Original Research Article

Zea mays (CORN) DIET PROTECTS THE GASTRIC TISSUE AGAINST INDOMETHACIN-INDUCED ULCER IN EXPERIMENTAL RATS

ABSTRACT

Introduction: One of the most prevalent gastrointestinal ailments is gastric ulcer, which is caused by an imbalance between protective and aggressive factors. *Zea mays* Corn is a significant cereal crop containing natural phytochemical substances that are sources of nourishment. The methanolic extract of Corn, according to a previous study, lowers stomach acidity and inhibits the percentage of gastric ulceration with no knowledge on the mechanisms involved.

Aim: This study investigated the underlying gastroprotective mechanisms of the Corn diet (ZD).

Materials and Methods: Sixty male Wistar rats were used, randomly grouped into 6; 1(Normal control), 2(Ulcerated control), 3, 4, 5 (prefed with ZD -55%, 65%, 75%) and 6 (cimetidine- 25mg/kg) for 28 days. Gastric ulcer was induced by oral administration of indomethacin (40mg/kg) and animals were sacrificed after 4 hours. The stomach was excised and cleaned, it was then homogenized and centrifuged for biochemical assays.

Results: There is a significant reduction in gastric ulcer area in all treated groups. Significant increase in gastric tissue mucin content and gastric mucosal SOD, NO and PGE2 levels and significant reduction in the MDA was observed in the ZD and cimetidine group. Histological evaluation showed tubular glands closely packed and separated from each other by laminar propia, however there is mild presence of inflammatory cells within the laminar propia in the ZD groups compared to ulcerated control group that showed moderate oedema with infiltration of inflammatory cells with mild vascular congestion in the mucosa. There is significant reduction in the macroscopic gastric mucosal lesions with percentage inhibition of 90%, 92%, 90% and 92% in the ZD (55%, 65% and 75%) and cimetidine group respectively.

Conclusion: Results obtained from this study suggests that Zm diet may have anti-ulcerogenic properties by enhancing antioxidant enzymes as well as, nitric oxide and prostaglandin E2 mechanisms.

Keywords: *Zea mays* Diet, Gastroprotective, Indomethacin, Cimetidine

1. INTRODUCTION

One of the most prevalent gastrointestinal tract disorders, gastric ulcers affect about 5% of the global population and have a mortality rate of one death per 10,000 cases. A number of factors, including an imbalance between aggressive and intrinsic defensive factors, have been linked to its development [1–3]. Alcohol, NSAIDs, mental stress, and Helicobacter pylori infection are among the aggravating factors. Cytoprotective intrinsic factors include mucosal blood flow, bicarbonate, mucus, cell renewal, growth hormones, NO, and prostaglandins [4]. The development of ulcer has been linked to elements including stress, a sedentary lifestyle, smoking, spicy meals, nutritional deficiencies and bacterial infections [5].

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) (Indomethacin, aspirin etc.) are widely used for their analgesic, anti-inflammatory and antipyretic properties. Thereby, contributing to its higher ulcerogenic activities in both animals and humans [7].

It has been suggested that the main factor in the cause of peptic ulcer might be the presence or absence of protective substances. This might be either as a result of refining the staple carbohydrate diet or as a result of an associated low intake of supplementary foods containing the protective substances [8,9]. Natural products have been reported to guard against gastrointestinal inflammation because of their antioxidant and anti-inflammatory properties [10,11]. Therefore, foods derived from natural sources that has antioxidant characteristics and the ability to alter the levels of nitric oxide (NO) and prostaglandin (PG) in gastric tissues may be beneficial in the prevention of indomethacin-induced gastric ulcer.

Maize or Corn (*Zea mays* L.) is an important annual cereal crop of the world belonging to the family Poaceae. The plant has been reported to be used for the treatment of several diseases. The silk has been reported to possess antihyperglycemic, antibacterial, antimicrobial, antihyperlipidemic, and antioxidant activity [12–14].The husk has been reported to possess analgesic, anti-inflammatory, antidiabetic, hypolipidemic, antimalarial, antiplasmodial activities [15–18], The Corn of the *Zea mays* has been reported to enhance ulcerative colitis healing [19]and also decrease gastric acidity and reduce ulcerogenesis by inhibiting percentage ulceration [20]. However, the mechanisms underlying the antiulcerogenic activity have not been understood, therefore, this study aimed at evaluating the gastroprotective mechanisms of *Zea mays* diet.

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2. MATERIALS AND METHODS

2.1 Collection of Plant

Zea Mays (Corn) was purchased in Bodija market in Ibadan, Oyo state. It was dried under shade before further processing. Identification and authentication of the plant were at the University of Ibadan Herbarium, where voucher specimen was assigned as UIH-23046.

2.2 Feed Formulation

Corn was purchased in Bodija market in Ibadan, Oyo state. It was dried under shade before further processing. Then, the dried corns are removed from the cobs, and then grounded in an electrical grinder to almost fine powder. The powdered corns were used in the feed formulation, using the standard composition of laboratory animals' diet (Table 1).

Table 1: Composition of Standard pelletised feed (Ladokun feeds).

COMPONENT	**AMOUNT**
Carbohydrate	60%
Protein	21%
Fat	9%
Fibre	6%
Calcium	0.8%
Phosphorus	0.8%

2.3 Animals

Male Wistar rats weighing 132 ±5.0 g were obtained from the Central Animal house of the Faculty of Basic Medical Sciences, College of Medicine, University of Ibadan, Ibadan, Nigeria. The animals were maintained under standard laboratory conditions and acclimatized for two weeks prior to the commencement of the experiment.

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2.4 Animal Grouping and Treatment

Sixty (60) male wistar rats were divided into two experimental sets of thirty animals per set. Each set was further divided into six (6) groups of five (5) animals per group.

Group 1 (**Normal Control; not induce with ulcer**)

Group 2 (**Ulcerated Control, n=5**)

Group 3 (**CMTD, n=5**) 40mg/kg

Group 4 (**ZD, n=5**) received 55% ZD

Group 5 (**ZD, n=5**) received 65% ZD

Group 6 (**ZD, n=5**) received 75% ZD

The *zea mays* diet (ZD) was given to the animals through feeding and cimetidine (CMTD) was administered by orally with the use of oral gavage which lasted for 28 days. CMTD was grounded into fine powder and dissolved in distilled water, and it was freshly prepared each day.

