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Anti-ulcerogenic mechanism of magnesium in indomethacin induced gastric ulcer in rats

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Summary: The gastric mucosa is continuously exposed to various agents like food condiments, spices, alcohol, acids and drugs, some of which are implicated in the pathogenesis of gastric ulcer. Magnesium compounds commonly used as laxatives and antacids have been reported to prevent ulcer formation but the mechanisms underlying this potential is unknown. This study therefore seeks to evaluate the gastro-protective mechanism of magnesium in the stomach through its effect on the parietal and mucus cells. Thirty-six male albino rats divided into 6 groups of 6 rats each were used. Group 1 was control, Group 2 was ulcer induced and untreated, Group 3 was treated with 500mg/kg b.w magnesium alone, Group 4 was pre-treated with 500mg/kg b.w magnesium before inducing ulcer, Group 5 was pre-treated with 500mg/kg b.w magnesium and 20mg/kg omeprazole 4 hours before inducing ulcer, Group 6 was treated with 20mg/kg omeprazole 4 hours before inducing ulcer. Animals were sacrificed 6 hours after ulcer induction and their stomachs were removed for ulcer scoring and histological analysis. A significant reduction was observed in the ulcer scoring of magnesium pre-treated ulcerated rats (9.4±0.8) compared with ulcerated untreated (20.8±0.9) groups. Parietal cell count of magnesium pre treated ulcerated group significantly decreased (169.7±18.9) compared with ulcerated untreated group (310.5±34.7). Mucous cell count of magnesium pre-treated ulcerated group (264.6±8.3) significantly increased compared with ulcerated untreated group (170.0±17.7). This study shows that magnesium possesses anti-ulcerogenic properties due to its ability to reduce the number of parietal cell and increase mucous cell counts.

Keywords*:* Magnesium, Ulcer, Parietal Cell, Mucus Cell

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INTRODUCTION

The stomach, in particular the gastric mucosa is continuously exposed to various agents such as food, acid, alcohol, pepsin, food condiments /spices, bacteria (*Helicobacter pylori*) and drugs which could sometimes be injurious to the stomach (Peskar *et al.*, 1998). Increased gastric acid secretion, pepsin secretion, inhibition of prostaglandin synthesis, cell proliferation, diminished gastric blood flow and gastric motility have been implicated in the pathogenesis of gastric ulcer (Toma *et al.*, 2005).

Ulcer is an erosion of the mucosal layer or excavation of the surface of a tissue as a result of the sloughing of inflammatory necrotic tissue (Yang *et al.*, 2006). The normal stomach maintains a balance between protective factors and aggressive factors (Rifat *et al.*, 2004). Gastric ulcers therefore develops when aggressive forces (increased hydrochloric acid and pepsin, parietal cell mass and gastrin production) overcome the protective factors (prostaglandins and increased mucous cells) (Wallace 2001 ; Zhu *et al.*, 2008). Drug treatment of peptic ulcer is targeted at either counteracting aggressive factors like acid, pepsin, active oxidants, Platelet Aggravating Factor 'PAF', leukotrienes, and exogenous factors including Non Steroidal Anti inflammatory Drugs (NSAIDs) or stimulating the mucosal defences such as mucus, bicarbonate, normal blood flow, prostaglandins and nitric oxide (Borelli *et al.*, 2000). The topical effects of NSAIDs are superficial gastric erosions and petechial lesions (Wallace, 2005).

The goal of treating ulcer disease are to relieve pain, heal the ulcer and prevent its' reoccurrence; since appropriate treatment regimen has not been found, efforts are still on to find suitable treatments for ulcer (Ibrahim *et al.*, 2008).

Some natural rich sources of magnesium include whole grains, green leafy vegetables, almonds, cashew, black walnuts, legumes (Marrier, 1986) but few metal elements have been known to possess anti – ulcer potentials, one of such is magnesium (Barragen *et al.*, 2008). Magnesium compounds are used as laxatives (Milk of magnesia) and in numerous conditions to help stabilize abnormal nerve excitation and blood vessel spasm. It is a co – factor of many enzymes especially those utilizing high phosphate bonds (Holmgren *et al.*, 1963). It is used in the formulation of antacids which act by neutralizing

stomach acid and also by reducing gastric acid secretion thereby providing suitable medium for healing to occur (Grubel *et al.,* 1997*).* In spite of the multi-functional properties of magnesium, its gastro-protective mechanism has not been fully elucidated. This study therefore seeks to investigate further the gastro-protective mechanism of magnesium through its effects on the parietal and mucous cells in male albino rats induced with ulcer.

