated using the aspirin induced ulcer model, showing dose-dependent inhibition percentages of 53.26% and 63.23% compared to the ulcer control. The standard drug Ranitidine HCL (20mg/kg) showed a percentage inhibition of 71.48% when compared to the ulcer control.

The study also found that the extract can reduce reactive free radicals that might cause oxidative damage to tissue. It also reduced polymorphonucleur infiltration, TNF expression, and ROS formation in peptic mucosa. The anti-ulcerogenic activity of the extract may add to its beneficial effect against peptic ulcer disorder.

Keywords: Peptic Ulcer, Annona squamosa *linn,* Acid Secretion, Inflammation, Mucosa

Introduction:

Peptic ulcers are acid-induced lesions of the digestive tract, typically located in the stomach or proximal duodenum. They are characterized by denuded mucosa with defects extending into the submucosa or muscularis propria. The prevalence of peptic ulcer disease is estimated to be 5-10% in the general population, but recent epidemiological studies have shown a decrease in incidence, rates of hospital admissions, and mortality associated with peptic ulcer.

The risk of complications of peptic ulcer is increased four times in NSAID users and two times in aspirin users. The concomitant use of NSAIDs or aspirin with anticoagulants, corticosteroids, and selective serotonin reuptake inhibitors increases the risk of upper gastrointestinal bleeding. A meta-analysis of observational studies concluded that NSAIDs, aspirin use, and H. pylori infection increase the risk of peptic ulcer disease independently. [1-3]

The main mechanism of NSAID-associated damage of the gastroduodenal mucosa is the systemic inhibition of constitutively expressed cyclooxygenase-1 (COX-1), which is responsible for prostaglandin synthesis. This is associated with decreased mucosal blood flow, low mucus and bicarbonate secretion, and the inhibition of cell proliferation. The co-administration of exogenous prostaglandins and cyclooxygenase-2 (COX-2)-selective NSAIDs reduces mucosal damage and the risk of ulcers. However, the different physicochemical properties of NSAIDs cause differences in their toxicity. [4-7]

In traditional medicine, several plants and herbs have been used to treat gastrointestinal disorders, including gastric ulcers. The first drug effective against gastric ulcer was carbenoxolone, discovered through research on Glycyrrhiza glabra, cabbage, banana fruit, Campanulaceae species, solon, Melia azedarach, and Santalum album stem. [8]

Materials and Methods:

Annona squamosa Linn. Was obtained from a local nursery, Ethanol and CMC was obtained from S.D. Fine Chem, Mumbai, Distilled water was procured from Loba Chem, Mumbai. The standard Ranitidine HCL was procured from Yarrow Chem, Mumbai. All other chemicals and reagents used were of analytical grade.

Preparation of Extract:

The roots of *Annona squamosa* were shade dried and then ground till they became coarse powder in a mortar-pestle. The powdered material thus obtained was subjected to extraction using Ethanol. The extracts obtained were distilled to remove excess of the solvent and then evaporated at 40^{o}C to get a semi-solid mass. These extracts were subjected to phytochemical tests. [9-10]

Animals:

Wistar rats of either sex (150-200gms) were housed in separate cages at controlled room temperature (24 ±2^{o}C; relative humidity 60-70%) in a 12hr light- dark cycle. They were fed with standard pellet diet and water *ad libitum*.

Determination of Acute Oral Toxicity (Ld_{50}) Of *Annona Squamosa Linn* (Root)

Test Substance Details:

Name of the test substance: Ethanolic extract of *Annona Squamosa Linn* (Root).

Color: Greenish Black

Nature of the Test Substance: Gummy

Study Procedure:

The Organization for Economic Cooperation and Development (OECD) guideline 425 methodology were used when assessing acute oral toxicity. A specifically made oral needle for mice was used to gavage the extract in a single dosage. The day before the dose, the animals fast (no water, only no food). (OECD Chemical Testing Guidelines, 425). Prior to conducting the study on animals, institutional animal ethics committee clearance was obtained for the handling of the animals and the procedures utilized in the study. The number of the proposal is 22MP01DEC10.

Housing and Feeding Condition:

The temperature in the experimental animal room was kept 22±3^{o}C. Artificial lighting was provided. The animals were acclimatized to standard laboratory conditions of temperature (22 ± 30^{o}C) and maintained on 12:12 h light: dark cycle. The animals were housed in sanitized polypropylene cages containing sterile paddy husk as bedding. They were provided with regular rat chow diet and distilled water ad libitum. [11]

Preparation of Animals:

The animals were randomly selected and kept in their cages for at least 5 days prior to dosing to allow for acclimatization to the laboratory conditions.

Extracts & Standards Used:

Extract used: *Annona squamosa linn* (Root) Ethanolic extract.

Standard Used:

Ranitidine HCL: 20 mg/kg b.w.

Drugs, viz, Ranitidine HCL and the test extract of *Annona squamosa linn* (Root) were suspended in 0.5% CMC and used for anti-ulcer studies. Each drug suspension was freshly prepared just before administration.

