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Coartem Modulates P53, Antioxidants and Biochemical Parameters in Ethanol: Hydrochloric Acid Induced Ulcer in Mice

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Abstract

Coaretem was repurposed in the treatment of ethanol:HCl acid induced ulcer in mice. Forty mice were grouped into four groups (ten mice each group). Control group had free access to water and mice feed. Group 2 received ethanol:HCl orally after fast. Group 3 received ethanol:HCl acid and omeprazole (20mg/kg b.w). Group 4 received Ethanol:HCl acid and coartem (5mg/kg b.w). Stomach tissues were processed for gastric ulcer index, biochemical assays, antioxidants enzyme assays, histopathology and immunohistochemistry staining of p53. The results revealed that the coartem group reduced the burden of ulcer as shown in the percentage inhibition of ulcer index (table 1). The activities of aspartete aminotransferase (AST), alanine aminotransferase and alkaline phosphatase were moderate due to the modulating effect of coartem as shown in the coartem treated group. Superoxide dismutase (SOD), Catalase (CAT), glutathione peroxidase (GPx) and glutathione (GSH) activities and levels decreased in the Ethanol:HCl acid induced group, however in the coartem treated group the activities and levels were increased significantly as compared to the control group. Malondialdehyde and protein carbonyl content levels and p53 expression were increased in the Ethanol:HCl acid induced ulcer group, but in the coartem treated group, the levels of malondialdehyde and protein carbonyl contents decreased significantly as compared to the Ethanol: HCl acid group. The histopathology revealed ulceration marked, injury and edema in Ethanol: HCl acid group, but in the coartem group no injury and edema. In conclusion coartem showed potentials in modulating ethanol:HCl acid induced ulcer by acting as a defensive agent against gastric secretion.

Key words: *Coartem, Ulcer, p53, Antioxidant, Biochemical assays*

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1. Introduction

Gastric ulcer is a disease due to open sores in the walls of the stomach leading to stomach pains, loss of appetite, bleeding, vomiting and it is caused by *Helicobacter pylori*. Other causes of gastric ulcer are excessive usage of (NSAIDs), excessive usage of alcohol, antacids, lifestyle (Njam, 2011). Alcohol consumption over the years can damage the stomach leading to inflammation and gastric ulcer formation (Sagun *et al*., 2017). The mechanism by which alcohol can lead to gastric ulcer formation can be direct toxicity, impaired mucosal defence and increased acid production (Suervaum and Michei, 2002). Non-steroid anti-inflammatory drugs can also cause ulcer by their inhibitory action against prostaglandins. Prostaglandins stimulate the production of bicarbonate that protects gastric lining from the toxicity of acid and pepsin (Wallace, 1986). Ulcer can also be managed by minimizing stress, avoidance of alcohol, avoidance of certain food, smoking and carrying out light exercise (Laine and Jensen, 2012). When the gastric mucosa is destroyed by ethanol or hydrochloric acid, neutrophiles are release and many pro-inflammatory cytokines (Amirshahrokhi and Khalili, 2015). This cascade can give rise to the production of free radicals, therefore antioxidants becomes players in the treatment and management of ulcers (Zhang *et al*., 2015).

Omeprazole belongs to a class of medication that inhibits proton pumps, as its mechanism. It is used in the treatment of gastric ulcers (Massoomi *et al*., 1993). Omeprazole works by inhibiting excessive acid secretion in the gastric lining due to the proton pump inhibition. The reduction in the amount of acidity alleviates heart burn, difficulty in swallowing and regurgitation (Wallace, 1986).

Coartem a combination of artemether and lumefantrine is a medication used for the treatment of malaria. Malaria is a tropical disease caused by a parasite called plasmodium. Mosquitoes are the vectors of the parasite. Artemether acts faster on the parasites especially in the blood and lumefantrine also acts to eliminate the parasite but much slower. The combination makes coartem more effective even against resistant parasite (Warhust *et al*., 2001). Since the management and treatment of ulcer involves protecting the linings of the stomach acids, elimination of the parasite *H. pylori* coartem was chosen to investigate its anti-ulcer properties.

