

Original Research Article

Gastro-protective activities of misoprostol and omeprazole on aspirin-induced gastric ulceration in rat model

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Abstract

Purpose: To evaluate the gastroprotective effects of misoprostol and omeprazole co-administration on aspirin-induced gastric ulceration in Wistar rats.

Method: Gastric ulcers were induced in Wistar albino rats by oral administration of aspirin (200 mg/kg) once daily for six consecutive days. Animals were divided into five groups of five rats each: normal control, aspirin control, and three treatment groups receiving misoprostol (2 mg/kg), omeprazole (20 mg/kg), and a combination of both drugs, respectively, at the same doses. All treatments were given orally once daily, simultaneously for six days. Ulcer index, pH levels, antioxidant indices, and histological changes were assessed 24 hours after the last treatment, following sacrifice.

Result: Aspirin administration significantly ($p < 0.05$) decreased pH and increased the ulcer index in rats. Treatment with misoprostol and omeprazole significantly ($p < 0.05$) improved acidity levels and inhibited ulceration, with combination therapy showing the best protection. Aspirin-induced ulceration is associated with increased lipid peroxidation and reduced superoxide dismutase and catalase activities. All treatments significantly ($p < 0.05$) improved the antioxidant parameters, with omeprazole alone exhibiting the most potent antioxidant activity. Histological examination revealed significant changes in the gastric histoarchitecture of the aspirin-treated rats, including vascular congestion, degenerated epithelial mucosa, and inflammatory cell infiltration. These changes were significantly reduced in the misoprostol- and omeprazole-treated groups, although much more significant with the combination group.

Conclusion: Misoprostol and omeprazole have demonstrated significant gastroprotective effects against aspirin-induced gastric ulceration in Wistar rats, with combination therapy showing the most promising results. These findings support the use of these drugs, particularly in combination, to prevent and treat NSAID-associated gastric damage.

Keywords: Gastric ulcer, Aspirin, Gastroprotective, Misoprostol, Omeprazole, Antioxidant, Histological

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INTRODUCTION

Gastric ulcer is a prevalent gastrointestinal tract illness that impacts over 10% of the global population [1]. It is defined by gastrointestinal

tract haemorrhage, perforation, and erosion of the mucosal wall resulting from an imbalance between aggressive factors (acid, pepsin, and *Helicobacter pylori*) and protective factors (mucin, prostaglandin, bicarbonate, nitric oxide,

mucosal blood flow, and growth factors) [2]. The aetiology of this condition is multifaceted, encompassing *Helicobacter pylori*, non-steroidal anti-inflammatory medicines (NSAIDs), tobacco use, stress, chronic alcohol intake, disrupted prostaglandin E series metabolism, and suboptimal dietary practices [3].

Aspirin is acetylsalicylic acid, commonly utilised for the alleviation of pain, fever, and inflammation, although it is capable of causing peptic ulcer formation [4]. Several treatment options are available for peptic ulcers, such as proton pump inhibitors (omeprazole and lansoprazole), Histamine-2 (H_2) receptor blockers (cimetidine and ranitidine), prostaglandin-like substances (misoprostol), antacids, and antibiotics [5].

This study aimed to evaluate the protective effects of misoprostol and omeprazole and their combination against gastric ulcers in Wistar rats exposed to aspirin, and justify their use in clinical practice.

EXPERIMENTAL

Drugs and chemicals

Aspirin 300 mg tablets (SKG-Pharm Ltd, Nigeria; 721AC/NG02), misoprostol 200 µg tablets (Naari Pharma Private Ltd, India; NR00827B), and omeprazole 20 mg tablets (McCOY Pharma Pvt. Ltd, India; L20137) were procured for the study. The assay kits used were from Randox Laboratories Limited, United Kingdom. The rats were housed in a standard laboratory environment with a 12-hour cycle of equal light and dark, and they were given unlimited access to food and water before the experiment.

Animals

Male Wistar rats weighing 120 - 150 g were procured from the animal holding facility of the Faculty of Basic Medical Science, Delta State University, Abraka, Nigeria. They were housed in the animal house of the Faculty of Basic Medical Science, Delta State University, Abraka, allowed to acclimatize for a period of two weeks before the commencement of the study under a standard laboratory environment with a 12-hour cycle of equal light and dark, and were placed on Growers' feed and clean water *ad libitum*. Animal handling was performed in accordance with the ethical standards of the Institutional Animals Ethics (IAEC), as adopted by the Research and Ethics Committee of the Faculty of Basic Medical Science, Delta State University, Abraka, Nigeria (approval no. RBC/FBMC/DELSU/24/338).