2.5 Induction of Ulcer

Gastric ulceration was induced in the animals according to the procedure described by Sayanti [21]. Rats were orally administered with a single dose of indomethacin (INDO) (30mg/kg body weight). They were deprived of food but had free access to water 24 hours prior to ulcer induction. Various degrees of ulceration have manifested 4 hours after indomethacin administration.

2.6 Scoring Criteria of Gastric Ulcer

Gastric ulcer scoring was determined using the modified method of Alphin and Ward (1967) as described below [22].

0 - Normal gastric mucosa; no ulcer
0.5 - Punctuate hemorrhage / pinpoint ulcer
1.0 - Two or more hemorrhage ulcer (approximately 2 mm)
2.0 - Ulcer greater than 3 mm in diameter

2.7 Determination of the Ulcer Index

Ulcer index (UI) was calculated as described by Marton-Aragon [23].

UI = Mean ulcer score **x** Number of animals in a group **/**100

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2.8 Determination of Percentage Inhibition

Percentage Inhibition (%) was calculated as:

PI (%) = {Ulcer index of control -Ulcer index of treated/Ulcer index of control} X100

2.9 Histological Studies

Sections were prepared from strips removed from the fundic area of the stomach. The tissues were fixed in 10% formalin and subsequently prepared for histology. Sections were stained as described by Sheehan and Hrapchak (1987), using the Hematoxylin and Eosin stain [22].

2.10 Preparation of Stomach Homogenate and Assay of Antioxidant Indices

The rats stomach tissue used for ulcer scoring was homogenized using a Tefflon Homogenizer and the resulting homogenates were centrifuged at 10 000 revolution per minute (rpm) and the supernatant fraction was collected and stored at $4^{o}C$ for biochemical estimations.

2.11 Determination of Biochemical Parameters

Activity of superoxide dismutase (SOD) and malondialdehyde were respectively assayed with the stomach homogenate by using the methods of Misra and Fridovich (1972) and Adam-Vizi and Seregi (1982). Mucin concentration was determined according to the method of Winzle (1995). Nitric Oxide Level wa**s** assayed via indirect determination of nitric oxide (NO) through the determination of total nitrite [24]. Prostaglandin level was measured using ELISA kits obtained from Bioassay Technology Laboratory (Shanghai, China) according to manufacturer protocols.

2.12 Statistical Analysis

The mean, standard deviation and standard error of mean were calculated. The results were expressed as Mean ± SEM. One-way ANOVA was used to analyze the differences among data. Comparisons between two groups were done using student's t-test. The statistical difference was taken to be significant at $P<0.05$.

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3. RESULTS

3.1 Histopathology

In line with the findings about the UI and percentage inhibition, compared to the sections obtained from normal control (Fig. 1), Stomach sections from ulcerated control (Fig. 2) shows gastric tissue showing moderate inflammation of mucosa, moderate inflammation of the submucosa, moderate oedema with infiltration of inflammatory cells. There is mild vascular congestion in mucosa. Sections from CMTD (Fig. 3) and corn diet group shows round tubular glands closely packed and separated from each other by laminar propia.

3.2 Effect on the Macroscopic Assessment of Indomethacin-Induced Gastric Ulceration

Table 2 show the effect of ZD on the macroscopic assessment of indomethacin induced gastric ulcerated rats (mean ulcer score, ulcer index, and percentage inhibition). The Normal Control group was not induced with ulcer and had a mean ulcer score of (0.00±0.00). The Ulcerated Control group had a mean ulcer score of (13.33±2.33) which was significantly reduced in the 55% (1.33±0.33), 65% (1±0.58), 75% (1.33±0.67) ZD groups and CMTD group (1±1.00) Percentage inhibition of 90%, 92%, 90% and 92% was observed in the ZD groups (55%, 65%, 75%) respectively and 92% in the CMTD group ($p<0.05$).

3.3 Effect on Gastric Mucin Content

Indomethacin caused a significant decrease in gastric tissue mucin level in the ulcerated group when compared to the normal control rats (Figure 11). Pretreatment with CMTD and ZD (75%) led to significant increase in gastric mucin level when compared with ulcerated control and lower concentration of ZD (55% and 65%). (Fig. 4.).

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Table 2: Effect on Mean Ulcer Score, Ulcer Index and Percentage Inhibition

TREATMENT	MEAN ULCER SCORE (MEAN±SEM; mm)	ULCER INDEX (mm^2)	PERCENTAGE INHIBITION (%)
Normal Control	0.00	0.00	0.00
Ulcerated Control	13.33±2.33[a]	0.40	0.00
ZD (55%) + INDO	1.33±0.33[a]	0.04	90%
ZD (65%) + INDO	1±0.58[b]	0.03	92%
ZD (75%) + INDO	1.33±0.67[b]	0.04	90%
CMTD 40 + INDO	1.00±0.00[b]	0.03	92%

Data expressed as Mean ± SEM; n=5, Values are significantly different when $p<0.05$

a = statistically significant when compared with normal control group

b = statistically significant when compared with ulcerated control

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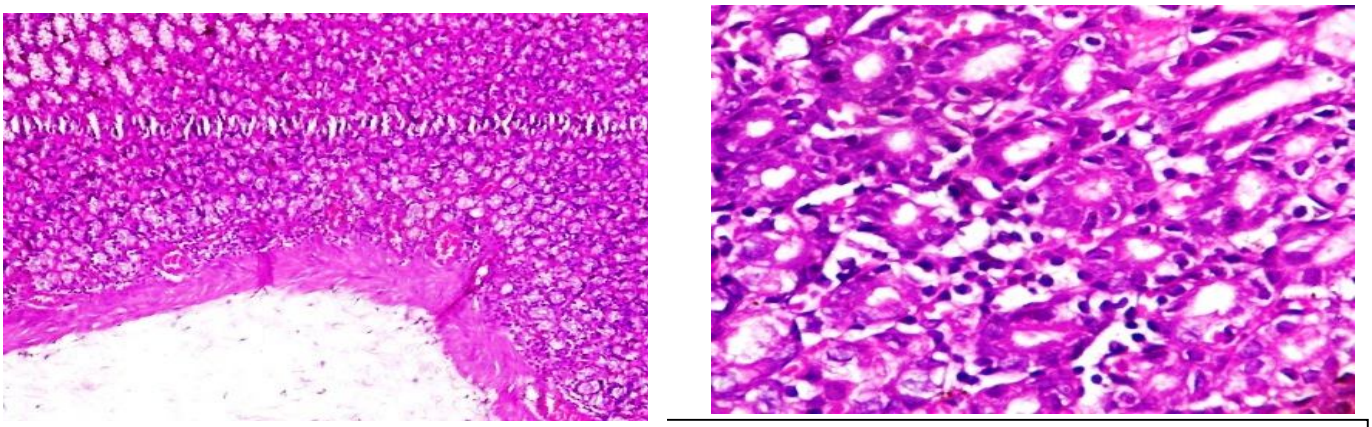