MATERIALS AND METHODS

Animals: Thirty–six (36) male albino Wistar rats weighing 240g to 260gs were used for this study. The rats were obtained from the Central Animal House, College of Medicine, University of Ibadan. All the animals were maintained under standard conditions (12 h light and 12 h dark), acclimatized for 2 weeks and had free access to clean water and rats chows. Animals were kept in ventilated cages at room temperature (28-30^{o}C). Rats handling and treatments conform to guidelines of National Institute of Health (NIH publication 85-23, 1985) for laboratory animal care and use.

The animals were divided into six groups of six animals each. Group 1 (control) consists of normal rats that had free access to clean water and rat chows. Group 2 animals were induced with ulcer using 40mg/kg b.w of indomenthacin after 24h fast. Group 3 consist of animals pre-treated with 500mg/kg b.w of magnesium daily for 14 days. Group 4 animals were pre-treated with 500mg/kg b.w of magensium daily for 14 days, fasted for 24 hours before ulcer induction with 40mg/kg b.w of indomethacin and sacrificed 6 hours after ulcer induction. Group 5 consist of animals pre-treated with 500mg/kg b.w magnesium daily for 14 days then 20mg/kg of omeprazole 4 hours prior to induction of ulcer with 40mg/kg b.w of indomethacin. The animals were sacrificed 6 hours after ulcer induction. Group 6 animals were treated with 20mg/kg of omeprazole 4 hours prior to induction of ulcer with 40mg/kg b.w of indomethacin. Animals were sacrificed by cervical dislocation 6 hours after ulcer induction; the stomachs were removed and cut open for ulcer scoring, parietal and mucus cell count.

Preparation of drugs

Magnessium: Magnesium Sulphate salt (Triveni Chemicals, Vapi, India) given at a dose of 500mg/kg b.w orally. Magnesium sulphate (20g) was dissolved in 100mls of distilled water.

Omeprazole: Omeprazole (JiangSu Ruinian Qianjin Pharmaceutical Ltd, JiangSu, China) purchased from Danax Pharmacy in Ibadan. The dose administered was 20mg/kg b.w orally 4 hours before ulcer induction (Tari *et al,* 1996).

Ulcer Induction:

Indomethacin (Embassy Pharmaceutical and Chemical Ltd) was purchased from Danax Pharmacy, Ibadan. The dose used for ulcer induction was 40mg/kg b.w. administered orally (Moustafa *et al.,* 2013).

Indomethacin preparation: Indome-thacin (100mg) was dissolved in 0.5mls of 1.25% sodium bicarbonate and administered 6 hours prior to sacrifice (Frucht-Pery *et al,* 1999).

Ulcer scoring: 6 hours after ulcer induction, animals were sacrificed by cervical dislocation and their stomach excised surgically by cutting through the *linea alba* on the anterior abdominal wall. The stomach was opened up by an incision along the greater curvature, rinsed with normal saline and examined with the aid of a hand lens for ulcer scoring after which it was fixed in 10% formalin for 48 hours before histological preparation and analysis of parietal and mucous cells were done.

Macroscopic scoring of ulcer: This was done according to the method of Alphin and Wards (1967), modified by Elegbe (1974).

Determination of gastric parietal and mucous cell population

The animals were sacrificed and the stomach removed as quickly as possible into normal saline. The stomach was opened along the greater curvature, washed and transferred into 10% formalin. Sections were prepared from strips removed from the fundic area of the stomach and stained using the method of Marks and Drysdale (1957) as modified by Oluwole *et al* (2007), using Hematoxylin and Eosin stain. The various gastric mucosal secretory cells were clearly differentiated, taking up different colours. The nuclei of the parietal cells were stained deep blue while the mucous cells were clearly vacuolated. Five counts from randomly selected fields were made on each section and the average count per unit area was calculated for each stomach by dividing the number of cells seen by the number of counts made.