Anti-ulcer study

Aspirin (200 mg/kg) has been previously used to induce gastric ulceration [6]. Twenty-five (25) animals were divided into five groups of five animals each. Animals in Group 1 (normal control) received only distilled water orally. Group 2 (aspirin control) received aspirin 200 mg/kg alone orally. Rats in Groups 3, 4, and 5 were treated orally once for six consecutive days with misoprostol (MIS; 2 mg/kg), omeprazole (OME; 20 mg/kg), and a combination of misoprostol and omeprazole (MIS+OME), respectively. All animals were fasted for 12 h before the administration of aspirin. Gastric ulcers were induced in rats by administering aspirin 200 mg/kg orally once daily for six consecutive days in 10 % Tween 80 solution 30 min before the administration of the test drugs. On the seventh day, the animals were sacrificed using ether [7] and their stomachs were opened along the greater curvature, and the ulcers were scored [6]. Scoring was performed as follows: Normal Stomach (0), red coloration (0.5), spot ulcer (1), hemorrhagic streak (1.5), deep ulcer (2) and perforation (3). The mean ulcer score for each animal is expressed as the ulcer index.

The ulcer index (UI) was calculated using Eq 1, while the percentage (%) inhibition of ulceration (I) was calculated using Eq 2 [8].

$$UI = UN + US + UP \times 10^{-1} \dots\dots\dots (1)$$

$$\text{Inhibition of ulceration (\%)} = (UI_{\text{control}} - UI_{\text{Test}}/UI_{\text{control}})100 \dots\dots\dots (2)$$

Where UI is Ulcer Index, UN is the average number of ulcers per animal, US is the average severity score, and UP is the percentage of animals with ulcers

Antioxidant indices assay

Stomach homogenate was prepared using the method described by Sabiu *et al* [9]. Whole stomach tissues were pulverized with liquid nitrogen in a mortar; thereafter, each sample (0.5 g) was homogenized in ice-cold phosphate saline buffer (0.1 M, pH 7.4), the homogenates were centrifuged at 2500 rpm for 10 min at 4 °C, and the resulting supernatants were used for the antioxidant indices assay. Catalase (CAT) and superoxide dismutase (SOD), and the level of lipid peroxidation, measured in terms of malondialdehyde (MDA), were assayed in the stomach homogenate using the methods of Gutteridge and Wilkins, and Sinha [10,11].

Histology of the stomach

Histopathological examinations of gastric tissues were performed according to a previously reported protocol [12]. The gastric tissues were embedded in paraffin after fixation with formalin. Subsequently, 5 μ m microtome sections were stained with hematoxylin. Eosin staining (an acidic dye that binds to the basic components of cells) was used to evaluate inflammation and necrosis in the stomach. Light microscopy was used to analyze the sections, and photographs at a magnification of $\times 100$ were acquired.

Statistical analysis and data presentation

Ulcer-inhibitory level was expressed as a percentage. Other data obtained were expressed as mean $\pm$ standard error of mean (SEM) and analyzed by one-way analysis of variance (ANOVA) followed by Tukey's post-hoc test. Analyses were performed using GraphPad Prism version 7.0 (GraphPad Software, San Diego, CA, USA). Statistical significance was set at $p < 0.05$.

RESULTS

The effects of misoprostol and omeprazole on the acidity (pH), ulcer index, and percentage (%) inhibition of ulcers in the experimental animals are shown in Figures 1-3, respectively. Following oral administration of 200 mg/kg of aspirin (ASP), there was a significant ($p < 0.05$) decrease in pH and a significant ($p < 0.05$) increase in the degree of ulceration (ulcer index) in rats. However, significant ($p < 0.05$) improvements in acidity and inhibition of ulceration were observed in animals treated with misoprostol (MIS; 2 mg/kg) and omeprazole (OME; 20 mg/kg). The combination of both misoprostol and omeprazole (MIS + OME) provided better protection against gastric ulceration.

Figure 4 shows the effects of MIS and OME on lipid peroxidation and superoxide dismutase (SOD) and catalase activities in the gastric mucosa of aspirin ulcerated rats. MDA levels significantly increased ($p < 0.05$) in ulcerated animals (Figure 4A). There was also a significant reduction ($p < 0.05$) in the activities of SOD and catalase (Figure 4B, 4C) in aspirin-induced ulcerated animals. Notably, all treatments (MIS, OME, and MIS+OME) resulted in significant improvement ($p < 0.05$) in these parameters. Omeprazole treatment resulted in the highest antioxidant activity among all treatments in this study.