Preparation and Administration of Doses:

The extract was solubilized in 0.5% Carboxy Methyl Cellulose prior to experimental use to obtain the desired concentrations (200 and 400 mg/kg body weight) in 1 ml. The test substances were administered in a single dose using a gastric intubation tube after fasting for 3 to 4 hrs.

Anti-Ulcer Activity: [12-15]

Aspirin Induced Gastric Ulcers:

Albino rats were divided into four groups of six animals each. The weight of the animals chosen was between 150 and 180gms. The animals were fasted 36 hrs prior to the commencement of the experiment but were allowed free access to water.

- Group I (control): 0.5% CMC
- Group II: 20mg/kg Ranitidine HCL.
- Group III: ethanolic extract at dose 400mg/kg.
- Group IV: ethanolic extract at dose 200mg/kg.

All the animals received 200mg/kg of aspirin orally to the rats. In the treatment group, drugs were administered orally 1hr before the administration of aspirin. After 2hrs of treatment with aspirin, animals were sacrificed by an excess dose of ether. The stomachs were removed, opened along the greater curvature and examined for lesions. Lesions severity was determined by ulcer index. The ulcers were scored according to the following scale:

- Normal Coloration – 0
- Red Coloration – 0.5
- Spot Ulcer – 1
- Hemorrhagic Streaks – 1.5
- Ulcer - 2
- Perforation - 3

Mean ulcer score for each animal will be expressed as ulcer index. The percentage of ulcer protection was determined as follows:

$$\% \text{ Protection} = \frac{\text{Control Mean Ulcer Index- Test Mean Ulcer Index}}{\text{Control Mean Ulcer Index}} \times 100$$

Stati

Statistical analysis was carried out using Graph Pad Prism5 software version 5.04 (Graph Pad prism software Inc.) The values were expressed as mean ± SEM. The statistical analysis was carried out by one way analysis of variance (ANOVA) followed by Dunnet's t-test. P values< 0.05 were considered significant.

Pylorus Ligation Induced Gastric Ulcers:

Rats were divided into four groups of six animals each. All the animals selected for the study were of weight between 200-250gms.

- Group I (control), received, 0.5% CMC.
- Group II (reference standard) was treated with 20mg/kg Ranitidine HCL.
- Group III treated with 400 mg/kg ethanol extract.
- Group IV was treated with 200mg/kg ethanolic extract.

Animals in all the groups were fasted for 36 h after the respective assigned treatment and were anaesthetized with anesthetic ether. The abdomen was opened by a small midline incision below the xiphoid process and pylorus portion of stomach was lifted out and ligated. Precaution was taken to avoid traction to the blood supply. The stomach was sutured with interrupted sutures. Animals were allowed to recover and stabilize in individual cages and were deprived of water during post-operative period. Four hours after the pyloric ligation, the animals were sacrificed by an excess dose of ether. The stomach was carefully removed and the

gastric contents were collected. The gastric juice was centrifuged at 1000rpm and gastric volume was measured. Free and total acids of the supernatant were determined by titration with 0.1 N NaOH and expressed as mEq/ L /100 gms. The stomach was cut open along the greater curvature and pinned onto a soft board for evaluating the gastric ulcers and to calculate ulcer index. Ulcer scoring is done according to the scale mentioned below.

Ulcer Index:

After the incision of the stomach at the greater curvature the ulcers were observed. And the number of ulcers was counted using a magnifying glass and the diameter of the ulcers were measured using vernier calipers. The following arbitrary scoring system was used to grade the incidence and severity of lesions.

- Normal coloration – 0
- Red coloration – 0.5
- Spot ulcer – 1
- Hemorrhagic streaks – 1.5
- Ulcer - 2
- Perforation - 3

Determination of Free Acidity and Total Acidity:

The gastric contents were centrifuged at 1000rpm for 10mins. 1ml of supernatant was diluted with 9ml distilled water. A volume of 2ml diluted gastric juice was treated with 0.1 N sodium hydroxide run from a micro burette using 3-4 drops of Topfer's reagent as indicator until a canary yellow colour was observed. The volume of NaOH run down was noted. This corresponds to free acidity.

Further, 2-3 drops of phenolphthalein was added and titrated with NaOH until pink colour was restored. This gives total acidity. Free acidity and Total acidity are expressed in terms of ml of 0.1N HCl per 100 gms of gastric contents. This is the same as mEq/lit. [16] Acidity may be calculated by using the following formula:

$$\text{Acidity} = \frac{\text{Volume of NaOH} \times \text{Normality of NaOH}}{0.1} \times 100$$

Histopathological Evaluation:

The gastric tissue samples were fixed in neutral buffered formalin solution for duration of 24 hrs. Sections of tissue from stomachs were examined histopathologically to study the ulcerogenic and/ or anti-ulcerogenic activity of ethanolic extract of ***Annona squamosa linn*** **(Root)**. The tissues were fixed in 10% buffered formalin and were processed using a tissue processor. These sections were stained with hematoxylin and eosin using routine procedures. The slides were examined microscopically for Pathomorphological changes such as congestion, haemorrhage, oedema and erosions using an arbitrary scale for the assessment of severity of these changes. [17]