Statistical Analysis

Experimental data were analyzed using one way analysis of variance (ANOVA) and multiple range tests to determine significant difference between means. Difference between means were regarded as significant at $p<0.05$

RESULTS

Macroscopic scoring of ulcer

There was a significant decrease ($p<0.05$) in the ulcer score of Magnesium pre-treated ulcerated (group 4) (9.42± 0.80), Magnesium + Omeprazole treated

ulcerated (group 5) (2.00 ± 0.62) and Omeprazole pre-treated and ulcerated (groups 6) (1.67±0.40) compared with ulcerated untreated (group 2) (20.83 ± 0.85). There was no evidence of ulcer in control (group 1) and Magnesium pre–treated normal (group 3) as shown in Table1.

Table 1: Anti-ulcerogenic effect of magnesium pretreatment on ulcer formation.

GROUPS	Treatments.	SCORE (mm)
1	Normal rats	0
2	Ulcerated untreated	20.83± 0.85
3	Mg^{2+}treated normal rats	0
4	Mg^{2+} treated ulcerated rats	9.42±0.8
5	Mg^{2+}+Omeprazole normal rats	2.00± 0.62
6	Omeprazole-treated ulcerated rats	1.67 ± 0.4

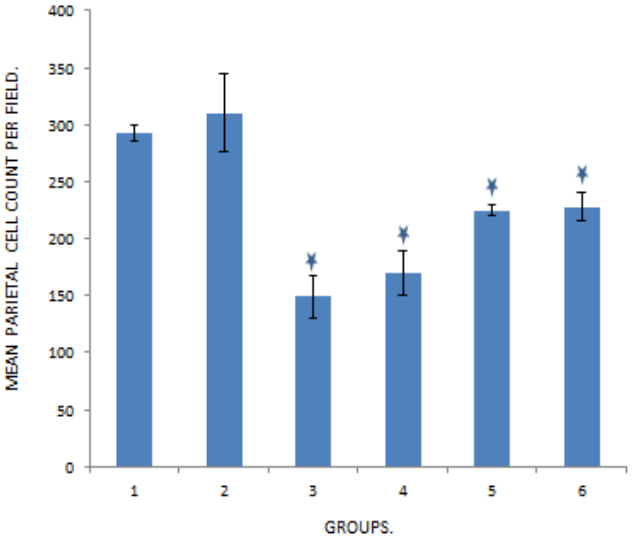

Figure 1: Effect of magnesium on Parietal cell counts in 1=normal, 2=ulcerated, 3 = Magnesium pre-treated normal, 4=Magnesium ulcerated, 5=Magnessium+Omeprazole treated ulcerated and 6= Omeprazole only treated ulcerated rats.* significant p<0.05 reduction when compared with Ulcerated untreated

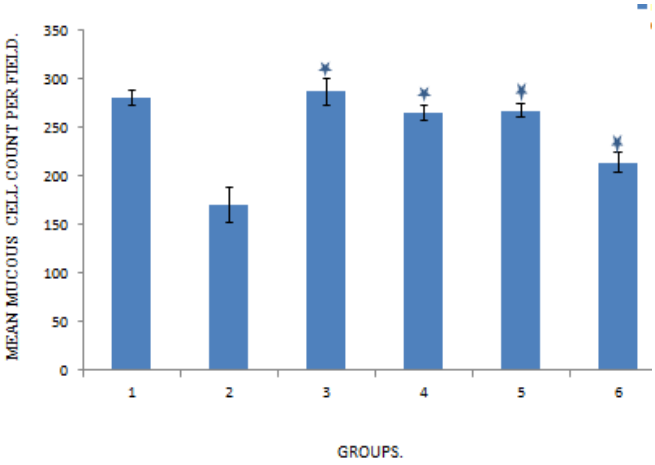

Figure 2: Effect of magnesium on mucus cell count in 1=normal, 2=ulcerated, 3=Magnesium pre-treated normal, 4=Magnesium ulcerated, 5=Magnessium+Omeprazole treated ulcerated and 6 = Omeprazole only treated ulcerated rats. *p<0.05 increase when compared with Ulcerated untreated