Stomach tissue sections showed normal histological structures in the control group. The

histological evaluation scores are shown in Figure 5. Significant changes in gastric histoarchitecture were observed in the ASP group, including vascular congestion, degenerated epithelial mucosa, and inflammatory cell infiltration. However, these changes were significantly ($p < 0.05$) reduced in animals treated with MIS and OME (Figures 5 c - e).

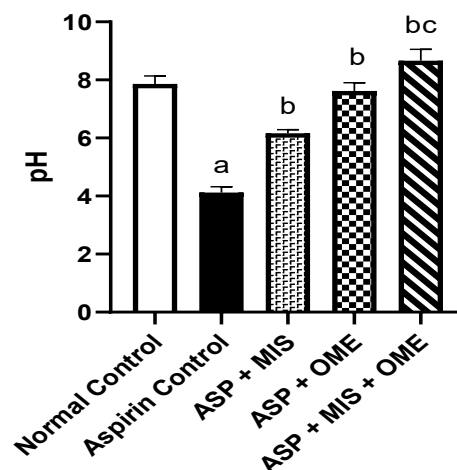


Figure 1: Effect of misoprostol and omeprazole on the pH value of aspirin ulcerated rats. (n = 5; mean $\pm$ SEM). Superscript letters indicated the statistical differences between groups; ^a $p < 0.05$ vs normal control, ^b $p < 0.05$ vs aspirin control, and ^c $p < 0.05$ vs ASP + MIS. ASP, aspirin; MIS, misoprostol; OME, omeprazole

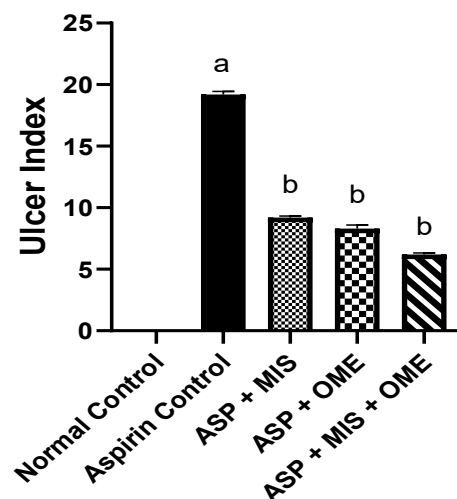


Figure 2: Effect of misoprostol and omeprazole on the ulcer index of aspirin ulcerated rats. (n = 5, mean $\pm$ SEM). Superscript letters indicated the statistical differences between groups; ^a $p < 0.05$ vs normal control, ^b $p < 0.05$ vs aspirin control. ASP, aspirin; MIS, misoprostol; OME, omeprazole

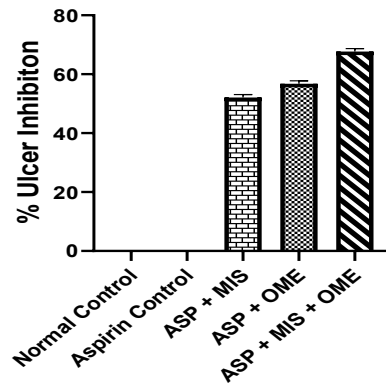


Figure 3: Effect of misoprostol and omeprazole on degree of protection against ulceration in aspirin ulcerated rats. (n = 5, mean $\pm$ SEM). Bars represent degree of protection offered against ulceration. ASP, aspirin; MIS, misoprostol; OME, omeprazole