2. Materials and methods

2.1. Chemicals and reagents

Ethanol, pyrogallol, EDTA, DTNB, hydrochloric acid, glutathione, sodium azide, hydrogen peroxide, sodium hydroxide, thiobarbituric acid, Dinitrophenylhydrazine, phosphoric acid, potassium chloride, ALT, AST, ALP Kits, trichloroacetic acid, Tris(hydroxymethyl)aminomethan were obtained from sigma Aldrich USA and Randox London.

2.2. Experimental animals

Wistar strain of albino mice weighing 20-28 g (five weeks old) males were adopted in carrying out this experiment. Forty mice were obtained from the animal house of the department of pharmacology, University of Port Harcourt, Rivers State. They were later housed in the department of pharmacology, Niger Delta University, Bayelsa State. The mice were maintained in a germ free house of 12 hours light and 12 hours darkness.

2.3. Preparation of ethanol: hydrochloric acid

A 100ml solution of 70% ethanol was prepared and used to prepare 150 mM HCl to form 100 ml 70% ethanol / hydrochloric acid (150mM). This solution was used for the induction of ulcer after 24 hours fast (Sung *et al*., 2019).

2.4. Induction of gastric ulcer

After 24 hours of food fast, all animals were divided into four groups, they were administered 0.2 ml of 70% ethanol / 150mM HCl except group one and were treated with either omeprazole (20 mg / kg) as standard or (coartem 5 mg / kg) for 7 days. At the end of the 7th day animals were sacrificed using a chamber filled with chloroform and later by cervical dislocation. Stomach tissues of mice were harvested and divided for ulcer scoring, p53 staining, histopathology and biochemical analysis.

2.5. Biochemical and antioxidant assays

Stomach tissues suspended in phosphate buffer were homogenized in cold centrifuge 4 ^{0}C and centrifuged at 3000 rpm for 10 minutes and supernatant was used for AST, ALT, ALP, superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), GSH, protein carbonyl content and lipid peroxidation (MDA).

2.6. Aspartate aminotransferase

One millilitre of AST reagent (prepared by mixing reagent R1 and R2 as 1ml and 4ml respectively) was added to 0.1ml of stomach tissue homogenate and mixed. Oxidation of NADH was measured kinetically at 340nm using AST reagent as blank for 2 minutes at interval of 30s. AST activity was expressed as (U / L).

2.7. Alanine aminotransferase

Reagent 1 and 2 were appropriately mixed to form ALT reagent. The ALT reagent 1ml was added to 100uL of stomach homogenate and thoroughly mixed. The oxidation of NADH was monitored kinetically at 340nm utilizing ALT reagent as blank for 2 minutes at 30s intervals. ALT activity was expressed as (U / L).

2.8. Alkaline phosphatase assasy

In a test tube ALP reagent 0.1ml was added and also ALP working reagent 0.4ml was also added, followed by 20 uL of stomach homogenate and was catalysed by ALP to P-nitrophenyl and phosphate. The P-nitrophenyl was measured at 405 nm kinetically for 30s intervals. ALP activity was then calculated and expressed as (U / L).

2.9. Superoxide dismutase activity

Marklund and Marklund (1974) method was adopted for the determination of superoxide dismutase. Tris-HCl buffer (50mM) 2.4ml consisting of EDTA (ImM) pH 7.6, was added to 0.3ml pyrogallol (0.2mM) and 0.1ml of stomach homogenate. The absorbance increment was determined at 420nm against blank that was devoid of stomach homogenate at 10s increment for 3 minutes. The enzyme activity was expressed as (units / ml).

2.10. Catalase activity

The method described by Aebi (1984) was utilized stomach homogenate 50µL was added into the cuvette that was already containing 2.95ml of 100mM phosphate buffer and 500mM H_20_2 prepared in phosphate buffer. Absorbance at 240nm was monitored for 3 minutes at 1 minute interval. Catalase activity was calculated and expressed as (units / ml).

2.11. Glutathione peroxidase

The method of Rotruck *et al*. (1973) was followed, in a 2ml reaction containing 500µl phosphate buffer, pH 7.4, 100µl of sodium azide, 200uL of reduced glutathione (GSH), 100 µL of hydrogen peroxide, 500 µL of stomach homogenate and 600µl of distilled water.