Effect of magnesium pre–treatment on parietal cell count

A significant decrease in the parietal cell count of Magnesium pre-treated normal (group 3) (149.00 ± 18.96), Magnesium pre-treated ulcerated (group 4) (169.67 ± 18.94), Magnesium + Omeprazole treated ulcerated (group 5) (233.33 ± 4.55) and Omeprazole only treated ulcerated rats (group 6) (228 ± 12.46) was observed when compared with ulcerated untreated (group 2) (310.50 ± 34.65), Figure 1.

Effect of magnesium pre–treatment on mucous cell count

There were significant increase in the mucous cell count of Magnesium pre-treated normal (286.20±13.54), Magnesium pre-treated ulcerated (264.60 ± 8.28), Magnesium+Omeprazole pre-treated ulcerated (266.60±7.05) and Omeprazole

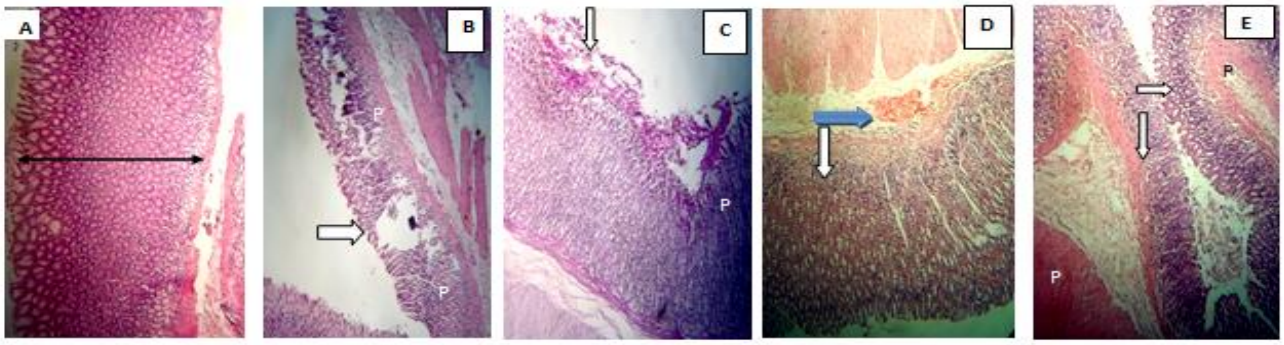

Figure 3. Photomicrograph showing parietal cells from H&E stained stomach sections (X 100) of **A** – normal rats showing normal mucosa, sub mucosal and muscular layer (spanned)., **B** – ulcerated untreated rats showing moderate ulcer (white arrow) within the mucosal layer and mild infiltration of submucosal by inflammatory cells, the parietal cells (P) are present, **C** –magnesium pretreated normal rats showing mild infiltration of submucosa and lamina propria by inflammatory cells (white arrow), the parietal cells (P) are present and of low, **D** – magnesium pretreated ulcerated rats showing infiltration of submucosa and lamina propria by inflammatory cells, (white arrow), there is haemorrhage (blue arrow) at the submucosa area,the parietal cells (P) are present and of moderate quantity, **E** – magnesium and omeprazole pre-treated ulcerated rats showing submucosa, mucosa layers mildly infiltrated by inflammatory cells(white arrow), the parietal cells (P) are present and of moderate quantity.