Biochemical studies:

The ulcer induced part were utilized to perform the different biochemical studies for the assessment of myeloperoxidase, catalase (CAT), superoxide dismutase (SOD), lipid peroxidation (malonaldehyde MDA), protein carbonyl (PCO), and MPO.[18-21]

RESULTS:

Results of Preliminary Phytochemical Evaluation:

The colour of the Alcoholic test extract (Ethonolic extract of ***Annona squamosa linn*** **(Root)**) was found to be dark green in colour and the consistency was found to be sticky. The extracts were subjected to phytochemical screening for the presence of type of phyto-constituents. The phytochemical screening revealed that ethanolic extract contains resins, alkaloids, Phytosterols, Phenols and Flavonoids. Of the phytosterols, the ones identified were triterpenes. The results has been tabulated in the Table No.1 showing various phytoconstituents in the extract.

Table No. 1: Various Phytoconstituents in the Extract

Phytoconstituents	Ethanolic Extracts
Carbohydrates	+
Glycosides	-
Alkaloids	+
Phyto steroids	-
Flavonoids	+
Protein and amino acids	-
Saponin	-
Phenols & tannins	+
Antha quinone Glycosides	-
Triterpenoids	+

(-) Represents Absence; (+) Represents Presence.

Acute Toxicity Study:

Up to a dosage level of 2000 mg/kg body weight, the ethanolic extract of Annona squamosa *linn* (Root) did not cause any toxic symptoms or fatality. During the observations up to a 24-hour period for mortality, there

was no evidence of toxicity or alteration in behavioral pattern. As a result, the extract was deemed safe for pharmacological analysis. The biological assessment was conducted using dosages of 200 and 400 mg/kg.

Toxicological evaluations of ethanolic extract of *Annona squamosa linn. (Root):*

Study on the effects of Annona squamosa *linn*. (Root) ethanolic extract on mice revealed that, when given orally at doses of up to 2000 mg/kg, the extract did not cause any toxicity or death in the mice.

Table No 2: Acute Oral Toxicity Study (425) Observations.

S.NO	Response	
1	Alertness	N
2	Grooming	A
3	Anxiety	A
4	Roaming	N
5	Sniffing	N
6	Tremors	A
7	Convulsion	A
8	Depression	N
9	Gripping strength	N
10	Scratching	A
11	Defecation	A
12	Writhing	N
13	Pupils	N
14	Urination	N
15	Salivation	N
16	Skin colour	N
17	Lacrimation	N

N-Normal, A-Absent

Anti-Ulcer Evaluation:

Aspirin Induced Gastric Ulcers:

Table 3 displays the apparent effect of Ranitidine HCL and Extract on the Ulcer Index and the level of mucosal damage in the stomach. In Group I (control animals), oral aspirin treatment resulted in distinctive lesions in the glandular area of the rat stomach, which showed as elongated bands of thick, black, and dark red lesions. Group II animals pretreated with the standard medicine, Ranitidine HCL, demonstrated significant protection from ulcers in the stomach mucosa, and in Group III and IV, EEAS considerably decreased the ulcer Index at 400mg/kg and 200mg/kg dosages, respectively. Ranitidine HCL, as a reference,

provided ulcer prevention. Pretreatment considerably decreased the severity of haemorrhage and lesions, demonstrating EEAS' protective impact.

Table No. 3: Results of Anti-Ulcer Evaluation by Aspirin Induced gastric Ulcers

Groups	Ulcer Index	% Protection
Group I- Control	12.24±0.06	--
Group II- Standard (Ranitidine HCL)	3.49±0.08***	71.48 %
Group III – *Annona squamosa linn.* Extract 400mg	4.5±0.10***	63.23%
Group IV – *Annona squamosa linn.* Extract 200mg	5.72±0.05*	53.26 %

All values represent Mean ± SEM, n=6 in each group. P < 0.05. Control group (Group I) is compared with standard and extract doses, * represents significance.

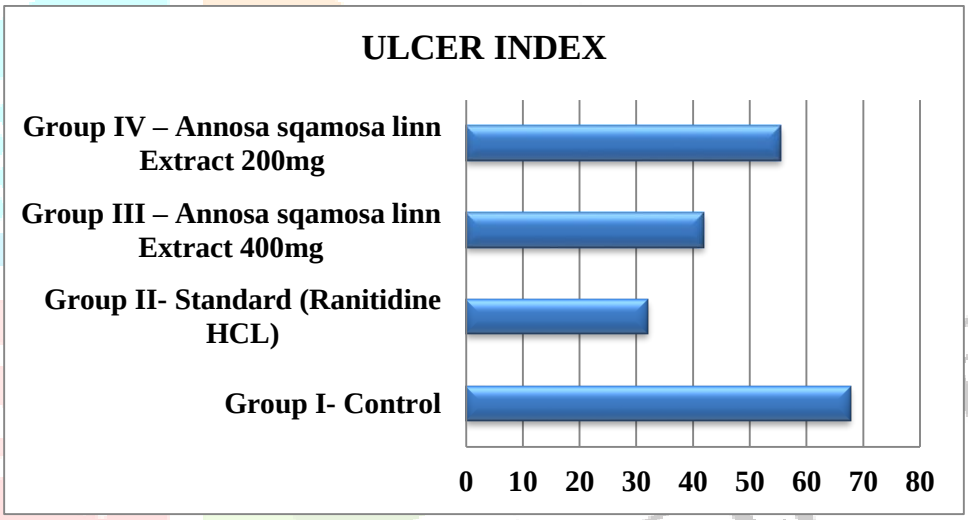

Figure 1: Graphical Representation of Anti-Ulcer Evaluation by Aspirin Induced gastric Ulcers