2.12. Lipid peroxidation

The concentration of malondialdehyde was determined by the procedure explained by Yagi (1984). A solution containing 15% of trichloroacetic acid (w / v) in 0.25 M hydrochloric acid and 0.37% of thiobarbitric acid. One ml of stomach homogenate was added to 2ml of the solution in a centrifuge tube, mixed and heated for 15 minutes in a water bath at 100 ^{0}C. After cooling on ice, it was then centrifuged at 1000xg for 15 minutes to remove debris. Absorbance was determined at 532nm against a blank that do not contain sample. The levels of MDA were expressed as (units / ml).

2.13. Glutathione content

The stomach homogenate were centrifuged at 3000rpm for 10 minutes to obtain supernatant. The clear supernatant (2ml) was carefully added to 4ml of 0.4 M Tris buffer (pH 8.0). The solution was mixed and 0.1ml of 0.01M DTNB was also added. The absorbance was read after 5 minutes at 412nm according to the method of Anderson and Meister (1985).

2.14. Ulcer scoring

The stomach in control and experimental groups were cut open and rinsed properly with phosphate buffer saline. The gastric lesions in stomach tissues were photographed and processed by image J Soft ware. Pertcentage inhibition was calculated and ulcer index reported in percentages (Wasman *et al*., 2012; Ku *et al*., 2009).

2.15. Histopathology

The stomach tissues preserved in 10% formalin, were later embedded in paraffin wax and were sliced into tiny bits. The slices were later stained in eosin dye and hematoxylin. The slides were later observed under a light microscope (Becur *et al*., 1990).

2.16. Immunohistochemistry

p53 Immunohistochemistry staining of gastric tissues of control, experimental and treated groups were dissected into tiny slices of 3-4 um thick and were stained immunohistochemically using p53 antibodies diluted at 1:100 (Santa Cruz USA). The stained slides were examined utilizing microscope (Omar *et al*., 2017).

3. Statistics

All data were computed as mean ± S.D (n = 10) $p < 0.05$ was computed through one-way analysis of variance using GraphPad prism software.

4. Results

The results revealed that the control group, used as a reference, exhibited complete protection (100%) against ulcers. In contrast, the ethanol group showed no protective effects (0%). However, the combination of omeprazole and ethanol demonstrated a significant protective effect, with a 70.6% reduction in ulcer formation. Meanwhile, the coartem and ethanol group showed a moderate protective effect, with a 20.2% reduction in ulcer formation (Table 1).

Table 1: Ulcer index and percentage protection in control. Group 2, 3 and 4 of ethanol:HCl acid induced ulcer

Groups	Ulcer Index	Protection (%)
Control Group	0	100
Ethanol:HCl Group	44.94	0
Omeprazole and Ethanol:HCl acid group	15.21	70.6
Coartem and Ethanol:HCl acid group	35.86	20.2

The ALT, ALP and AST activities increased significantly in the ethanol:HCl control group ($p < 0.5$). These activities were modulated at the end of the 7 days treatment in omeprazole + ethanol:HCl and coartem + ethanol:HCl groups. This suggested that both omeprazole and coartem modulates ALT, ALP and AST activities (Figure 1).