Fig 1. (Normal control): Photograph (x100, x400) showing normal gastric mucosa with no histopathological

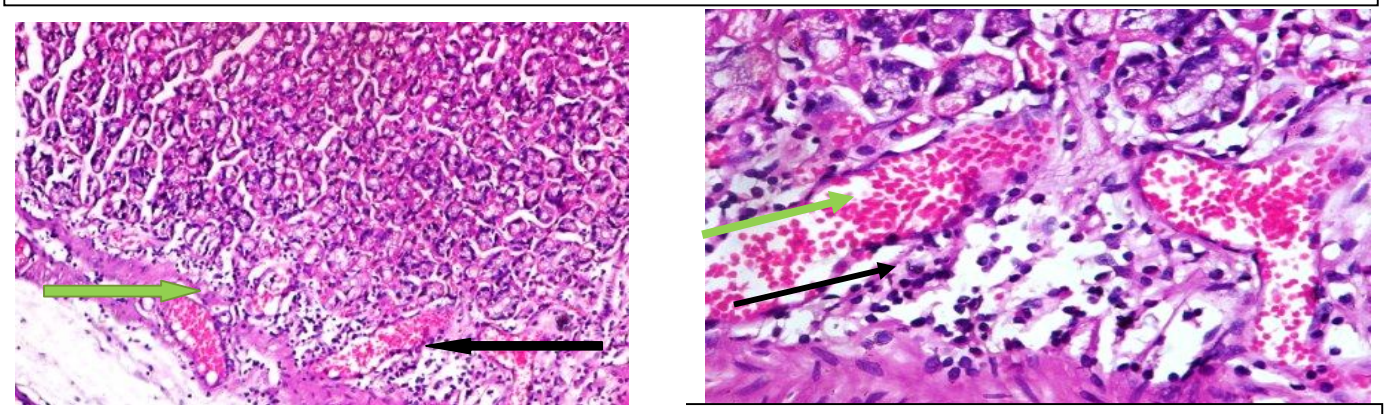

Fig 2. (Ulcerated control): Photomicrographs (x100, x400) of gastric tissue Photomicrographs of gastric tissue show moderate inflammation of mucosa (black arrow), moderate oedema (blue arrow) with infiltration of inflammatory cells and fibroblasts cum mild angiogenesis. There is mild vascular congestion in mucosa (green

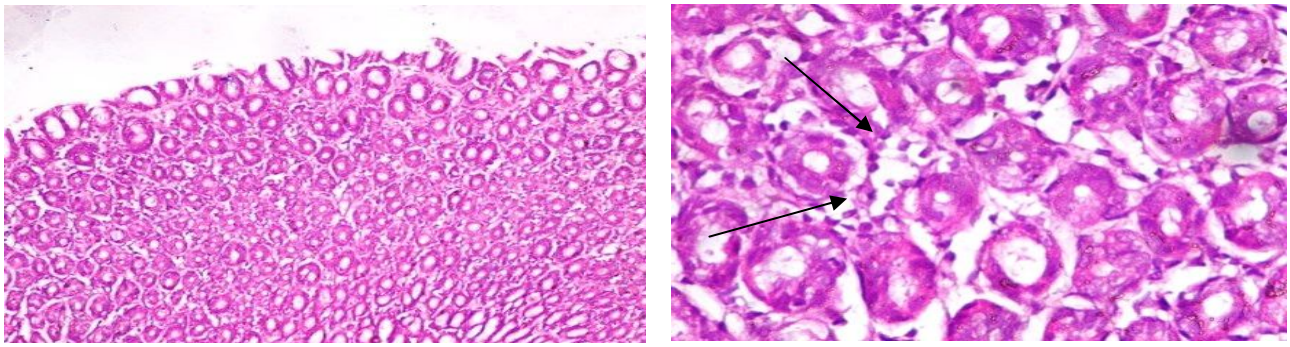

Fig 3. (CMTD 40mg/kg)

Photomicrographs of gastric glands show round tubular glands closely packed and separated from each other by laminar propia, however there is mild presence of inflammatory cells within the laminar propia (thin arrow).

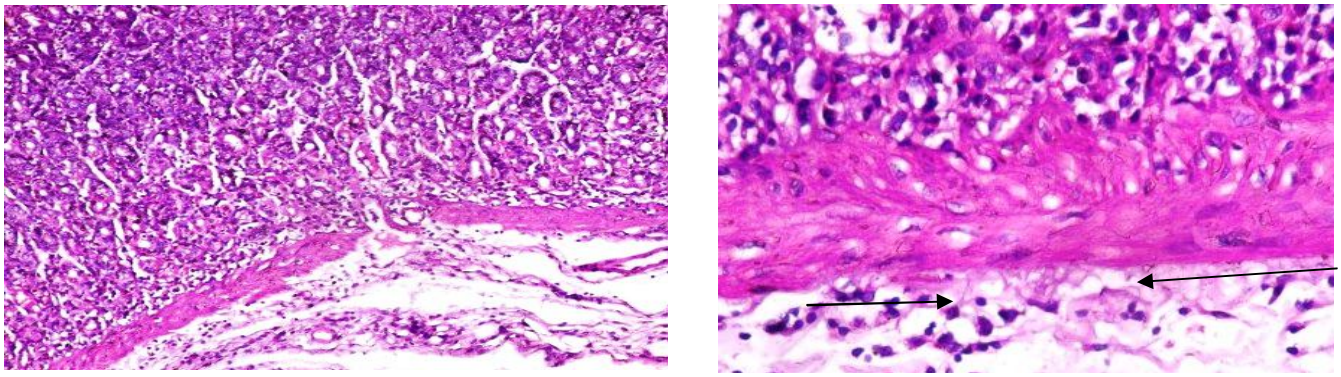

Fig 4. (ZD 55% + INDO) Photomicrograph (x100, x400) of gastric tissue show moderate inflammation of the submucosa (thin arrow), moderate oedema (blue arrow) with infiltration of inflammatory cells and fibroblasts cum mild angiogenesis.