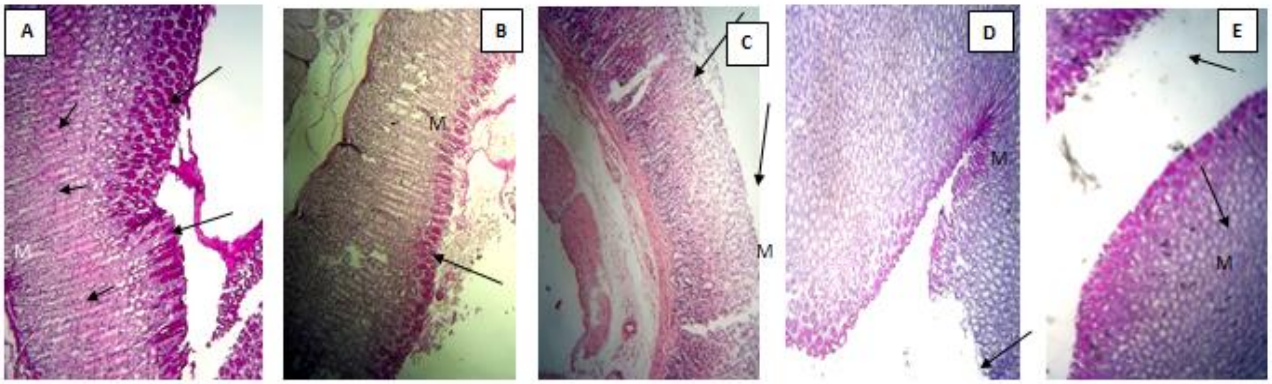

Figure 4. Photomicrograph showing mucous cells from PAS(periodic acid shiff) stained stomach sections (X 100) of **A** – normal rats showing intracellular glandular mucin production (slender short arrows) and abundant surface epithelia mucus production appearing normal (slender long arrows), **B** – ulcerated untreated rats showing mucous cells (M), there is no intracellular glandular mucin production (slender arrow) but there is moderate surface epithelia mucus production. (slender arrow), **C** - magnesium pre-treated normal rats showing mucous cells (M), there is mild intracellular glandular mucin production (slender arrow) but normal surface epithelia mucus production (slender arrow), **D –** magnesium pretreated ulcerated rats showing mucus cells (M), there is mild intracellular glandular mucin production (slender arrow) but moderate surface epithelia mucus production, **E** - ulcerated rats pre-treated with magnesium and omeprazole showing mucus cells (M), there is mild surface epithelia mucus production. (slender arrow).

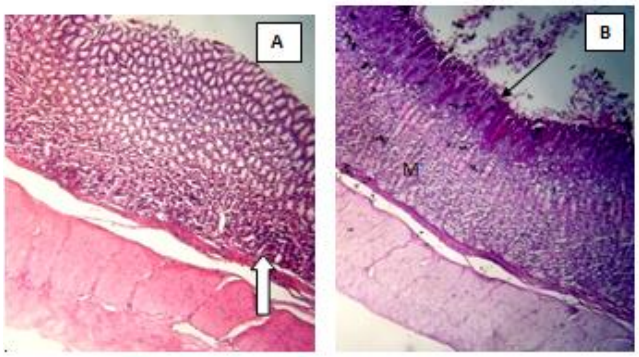

Figure 5: Photomicrograph showing parietal and mucous cells from H&E **(A)** and PAS **(B)** stained stomach sections (X100). **A** – shows submucosa infiltrated by inflammatory cells(white arrow). Mucosa and lamina propria are not infiltrated, the parietal cells are present and of moderate quantity. **B** - shows mucous cells (M), there is moderate surface epithelia mucus production. (slender arrow)

pre-treated ulcerated (213.50±10.12) when compared with ulcerated untreated (170.00±17.73), Figure 2. This result showed that pre-treatment with magnesium stimulated increased mucus cell production thereby increasing the thickness of mucus layer and preventing direct contact with the sub-mucosa layer(Figures 3-5)

