# Studying the protective effect of Moringa Oleifera and lansoprazole contra indomethacin – induced gastric ulceration in male rats through prostaglandin modulation and restoration of histological changes

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***Abstract*—** Moringa oleifera is a medicinal plant widely recognized for its rich content of bioactive compounds such as flavonoids, phenolic compounds, alkaloids, tannins, saponins, vitamins, and antioxidants that contribute to its therapeutic potential against various pathological disorders, including gastric ulceration. The present study aimed to evaluate the therapeutic effects of Moringa oleifera extract and lansoprazole against indomethacin-induced gastric ulcers in rats. Ulcer-induced rats exhibited several clinical manifestations, including lethargy, anorexia, and melena, accompanied by a significant decrease ($P < 0.05$) in body weight to accomplish this, Forty adult Wistar rats were divided to 5 groups(n=8): control (C−) Administration of Distilled water (D.W) for 4weeks (orally) and other 4 groups induced gastric ulcer by administration with a single oral dose of indomethacin (30 mg/kg BW). Control positive (C+): (8 rat) Induced with acute gastric ulcer without any treatments. G1:(Moringa treatment): after 3 days of ulcer induction, administration with 200 mg/kg of Moringa leaf extract orally, for 4 weeks. G 2: (lansoprazole treatment): after 3 days of ulcer induction, administration with 20 mg/kg of lansoprazole orally for 4 weeks. G3: after 3 days of ulcer induction, administration with combination of MO (200mg/kg) and lansoprazole (20mg/kg) orally for 4 weeks. following ulcer induction. Treatment with Moringa oleifera extract significantly improved ($P < 0.05$) body weight and clinical condition compared with the untreated ulcer group, while rats treated with lansoprazole demonstrated a greater degree of recovery. Notably, the combination therapy produced the most pronounced therapeutic effect, showing significant amelioration ($P < 0.05$) of clinical signs and restoration of body weight compared with all other treated groups. Prostaglandin levels were significantly elevated ($P < 0.05$) in all treated groups relative to the untreated ulcer group. The highest prostaglandin concentration was observed in the combination-treated group, followed by the lansoprazole-treated group, whereas the Moringa oleifera-treated group showed the lowest increase among the treated groups. Histopathological examination further confirmed the therapeutic efficacy, revealing marked improvement in gastric mucosal architecture and a significant reduction in tissue damage in treated animals, particularly in the combination therapy group. These findings suggest that Moringa oleifera possesses significant anti-ulcer activity and may enhance the therapeutic efficacy of lansoprazole through prostaglandin modulation and improvement of gastric histopathological alterations.

Keywords: Moringa oleifera, gastric ulcer, indomethacin, lansoprazole, prostaglandins, histopathology, rats.

## INTRODUCTION

Peptic ulcer is one of the most common of disorders affecting 10% of the world's population. Damage to the stomach's superficial and deeper muscularis mucosa, (1) and (2), causes the condition. However, when risk factors like smoking and excessive drinking, stress, spicy food and frequent over the counter use of non-steroidal anti-inflammatory drugs (NSAIDs) outweigh protective factors, such as gastric hormones, mucus phospholipids, bicarbonate buffers, prostaglandins and mucus gel, peptic ulcers develop. Among the most harmful NSAIDs is indomethacin (INDO) which is especially damaging to the mucosa of the gastrointestinal tract (GI). This is often used to investigate the gastrointestinal side effect of NSAIDs and effect of their potential therapeutics (4). PPIs (for example lansoprazole) have long-lasting and irreversible effects on the gastric acid

producing mechanism and have a relatively long duration of action when compared with other gastric acid inhibitory drugs (5, 17).

