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Ameliorative Activity of Unripe *Musa paradisiaca* Peels Fractions against Omeprazole and Cimetidine Drugs in Gastric Ulcer - A Comparative Study

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ABSTRACT

Gastric ulcer is a prevalent gastrointestinal disorder affecting millions of the human population, globally. This chronic disease can be combated using synthetic drugs like Omeprazole and Cimetidine, including medicinal herbs like guava leaves, ginger roots, and cabbage. These synthetic drugs pose a wide variety of side effects and have varying efficacies, prompting the need for safer and more efficient alternatives. This research compares the ameliorative activity of *Musa paradisiaca* peels fractions with standard drugs, Omeprazole and Cimetidine in healing experimentally-induced ulcers. Forty rats were divided into eight groups, and starved for 24 h: Groups A and B served as the control groups administered 10 mL/kg of distilled water; Groups C – F were induced with ulcer using 0.5 mL of 90 % ethanol and administered with 97.98 mg/kg *Musa paradisiaca* fractions; Group G received 0.29 mg/kg Omeprazole; Group H were given 5.71 mg/kg Cimetidine. The administration was oral and lasted for 28 days. On the last day of the administration, the forty animals were sacrificed after being anaesthetized with ketamine hydrochloride intraperitoneally, and the stomach excised and fixed in 10 % formal saline for biochemical analysis and histological studies. Results obtained revealed that *Musa paradisiaca* fractions, particularly dichloromethane, showed a significant decrease in the level of malondialdehyde and a substantial increase in total antioxidant capacity, proving that the fractions possess anti-inflammatory properties that reduce inflammation and lower the production of malondialdehyde. *Musa paradisiaca* fractions neutralize reactive oxygen species and therapeutically suppress lipid peroxidation, which enhance antioxidant reserves, offering protection to gastric tissues and cells from oxidative damage, outperforming Cimetidine and Omeprazole. Cimetidine, on the other hand, demonstrated superior ameliorative effects over Omeprazole. Histological findings revealed a substantial elimination of inflammatory cells, retention of glycogen stores for mucin production, and strengthened mucosal integrity as well as absence of apoptotic cells in the treated groups. The study therefore concludes that *Musa paradisiaca* peel fractions hold promising potential to act as a natural antiulcer agent as its efficacy is higher than that of conventional drug therapies.

Keywords: *Musa paradisiaca* fractions, Omeprazole, Cimetidine, Dichloromethane, Gastric ulcer

1. INTRODUCTION

Gastric ulcer disease (GUD) is a prevalent gastrointestinal disorder characterized by erosion of the inner muscularis mucosae lining. Gastric ulcer disease is caused by gastric acid influx, creating wounds and bruises in the mucosal lining. Ulcers can occur in the stomach, in the duodenum, and in the inferior part of the oesophagus. Accompanied by intense abdominal pain, described as a burning dull ache, which may intensify during eating. The symptom is also accompanied by belching, vomiting, loss of appetite, and weight loss (Najm, 2011). Princess Henrietta of England first detected a perforated peptic ulcer (Milosavljevic et al., 2011) in the year 1670. Common causes include infection from *Helicobacter pylori*, excessive smoking, use of non-steroidal anti-inflammatory drugs, alcohol, and stress. For years, millions of humans experiencing peptic ulcer at certain points in their lives have been treated using synthetic drugs like Omeprazole and Cimetidine. The long-term use of these drugs poses adverse health challenges ranging from drug resistance to relapse, abortion, and cardiovascular diseases (Eraslan et al., 2020). In local communities with poor medical facilities and amenities, people tend to rely more on local medicinal herbs, plants, and ingredients found around their environs, farms, and kitchen in bid to alleviate the pain caused by the disease. This motivated modern researchers to search for plants and herbs that possess natural bioactive compounds with gastroprotective potential for healing gastric ulcer. One of such medicinal plants is *Musa paradisiaca*, which from ancient times has been used medically to treat burns and wounds on wounded soldiers. Some communities use it to remove bitterness in vegetables like *Editan*, and to bleach palm oil for special meals, like *nkwobi*, and in soap making. In ethnomedical cases, it has been employed in the treatment of bronchitis, arthritis, pneumonia, and to regulate blood sugar levels in diabetic patients (Al-Zahrani et al., 2015). Although the plant bulb and chunks has been extensively researched, the peels which have often been neglected and considered as waste, are now emerging as a potent source of bioactive compounds containing essential phytochemical compounds ranging from phenols, flavonoids, steroids, tannins, cardiac glycosides, anthraquinones, and saponins (Olatunde et al., 2023). Thus, *Musa paradisiaca* contains anti-oxidatory, anti-inflammatory, antidiabetic, wound healing, and analgesic properties. This study focuses on evaluating the ameliorative potential of solvent fractions – n-hexane, dichloromethane, ethyl acetate, and n-butanol of unripe *Musa paradisiaca* peels in an experimentally-induced gastric ulcer rat model and compare their gastroprotective efficacy with Omeprazole and Cimetidine.