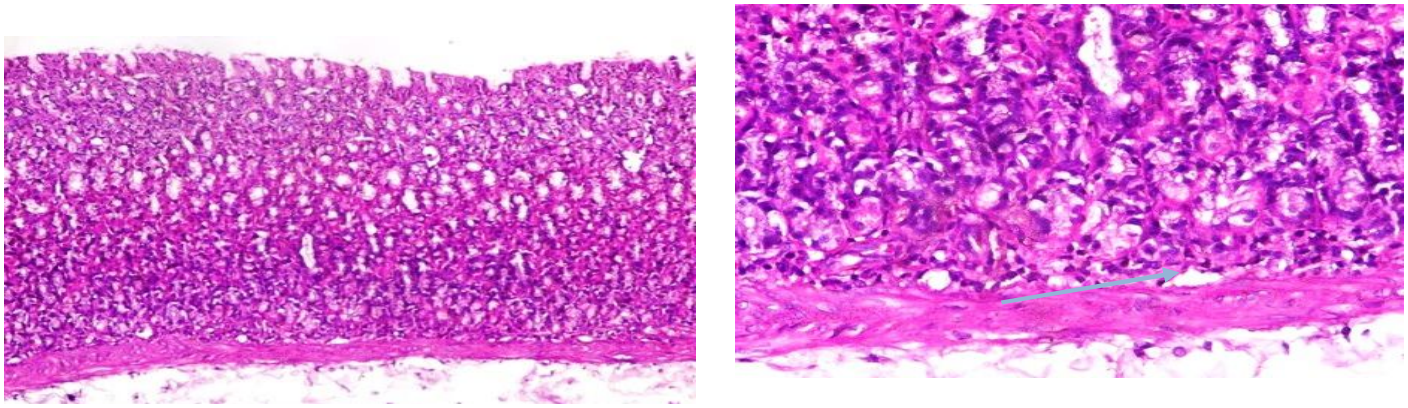

Fig 5. (ZD 65% + INDO) Photomicrograph (x100, x400) of gastric tissue show moderate oedema (blue arrow) with mild infiltration of inflammatory cells (thin arrow).

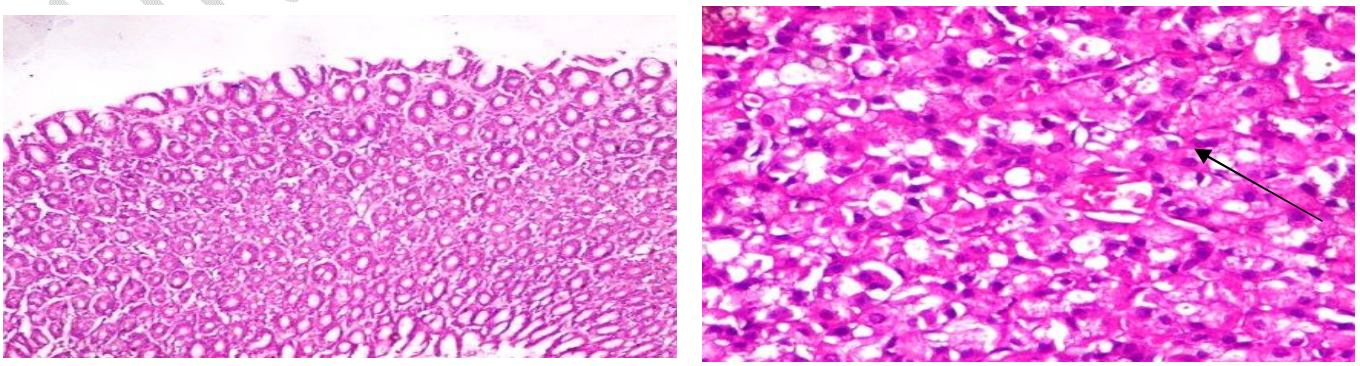

Fig 6. (ZD 75% + INDO) Photomicrograph (x400) of gastric glands show round tubular glands closely packed and separated from each other by laminar propia, however there is very mild infiltration of inflammatory cells within the laminar propia (thin arrow).

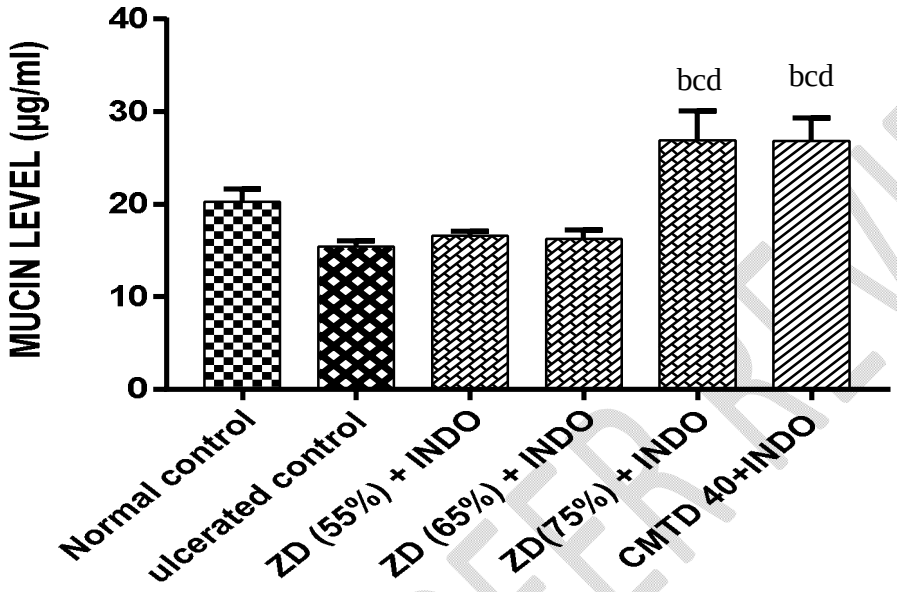

Fig 7. Effect on Gastric Mucin level

Values are significantly different when $p<0.05$ **.**b= statistically significant when compared with ulcerated control; c= statistically significant when compared with ZD (55%) group; d= statistically significant when compared with ZD (65%) group.

