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Protective Effects of Alogliptin Against Indomethacin-Induced Gastric Ulcers in Rats

Abdunaser S. A. Aklan[1]*, Mohammed A. Al-khawlani[2], Hassan M. Al-Mahbashi[1, 3], Abdul-Malik Abudunia[1], Mohammed A.N. Abbas[1] and Abdullah S.A. Ahmed[1]

[1]**Department of Pharmacology Therapeutics, Faculty of Medicine and Health Sciences, Sana'a University, Yemen,**
[2]**Department of Pharmacology, Faculty of Pharmacy, Sana'a University, Sana'a, Yemen,**
[3]**Department of Forensic Medicine and Clinical Toxicology, Faculty of Medicine, Sana'a University, Yemen.**

*Corresponding author: E-mail: nasershami12345@gmail.com

Abstract

Background: Notwithstanding the availability of efficacious antiulcer drugs, concerns over their safety have motivated the lookup of alternate or adjunctive therapies. Drug repurposing is a practical, low-risk, and cost-effective approach. Dipeptidyl peptidase-4 (DPP-4) inhibitors, such as alogliptin, have pleiotropic effects beyond glucose regulation, including antioxidant and anti-inflammatory activities, which may protect the gastric mucosa.
Objectives: To evaluate the gastroprotective potential of alogliptin against indomethacin-induced gastric ulcers in rats.
Methods: Albino rats were assigned randomly to four groups (n = 6): normal control, positive control, omeprazole (20 mg/kg), and alogliptin (3 mg/kg). The treatments were administered for eight consecutive days. All pretreatment groups, except the normal control group, received a single oral dose of indomethacin (50 mg/kg) to induce gastric ulceration. The rats were sacrificed after 6 h, and their stomachs were collected for assessment. Gastric juice volume and pH were measured, and gastric tissues were evaluated both macroscopically and microscopically. Antioxidant markers, including GPx, SOD, and MDA, were measured.
Results: Pretreatment with alogliptin significantly reduced ulcer number by 32.1% and severity by 37.9%. GPx and SOD activities were significantly restored by 44% and 43%, respectively. It also significantly decreased MDA levels by 45.6% compared to the positive control group. Histopathology revealed marked preservation of the gastric mucosal architecture, with reduced necrosis and inflammatory cell infiltration.
Conclusion: Alogliptin exhibits gastroprotective effects, likely via antioxidant mechanisms, suggesting its potential as an adjunct therapy for patients at risk of NSAID-induced gastric ulcers, especially in diabetic populations.

Article Info

Keywords:
Alogliptin, Gastric ulcer, DPP-4 inhibitor, Antioxidant, Indomethacin

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1. INTRODUCTION

Peptic ulcer disease (PUD) is one of the most prevalent gastrointestinal disorders worldwide [1]. Several etiological factors have been implicated in the progression of this condition, including *Helicobacter pylori*infection, excessive alcohol consumption, hypersecretion of hydrochloric acid and pepsin, bile acids, cigarette smoking, psychological stress, and long-term non-steroidal anti-inflammatory drugs [2, 3]. In addition, oxidative stress and inflammatory responses within the gastric tissue play pivotal roles in the progression and pathogenesis of peptic ulceration. Moreover, reactive oxygen species (ROS) generated by infiltrating neutrophils and monocytes induce protein oxidation and lipid peroxidation, leading to oxidative damage to gastric mucosal cells and subsequent ulcer formation [4].

Although effective antiulcer therapies are currently available, concerns regarding their long-term safety profiles remain, which has stimulated the search for safer alternative or complementary therapeutic agents [5].

NSAIDs are among the most widely prescribed medications. Indomethacin, a prototypical NSAID, is commonly used and serves as a clinically relevant experimental model for inducing severe gastric ulcers [6]. Indomethacin-induced extensive gastric injury results not only from the inhibition of prostaglandin synthesis but also from the disruption of enzymatic and non-enzymatic antioxidant defense systems, including catalase (CAT), reduced glutathione (GSH), superoxide dismutase (SOD), and elevated myeloperoxidase (MPO) activity and malondialdehyde (MDA) levels [7]. Moreover, NSAIDs, such as indomethacin, enhance gastric mucosal permeability, promote neutrophil infiltration, and promote the overproduction of reactive oxygen species (ROS), thereby aggravating oxidative stress and accelerating gastric ulcer development [8, 9].