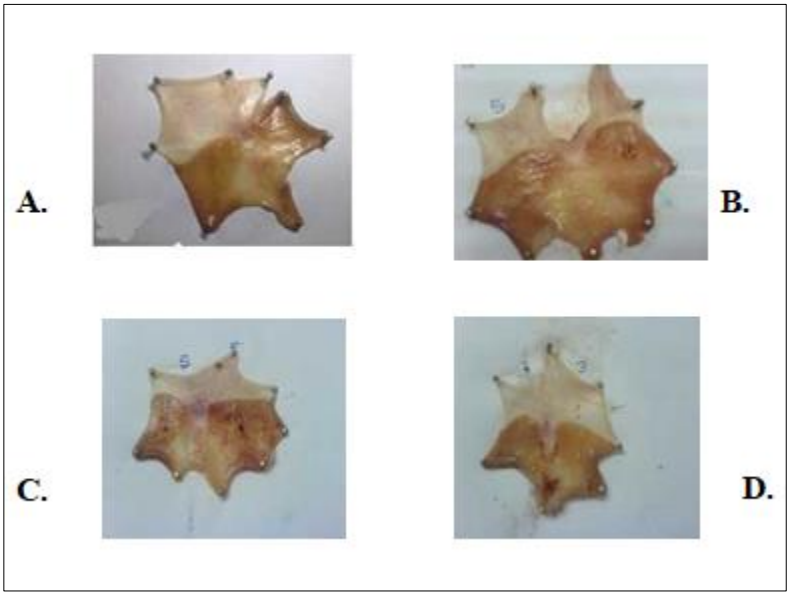

Figure 2: Aspirin Induced Ulcers and their Treatment (A) – Control; (B) – Standard; (C) – Extract 400mg/kg; (D) – Extract 200mg/kg

Pylorus Ligation Method:

In the pyloric ligation induced ulcer model, oral administration of EEAS at two distinct dosages (200mg/kg and 400mg/kg) resulted in a substantial reduction in ulcer index, stomach volume, free acidity, and total acidity when compared to the control group. In comparison to the control, EEAS showed a protection index of 52.3% and 36.28% at doses of 400mg/kg and 200 mg/kg, respectively, whereas Ranitidine HCL, the reference standard medicine, showed a 70% protection percentage. The ulcer protection percentage of EEAS at 200mg/kg is 36.28%, which is regarded less significant in the context of the research.

Table No. 4: Results of Anti-Ulcer Evaluation by Pylorus Ligation Method

Groups	Ulcer Index	% Protection
Group I- Control	11.3 ± 0.11	--
Group II- Standard (Ranitidine HCL)	3.39 ± 0.07***	70%
Group III – *Annona squamosa linn.* Extract 400mg	5.48 ± 0.07***	52.3%
Group IV – *Annona squamosa linn.* Extract 200mg	7.2 ± 0.06*	36.28%

All values represent Mean ± SEM, n=6 in each group. P < 0.001. Control group is compared with standard and extract doses.

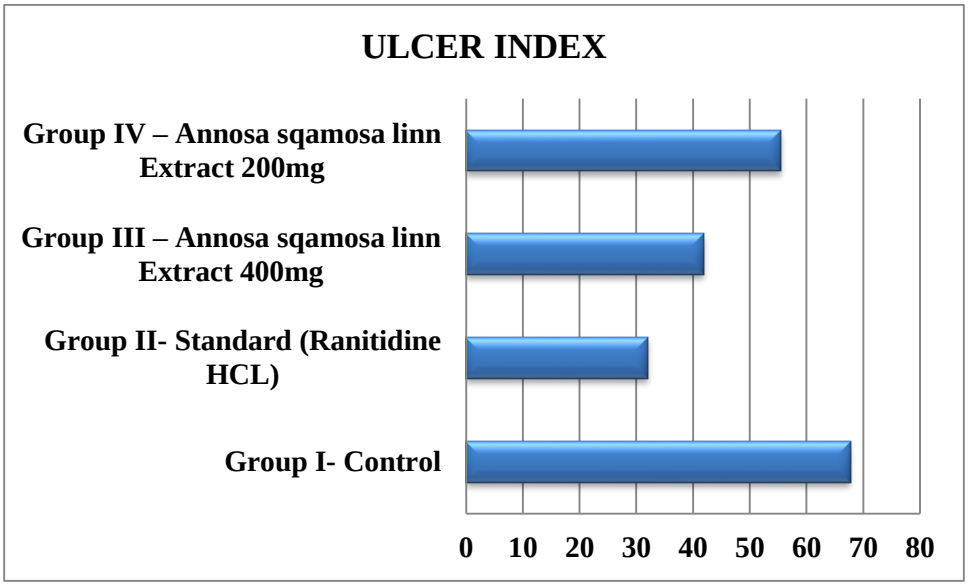

Figure 3: Graphical Representation of Anti-Ulcer Evaluation by Pylorus Ligation Method