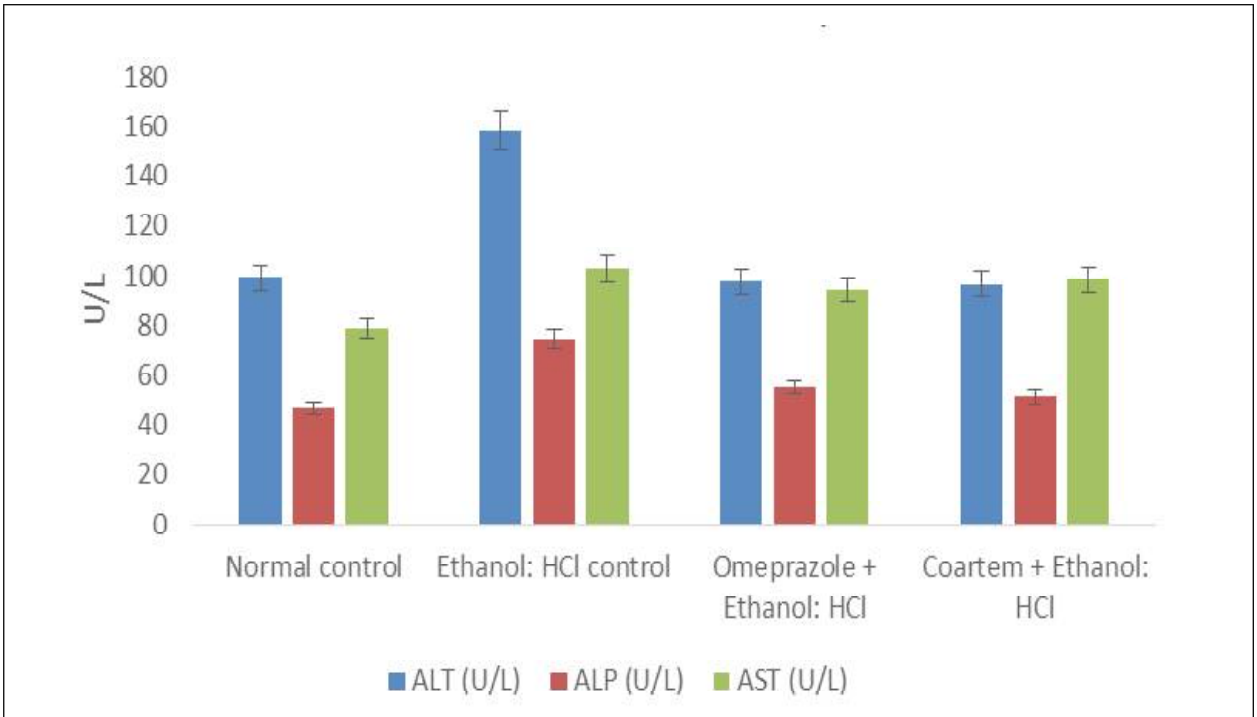

Figure 1: ALT, ALP and AST activity in stomach tissues in the different experiment groups (n=10) after 7 days of treatment.

The Catalase and SOD activities decreased significantly in the ethanol:HCl control group ($p < 0.5$). These activities were modulated at the end of the 7 days treatment in omeprazole + ethanol:HCl and coartem + ethanol:HCl groups. This suggests that both omeprazole and coartem modulates the Catalase and SOD activity (Figure 2).

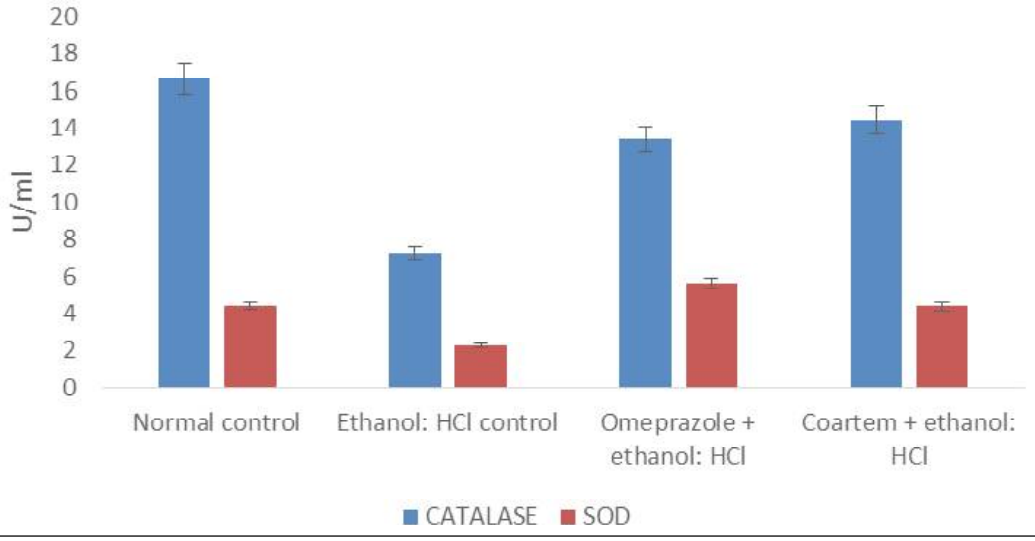

Figure 2: Catalase and SOD activity in stomach tissues in the different experiment groups (n=10) after 7 days of treatment

The GPx and GSH activity and levels decreased significantly in the ethanol:HCl control group ($p < 0.5$). These activity and levels were modulated at the end of the 7 days treatment in omeprazole + ethanol:HCl and coartem + ethanol:HCl groups. This suggests that both omeprazole and coartem modulates the GPx and GSH activity and levels (Figure 3).

