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Prophylactic Anti-Ulcer Effect of Aqueous Leaf Extract of *Mormodica foetida* (Schumach & Thonn) Against Indomethacin-Induced Ulcers in Wistar Rats

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ABSTRACT

Peptic ulcer disease (PUD) remains a global health concern affecting millions worldwide, with significant morbidity and mortality. The limitations and side effects of existing treatments necessitate exploring alternative remedies. *Momordica foetida*, a traditional plant with reported medicinal properties, holds the potential for antiulcer activity due to its phytochemical constituents. This study evaluated the prophylactic anti-ulcer effects of the Aqueous Leaf Extract of *Momordica foetida* using an indomethacin-induced gastric ulcer model in rats. Aqueous leaf extract of *Momordica foetida* was administered at doses of 250 mg/kg and 500 mg/kg, while omeprazole served as a standard anti-ulcer drug. Ulcer index, oxidative stress markers, and histopathological changes were assessed. Aqueous leaf extract of *Momordica foetida* exhibited a dose-dependent reduction in ulcer index, with the 500 mg/kg dose offering superior protection. Indomethacin-induced ulceration was linked to oxidative stress and impaired antioxidant enzyme activity. Microscopic analysis revealed improved gastric mucosa in the aqueous leaf extract of *Momordica foetida*-treated rats, especially at 500 mg/kg. The study highlights the significant antiulcer potential of *Momordica foetida*, supporting its traditional use. These findings contribute to the growing body of evidence suggesting the therapeutic value of natural remedies like *Momordica foetida* in managing peptic ulcers.

***Keywords*:** *Mormodica foetida*, antiulcer, prophylactic, indomethacin-induced ulcer, medicinal plants, phytochemical constituents.

Introduction

Peptic-ulcer disease (PUD) is a common gastrointestinal disorder characterized by lesions in the stomach or proximal duodenum, often induced by excessive stomach acid, leading to the denuded mucosa that can extend into deeper layers of the digestive tract.[1] The clinical presentation of PUD includes abdominal stress, frequently in the upper abdomen and epigastric region, along with superficial or deep erosions that may perforate the stomach (gastric ulcer) or the small intestine (duodenal ulcer).[2]

Despite medical advancements, PUD remains a significant global health concern, affecting approximately 8 to 10% of the world's population.[2] Annually, four million individuals worldwide are diagnosed with PUD.[3] In Western Uganda, PUD affects 11.4% of the population; however, this prevalence may be underestimated due to a substantial number of patients seeking treatment from traditional healers.[4] The impact of ulcers is profound, significantly impinging on the quality of life for millions, and contributing to morbidity and mortality rates.[5] Notably, ulcers are responsible for 15 out of every 15,000 gastrointestinal-related deaths annually, indicating their severity and importance.[6,7]

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The primary causative factor of PUD is the bacterium *Helicobacter pylori*, complemented by lifestyle elements such as diet, smoking, alcohol consumption, and stress.[8] Additional contributors include anticoagulant and corticosteroid use, non-steroidal anti-inflammatory drugs (NSAIDs)' consumption, and a history of PUD, accompanied by factors like Tumor Necrosis Factor (TNF), Reactive Oxygen Species (ROS), histamine release, apoptosis incidence, and bile acid secretion.[5,6]

While the current management of PUD involves drugs like H_2-blockers and proton pump inhibitors to reduce gastric acid production, as well as sucralfate and similar agents to enhance mucosal protection, these medications are associated with adverse effects and limitations.[2,6] Therefore, there is a growing need to explore alternative treatment options with fewer side effects and enhanced cost-effectiveness, potentially sourced from herbal medicines.[9]

One promising candidate is *M. foetida*, a traditional plant belonging to the Cucurbitaceae family and widely distributed throughout tropical Africa.[10] Locally known as "bitter cucumber," this plant has been used in traditional medicine to manage various conditions including peptic ulcers.[11] Despite its extensive use, scientific validation of its antiulcer potential remains limited. Hence, the present study investigated the prophylactic anti-ulcer potential of the Aqueous Leaf Extract of *Momordica foetida* (ALEMF) in a rat model with indomethacin-induced gastric ulcers.

The persistent prevalence of peptic-ulcer disease and the limitations of current treatments underscore the importance of exploring alternative therapeutic options. *M. foetida*, a traditional plant with historical use in managing various ailments, offers a promising avenue for investigation into its antiulcer property. This study aims to investigate the prophylactic antiulcer potentials of aqueous leaf extract of *Momordica foetida*.