Alogliptin (ALO) is a selective dipeptidyl peptidase-4 (DPP-4) inhibitor widely used as an oral antidiabetic agent [10]. DPP-4 degrades the incretin hormone glucagon-like peptide-1 (GLP-1); therefore, inhibition of this enzyme enhances and prolongs the biological activity of GLP-1 [11].

Recent evidence suggests that incretin-based therapies exert pleiotropic effects beyond glucose regulation, including antioxidant, anti-inflammatory, and immunomodulatory effects [12, 13]. Elevated GLP-1 levels have been reported to counteract oxidative stress and attenuate tissue injury [14]. Furthermore, alogliptin has demonstrated protective effects against cyclophosphamide-induced toxicity in various organs, attributed to its antioxidant, anti-inflammatory, and antifibrotic properties [15–18].

Therefore, the present study aimed to assess the gastroprotective effects of alogliptin against indomethacin-induced gastric mucosal injury in rats using macroscopic evaluation, biochemical analyses, and histopathological assessment.

2. MATERIALS AND METHODS

2.1. Animals

Twenty-four adult female Wistar albino rats, each weighing between 150 and 250 g, were procured from the animal care facility at the Faculty of Science, Sana'a University. The animals were individually housed in wire-mesh plastic cages and allowed to acclimatize for seven days prior to experimentation. Rats were maintained under standard laboratory conditions with a relative humidity of 30 ± 5%, controlled temperature of 25 ± 2℃, adequate ventilation, and a 12 h light/dark cycle. The rules for the use and care of laboratory animals were followed in all experimental procedures, which were authorized by the Ethical Committee of the Faculty of Medicine and Health Sciences, Sana'a University, Sana' a, Yemen. Serial No.: (26) 10–11/2026.

2.2. Drugs

Alogliptin was obtained from a local market (Al-Hikma Pharmaceutical Co., Egypt). Indomethacin was obtained from Pharco Pharmaceuticals Co. (Egypt), and omeprazole was purchased from Ciplamedica Co. (India). All drugs were freshly prepared in 5% Tween 80 dissolved in distilled water before oral administration.

2.3. Chemicals

Distilled water (Echotchem etd, UK), formalin solution (Chemacool, Saudi Arabia), Tween 80 (Himedia, India), normal saline (Pharmaceutical Solutions Industry, Yemen), and kits for superoxide dismutase (T-SOD) (Elabscience Biotechnology Inc., China, catalog number E-BC-K020-M), malondialdehyde (MDA) (Elabscience Biotechnology Inc., China, catalog number E-BC-K025-M), and glutathione peroxidase (GSH-Px) (Elabscience Biotechnology Inc., China, catalog number E-BC-K096-M) were used.

2.4. Experimental Design

The animals were randomly divided into four groups. The sample size (n = 6) was determined based on previously published studies employing similar experimental models, in which this number was sufficient to detect statistically significant differences in the results. The test drugs were administered orally once daily for eight consecutive days using an oral gavage needle [19].

Group 1: (normal control group): received vehicle (5% Tween 80, 2 mL/kg/day, p.o.).
Group 2: (positive control group): received vehicle (5% Tween 80, 2 mL/kg/day, p.o.), followed by indomethacin (50 mg/kg/day, p.o.).
Group 3: pretreatment with omeprazole (20 mg/kg/day, p.o.).
Group 4: pretreated with alogliptin (3 mg/kg/day, p.o.).

2.5. Indomethacin-Induced Gastric Ulcer Model

All animals were fasted for twenty-four hours before ulcer induction, with continuous free access to water. One hour after the final treatment, a gastric ulcer was induced by a single dose of indomethacin (50 mg/kg), with the exception of the normal control group, which received only the vehicle [20]. The rats were sacrificed six hours after indomethacin administration. The stomachs were then dissected, longitudinally incised along the greater curvature, rinsed with ice-cold saline, and examined for macroscopic gastric lesions. The stomachs were photographed, and the tissue samples were divided for histopathological and biochemical analyses. Samples intended for oxidative stress assays were stored

at -80℃[21].