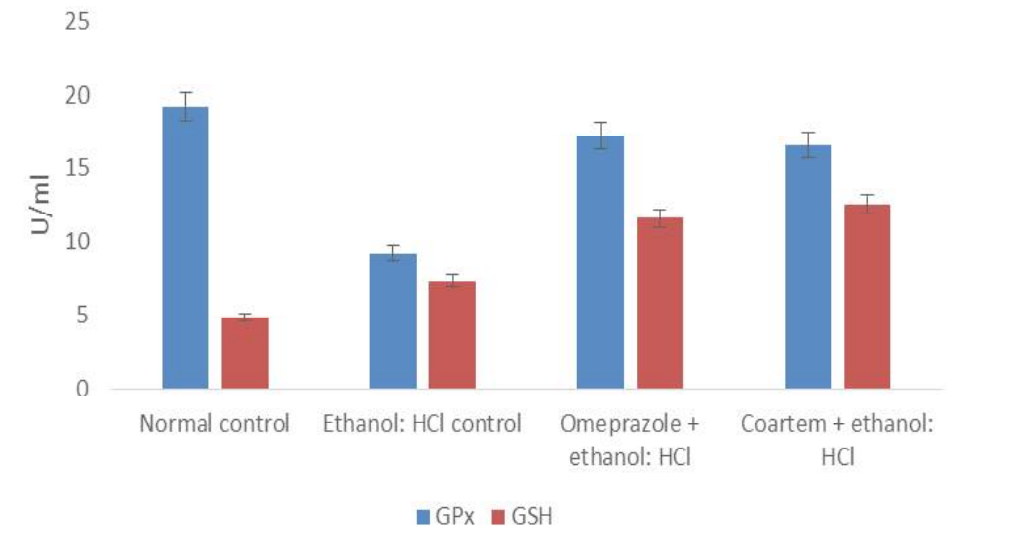

Figure 3: GPx and GSH activity and levels in stomach tissues in the different experiment groups (n=10) after 7 days of treatment

The levels of MDA and Protein carbonyl content increased significantly in the ethanol:HCl control ($p < 0.5$). These levels were modulated at the end of the 7 days treatment in omeprazole + ethanol:HCl and coartem + ethanol:HCl groups. This suggests that both omeprazole and coartem modulates the level of MDA and Protein carbonyl content (Figure 4).

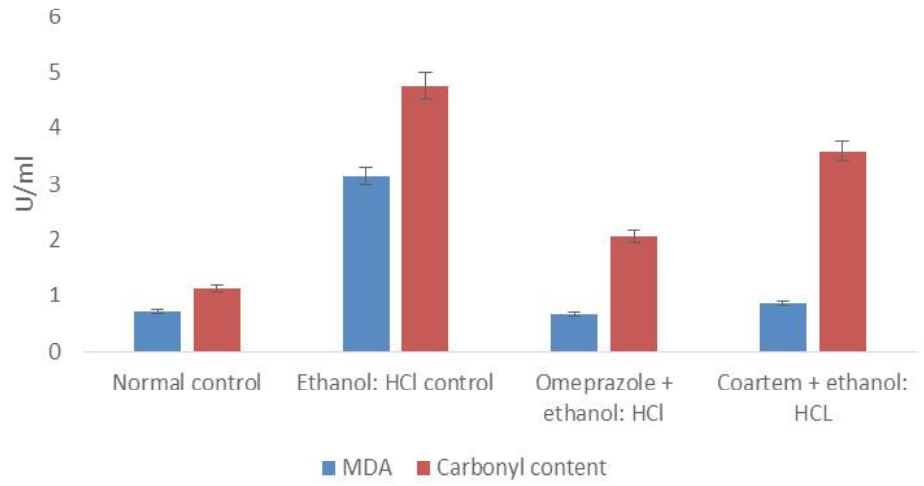

Figure 4: MDA and Protein carbonyl content in stomach tissues in the different experiment groups (n=10) after 7 days of treatment