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Materials and Method

Plant Collection and Identification

The leaves of *M. foetida* were obtained from *Rukararwe* forest Bushenyi district, Uganda, in July 2022. The leaf samples were identified and authenticated by Dr. Olet Eunice of the Department of Botany, Mbarara University of Science and Technology, Uganda, where a voucher specimen (SN00894) was deposited.

Extraction of Plant Material

The fresh leaves of *M. foetida* were air-dried until constant weight was obtained. The dried leaves were made into powdered form with the aid of a mortar and pestle. The powdered leaf material was soaked in water in the ratio 1:10 (w/v, g/ml) for 72 hours, with intermittent agitation. The solution was sieved, and filtered with Whatman's filter paper; the filtrate was concentrated in an oven set at 50ºC.[12] The extract was placed in a desiccator until when it was ready for use. The extract was reconstituted with distilled water before being administered to the experimental rats.

Extract Yield

The percentage yield of the extract was obtained after extraction using the formula;

$$Percentage\ yield\ (\%) = \frac{\text{weight of extract}}{\text{weight of powder}} \times\ 100$$

Materials and Chemicals

The materials that were used for this study included; indomethacin, omeprazole, (Bliss Pharma, India), normal saline, distilled water, ALEMF, eosin and haematoxylin, mortar and pestle, Whatman's filter paper, a microscope, centrifuge, spectrophotometer.

Experimental Animals

Wistar rats weighing 150 to 200 g were used. The rats were sourced from the Pharmacology and Toxicology Departmental Animal House Facility at Kampala International University, Western Campus, Ishaka-Bushenyi. They were housed in plastic cages and maintained under typical environmental conditions; optimal temperature of 25°C with humidity levels of 50%. Additionally, the rats were provided with standard rat food and had unrestricted access to water.[8,13]

Animal Grouping and Dosing

Twenty-five rats were randomly divided into five groups (n=5). The animals were pretreated for 14 days before the ulcer induction. Groups I and II animals received distilled water, 10 mL/kg; group III was administered omeprazole 20 mg/kg; while groups IV and V were administered graded doses of aqueous leaf extract of *Momordica foetida* (250 and 500 mg/kg) respectively, for 14 days. The animals were fasted 24 hours before the ulcer induction on day 15.

Induction and Quantification of Gastric Ulcers in Experimental Animals

Rats were denied food but given access to water 24 hours before ulcer induction. The rats were administered with a single oral dose of indomethacin (25 mg/kg body weight). Ulcerations manifested 4 hours after indomethacin administration in various degrees. Grading the ulcers was done on a 0–3 scale, based on the severity of hyperemia and hemorrhagic erosions:

0- normal stomach,
0.5-red coloration,
1- spot ulcer,
1.5- hemorrhagic streaks,
2- ulcers greater than 2 mm but less than 3.5 mm
3- ulcers greater than 3.5 mm

Ulcer index = total number of ulcers + severity of ulcer

Healing index [%] = $\frac{Control[ulcer\ index] - Drug\ [ulcer\ index]}{control[ulcer\ index]} \times 100$

Isolation of Stomach and Grading of Ulcers

On day 15, four hours after ulcer induction, the rats were sacrificed through cervical dislocation and the abdomen opened. The stomach was excised and opened along the greater curvature. The stomach was washed with normal saline and the ulcer scored.

Preparation of Stomach Homogenate

Whole stomach tissues were crushed in a mortar right after ulcers were scored. The ground tissues were homogenized in ice-cold 0.1 M phosphate buffer (1:4 w/v. pH. 7.4) and followed by centrifugation at 2500 rpm for 10 mins. Supernatants were then frozen at - 20ͦ C to the maximum to release enzymes located in the tissue.[14]

Histopathological Examination

The stomach was placed in 10% neutral buffered formalin for 24 hours to ensure fixation of the tissue. The tissues were trimmed and processed using an automated vacuum tissue processor (TP-1020). The tissue processing stages included dehydration in graded ethanol (70%, 80%, 90%, and absolute ethanol), clearing using xylene, infiltration using molten paraffin wax, and embedding in paraffin to ensure the hardening of the tissue for microtomy. The processed tissues were cut at a thickness of 6µ using a Leica RM2245 semi-automated rotary microtome to obtain tissue ribbons, which were subsequently placed on a slide and stained using hematoxylin and eosin (H & E). The stained slides were examined and photo-micrographs were taken using Leica's Upright DM1000 Research Microscope. Then histopathological features like erosions, hemorrhage, edema, inflammation and necrosis were evaluated by a pathologist.[16]