2.6. Assessment of Ulcer Number and Severity

The gastric mucosa was assessed macroscopically for hemorrhagic streaks and necrotic lesions, and images were captured using a digital camera [22]. The number of ulcers was counted, and ulcer severity was scored as follows:

– Absence of ulceration = (0).
– Lesion size $\leq$ 1 mm = (1).
– Lesion of size 1-2 mm = (2).
– Lesion of size 2-3 mm = (3).
– Lesion of size 3-4 mm = (4).
– Lesion size > 4 mm = (5).

2.7. Determination of Gastric Juice Volume and pH:

The resected stomach was longitudinally incised along the greater curvature and washed with five milliliters of ice-cold distilled water. Gastric washings were collected and centrifuged for 10 min at 3000 rpm, and the supernatant was collected for pH determination using a calibrated pH meter [19].

2.8. Determination of biochemical parameters

Specimens from dissected stomachs of all experimental animals were collected, with the quantity required for each assay set at 20 mg. Tissue specimens were rinsed with cold phosphate-buffered saline (PBS) (0.01 M, pH 7.4). Each 20 mg tissue specimen was homogenized in 180 µL of 0.9% NaCl using a Dounce homogenizer. The mixture was centrifuged for 10 min at 4℃ at 10,000×g to eliminate insoluble material. The supernatant was collected and kept on ice for further analysis. SOD, GPx, and MDA levels were measured using commercial kits (Elabscience, USA) according to the manufacturer's instructions. Absorbance was measured using a microplate reader (BioTek, USA) at specific wavelengths (SOD: 450 nm, GPx: 340 nm, and MDA: 532 nm). Standard curves were used for quantification of the data.

2.9. Histopathological analysis:

Immediately after the animals were sacrificed, small fragments of the stomach were collected and thoroughly rinsed with ice-cold saline solution. The tissue samples were preserved in 10% neutral buffered formalin [23] and carefully sectioned along the longitudinal axis. Dehydration was performed using a series of ethanol solutions with increasing concentrations (70%, 80%, 90%, and 100%). Thereafter, the tissues were cleared with xylene and embedded in paraffin wax. Once infiltration was complete, the paraffin blocks were sectioned into 5 μm-thick slices using a microtome. The sections were then mounted on glass slides and stained with hematoxylin and eosin (H&E). Finally, the prepared slides were examined under an optical microscope to assess pathological changes in the gastric tissue [24].

2.10. Statistical analysis:

The results are presented as mean ± SD (n = 6). One-way analysis of variance (ANOVA) was used for group comparisons, and Tukey's test was applied for multiple comparisons. The groups were compared with the indomethacin-treated group. Statistical significance was attained when the P-value was <.05 in the obtained results. Statistical analysis was performed using GraphPad Prism version 10.6.0 (890).

3. RESULTS:

3.1. Effect on Gastric Ulcer Number and Severity

Administration of indomethacin induced extensive gastric mucosal injury, as evidenced by a significant increase in the number of ulcerations (56.67 ± 16.7) and ulcer severity score (4.83 ± 0.41) compared to the normal control group. In contrast, pretreatment with omeprazole (20 mg/kg, p.o.) or alogliptin (3 mg/kg, p.o.) significantly reduced the number of ulcerations by 96.5% and 32.1%, respectively. Similarly, ulcer severity was significantly decreased by 82.8% and 37.9%, respectively, compared with that in the positive control group (Figs. 1 and 2).

Representative macroscopic images illustrating gastric mucosal damage and protection are presented in Fig.3.

3.2. Effect on Gastric Juice Volume and pH

Indomethacin significantly increased gastric juice volume (0.67 ± 0.10 mL) and reduced gastric pH (3.67 ± 0.75) compared to the normal control group. The omeprazole-pretreated group showed a significant decrease in gastric juice volume by 56% and a significant increase in gastric pH by 89.5% compared to the positive control group. Alogliptin therapy showed a balanced normalization of both parameters (Figs. 4 and 5).