Moringa oleifera is one member of the Moringaceae family that is tolerable to dry periods and grows fast. In common parlance, the tree is called many names: miraculous, ben oil, drumstick, horseradish and moringa. Being able to adapt to a variety of environments. Moringa oleifera is one of the richest nutritionally abundant edible plants (6). High in polyphenols, minerals, vitamins and important amino acids. This plant is rich in a variety of phytochemicals, among which include flavonoids, anthocyanins, isothiocyanates, anthraquinone, alkaloids, tannic acid, steroids, terpenoids and cardiac glycosides, just to list a few (7). It has become more and more attractive for the scientific community in the recent years due to its significant pharmacological activities such as anti-inflammatory, antioxidant, anti-diabetic, antidiabetic, anti-urolithiasis, antihypertensive, antifertility, hepatoprotective, cholesterol-lowering, nutraceutical, and antimicrobial activities (8).

The work aims to evaluate the therapeutic and synergistic effects of *Moringa Oleifera* extract alongside lansoprazole against experimentally induced gastric ulcers in male rats as reflected by prostaglandin levels and other biochemical indication

## Materials and methods

**Drugs**

Lansoprazole (enteric-coated capsules of 30 mg) was manufactured by ACTOVERCO Pharmaceutical and indomethacin was manufactured by LOGHMAN Pharmaceutical (Iran). Al-Qasim nursery was the source for the Moringa Oleifera leaves that were harvested.

**Animals**

The mature male albino Wistar rats (weighting 200–250g) apiece were used in the investigation. All of these animals were taken from the animal house of Al-Kufa University College of Veterinary Medicine. Before the experiment the rats were kept in cages one to a row provided with tap water and food of the laboratory pellets for one week. The rats were then subjected to a 24 hour fast and water deprivation for 2 hours, following which they were ready for the experiment.

**Animal grouping and treatments**

The five groups of eight albino rats in each group were randomly selected. C- group (control animals) was provided with just distilled water. In the C+ group of rats, which were the ulcerated control the single oral dosage was applied, 30 mg/kg of indomethacin (9) G1 :animals were administered with 200 mg/kg B.W of Moringa leaf extract orally, after 3 days from receiving indomethacin dose for 4 weeks. (10, 11). G 2: (lansoprazole treatment): Induced with ulcers by receiving Indomethacin Administration their treatment with 20 mg/kg of lansoprazole orally after3 days from receiving indomethacin dose for 4 weeks. (12)G3: after 3 days of ulcer induction (10) administration with combination of MO (200mg/kg) and lansoprazole (20mg/kg) orally for 4 weeks.

**Ulcer induction**

Gastric ulceration was induced in the animals according to the procedure described by (9). Briefly, rats were administered with a single oral dose of indomethacin (30 mg/kg body weight). They were deprived of food but had free access to water 24 h prior to ulcer induction. Various degrees of ulceration have manifested 4 h after indomethacin administration**.**

**Samples Collection**

The male rats were sacrificed after all animals were anesthesia by mixed of ketamine and xylazine (90 mg/kg and 40 mg/kg) (13). respect inly by intramuscular IM injection in the day 31 for all groups. Blood collected aseptically by heart puncture using a disposable syringe(5ml) for assessment of Prostaglandin E2 (PGE2). The blood was left at room temperature till being clotted, then, it was centrifuged at (3000) rpm for (15 minutes), the serum was aspirated from the tube into a new Eppendorf tube and stored at (- 20 C) until used for measurement of PGE2 and then the abdominal lumen was opened. The Gastric was removed, the Gastric was kept in plastic containers containing formaldehyde sol. (10%) for histological examination.

**Ethical Approval**

All the procedures in this study were conducted in accordance with College of Veterinary, Medicine, Qassim Green University's Ethics Committee and international animal welfare guidelines. Approval number: qgec /14/2025

**Histological Examination**

Histopathological study: Small pieces of the stomach were fixed in formalin 10 % and embedded in paraffin. All sections of 5µm thickness were stained with Harris's hematoxylin and eosin satin (H and E) for histopathological examination. Images were captured at 10X and 40X magnification using a Leica DM3000 LED microscope (14).