3.4 Effect on Gastric MDA and SOD

Indomethacin caused a significant increase in gastric tissue MDA levels in ulcerated control group compared to the normal control rats (Fig. 10). Animals pretreated with cimetidine or Zm diet fed group showed significant decreases in gastric MDA when compared to the ulcerated control group. On the other hand, SOD levels were significantly decreased in the ulcerated control group (Figure 11) while cimetidine pretreated and Zm diet fed group corrected the gastric SOD level compared to levels in the ulcerated control group.

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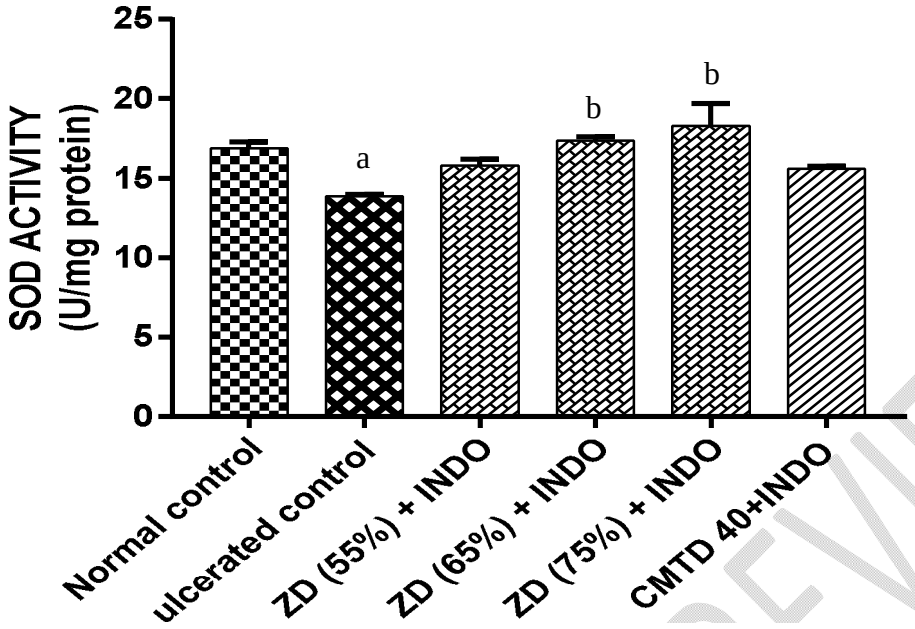

Fig 8. Effect of Zm diet on Gastric Superoxide Dismutase (SOD) level

Values are significantly different when $p<0.05$. a= statistically significant when compared with normal control group

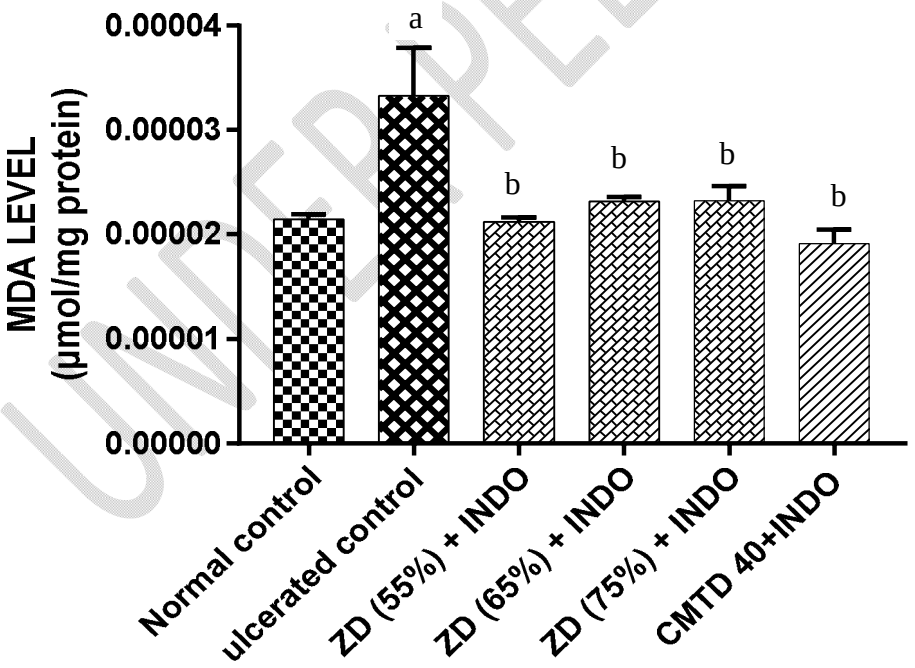

Fig 9. Effect on Gastric Malondialdehyde (MDA) level

Values are significantly different when $p<0.05$. a= statistically significant when compared with normal control; b= statistically significant when compared with ulcerated control

3.5 Effect on Nitric Oxide Level

There was statistical increase in the nitric oxide level in the Zm diet (75%) group when compared with the normal control group. Increase nitric oxide level observed in Zm diet (75%) group and Cimetidine (40mg/kg) group were statistically significant when compared with Ulcerated group, Zm diet (55%) group and Zm diet (65%) group. The decreased nitric oxide level observed in the Cimetidine (40mg/kg) group was statistically significant when compared with Zm diet (75%) group ($p<0.05$) (Fig. 11.).