3.3. Antioxidant Activity

3.3.1. Gastric Glutathione Peroxidase (GSH-Px)

Indomethacin administration significantly reduced gastric GSH-Px activity to approximately 49% of the normal control value, indicating marked oxidative stress. Pretreatment with omeprazole or alogliptin therapy significantly

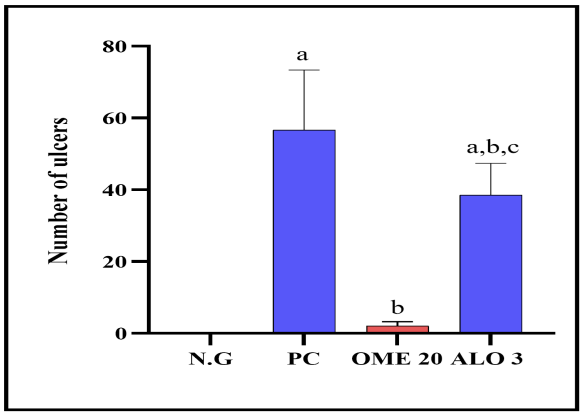

Figure 1. Effect of alogliptin on ulcer number against indomethacin-induced gastric ulcerated rats. Each value of ulcer number is expressed as the mean ± SD (n = 6 per group). Statistical evaluation was performed using one-way analysis of variance (ANOVA), followed by Tukey's post hoc test. a Significant difference relative to N. G. group at $p < 0.05$. b Significant difference relative to P. C. group at $p < 0.05$. cSignificant difference relative to the OME (20 mg/kg) group at $p < 0.05$.
N.G: Normal control group; P.C: Positive control; OME: Omeprazole; ALO: Alogliptin.

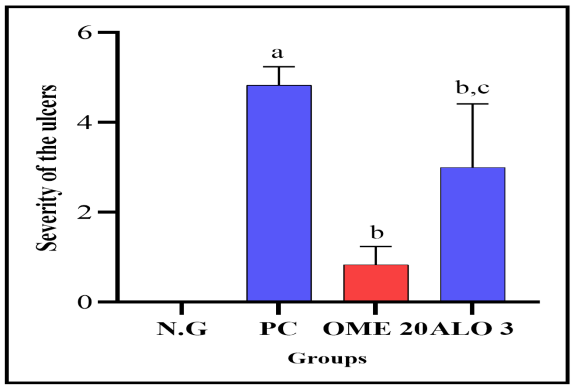

Figure 2. Effect of alogliptin on ulcer severity against indomethacin-induced gastric ulcerated rats.
Each value of the ulcer severity or ulcer number is expressed as mean ± SD (n = 6 per group). Statistical evaluation was performed using one-way analysis of variance (ANOVA), followed by Tukey's post hoc test. a Significant difference relative to N. G. group at $p < 0.05$. b Significant difference relative to P. C. group at $p < 0.05$. cSignificant difference relative to the OME (20 mg/kg) group at $p < 0.05$.
N.G: Normal control group; P.C: Positive control; OME: Omeprazole; ALO: Alogliptin.

restored GSH-Px levels compared to the positive control group. (Fig. 6).

3.3.2. Gastric Superoxide Dismutase (SOD)

Indomethacin markedly decreased gastric SOD activity to approximately 55% compared to the normal control group. Omeprazole or alogliptin pretreatment significantly increased SOD activity compared to that in the positive control group. (Fig. 7).

3.3.3. Gastric Malondialdehyde (MDA)

Indomethacin administration significantly elevated gastric MDA levels (≈122% increase), reflecting enhanced lipid peroxidation. Pretreatment with omeprazole or alogliptin significantly reduced MDA levels compared to that in the positive control. (Fig. 8).