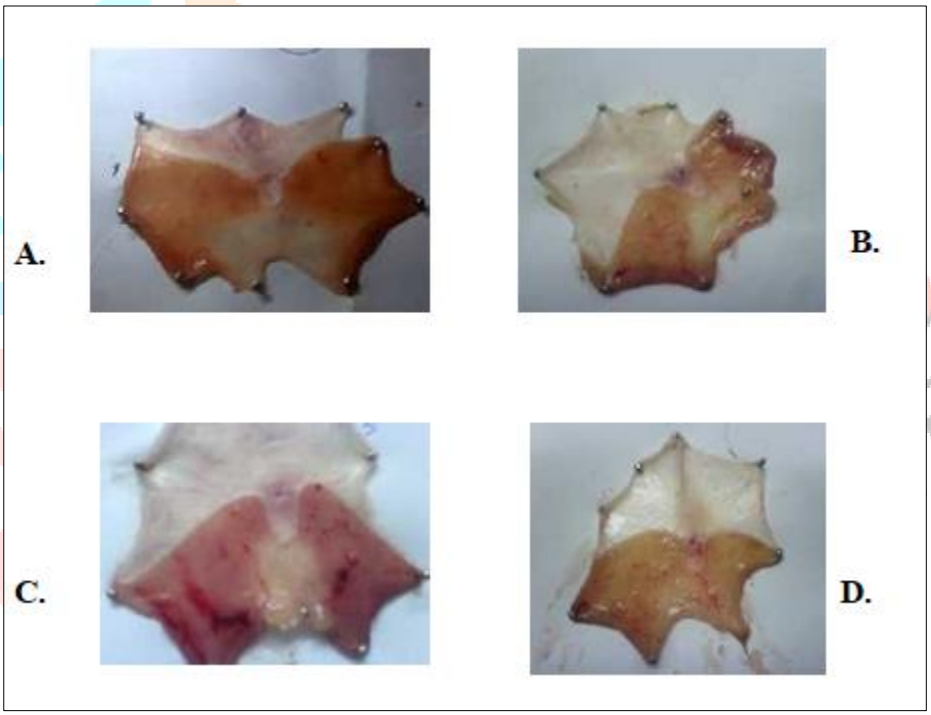

Figure 4: Pylorus Ligation Method and their Treatment (A) – Control; (B) – Standard; (C) – Extract 400mg/kg; (D) – Extract 200mg/kg

Histopathology Examination:

The photos and reports show a submucosal edema with mixed inflammatory infiltrate, including lymphocytes and neutrophils. The muscularis propria appears to be normal, and macrophage and neutrophil aggregation can be detected on the epithelial cell lining. In Group II, the conventional group demonstrated no stomach mucosal injury. The histological sections of group III treated with EEAS 400 mg/kg indicate mucosal moderate edema, scattered chronic inflammatory infiltration, and congested vascular spaces. The

muscularis propria seems normal. The slice of IV-group rats demonstrates mucosal edema with inflammatory infiltrate. The muscularis propria looks to be normal.