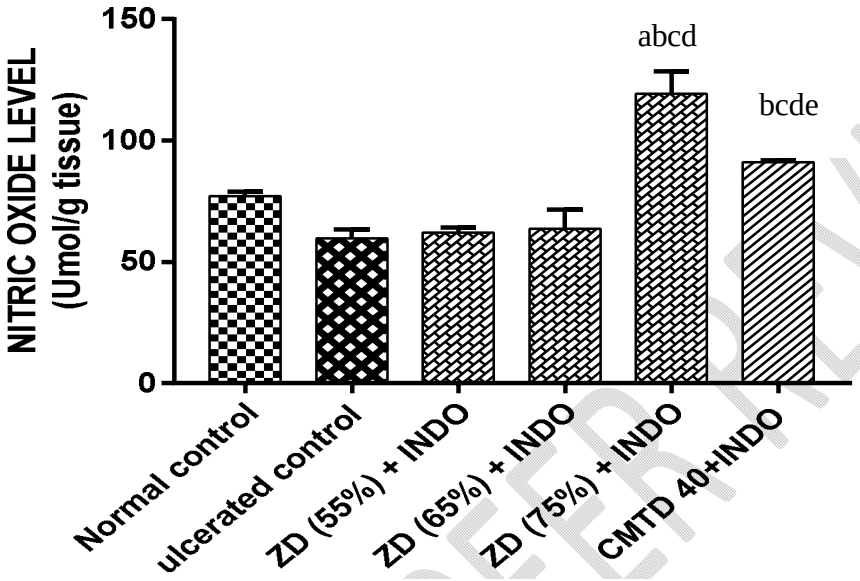

Fig 10. Effect of Zm diet on Nitric Oxide (NO) level

Values are significantly different when $p<0.05$. a= statistically significant when compared with normal control; b= statistically significant when compared with ulcerated control; c= statistically significant when compared with ZD (55%) group; d= statistically significant when compared with ZD (65%) group; e= statistically significant when compared with ZD (75%) group.

3.6 Effect on Prostaglandin Level

The prostaglandin level of ulcerated control group was significantly reduced when compared with normal control group. Prostaglandin level increase significantly in the ZD (65%, 75%) and CMTD group when compared with ulcerated control group ($p<0.05$). The increase observed in the ZD groups was dose-dependent (Fig. 8).

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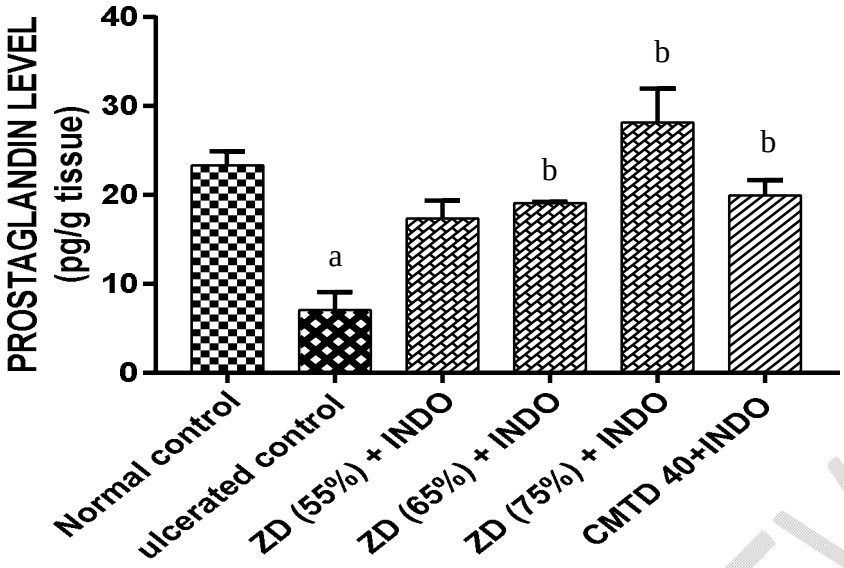

Fig 11. Effect of Zm diet on Gastric Prostagladin level

Values are significantly different when $p<0.05$. a= statistically significant when compared with normal control group, b= statistically significant when compared with ulcerated control group

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4. DISCUSSION

The stomach is exposed to a wide range of substances such as hydrochloric acid, digestive enzymes and bile with the potential to harm the epithelium. The mucosal tissue can, however, occasionally sustain considerable injury. In typical circumstances, the gastric mucosa has the capacity to preserve both its structural integrity and function, while being directly exposed continuously to a variety of harmful elements. Gastric mucosal injuries, however, may happen when aggressive elements succeed in overcoming an intact mucosal barrier or when the mucosal defensive systems are weak.

Maize is an important cereal crop in the world, besides providing nourishment, it also contains phytochemical substances (phenolics, carotenoid and phytosterols) [25]. Phytochemicals are known to have antiulcer action because of their cytoprotective, antisecretory, and antioxidant properties [26]. According to reports, resistant starch (RS) from maize plays a crucial function in maintaining digestive health (pH, epithelial thickness and apoptosis of colorectal cancer cells).

Non-steroidal anti-inflammatory drugs (NSAIDs) are crucial for the treatment of arthritic conditions and other musculoskeletal disorders. They are also used as analgesics in a wide range of clinical situations, but their use has been restricted due to their link to mucosal injury, particularly upper gastrointestinal bleeding and perforation [29,30].

Sizes of generated gastric mucosa lesions are assessed macroscopically and microscopically to determine any drug's or agent's capacity to provide cytoprotection [22]. Macroscopic observation (i.e ulcer score) from this study shows that ZD ameliorated gastric ulceration by reducing ulcer index and significantly increasing percentage inhibition evident by severely eroded mucosal epithelial layer with severe hemorrhagic mucosal ulceration from histological evaluations.

Histopathological studies on the gastric mucosa revealed that administration of indomethacin induced a mucosal ulceration associated with significant increase in lipid peroxidation, as evidently shown by the severely eroded mucosal epithelial layer with severe hemorrhagic mucosal ulceration, moderate inflammation of the submucosa and moderate oedema with infiltration of inflammatory cells. From this study, there was reduced gastric ulceration in the entire ZD and Cimetidine groups when compared with the Ulcerated Control group.

The whole gastrointestinal mucosa is covered in a viscous, elastic, adherent, and translucent gel called gastric mucus, also known as mucin. Mucin is composed of 95% water and 5% glycoproteins. Mucus can also function as an antioxidant, which helps lessen mucosal damage brought on by oxygen free radicals [29]. In this study, increased mucin secretion observed in the 75% Zm diet supplemented indicated improved ability of the mucosal membrane to protect the mucosa from physical damage and back diffusion of hydrogen ions. Mucosal damage can be easily produced by the generation of exogenous and

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endogenous active oxygen and free radicals [30]. An increase in mucus production usually assists the healing process by protecting the mucosa lining against irritant secretions such as, HCl and pepsin thereby enhancing the rate of the local healing process, this is so reflected above. Apparently, the free radicals scavenging property of the *zea mays* diet might contribute in protecting the oxidative damage to gastric mucosa.