**Statistical Analysis:**

Statistical analysis of the results by using computer program (SPSS), Version 23 one-way and ANOVA of variance (15). The difference was considered significant at ($P \leq 0.05$). Descriptive statistics: mean± standard error statistical analysis of data was performed on the basis with least significant difference LSD.

## Results and Discussion

**Clinical signs**

Clinical signs appears after six hours following oral administration of indomethacin (30 mg/kg, single oral dose), clinical signs observed in all experimental groups included: dark black stools with slightly soft consistency, dehydration, abdominal pain, back arching, lethargy, anorexia, gastric discomfort, reduced food intake, piloerection, hunched posture, decreased physical activity, weight loss, and dark colored stool (melena), rough hair coat, and reduced movement.

**Effect of Moringa Oleifera, Lansoprazole and combination of Lansoprazole and Moringa Oleifera extract: body weight in male rats.**

According to the results presented in (table 1), all the groups showed similar starting body weights. However, after

induction of ulcers, there was a noticeable reduction in weight among all the experimental groups but a continuous increase physiologically within the healthy control group. At the end of the experiment, the untreated control group showed consistent weight loss due to tissue destruction. On the other hand, there was improvement in the trend in terms of weight gain in all experimental animals that were under therapy. This was more pronounced in the combined therapy where there was a full return of weight gain to physiological levels.

**Table 1.** Body weights of ulcer rats treated with Moringa Oleifera, Lansoprazole and combination of Lansoprazole and Moringa Oleifera extract

| Groups / Time | C- | C+ | G1 | G2 | G3 |
|---|---|---|---|---|---|
| 0DAY | 241.4 ±2.9 Ba | 240.9 ±1.5 Aa | 241.7 ±1.9 Ba | 242.1 ±1.8 Ba | 242.4 ±2.08 Ba |
| 3 days after induction | 246.4 ±2.9 Ba | 224.1 ±1.6 Bb | 224.6 ±1.6 Cb | 224.5 ±1.4 Cb | 225.4 ±1.8 Cb |
| Treatment period (after 30 days) | 321.1 ±3.8 Aa | 216.7 ±1.4 Cc | 289.6 ±1.6 Ab | 299.5 ±1.6 Ab | 313.7 ±1.5 Aa |
| LSD | 3.7 | | | | |

control negative group, G+ control positive group (Gastric Ulcer Induction) group treated with moringa oleifera, G2 Group treated with Lansoprazole and G3 group treated mix Moringa oleifera+ Lansoprazole

No: 8, Values represent mean ± S.E Means followed by different small letters in the same column are significantly different*(P≤0.05), while Means followed by different small letters in the same row are significantly different. * (P≤0.05).

The positive control group (C+) showed a statistically significant decrease in body weight in comparison to the negative control (C-). The reason behind this weight loss is the ulceration of the gastric mucosa induced by indomethacin, causing abdominal pain, oxidative stress, and inflammation, which affect the nutritional and body mass of the organism (16). On the other hand, the Moringa oleifera extract group (G1) exhibited a statistically significant body weight gain compared to the positive control group (C+). This was because of the rich nutrition in Moringa leaves, being full of proteins, vitamins, and antioxidants, in addition to their ulcer-healing properties (18).

Similarly, those subjected to lansoprazole treatment (G2) showed some significant restoration in body weight. Lansoprazole is an antagonist to gastric acid secretion and acts by reducing ulcers, improving mucosal lining, enhancing digestion processes, and relieving pain-related anorexia (17).

Remarkably, the combination treatment group (G3) showed superior quality in recovering the body weight compared to other individual treatments, with body weights reaching higher levels compared to G1 and G2. The synergy helped to restore body weights fully, reaching statistical equivalence with the control negative group (C-), confirming that the proposed protocol was successful in restoring physiological well-being (17, 18).