DISCUSSION

Magnessium has been reported to reduce acid secretion and prevents ulcer formation (Mathias *et al.*, 2005, Christiansen *et al.*, 1979). Indomethacin, a known Non Steroidal Anti Inflammatory Drug used in the treatment of fever, pain, stiffness and swelling is a known inhibitor of prostaglandin synthesis (Koji, 2012). These NSAIDs have been reported to cause ulcer by inhibiting prostaglandin. Prostanglandins on the other hand have significant roles in cytoprotection by exerting a positive influence on mucus and bicarbonate secretion on surface epithelial cells, mucosal circulation, prevention of hemorrhagic lesion and by aggregating platelets when required thus having protective effect on the gastric mucosa (Faggio *et al.*,2000; Vane and Botting, 2003; Dey *et al.*, 2006; Wallace, 2008). Free carboxyl group present in all NSAIDs form a strong electrostatic bond with postively charged head group of zwitterionic phospholipids of mucus layer. The increase in the solubility of the phospholipids thereby neutralizes its surface activity. Thus NSAIDs topically act on tissue to disrupt the hydrophobic protective lining of the mucus gel layer (Al-Harbi *et al.*, 1997 ; Jainu *et al.*, 2006). In the ulcer induced and untreated group (Figure 3B), the mucus layer was eroded by the presence of indomethacin. This is similar to the reports of Vane,1971; Zhu and Kaunitz, 2008; Lanza *et al.*, 2009 in which prostaglandin and mucus protective function were inhibited by NSAIDs. This shows the vital roles of prostaglandin and mucus in cytoprotection of the stomach. The mild infiltration of inflamatory cells and reduced quantity of parietal cells in the magnessium alone pre-treated group (Figure 3C) showed the ability of magnessium to reduce the quantity of acid secreting cells while it enhances mucus production (Christiansen *et al.*, 1975, 1979 and Stephanie *et al.*, 2005). The effect of magnessium could also be seen in the magnessium pretreated and ulcerated group as the parietal cells are of moderate quantity (Figure 3D) even though the indomethacin

administration resulted in some haemorrahge but not as erosive as in Figure 3B. In the group treated with magnesium and omeprazole (an anti-ulcer drug), mild infiltration of the mucosa by inflamatory cells and moderate quantities of parietal cells showed that omeprazole and magnessium reduced significantly, the number of parietal cells thereby reducing acid secretion and possible ulcer formation (Zhu and Kaunitz, 2008). In Figure 4C, D and E, pre-treatment with magnessium prevented complete absence of glandular mucin and epithelia mucus just like in the normal stomach (Grubel *et al* 1997). The absence of intracellular glandular mucin in the ulcerated untreated group, (Figure 3B) clearly showed the vital role of postaglandin which was inhibited by administration of indomethacin. Administration of omeprazole (an anti-ulcer drug) prevented ulceration though the parietal cells were present in moderate quantity. This is in line with the reports of Tore *et al.*, 1983, Andrews *et al.*, 1992, Kaushik *et al.*, 2003 and Viswanatha swamy *et al.*, 2011 in which omeprazole significantly inhibited both basal and stimulated gastric acid secretion.

Results obtained from this study suggests that oral administration of magnesium caused a reduction in parietal cell count when compared with control and ulcer untreated groups (Figure 1 and 3). A significant difference was also observed in the parietal cell count of magnesium pre-treated ulcerated rats when compared with omeprazole pretreated ulcerated rats.This result supports the reports of Takeguchi (1972) which states that indomethacin blocks synthesis of prostaglandins leading to an increased parietal cell number as well as increased gastric acid secretion. It also supports the findings of Karam and Forte (1994), in which subcutaneous 12 hourly injection of 1mg/kg omeprazole for 5 days resulted in inhibition of acid secretion (H^+/K^+ATPase blockade) and enhanced degeneration of parietal cells in rabbits.

This study showed that there was a significant increase in mucus cells production of magnesium pre-treated groups when compared to ulcerated untreated group (Figure 2). This result indicated that the anti-ulcer property of magnesium might be associated with its ability to rapidly stimulate gastric mucus production thus protecting the gastric mucosa (Azzumi *et al.*, 1993; Jainu *et al.*, 2006).

The significant increase in mucous cell counts in animals pretreated with magnesium as shown in Figure 4 compared to ulcer control further support the observed increase in gastric mucus secretion (Jainu *et al.*, 2006).

Magnesium in addition to its ability to reduce stomach acid production has also been reported to stimulate endogenous production of prostagladins in vascular cells (Satake *et al.*, 2004). It is likely therefore, that the anti-ulcerogenic and gastroprotective effects of magnesium is due to its ability to block indomethacin action and stimulate production of prostanglandins.

This study showed that oral administration of magnesium reduced parietal cell count and increased mucus cells in indomethacin induced ulcerated rats. It is likely that the mechanism by which magnesium exerts its antiulcer property is by reducing the parietal cell mass, stimulate production of prostaglandin which then stimulates copious production of mucous cells.

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