In this study, Cimetidine treatment along with ZD significantly reduced MDA levels. This significant reduction in MDA levels suggest decreased lipid peroxidation and antioxidant activity of Cimetidine [31]. ZD provided a marked suppression of oxidative damage due to its radical scavenging capacity along with significant increase in SOD level in the ZD group. This significant reduction in MDA levels along with significant increase in SOD level suggest decreased lipid peroxidation and antioxidant activity of *zea mays* diet.

Nitric oxide (NO) has gastroprotective capabilities against several types of hostile substances and is an endogenous protective factor for gastric cells [32]. It may protect against NSAID damage by promotion of prostaglandin synthesis [33]. It is synthesized by the action of the enzyme nitric oxide synthase (NOS) on nitric oxide donor such as L-arginine. Recently, NO has been reported to be beneficial in gastric healing as administration of NO donors enhances healing [22]. In this study NO concentration was seen to be increased at 75% *zea mays* diet and also, Cimetidine group. This indicates adequate blood supply to the stomach and probably a mechanism by which severity of gastric ulcer formed was reduced.

Prostaglandin, a key molecule involved in the stimulation of the complex array of ulcer healing mechanism, is synthesized in the mucosal cells by cyclooxygenase (COX) enzymes. It stimulates the secretion of bicarbonate, mucus, maintains mucosal blood flow, regulates mucosal turn over and repairs [36,37]. Indomethacin typically increases the sensitivity of the stomach to mucosal damage and gastroduodenal by suppressing prostaglandins production through the inhibition of the cyclooxygenase enzymes [36]. The results obtained in this study showed significant reduction in gastric mucosal prostaglandin E_2 (PGE_2) level in ulcerated control group compared to normal control group and ZD groups significantly increase PGE_2 level when compared to ulcerated rats.

5. Conclusion

In conclusion, Zm diet can protect indomethacin induced gastric ulceration due to its anti-ulcerogenic properties, with the mechanisms related to increase gastric blood flow (dose-dependent), increase gastric mucin concentration at 75% *zea mays* diet and Cimetidine treated, increase SOD (dose-dependent), decrease MDA, increase NO at 75% Zm diet only and increase PGE_2 level (dose-dependent). The presence of resistant starch and phytochemical compounds in corn, particularly phenolics, carotenoids and phytosterols, might be responsible for these anti-ulcerogenic actions.

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Ethical Approval

The study was carried out following approval from the Animal use and care research ethics (ACUREC), University of Ibadan (Assigned number- UI-ACUREC/190075).

REFERENCES

[1] A. Augusti *et al.*, 'Antiulcerogenic activity of Scutia buxifolia on gastric ulcers induced by ethanol in rats', *Acta Pharm. Sin. B*, vol. 4, no. 5, pp. 358–367, 2014, doi: 10.1016/j.apsb.2014.05.001.

[2] F. S. Oluwole, 'Bran in Nigerian Local Rice Confers a High Degree of Protection against Indomethacin-Induced Peptic Ulceration in Albino Rats', no. May, 2016.

[3] K. Koc *et al.*, 'Gastroprotective effects of oleuropein and thymol on indomethacin-induced gastric ulcer in Sprague- Dawley rats', *Drug Chem. Toxicol.*, vol. 43, no. 5, pp. 441–453, 2020, doi: 10.1080/01480545.2018.1530261.

[4] A. M. Abbas and H. F. Sakr, 'Effect of selenium and grape seed extract on indomethacin-induced gastric ulcers in rats', 2013, doi: 10.1007/s13105-013-0241-z.

[5] V. Prabhu and A. Shivani, 'An overview of history, pathogenesis and treatment of perforated peptic ulcer disease with evaluation of prognostic scoring in adults', *Ann. Med. Health Sci. Res.*, vol. 4, no. 1, p. 22, 2014, doi: 10.4103/2141-9248.126604.

[6] 'simon1993.pdf'. .

[7] H. Suleyman, A. Albayrak, M. Bilici, E. Cadirci, and Z. Halici, 'Different mechanisms in formation and prevention of indomethacin-induced gastric ulcers', *Inflammation*, vol. 33, no. 4, pp. 224–234, 2010, doi: 10.1007/s10753-009-9176-5.

[8] F. I. T. and M. Tunstall, 'Progress report Duodenal ulcer in black populations in Africa south of the Sahara', no. 3, pp. 564–576, 1975.

[9] G. T. Adedeji and F. S. Oluwole, 'Bran in Nigerian local rice confers a high degree of protection against indomethacin-induced peptic ulceration in albino rats', *African J. Biomed. Res.*, vol. 15, no. 3, pp. 177–180, 2012.

[10] B. R. Athaydes *et al.*, 'NU', *Food Res. Int.*, p. #pagerange#, 2018, doi: 10.1016/j.foodres.2018.10.057.

UNDER PEER REVIEW

[11] E. M. El Morsy and M. A. E. Ahmed, ‘Carvedilol attenuates l-arginine induced acute pancreatitis in rats through modulation of oxidative stress and inflammatory mediators’, *Chem. Biol. Interact.*, p. 109181, 2020, doi: 10.1016/j.cbi.2020.109181.

[12] J. Guo, T. Liu, L. Han, and Y. Liu, ‘The effects of corn silk on glycaemic metabolism’, 2009, doi: 10.1186/1743-7075-6-47.

[13] Z. Zhang, L. Yang, H. Ye, X. F. Du, Z. M. Gao, and Z. L. Zhang, ‘Effects of pigment extract from black glutinous corncob in a high-fat-fed mouse model of hyperlipidemia’, *Eur. Food Res. Technol.*, vol. 230, no. 6, pp. 943–946, 2010, doi: 10.1007/s00217-010-1242-6.

[14] Nessa, ‘Antimicrobial Activities of Extracts and Flavonoid Glycosides of Corn Silk (Zea mays L)’, *Int. J. Biotechnol. Wellness Ind.*, no. 8765, pp. 115–121, 2012, doi: 10.6000/1927-3037/2012.01.02.02.

[15] B. V Owoyele *et al.*, ‘Analgesic and Anti-Inflammatory Effects of Aqueous Extract of’, vol. 13, no. 2, pp. 343–347, 2010.

[16] K. Roh *et al.*, ‘Anti-inflammatory effects of Zea mays L . husk extracts’, *BMC Complement. Altern. Med.*, pp. 1–8, 2016, doi: 10.1186/s12906-016-1284-9.