**Effect on Serum Prostaglandin E2 (PGE2) Levels.**

The administration led to changes in both mean and standard error of PGE2. Graphs comparing different groups from the experiment can be seen in (Figure 1). The administration of Indomethacin alone led to a significant decrease in serum level of PGE2 compared to that of the normal control group ($P < 0.05$). However, the administration of Lansoprazole, Moringa, and their combinations (Lansoprazole plus Moringa) resulted in an increase in serum PGE2 compared to the ulcer group (rats on Indomethacin).

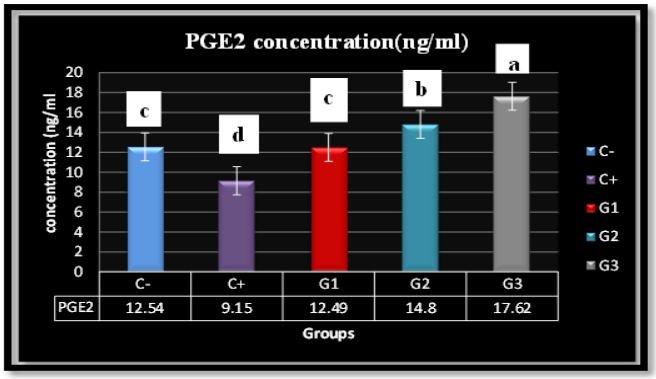


**Figure 1.** Effect of treatment on Serum PGE2 levels

Indomethacin treatment results in a reduction of the concentration of PGE2 by means of inhibiting both COX-1 and COX-2 enzymes (19,20). This leads to a weakening of the mucosal protection barrier, decrease in tissue perfusion and disruption of the bicarbonate-mucus barrier (21,22). Thus, a thinning of the mucus occurs resulting in back diffusion of H+ ions and pepsins, leading to acid damage of the mucous membranes (23, 24). At the same time, indomethacin increases oxidative stress and inflammatory cell migration, leading to ischemia (25).

Moringa oleifera leaf extract, which contains bioactive lipids, increases the level of prostaglandin E2 due to COX-1 activity on mucous tissue in stomach. Such changes improve local blood supply, stimulate production of mucus and bicarbonate as well as stabilize the cell membranes from the oxidative stress induced by indomethacin (18, 26, 27,28, 29). Likewise, lansoprazole undergoes conversion into sulfenamide metabolites that act on the hydrogen-potassium ATPase pump causing irreversible inhibition, thereby inhibiting acid production and enhancing the endogenous synthesis of PGE2 in the body for protection of the gastric lining, leading to rapid healing of ulcers (30, 31). Therefore, the use of both these drugs in conjunction produces significant biological synergism (potentiation) due to simultaneous reduction of acid production by lansoprazole and fortification of mucosal protection by moringa extracts (32).

**The effected of Moringa Oleifera, Lansoprazole and combination of Lansoprazole with Moringa Oleifera extract on the histological alteration of gastric tissue of Rats.**

In the H&E-stained slices obtained from the negative control group, a normal stomach mucosa was noted, with structures such as mucosa, submucosa, muscularis, and serosa.

The mucosa had a normal epithelial lining with well-organized gastric pits, and the fundic glands were distinctly identifiable with isthmus, neck, and basal regions. Below these structures were the well-structured lamina propria, muscularis mucosae, and submucosa .as (figure 2). Following this observation, Histopathologic examination revealed that the positive control group, which was exposed to indomethacin, showed profound changes in architecture, including deep ulceration penetrating the basement lamina of the glandular layer. The areas with ulcers were characterized by significant tissue necrosis with shed squamous epithelial cells. Additionally, an infiltration of mononuclear inflammatory cells was observed around the ulcerated areas. Other features included cyst formation in the glandular acinus, which suggests an obstruction of secretory products with resultant mucosal distress.as (Figure 3).