The Photomicrograph of a normal stomach showing mildly detached epithelium (EP), muscularis mucosa (M) and submucosa (SM) with Parietal cells (P) and chief cells of the stomach tissue (arrows). Detached mucosa with normal appearance of the stomach (Figure 5A). The Photomicrograph (H&E X400) of the stomach showing atrophy of the Mucosa with mild inflammation, muscularis mucosa and submucosa (arrows). Atrophied Mucosa of the stomach tissue (Figure 5B).

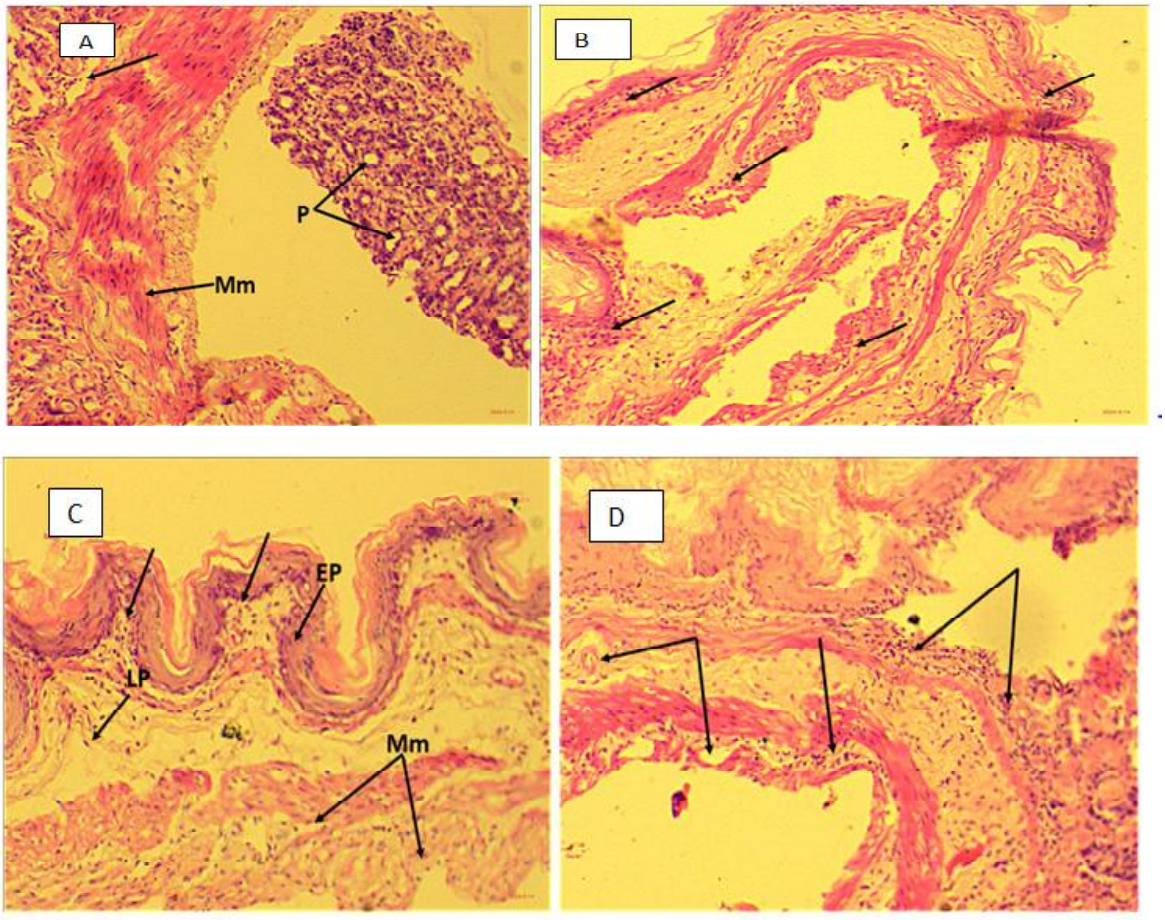

Figure 5: Showing the histopathology of the stomach tissues of control, group 2, 3 and 4