Assay of Anti-Oxidant Indices

Protocol for Superoxide dismutase activity was followed,[17] 15 mL tubes were obtained and labeled accordingly. Blank, 2.5 mL of 0.05 M carbonate buffer pH. 10.2 was added in the tube, 200 µL of the supernatant was added and this was used to equilibrate the spectrophotometer. Sample tubes, 2.5 mL of 0.05 M carbonate buffer pH. 10.2 was added in the 15 mL tube, 200 µL of supernatant was added, 300 µL of freshly prepared 0.0003 M of epinephrine was quickly added and mixed. The absorbance at 480 mm was read and recorded at 30 seconds and 180 seconds against the blank. Reference 15 mL tube, add 2.5 mL of 0.005 M carbonate buffer to the tube, then 200 µL of distilled water, then 300 µL of epinephrine. The absorbance was read at 30 and 180 seconds against the blank. The activity of Superoxide Dismutase (SOD) enzyme (as % inhibition) was calculated as,

$$\text{Percentage inhibition} = \frac{absorbance\ of\ sample}{absorbance\ of\ blank} \times\ 100$$

Where absorbance of sample was calculated thus: $\frac{\text{Absorbance @ 180s} - \text{Absorbance @ 30s}}{2.5}$

Statistical Analysis

The results were analyzed as Mean ± Standard Error of the Mean (SEM). The statistical analysis was conducted for Superoxide Dismutase Activity using a one-way ANOVA, followed by Dunnett's multiple comparison tests. Ulcer scoring was assessed using a non-parametric test, specifically the Kruskal-Wallis test. All statistical analyses were performed with GraphPad Prism software version 8. A significance level of $p \leq 0.05$ was used to determine statistical significance.

Ethical Consideration

Ethical approval was obtained from the Institutional Research and Ethics Committee for Biosafety (IREC) of Kampala International University- Western Campus (Number: KIU-2023-07). Handling of animals was done with care while carrying out the experiment to minimize pain and suffering. Clean cages with enough light and ventilation, water, and food were provided to the rats. All carcasses were disposed of by incineration. Chemical wastes were disposed of as protocol by the Kampala International University Pharmacy Laboratory guideline.

Results and Discussion

This study aimed to assess the prophylactic anti-ulcer property of the Aqueous Leaf Extract of *Momordica foetida* (ALEMF) in a rat model with indomethacin-induced gastric ulcers. Doses of 250 and 500

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mg/kg were chosen based on our prior investigation, which determined an LD_{50} exceeding 5,000 mg/kg.[13] Omeprazole was utilized as the standard reference for its established anti-ulcer effect. NSAIDs are commonly used for pain relief in various conditions but are associated with the generation of oxygen free radicals that contribute to mucosal injury.[18] Indomethacin, an NSAID, inhibits gastric cyclooxygenase, leading to decreased prostaglandins formation, and serves as a standard agent for inducing experimental gastric ulcers.[19]

The percentage yield of the aqueous leaf extract of *Momordica foetida* obtained after extraction was 10%. Extract yields can provide insights into the efficiency of an extraction process. Higher yields typically indicate a more efficient process, as more of the desired substance is being extracted from the plant material. The methanol extract yielded better than the ethanol extract, which was previously reported to be 5.7% yield.[20]

The effects of the aqueous leaf extract of *Momordica foetida* on the ulcer score and percentage inhibition against ulcers in the experimental animals are shown in Figure 1 and 2 respectively. The oral administration of aqueous leaf extract of *Momordica foetida* at doses of 250 and 500 mg/kg significantly protected the animals from ulcers by indomethacin. The 500 mg/kg had the highest protective effect against ulcers. The 250 mg/kg effect was lower than that of the standard drug (omeprazole).