However, when H&E-stained tissue sections were looked at from a fundic area of the Moringa oleifera group stomach, mucosal destruction was confined to the surface epithelial layer and pit area. This led to the gastric pits (superficial) becoming dilated in the shape of an egg and large dilated acini (cylinders) with built up secretions. The inflammatory infiltrates were mononuclear and were mild to moderate and extended downward over the area of the injury, suggesting an ongoing repair process at the injury site without significant disruption of the deep glandular architecture as seen in figure 4. As a first step in treatment, the histopathology results reveal a more potent ability of Lansoprazole to offer good protection and regeneration to the gastric mucosa compared to other medications. The treatment allows for effective restriction of tissue damage only to the surface epithelial layer, with the maintenance of normal structure and organization of glandular tissues at a deeper level. Moreover, there is a well-defined organization of gastric glands with no dilatation or distortion noted. There is also a marked reduction in inflammatory cells, with their presence strictly localized above the area of injury.as (figure 5). Finally, microscopic examination of rat stomach tissue treated with a combination of Moringa oleifera and Lansoprazole revealed significant mucosal protection and near-normal tissue architecture. Minimal injury was observed, restricted solely to the outermost surface layer with negligible necrotic debris. Notably, no damage was found in the gastric pits or deeper secretory glands, confirming that the deeper mucosal regions remained completely healthy and structurally intact .as (figure 6).

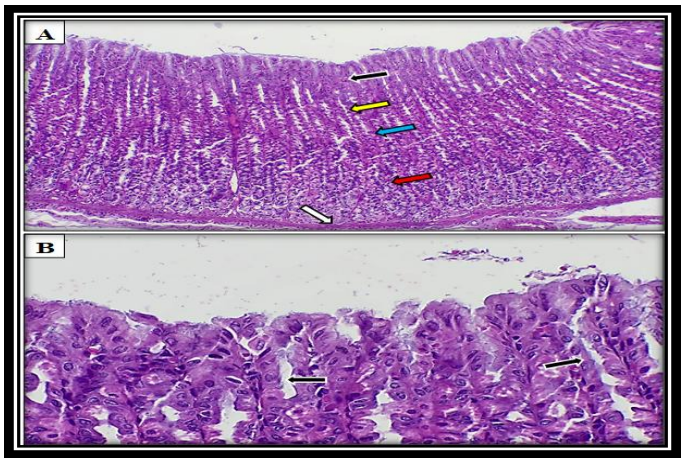


**Figure 2.** Cross histopathological section of fundic region of stomach of control negative group rat. A and B: Normal histological architecture of the gastric mucosa. The surface epithelium and gastric pit region (black arrow) are intact and well-defined. The fundic glands are packed in an organized, parallel arrangement, with clearly visible isthmus (yellow arrow), neck (blue arrow), and basal (red arrow) regions. The lamina propria (white arrow) remains thin and clear, and the underlying muscularis mucosae is continuous and healthy. H&E. A: 100x and B: 400x.