The Photomicrograph (H&E x400) of the stomach showing mild mononuclear activities with normal Mucosa; muscularis mucosa and submucosa of the tissue (arrows). Mild inflammation with Normal appearance of mucosa architecture of the stomach (Figure 5C). The Photomicrograph showing exfoliation and disruption of epithelial cells along the mucosal layer of the stomach with lymphocytic activities. Mild Inflammation and disruption of the stomach wall (Figure 5D).

Figure 6 shows Immunohistochemical sections of the gastric mucosa of mice in ethanol / hydrochloric acid induced ulcer model (10x). Images represent immunohistochemical staining of p53 (A) control group with very low expression of p53 (B) ethanol:hydrochloric acid group revealing deep expression of p53 (C) ethanol:hydrochloric acid plus omeprazole (20 mg / kg) group revealing very mild expression of p53 (D) ethanol:hydrochloric acid plus coartem group also revealing very moderate expression of p53.

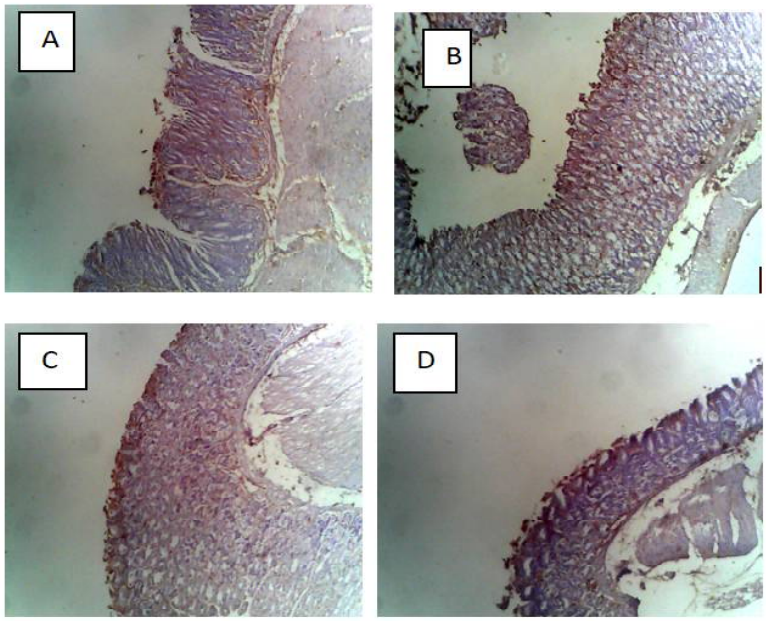

Figure 6: Immunohistochemical staining of p53 of the gastric mucosa of mice in ethanol/hydrochloric acid induced ulcer model

5. Discussion

A major public health concern that affects millions of people in the globe is gastric ulcer (Hossen *et al*., 2021). Therefore this research work was carried out to address this concern by using coartem as an intervention. In the present study coartem at 5 mg / kg and omeprazole at 20mg / kg respectively ameliorated the effect of ethanol:hydrochloric acid induced ulcer in mice. Gastric secretion and hydrochloric acid, aid digestion and inhibit bacteria respectively, but excessive increase of gastric secretion and acidity induced by ethanol can lead to gastric ulcers (Schubert, 2007). Signaling agents like histamine and acetylcholine can be activated by ethanol or hydrochloric acid leading to gastric secretion and ulcer formation (Puscas *et al*., 2001; Buzas and Supuran, 2016).

The present study of ethanol:hydrochloric acid induced ulcer shows great damage of gastric mucosa in the control group. However treatment with coartem or omeprazole drastically reduced the levels of ulcerative indices in the stomach of mice as shown in Table 1. The high damage of ethanol / hydrochloric acid could be due to acidity of the stomach and ROS (Al-Wajeeh *et al*., 2016). The ameliorative effect of either coartem or omeprazole could be due to their ability to act as free radical scavengers or as antacids. Our reports are similar to the findings of Al Asmaria *et al*. (2016) who also reported the gastric protection of vanillin.