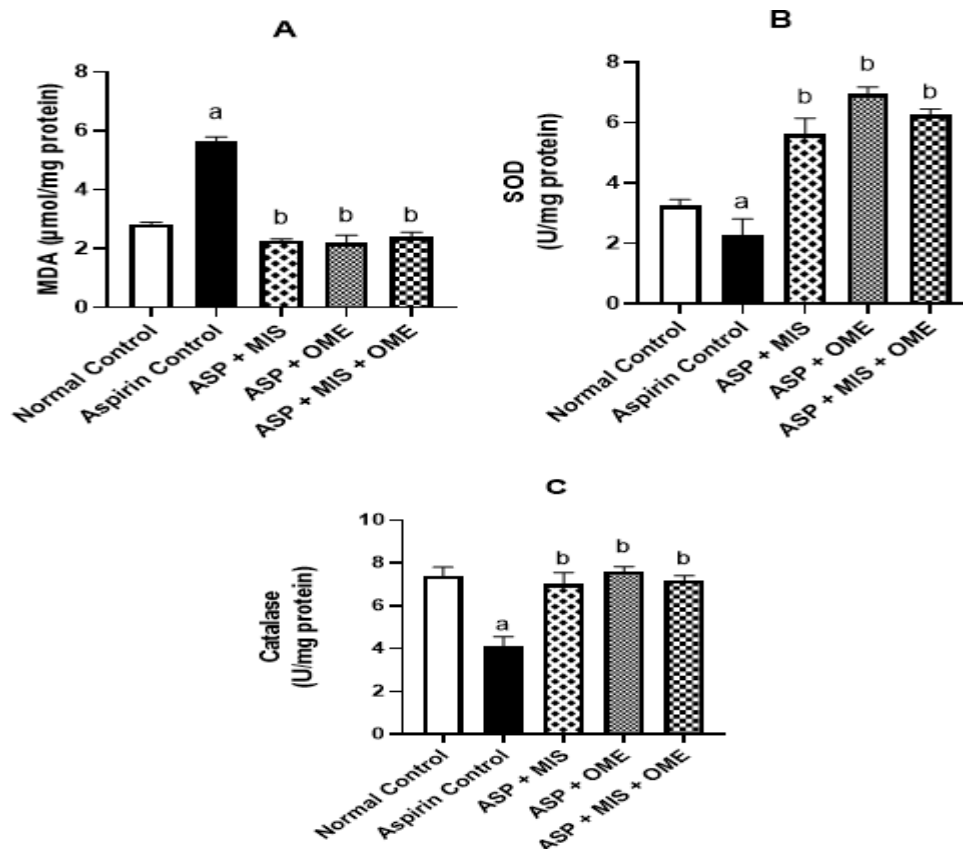


Figure 4: Misoprostol and omeprazole mitigate oxidative disruptions in aspirin ulcerated rats (n = 5, mean $\pm$ SEM): (A) malondialdehyde, MDA; (B) superoxide dismutase, SOD; (C) catalase. Superscript letters indicated the statistical differences between groups; ^a $P < 0.05$ vs normal control, ^b $p < 0.05$ vs aspirin control. ASP, aspirin; MIS, misoprostol; OME, omeprazole