The aqueous leaf extract of *Momordica foetida* was administered at doses of 250 and 500 mg/kg to evaluate its protective effects on gastric mucosa. The results indicated a dose-dependent reduction in ulcer index, with better protection observed at the 500 mg/kg dose compared to 250 mg/kg. This dose-dependent pattern of increased protection aligns with previous findings, including a study involving *Spondias mombin* in indomethacin-induced gastric ulceration.[14]

The histological examination of the gastric mucosa from the 10 mL/kg distilled water treated group revealed an intact gastric pit and intact gastric glands (Figure 4A). The group administered 10 mL/kg distilled water + indomethacin revealed intervillus hemorrhages in gastric mucosa, deep penetrating gastric mucosa erosion and desquamation (Figure 4B). The group administered omeprazole (20 mg/kg) + indomethacin showed improvement in the gastric mucosa with regions of intervillus hemorrhages in the gastric mucosa (Fig. 4C). The group administered aqueous leaf extract of *Momordica foetida* (250 mg/kg) + indomethacin showed intervillus hemorrhages in gastric mucosa and desquamation (Fig. 4D). The group administered ALEMF (500 mg/kg) + indomethacin showed improvement in the gastric mucosa showing intact gastric pit and intact gastric glands (Fig. 4E), Fig 3 (A-E), shows the macroscopic ulceration.

Macroscopic and microscopic examination supported the protective effects of aqueous leaf extract of *Momordica foetida.* Indomethacin-induced ulcers exhibited increased ulcer index, hemorrhagic lesions, and mucosal erosions, correlated with free radical formation and prostaglandin inhibition. The aqueous leaf extract of *Momordica foetida*-treated groups, particularly at the 500 mg/kg dose, demonstrated improved gastric mucosa with intact gastric pits and glands. The presence of intervillous hemorrhages and desquamation at the 250 mg/kg dose suggests a dose-dependent response of aqueous leaf extract of *Momordica foetida* for anti-ulcer effects. These findings align with prior research on indomethacin-induced gastric ulcers.[15]

Fig. 5 revealed the effects of the aqueous leaf extract of *Momordica foetida* on the SOD activity of the gastric mucosa in the indomethacin ulcerated Wistar rats. A significant reduction in the SOD activity was seen in the indomethacin-induced Wistar rats. Both doses of the extract showed significant improvement in these parameters ($p \leq 0.05$) against the indomethacin-treated group. The highest effect ($p \leq 0.01$) was observed in the standard control, Omeprazole.

Indomethacin-induced gastric ulceration is associated with inhibited prostaglandin synthesis and increased free radical formation. Indomethacin acts as an oxidant, initiating lipid peroxidation and ROS production, which damages tissues. The reduced activity SOD in indomethacin-induced ulcer rats contributes to facilitated lipid peroxidation and excessive free radical production, ultimately causing mucosal damage.[14]

Phytochemicals found in natural plants, such as the phenols, alkaloids, tannins, and flavonoids present in *Momordica foetida*, are known for their antioxidative properties. Phenolic compounds scavenge free radicals, chelate metals, reduce oxidative stress, and inhibit lipid peroxidation.[10] Flavonoids stimulate PG_{E2} formation in the gastric mucosa, while tannins possess anti-ulcer properties through their astringent and vasoconstrictive effects.[21]

Secondary metabolites detected in *M. foetida* are alkaloids, steroids, cardiac glycosides, tannins, phenolics, saponin, and flavonoids.[22] The protective effects of aqueous leaf extract of *Momordica foetida* against indomethacin-induced gastric ulcers can be assumed to be due to its phenolics and flavonoid constituents, as both phytochemicals are known for their anti-ulcer potentials.[14] This is consistent with another study on *M. foetida*, which highlighted its biochemical, nutritional, and medicinal properties.[22]

Conclusion

In conclusion, this study established that the aqueous leaf extract of *Momordica foetida* possesses significant antiulcer effects against gastric ulcers induced by indomethacin in rats. These findings substantiate the traditional use of *M. foetida* for ulcer management. However, further investigations are warranted to elucidate the precise mechanisms underlying the antiulcer activity of *Momordica foetida*.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

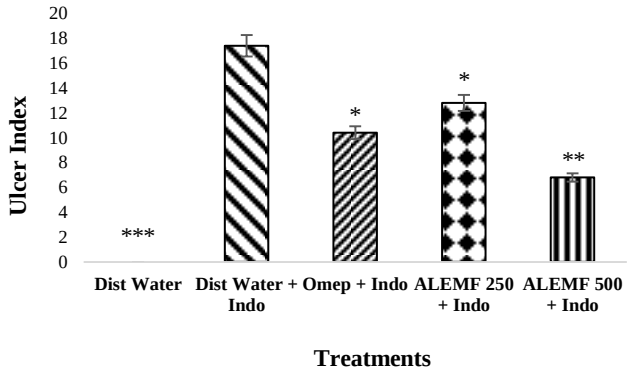

Figure 1: Ulcer Score
The results were analyzed as Mean ± Standard Error of the Mean. The statistical analysis was conducted using a non-parametric test (Kruskal-Wallis). * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$, against indomethacin treated group.