3.4. Histological examination

Histological examination of stomach sections from the normal control group revealed an intact mucosal architecture with normal glandular structures, submucosa, and muscular layers. (Fig. 9a). In contrast, indomethacin-treated rats displayed both deep and superficial ulcerations in the gastric wall, characterized by hemorrhage, inflammatory cell infiltration, dilated glands, and congested blood vessels (Fig.9b). Pretreatment with alogliptin revealed the presence of focal necrosis and superficial erosions, accompanied by mild vascular congestion. (Fig. 9d).

4. DISCUSSION:

Non-steroidal anti-inflammatory drugs (NSAIDs), particularly indomethacin, are well recognized for

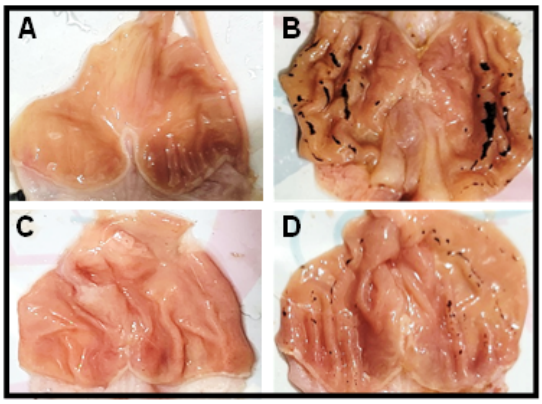

Figure 3. Macroscopic examination of gastric mucosa for gastric ulcers induced by indomethacin in rats. (A) Normal control group. (B) Positive control group: gastric mucosa manifesting as extensive erosion, visible as spots or strip hemorrhagic lesions (arrow). (C) omeprazole (20 mg/kg) and (D) alogliptin (3 mg/kg p.o.). This group exhibited reduced ulcer stripes and hemorrhagic spots. Black arrows indicate ulcer strips or hemorrhagic spots. The number of gastric lesions was enumerated, while their severity was graded using a scoring system as follows: absence of ulceration = (0), lesion size $\leq$ 1 mm = (1), lesion of size 1-2 mm = (2), lesion of size 2-3 mm = (3), lesion of size 3-4 mm = (4), and lesion of size > 4 mm = (5).

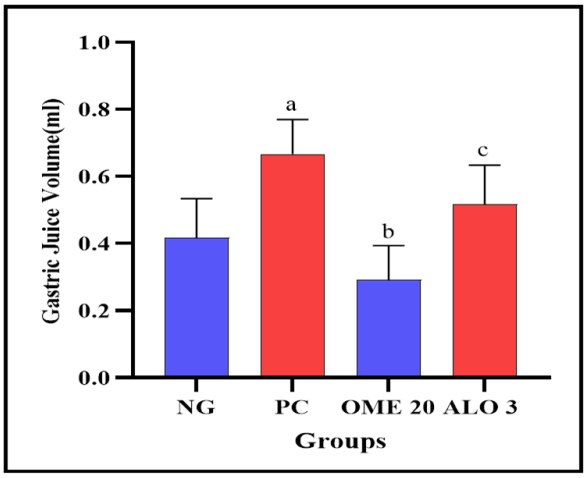

Figure 4. Effect of alogliptin on gastric juice volume against indomethacin-induced gastric ulcerated rats.
Each value of gastric juice volume is expressed as mean ± SD (n = 6 per group). Statistical evaluation was performed using one-way ANOVA, followed by Tukey's post hoc test. a Significant difference relative to the N. G. group at $p < 0.05$. b Significant difference relative to the P. C. group at $p < 0.05$. c Significant difference relative to the OME (20 mg/kg) group at $p < 0.05$.
N.G: Normal control group; P.C: Positive control; OME: Omeprazole; ALO: Alogliptin.

their ulcerogenic potential due to the inhibition of cyclooxygenase-derived prostaglandins, increased gastric acid secretion, oxidative stress generation, and infiltration of inflammatory cells. In the current study, indomethacin administration induced extensive gastric mucosal injury, as evidenced by a significant increase in the number of ulcerations and their severity (Fig. 1 and Fig. 2); elevated gastric acidity (Fig. 4 and Fig. 5); depletion of endogenous antioxidant enzymes GSH-Px and SOD (Fig. 66 and Fig. 7); increased lipid peroxidation MDA (Fig. 8); and profound histopathological alterations (Fig. 9a, b, and c). Similar results have been observed by other investigators [25–27]. The observed depletion of gastric antioxidant enzymes and elevation of MDA levels in the positive control group agree with previous studies demonstrating that indomethacin-induced gastric injury is closely associated with excessive generation of ROS and impairment of the gastric antioxidant defense system [28, 29]. Therefore, restoration of the antioxidant balance is a key target for gastroprotective interventions.