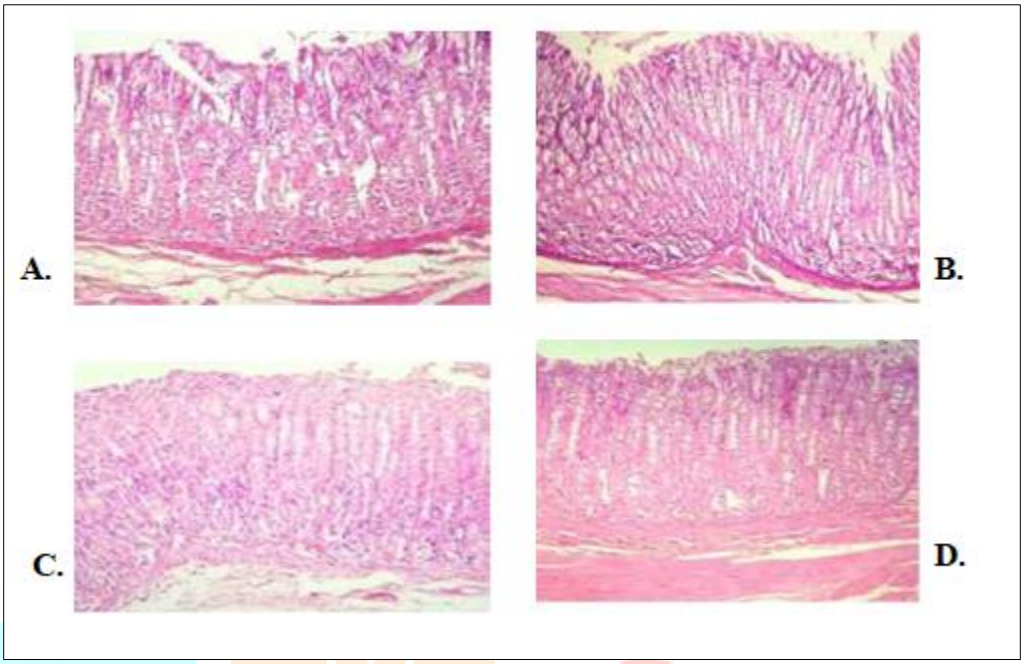

Figure 5: Histopathological Study of Aspirin Induced Ulcers and their Treatment

(A) – Control; (B) – Standard; (C) – Extract 400mg/kg; (D) – Extract 200mg/kg

The histological analysis of the rats' stomachs revealed a more detailed picture of the gastric lesions and mucosal damage. Acute stomach ulceration was seen in Group I, while Group (A) (control group rats) had mucosal ulcers comprised of necrosis, cellular debris, neutrophils, and degenerated epithelial cells. Group II(B) includes stomach mucosa with intact epithelium, lamina propria, and muscularis mucosa. Group (C) demonstrates an intact mucosa with lots of regenerating epithelial cells. Group (D) exhibits localised mucosal ulceration composed of degraded cells and a few regenerated epithelial cells.

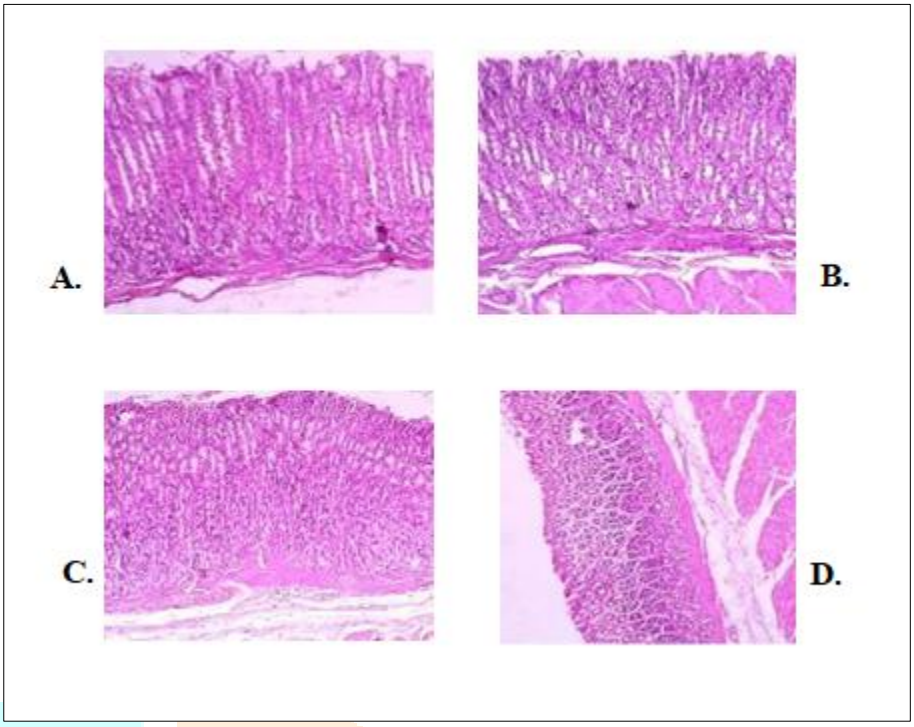

Figure 6: Histopathological Study of Pylorus Ligation Method and their Treatment

(A) – Control; (B) – Standard; (C) – Extract 400mg/kg; (D) – Extract 200mg/kg

Gastric volume, Free Acidity and Total Acidity:

Table 5 summaries the effects of several acid secretory parameters such as stomach volume, pH, free acidity, and total acidity of an ethanolic extract of Annona squamosa *linn* on pylorus ligation-induced gastric ulcers in rats. The control group showed considerably higher estimates of acid secretory parameters. EESP administration resulted in substantial ($p < 0.001$) reductions in all parameters, equivalent to the standard medication Ranitidine HCL 20 mg/kg. In the control group, the average gastric juice was 3.52ml. Ranitidine HCL, the standard medicine, reduced the mean stomach capacity (1.28ml), which was statistically significant. Aside from the standard, ethnologic extract exhibited a reduction in mean gastric juice at both 400 and 200mg/kg. The extracts lowered the average gastric juice volume to 1.59 and 1.86ml, respectively. The test extracts demonstrated a reduction in gastric juice volume compared to the control group, indicating an anti-secretary mechanism. This indicates the dose-dependent action of EEAS.