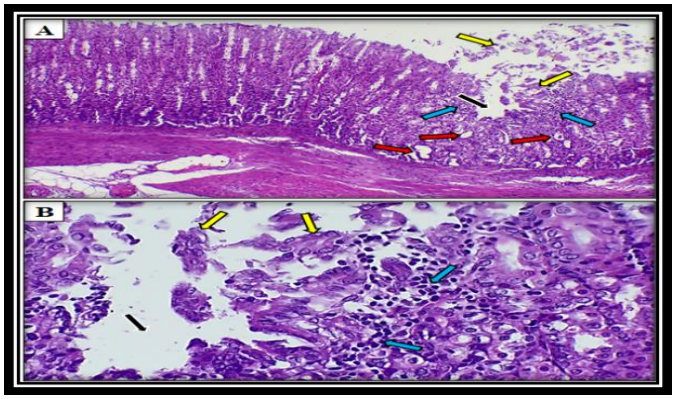


**Figure 3.** Cross histopathological section of fundic region of stomach of control positive group rat. A and B The fundic mucosa showing deep erosion (black arrow) reaching the basal glandular layer, extending through the pits, isthmus and neck regions. The ulcerated site is covered by sloughed necrotic epithelial debris (yellow arrow), where the necrotic cells debris were observed above the ulcer area and inside ulcer. A significant mononuclear inflammatory cell infiltrate (blue arrow) is evident at the base and on both lateral margins of the injury. Glandular outlet obstruction (red arrow) is seen with secondary mucosal distress, in the form of prominent cystic dilation of the glandular acini adjacent to the ulcer. H&E. A: 100x and B: 400x.

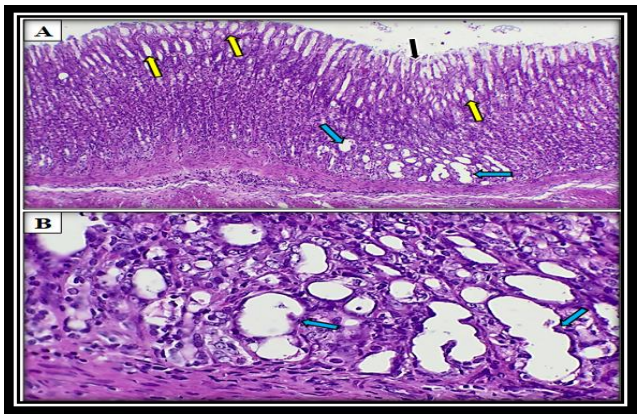


**Figure 4.** Cross histopathological section of fundic region of stomach of rat A and B of Moringa group: The surface epithelial destruction (black arrow) restricted to the pit region in the stomach. The deep glandular structure is well preserved in the group of control positives. On both sides of the injury gastric pits has an oval dilation (yellow arrow) and in the mid to deep mucosa, large circular cysts (number 1: dilated acini) due to the trapped liquid because of the superficial obstruction (number 2). The superficial lesion is also undergoing repair processes, evidenced by the continued presence of a mild to-moderate mononuclear cell infiltrate at the reading location. H&E. A: 100x and B: 400x.

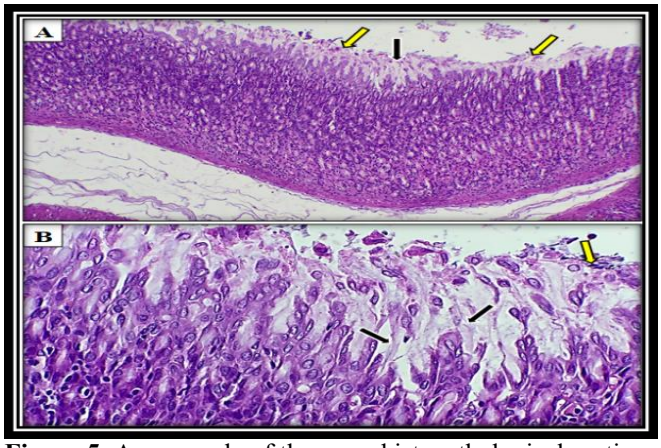


**Figure 5.** An example of the cross histopathological section of fundic region of stomach of Lansoprazole group rat. A and B: only surface epithelium being destroyed (black arrow). It is noteworthy that there are no cystic lesions or dilations of the glands noted in the pits or in the deep mucosa. The section is characterized by a normal gastric gland organization. The recovery of the mucosa is very high, there is only a very small infiltrate of mononuclear cells (signal 5: yellow arrow) over the superficial injury; no internal secretion pressure. H&E. A: 100x and B: 400x