Alogliptin, a selective DPP-4 inhibitor, prevents the degradation of incretins (GLP-1), thereby improving glycemic control in patients with diabetes. Beyond its metabolic effects, alogliptin exerts antioxidant, anti-inflammatory, and tissue-protective effects, potentially reducing drug-induced organ toxicity [12, 13]. This study aimed to determine whether these effects could also modulate the potential protective role of alogliptin

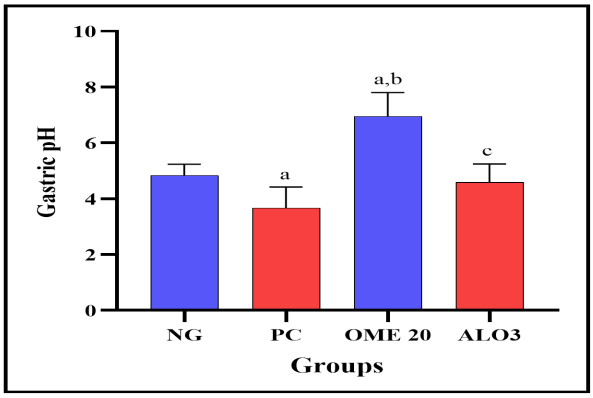

Figure 5. Effect of alogliptin on gastric pH against indomethacin-induced gastric ulcerated rats.
Each value of gastric pH is expressed as mean ± SD (n = 6 per group). Statistical evaluation was performed using one-way ANOVA, and subsequently subjected to Tukey's post hoc test. a showing a significant difference relative to N.G. at $p < 0.05$, b showing a significant difference relative to P.C. at $p < 0.05$, and c showing a significant difference relative to the OME (20 mg/kg) group at $p < 0.05$.
N.G: Normal control group; P.C: Positive control; OME: Omeprazole; ALO: Alogliptin.

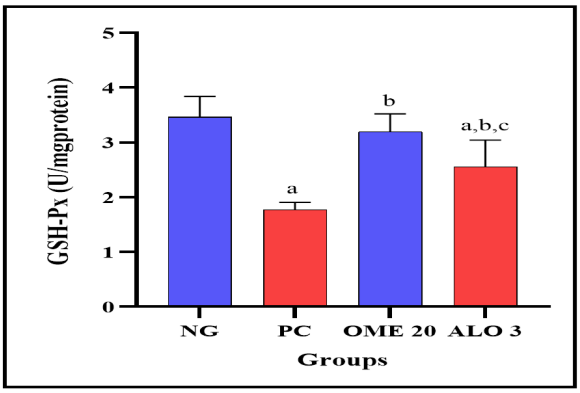

Figure 6. Effect of alogliptin on gastric GSH-Px content against indomethacin-induced gastric ulcerated rats.
Each value of GSH-pX content is expressed as mean ± SD (n = 6 per group). Statistical evaluation was performed using one-way ANOVA, and subsequently subjected to Tukey's post hoc test. a showing a significant difference relative to N.G. at $p < 0.05$, b showing a significant difference relative to P.C. at $p < 0.05$, and c showing a significant difference relative to the OME (20 mg/kg) group at $p < 0.05$.
N.G: Normal control group; P.C: Positive control; OME: Omeprazole; ALO: Alogliptin.