5.1. Immunohistochemistry

The p53 Immunohistochemistry staining of gastric tissues of control, experimental and treated groups were dissected into tiny slices of 3-4 um thick and were stained immunohistochemically using p53 antibodies diluted at 1:100 (Santa Cruz USA). The stained slides were examined utilizing microscope (Omar *et al*., 2017).

The activities of biochemical enzymes such as AST, ALT and ALP were also assessed in the present study. The results revealed higher activities in the ulcer induced group. These higher activities could be due to a mucosal damage leading to the influx of these enzymes into the interstitial space (Iqbal *et al*., 2016). In the intervention group of coartenm the activities of these biochemical enzymes were lowered just as in the normal group. These reports are similar to the works of Khana *et al*. (2024).

Ulcerogenesis is linked to inflammation and so are mediated by the action of free radicals. Lipid peroxidation is a product of free radical metabolism which leads to the production of peroxides that break down into carbonyl compounds and malondialdehyde (Khushtar *et al*., 2016). The lipid peroxidation and carbonyl content assays depicted that lipid peroxidation and protein carbonyl content were high in ethanol: HCl induced group. In contrast the coartem treated group significantly decreased the values of MDA and protein carbonyl content. This reversal could be as a result of antioxidant like activity of coartem (Lapenna *et al*., 1996). Our reports are also like the reports of Al-Asmaria *et al*. (2016); Abdoulrahman (2023).

GSH and GPx are two non protein and protein complementary antioxidants, these two play a role in the detoxifying of free radicals especially H_2O_2 (Sidahmed *et al*., 2015). The levels of GSH and the activity of GPx are lowered in the ethanol: HCl induced group. This is due to the fact that ethanol:HCl induces ROS (Leonard *et al*., 2004). Therefore these antioxidant molecules and enzyme activity decreases respectively (Alirezaei *et al*., 2012). These low levels were ameliorated in the two treatment groups of omeprazole or coartem. This is partly due to the fact that antioxidant enzyme and antioxidant levels can be boosted by omeprazole or coartem (Lapenna *et al*., 1996). Our report was similar to the reports of Abdoulrahman, 2023.

SOD and catalase are enzymes that can detoxify superoxide radical and hydrogen peroxide respectively. Superoxide and hydrogen peroxide when not detoxified can lead to the most dangerous radical, the hydroxyl radical (Khana *et al*., 2024). There was a decrease in the activities of SOD and catalase in the ethanol: HCl group due to the toxicity of ethanol or HCl in the gastric mucosa of mice. But in contrast the coartem group revealed an increase in activity of both SOD and catalase. This could be due to the fact that coartem may block histamine from binding to its receptor thereby not stimulating gastric secretion leading to increase activities of SOD and catalase (Schubert, 2007).

Administration of coartem at 5 mg / kg ameliorated ethanol:hydrochloric acid induced ulcer as shown in the histopathological slides. In the ulcer induced group there was gastric edema, lesions and injury due partly by ROS (Kountouras *et al*., 2001; Tabata *et al*., 1996). Whereas in the coartem treated group there was no injury, edema and lesions in the gastric mucosa of mice. Therefore the preventive properties of coartem could be due to proton pump inhibition, production of prostaglandins and antioxidants. Our reports are in line with the works of Al-Attar (2011).

p53 is a tumor suppressor gene, a transcriptional factor found in many oxidative stress related processes (Lazo, 2007). Increasing expression of p53 is linked to ethanol:hydrochloric acid or *H. pylori* induced gastric ulcers and carcinomas (Bellini *et al*., 2012). In the present study the immunohistochemical staining of p53 revealed higher expression of p53 in ethanol:hydrochloric acid induced ulcers. However the coartem treated group showed very low expression of p53 explaining the ameliorative role played by coartem.

6. Conclusion

Coartem is responsible for the modulatory effects found in this study. The results showed that coartem can be utilized in the treatment of ulcer as an alternative. Modulatory effects of coartem were evidenced by the ulcer index reduction, biochemical and antioxidant enzymes, lipid peroxidation and protein carbonyl biomarkers**,** histopathology and immunohistochemistry staining of p53.

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