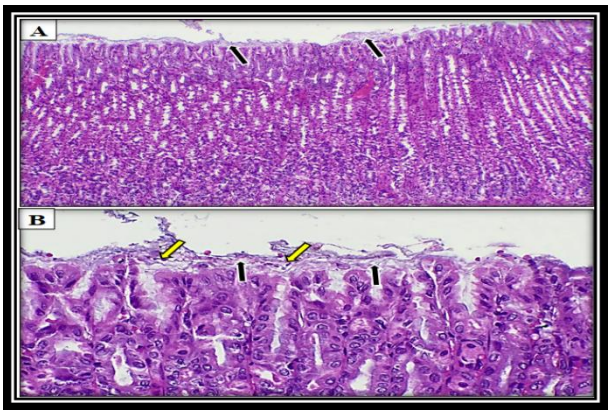


**Figure 6.** Cross histological section of fundic region of stomach of Moringa and Lansoprazole Group rat. A and B: The mucosa is almost totally intact, and the slight injury is confined to the submucosa which is filled with blood exudate and necrotic debris (black arrow). Destructive changes are not seen in the gastric pits or deeper glands, nor are any cystic changes seen. There is little (yellow arrow) mononuclear cell infiltration in the top few layers, where the deeper layers of the mucosa are well-protected and healthy. H&E. A: 100x and B: 400x

The positive control group showed acute mucosal injury, with glandular destruction which was attributed to the inhibitory effect of indomethacin on prostaglandin production (which must be protective) (33). This suppression resulted in significant mucosal barrier dysfunction resulting in a widespread loss of epithelial cells, necrotic, sloughed debris (34), and dense infiltrate of inflammatory cells in the ulcerated areas (35). These severe degenerative changes highlight the successful induction of gastric ulceration, and therefore provide a critical and reliable baseline and reference point for the evaluation of the protective and therapeutic efficacy of candidate interventions (36,37).

The extract stops further damage to the mucosal layer by suppressing pro-inflammatory cytokines and oxidative stress (11) The dilatation of the gastric pits and formation of cysts in the gastric wall are cases of cellular adaptation in response to tissue injury and mucus production in response to protection (38). Furthermore, the continuous mononuclear cell infiltration is a histological criterion of active repair that shows that the biochemistry of Moringa oleifera bioactive molecules promotes the healing speed of epithelium and re-establishes the gastric mucosal barrier (39).

Histological studies have shown that Lansoprazole is a key in maintaining the integrity of the gastric tissue. This effectiveness is the result of its ability to markedly decrease the inflammatory cell infiltrate and to limit damage to the epithelium. It has been argued that this structural preservation is the result of the drug's ability to increase the synthesis of mucosal defense factors and promote the migration of cells to damaged tissues to carry out repair processes; a protective effect that has been seen throughout all the studies performed (40). Lansoprazole has shown to have significant antioxidant activity in the inflamed stomach, where it can reverse the damages caused by oxidative insults and help maintaining the

structural integrity of gastric pits and the organization of the glandular structures (41).

The effectiveness of a combination of this type is due to their synergistic action of maintaining membrane integrity and preventing disruption of the tissue structure due to acid action, which occurs during the combination of Moringa and Lansoprazole with their ability to prevent tissue necrosis and protect the mucous membranes, respectively, and the capability of inhibiting H+/K+-ATPase that neutralizes acid-induced damage to the mucous membranes (42, 40). Such a strategy not only strengthens the body's mucous barrier but also leads to the improvement of gastric environment, while completely curbing inflammation within the superficial mucous layers, which can effectively shorten ulcer healing time and limit inflammation to superficial mucosal layers (39,43).

## Conclusion

The present study establishes that the combination of Moringa Oleifera (MO) extract and lansoprazole exhibits a more effective provides gastroprotective against indomethacin-induced ulcer compared to either treatment alone. This synergistic effect significantly enhances the gastric level of PGE2 and reduces oxidative stress through NF-κB inhibition, leading to an improvement in tissue healing, protection of mucosal integrity and accelerated glandular regeneration.

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**Conflict of interest** None.

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