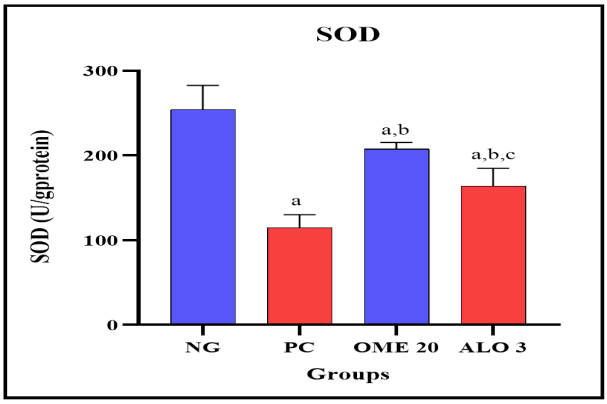

Figure 7. Effect of alogliptin on gastric SOD content against indomethacin-induced gastric ulcerated rats.
Each value of SOD content is expressed as mean ± SD (n = 6 per group). Statistical evaluation was performed using one-way ANOVA, and subsequently subjected to Tukey's post hoc test. a showing a significant difference relative to N.G. at $p < 0.05$, b showing a significant difference relative to P.C. at $p < 0.05$, and c showing a significant difference relative to the OME (20 mg/kg) group at $p < 0.05$.
N.G: Normal control group; P.C: Positive control; OME: Omeprazole; ALO: Alogliptin.

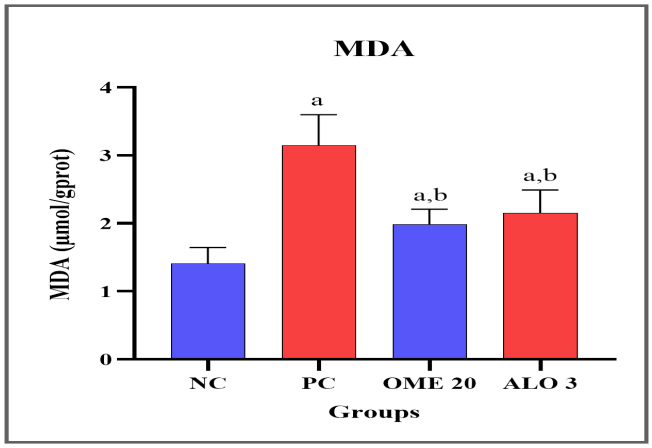

Figure 8. Effect of alogliptin on gastric MDA content against indomethacin-induced gastric ulcerated rats.
Each value of MDA content is expressed as mean ± SD (n = 6 per group). Statistical evaluation was performed using one-way ANOVA, and subsequently subjected to Tukey's post hoc test. a showing a significant difference relative to N.G. at $p < 0.05$, b showing a significant difference relative to P.C. at $p < 0.05$, and c showing a significant difference relative to the OME (20 mg/kg) group at $p < 0.05$.
N.G: Normal control group; P.C: Positive control; OME: Omeprazole; ALO: Alogliptin.

against indomethacin-induced gastric ulcerations in rats.

Pretreatment with alogliptin significantly attenuated indomethacin-induced gastric damage in the present study, as revealed by the improved morphology (Fig. 3) and ulcer scores (Fig. 1 and 2) and confirmed by histological examination (Fig. 9d).

Pretreatment with alogliptin also conferred appreciable protection against indomethacin-induced gastric injury, as evidenced by the improvement in oxidative stress markers. Alogliptin had a significant antioxidant effect, as evidenced by the decreased MDA levels (Fig. 8) and restored GSH-Px and SOD activities (Figs. 6 and 7), indicating attenuation of oxidative gastric injury. While our results suggest an antioxidant role, it is essential to consider whether the effect is due to DPP-4 inhibition alone or due to GLP-1 elevation. The literature suggests that both may contribute: GLP-1 analogs have direct antioxidant effects, whereas DPP-4 inhibition may also affect substrates beyond incretins. Future studies using GLP-1 receptor agonists or selective DPP-4 receptor blockers are needed to elucidate the precise molecular mechanisms. In accordance with our findings, Salama et al. reported that alogliptin attenuates oxidative stress by increasing the antioxidant enzyme GSH and decreasing the level of the lipid peroxidation marker MDA [16–18]. Furthermore, Zhang et al. observed similar outcomes in diabetic rats treated with alogliptin [30]. Additionally, Kabel et al. showed that alogliptin elevated the antioxidant (GSH-Px) levels in a rat model of doxorubicin-induced testicular toxicity. [15]. Furthermore, other DPP-4 inhibitors, such as linagliptin and sitagliptin, have been reported to protect gastric and intestinal tissues against NSAID-induced injury by modulating oxidative stress and activating cytoprotective pathways, including Nrf2/HO-1 signaling [12].