[17] J. E. Okokon *et al.*, ‘Antimalarial and antiplasmodial activity of husk extract and fractions of Zea mays’, *Pharm. Biol.*, vol. 0, no. 0, p. 000, 2017, doi: 10.1080/13880209.2017.1302966.

[18] J. E. Okokon, J. Obot, and L. U. Amazu, ‘Antiulcerogenic activity of husk extract of Zea mays’, no. July, 2018.

[19] S. Ige, M. Adeniyi, A. Olayinka, and I. Kehinde, ‘Role of dietary maize formulations in the healing of experimental acetic acid induced ulcerative colitis in male rats’, *Chin. J. Physiol.*, vol. 63, no. 4, pp. 156–162, 2020, doi: 10.4103/CJP.CJP_33_20.

[20] S. M. Jadhav, ‘PROTECTIVE EFFECT OF ZEA MAYS (POACEAE) ON EXPERIMENTALLY INDUCED GASTRIC ULCER IN RATS Department of pharmacy , Vidyabharati College of Pharmacy ’, no. 8, pp. 593–600, 2016.

[21] S. Bhattacharya, S. R. Chaudhuri, S. Chattopadhyay, and S. K. Bandyopadhyay, ‘Healing properties of some Indian medicinal plants against indomethacin-induced gastric ulceration of rats’, *J. Clin. Biochem. Nutr.*, vol. 41, no. 2, pp. 106–114, 2007, doi: 10.3164/jcbn.2007015.

[22] D. Usman, O. F. Sunday, and A. T. Gabriel, ‘Effects of L-arginine and L-citrulline on Indomethacin-Induced Gastric Ulceration and Gastric pH in Male Albino Rats’, vol. 4, no. 6, pp. 623–640, 2014.

UNDER PEER REVIEW

[23] S. Martín-Aragón, J. Benedí, and A. Villar, 'Studies on the antiinflammatory and antiulcerogenic activities of tuberaria lignosa extracts in experimental animals', *Pharm. Biol.*, vol. 32, no. 1, pp. 27–32, 1994, doi: 10.3109/13880209409082968.

[24] L. J. Ignarro, G. M. Buga, K. S. Wood, R. E. Byrns, and G. Chaudhuri, 'Endothelium-derived relaxing factor produced and released from artery and vein is nitric oxide.', *Proc. Natl. Acad. Sci. U. S. A.*, vol. 84, no. 24, pp. 9265–9269, 1987, doi: 10.1073/pnas.84.24.9265.

[25] T. R. Shah, K. Prasad, and P. Kumar, 'Maize — A potential source of human nutrition and health : A review', *Cogent Food Agric.*, vol. 54, no. 1, pp. 1–9, 2016, doi: 10.1080/23311932.2016.1166995.

[26] C. K. Sen, S. Khanna, and S. Roy, 'Vitamin E Byond tocopherols', *Asia Pac. Allergy*, vol. 1, no. 3, pp. 2088–2098, 2006.

[27] Z. Morise, D. N. Granger, J. W. Fuseler, D. C. Anderson, and M. B. Grisham, 'Indomethacin induced gastropathy in CD18, intercellular adhesion molecule 1, or P-selectin deficient mice', *Gut*, vol. 45, no. 4, pp. 523–528, 1999, doi: 10.1136/gut.45.4.523.

[28] J.-M. Park *et al.*, 'S-allyl cysteine alleviates nonsteroidal anti-inflammatory drug-induced gastric mucosal damages by increasing cyclooxygenase-2 inhibition, heme oxygenase-1 induction, and histone deacetylation inhibition', 2014, doi: 10.1111/jgh.12730.

[29] M. G. Repetto and S. F. Llesuy, 'Antioxidant properties of natural compounds used in popular medicine for gastric ulcers', *Brazilian J. Med. Biol. Res.*, vol. 35, no. 5, pp. 523–534, 2002, doi: 10.1590/S0100-879X2002000500003.

[30] Y. Naito *et al.*, 'Effects of oxygen radical scavengers on the quality of gastric ulcer healing in rats', *J. Clin. Gastroenterol.*, vol. 21, no. SUPPL. 1, pp. 2019–2021, 1995.

[31] M. Ito, T. Segami, T. Tsukahara, R. Kojima, and Y. Suzuki, 'Effect of cimetidine and omeprazole on gastric ulcer healing of rats with limited food intake time', vol. 263, pp. 245–251, 1994.

[32] M. Samini, L. Moezi, N. Jabarizadeh, B. Tavakolifar, H. Shafaroodi, and A. R. Dehpour, 'Evidences for involvement of nitric oxide in the gastroprotective effect of bromocriptine and cyclosporin A on water immersion stress-induced gastric lesions', *Pharmacol. Res.*, vol. 46, no. 6, pp. 519–523, 2002, doi: 10.1016/S1043661802002293.

[33] D. Salvemini, T. P. Misko, J. L. Masferrer, K. Seibert, M. G. Currie, and P. Needleman, 'Nitric oxide activates cyclooxygenase enzymes', *Proc. Natl. Acad. Sci. U. S. A.*, vol. 90, no. 15, pp. 7240–7244, 1993, doi: 10.1073/pnas.90.15.7240.

UNDER PEER REVIEW

[34] H. S. El-Abhar, ‘Coenzyme Q10: A novel gastroprotective effect via modulation of vascular permeability, prostaglandin E2, nitric oxide and redox status in indomethacin-induced gastric ulcer model’, *Eur. J. Pharmacol.*, vol. 649, no. 1–3, pp. 314–319, 2010, doi: 10.1016/j.ejphar.2010.09.012.

[35] J. L. Wallace, ‘Prostaglandins, NSAIDs, and gastric mucosal protection: Why doesn’t the stomach digest itself?’, *Physiol. Rev.*, vol. 88, no. 4, pp. 1547–1565, 2008, doi: 10.1152/physrev.00004.2008.

[36] K. Takeuchi and K. Amagase, ‘Roles of Cyclooxygenase, Prostaglandin E2 and EP Receptors in Mucosal Protection and Ulcer Healing in the Gastrointestinal Tract’, *Curr. Pharm. Des.*, vol. 24, no. 18, pp. 2002–2011, 2018, doi: 10.2174/1381612824666180629111227.

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