Table No. 5: Results of Gastric volume, Free Acidity and Total Acidity

Group	Gastric Volume	pH	Free Acidity	Total Acidity
Control	3.52 ± 0.02	1.41 ± 0.12	55.01 ± 2.28	67.79 ± 1.31
Std (Ranitidine HCL)	1.28±0.05***	5.21±0.13***	20.90±0.76***	32.06±3.316***
Extract 400mg	1.598±0.03**	3.5±0.08***	29.86 ± 0.77**	41.96±0.715***
Extract 200mg	1.86 ± 0.04**	4.63±0.14***	39.66 ± 1.14*	55.56 ± 0.99***

All values represent Mean ± SEM, n=6 in each group. P < 0.001. Control group is compared with standard and extract doses.

Biochemical Studies:

Biochemical experiments were performed on several enzymes in ulcerative colitis. The antioxidant properties were investigated by measuring the antioxidant enzyme Catalase (CAT). Biochemical experiments were performed on several enzymes in ulcerative colitis. The antioxidant properties were investigated by measuring the antioxidant enzyme Catalase (CAT). Catalase is the first-line defense enzyme against free radicals. The observation indicates that Catalase activity has greatly risen. This demonstrates that the formulation can minimise the number of reactive free radicals, which may cause tissue oxidative damage.

LPO levels were substantially higher in the current investigation, indicating that UC rats were under more oxidative stress than others. Acetic acid produced ulcerative colitis, as seen in the figure, with elevated LPO levels. Myloperoxidase (MPO) is an enzyme that is mostly present in neutrophil granules. It is an effective marker of inflammation, tissue damage, and neutrophil infiltration in gastrointestinal tissue. Pretreatment with the formulation reduced polymorphonucleur infiltration, as evidenced by a substantial reduction in MPO activity. The increase in SOD activity seen in peptic ulcer-induced groups suggested that the antioxidant defense system was functioning. When compared to test groups I and II, SOD in the control group (non-treated) increased. Increased levels of TNF (tumor necrosis factor) produced epithelial cell necrosis edema and neutrophil infiltration, as evidenced by histological examinations. TNF expression in animal macrophages in peptic tissues is considerably higher than in controls in a peptic ulcer model. The formulation considerably reduced the wet weight of distal peptic segments, the gross lesion score, and the generation of TNF. TNF can be mediated by either inhibiting or activating these pro-inflammatory mediators.