The histopathological findings strongly supported the biochemical and macroscopic results. Severe epithelial disruption, hemorrhage, and inflammatory cell infiltration observed in the positive control group were markedly attenuated in rats pretreated with alogliptin and the omeprazole-treated group, where a decrease in inflammatory cell infiltration and focal necrosis was also observed. These histological improvements are comparable to those reported in previous studies investigating gastroprotective agents in indomethacin-induced ulcer models, further confirming the protective potential of the tested interventions [23, 24].

Overall, the present results demonstrate that alogliptin exerts gastroprotective effects against indomethacin-induced gastric lesions through complementary mechanisms involving the attenuation of oxidative stress, suppression of lipid peroxidation, and preservation of mucosal integrity.

This study has several limitations. First, the mechanism focused primarily on the antioxidant pathway; other potential pathways, such as Nrf2/HO-1 signaling or direct anti-inflammatory effects, were not investigated. Second, only a single dose of alogliptin was tested, and the dose-response relationship was not explored. Third, extrapolation of these findings to humans requires further preclinical and clinical research.

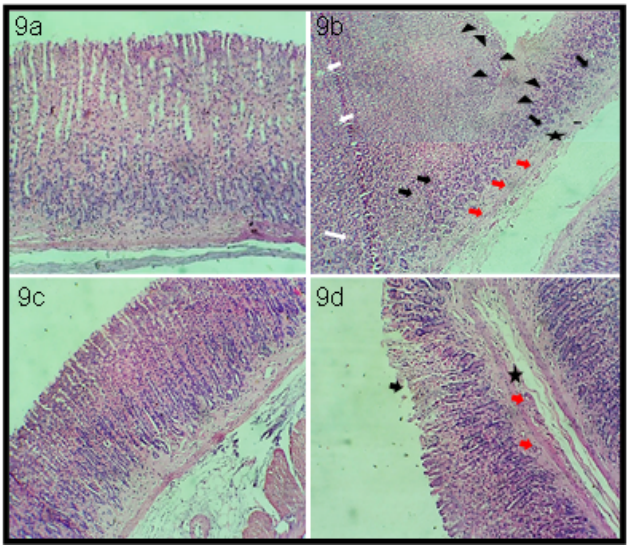

Figure 9. Effect of alogliptin on histopathological damage in the gastric mucosa of rats subjected to indomethacin (H&E, 100×) (n = 6 per group). (9a) Normal control group, (9b) positive control group, (9c) omeprazole-pretreated group (20 mg/kg), and (9d) alogliptin (3 mg/kg) group.
Necrosis and erosions (black arrows), dilated gastric glands (white arrows), congested blood vessels (red arrow), severe hemorrhages (triangle), and inflammatory cells' infiltration (black star).

5. CONCLUSION:

In conclusion, alogliptin exerted a protective effect against indomethacin-induced gastric ulcers in rats. This effect appears to be related to its antioxidant properties and ability to preserve gastric mucosal integrity. These findings suggest that alogliptin may be a potential adjunctive agent for reducing NSAID-associated gastric injury, particularly in diabetic populations.

AUTHORS' CONTRIBUTIONS

Abdunaser S. A. Aklan conducted the experiments, gathered information, interpreted findings, and participated in manuscript writing; Mohammed A. Alkhawlani designed and supervised the performance of the experiment and data collection; Hassan M. Al-Mahbashi and Abdul-Malik Abudunia conceived and supervised the study; Mohammed A.N. Abbas analyzed and interpreted results and wrote the manuscript; Abdullah S.A. Ahmed reviewed the discussions.

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