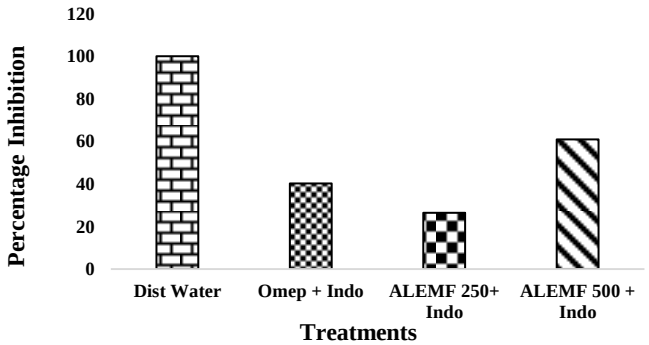

Figure 2: Percentage inhibition of ulcer

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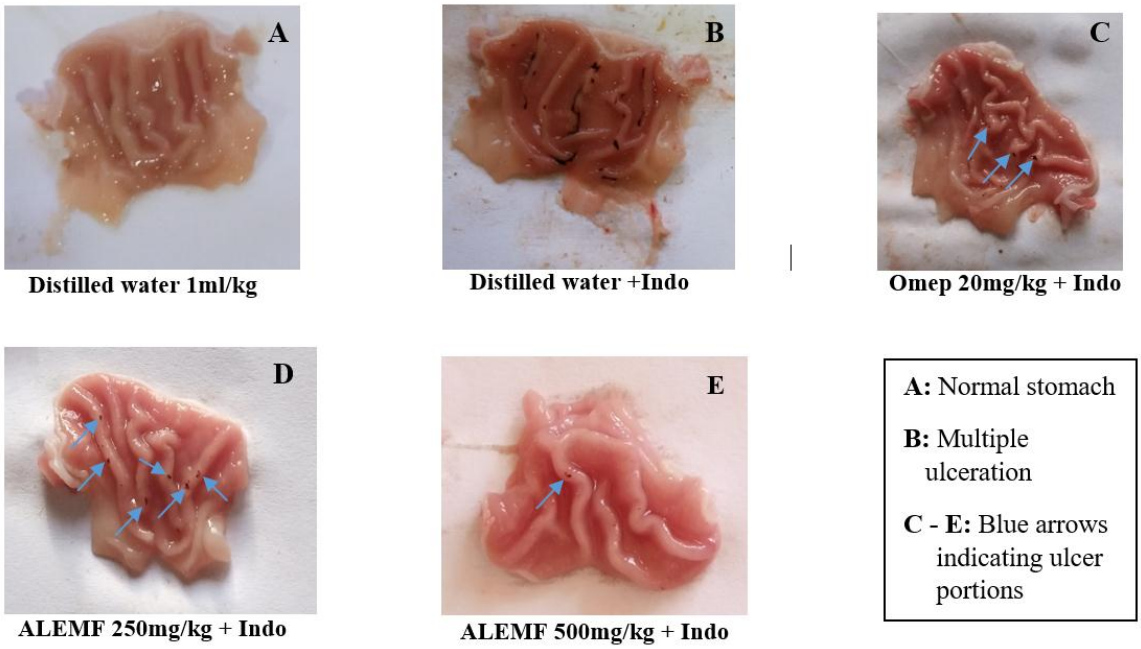

Figure 3: (A – E): Macroscopic evaluation of the ulcers: A, showing normal stomach without ulceration. B, showing multiple ulceration. C, D & E, blue arrows indicating ulceration.