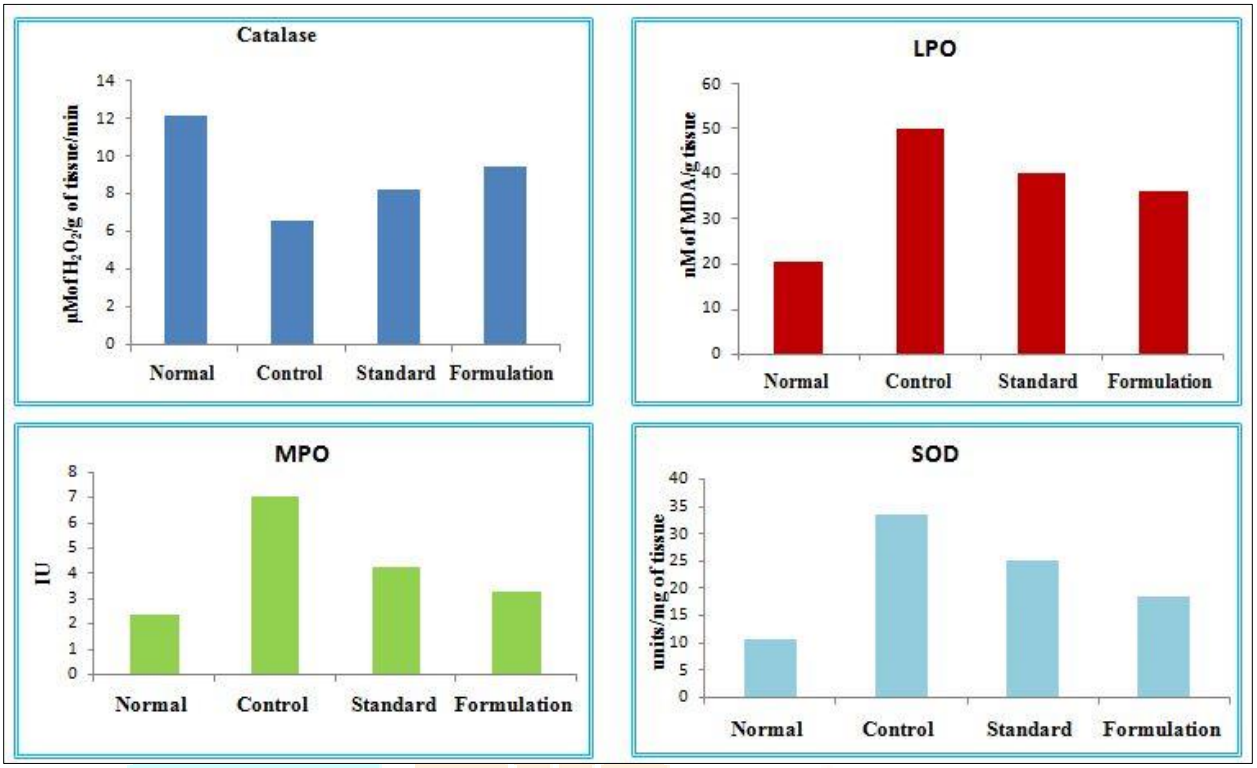

Figure 7: Various Biochemical Study in Peptic Ulcer

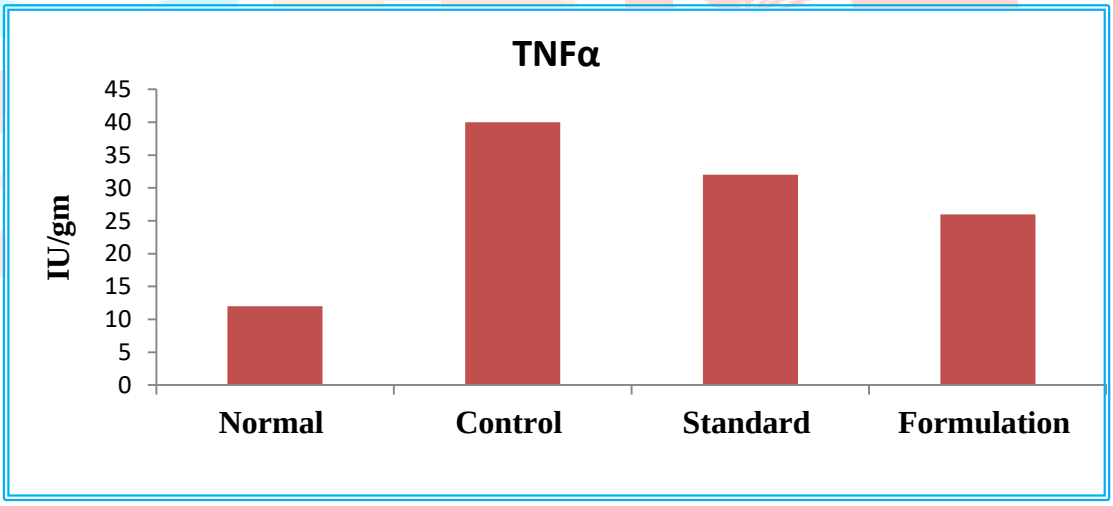

Figure 8: TNFα activity in Peptic Ulcer

Acetic acid promoted ROS production, as seen by elevated LPO levels, which overwhelmed SOD and CAT. Thus, the formulation has the potential to suppress free radical formation, as demonstrated in this study by restoring the redox state of the peptic mucosa, providing another rationale for anti-ulcerogenic efficacy. In addition, its anti-inflammatory and antioxidant properties may contribute to its favourable impact against peptic ulcer disease. The study assessed Catalase, SOD, MPO, and TNFα. The findings for the created formulation group were significant when compared to the Control and Standard groups.

DISCUSSION

This study investigates the anti-ulcer activity of the ethanolic extract of Annona squamosa *linn* (Root) against Aspirin induced and Pylorus ligated ulcers. Gastric ulcer disease is caused by an imbalance between mucosal defense factors and injurious factors, such as acid and pepsin. Ulcers caused by pylorus ligation result from increased accumulation of gastric acid and pepsin, leading to auto digestion of gastric mucosa and breaking down the gastric mucosal barrier. NSAIDs are frequently associated with peptic ulcers, and their effects are mediated systemically through suppression of the constitutive form of cyclooxygenase-1 (COX-1) in the mucosa and decreased production of cytoprotective prostaglandin (PGE2 and PGI). The anti-ulcer effect is supported by the decrease in aggressive factors like gastric volume, decrease in free and total acidity, and an increase in resistance factors like pH. The anti-ulcer agent may protect the mucosa from acid effects by selectively increasing prostaglandins, which have a vital protective role. The mucosal defense mechanism may be due to the epithelial cells of the gastric mucosa, which are impermeable to H+ ions and form a physical barrier. The ethanolic extract of Annosa sqamosa linn (Root) was evaluated using the aspirin induced ulcer model, and the oral administration of the extract at doses of 200 and 400mg/kg exhibited dose-dependent inhibition percentages of 53.26% and 63.23% respectively compared to the ulcer control. The standard drug Ranitidine HCL (20mg/kg) exhibited percentage inhibition of 71.48% when compared with the ulcer control. The study also examined the antioxidant effect of the extract on Catalase, SOD, MPO, and TNFα. The results for the tested group were significant compared to the control group and the standard group. The anti-ulcerogenic activity of the extract may be due to its ability to inhibit free radical generation and restore the redox state of peptic mucosa.

CONCLUSION:

This highlights the potential of Annona squamosa linn (Root) as a promising natural remedy for ulcers and inflammation. Further research is warranted to elucidate its mechanisms of action and to explore its therapeutic applications in clinical settings. The results indicate a promising potential for the extract as an effective treatment for ulcers. Further studies are needed to explore the underlying mechanisms and to determine the optimal dosage and administration protocols for achieving the best therapeutic outcomes. Additionally, long-term safety and efficacy of the extract should be evaluated to ensure its suitability for clinical use in the management of ulcer-related conditions.

Conflicts of Interest:

The authors declare no conflict of interest

Acknowledgement:

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