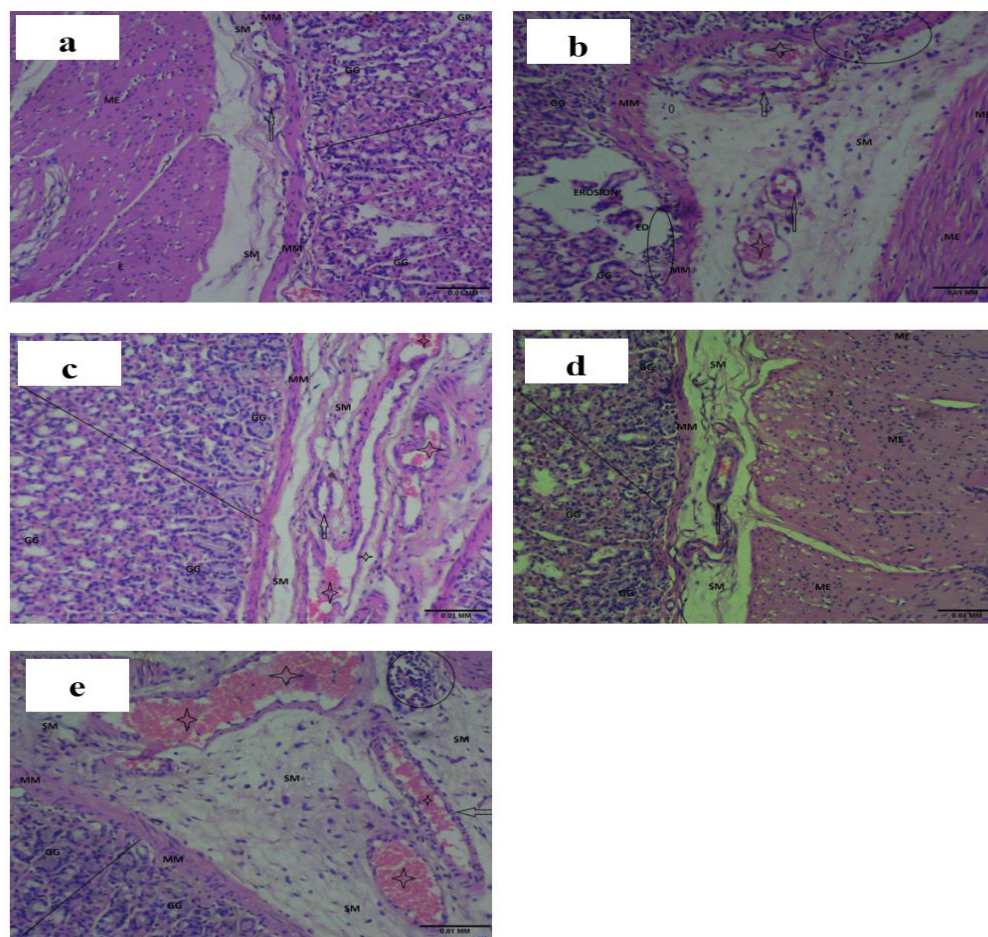


Figure 5: Effect of misoprostol and omeprazole on gastric histoarchitecture in aspirin ulcerated rats. (a) Normal control (b) aspirin control (c) aspirin + misoprostol (d) aspirin + omeprazole (e) aspirin + misoprostol + omeprazole. The tissues were stained with H&E and $\times 100$ magnification was used to capture the slides with light microscope. Arrows with ring indicate significant lesion.

DISCUSSION

The results of this study demonstrated the significant gastroprotective effects of misoprostol and omeprazole against aspirin-induced gastric ulceration in Wistar rats. Aspirin administration led to a marked decrease in gastric pH and an increase in ulcer index, indicating severe gastric damage [13]. This aligns with previous studies showing that aspirin and other NSAIDs can disrupt the gastric mucosal barrier and increase acid secretion, leading to ulceration [14]. The significant improvements in acidity levels and ulcer inhibition observed with misoprostol and omeprazole treatment highlight the efficacy of these drugs in countering the ulcerogenic effects of aspirin. Notably, combination therapy with misoprostol and omeprazole provided the greatest protection against ulceration. This synergistic effect may be attributed to the complementary mechanisms of action of misoprostol as a prostaglandin analog that enhances mucosal defense and omeprazole, a

proton pump inhibitor that suppresses acid secretion [15]. The superior efficacy of combination therapy supports the notion that using drugs with different mechanisms may be advantageous for treating gastric ulcers [16].

Antioxidant assays revealed that aspirin-induced ulceration was associated with increased lipid peroxidation and decreased activity of the antioxidant enzymes superoxide dismutase and catalase [17]. This oxidative stress likely contributes to mucosal damage. All treatments significantly improved the antioxidant parameters, with omeprazole exhibiting the most potent antioxidant activity. This suggests that the gastroprotective effects of these drugs may be partly mediated by antioxidant mechanisms. Histological examination provided further evidence for the protective effects of misoprostol and omeprazole. Severe mucosal damage, vascular congestion, and inflammatory cell infiltration observed in aspirin-treated stomachs were markedly reduced with drug treatment.

These findings corroborate macroscopic and biochemical findings. These results align with those of previous studies that demonstrated the efficacy of misoprostol and omeprazole in preventing NSAID-induced gastric damage [18]. However, this study provides new insights into the comparative and combined effects of these drugs as well as their impact on gastric antioxidant status.

Limitations of this study

Some limitations of this study include the relatively short treatment duration and lack of dose-response analysis. Future studies should explore long-term treatments, dose optimization, and additional mechanistic investigations.

CONCLUSION

This study has demonstrated that misoprostol and omeprazole, particularly in combination, provide significant protection against aspirin-induced gastric ulceration in rats. These gastroprotective effects appear to be mediated through multiple mechanisms, including acid suppression, mucosal defense enhancement, and antioxidant actions. These findings support the use of these drugs, particularly in combination, to prevent and treat NSAID-associated gastric damage. Further studies are warranted to optimize treatment strategies and explore their clinical applications.

DECLARATIONS

Acknowledgement/Funding

None.

Ethical approval

Ethical approval was obtained from the Research and Ethics Committee of the Faculty of Basic Medical Science, Delta State University, Abraka, Nigeria (Ethical No.: RBC/FBMC/DELSU/24/338).

Use of Artificial intelligence/Large language models

We also declare that we did not use Generative artificial intelligence (AI) and AI-assisted technologies in writing the manuscript.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the author(s) named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. EGM and Emuesiri Kohworho Umukoro conceptualized the study. Emuesiri Goodies Moke, Emuesiri Kohworho Umukoro, Ehriori Akponah and Winifred Eseoghene Demaki performed the experiments. Emuesiri Goodies Moke and Paul Chinwuba performed the analyses. All the authors drafted and approved the final version of the manuscript.

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