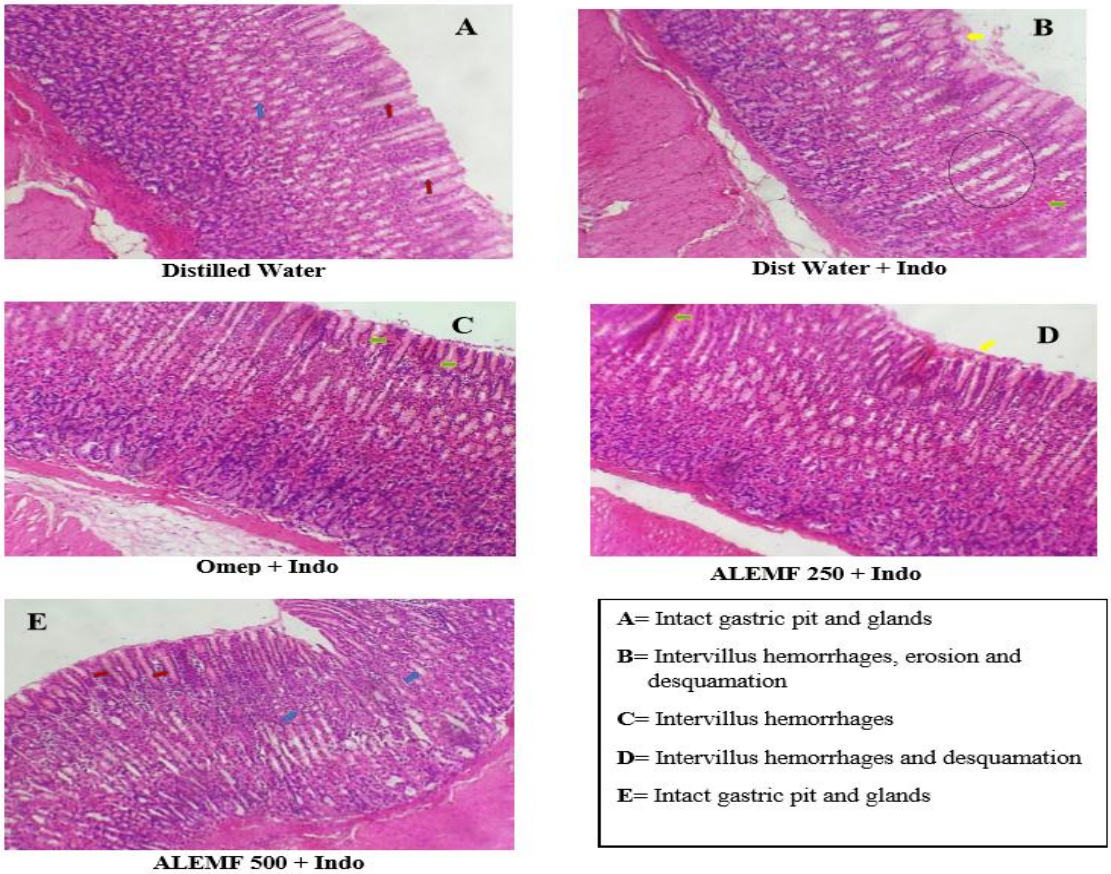

Figure 4: (A-E): Histological analysis of the mucosa lining of the stomach (H and E; ×100). A: Histology of the gastric mucosa showing intact gastric pit (red arrow) and intact gastric glands (blue arrow; B: Histology of the gastric mucosa showing intervillus hemorrhages in gastric mucosa (green arrow), deep penetrating gastric mucosa erosion (circled area) and desquamation (yellow arrow); C: Histology of the stomach showing improvement in the gastric mucosa with regions of intervillus hemorrhages in the gastric mucosa (green arrow); D: Histology of the gastric mucosa showing intervillus hemorrhages in the gastric mucosa (green arrow), and desquamation (yellow arrow); E: Histology of the stomach showing improvement in the gastric mucosa showing intact gastric pit (red arrow) and intact gastric glands (blue arrow).

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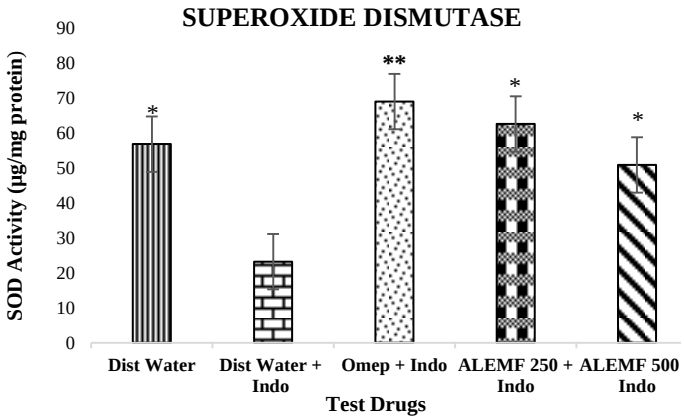

Figure 5: SOD activity
The results were analyzed as Mean ± Standard Error of the Mean (SEM). The statistical analysis was conducted using a one-way ANOVA, followed by Dunnett's multiple comparison tests. * $p \leq 0.05$, ** $p \leq 0.01$, against indomethacin treated group.

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