2. MATERIALS AND METHODS

Plant Materials and Drugs

Unripe *Musa paradisiaca* (plantain) peels were obtained from a local plantain farm in Uyo, Akwa Ibom State, to ensure that the plantains were grown naturally without the use of chemical fertilizers. The plant was identified at the Pharmacy department, Faculty of Pharmacy, University of Uyo with herbarium number UUPH51(a). Omeprazole (Omefast-20 20 mg) and Cimetidine (Tagacure® 400 mg) drugs were obtained from Anointed Brand Pharmacy (Uyo, Nigeria).

Plant Preparation

Six bunches of matured unripe *Musa paradisiaca* peels were collected between September and October, properly washed under running tap water to remove contaminants, rinsed in distilled water, sliced into tiny pieces, air dried for 2 weeks to remove their stickiness, ground into powder, then sieved, and stored in bottles for use. The dried thin peels were weighed with a triple beam balance and found to be 1.106 kg. The powdered form was soaked in 60 % ethanol solvent, covered, and kept for 72 hours with intermittent shaking using the method of maceration extraction. It was filtered using a funnel and cotton wool to get a filtrate, evaporated, and dried in a water bath at 40° - 45° C. This produced the crude extract (Uzairu and Kano, 2021).

Preparation of Fractions

To arrive at the fractions, 100 g of the crude extract was dissolved in distilled water, poured into a separation funnel, and passed through different organic solvents according to their level of polarity starting with the more polar compound to the less polar compound. N-hexane as the most polar organic solvent yield an N-hexanoic fraction; Dichloromethane organic solvent yield Dichloromethane fraction; Ethyl acetate solvent yield Ethyl acetic fraction; the less polar organic solvent N-butanol yield N-butanoic fraction. N-hexane, Dichloromethane, and Ethyl acetic fractions were air dried at room temperature for 72 hours to yield a dried compound of the fractions. N-butanoic fraction was dried in a water bath at 40° - 45° C for 72 hours to yield a dried compound of the extract and fractions.

Drug Administration

The drugs Cimetidine and Omeprazole were ground into powder using a ceramic mortar and pestle, and later dissolved in distilled water. The dosages administered were according to the standard dose regimen for each drug. Administration was done orally for 28 days using a hypodermic syringe attached to an oral cannula. Group G received Omeprazole (0.29 mg/kg); and Group H received Cimetidine (5.71 mg/kg).

Experimental Design

Forty Wistar rats weighing 150 – 240 g were purchased from and housed in the animal house of Faculty of Pharmacy, University of Uyo, according to the standard laboratory conditions. The rats were fed with standard rat pellets, given free access to water *ad libitum*, and acclimatized for two weeks. The rats were divided into eight groups with five rats in each group as shown in Table 1. The rats in Groups A and B served as the negative control groups, receiving 10 mL/kg of distilled water. Groups B – H were all induced with an ulcer using 0.5 mL of 90 % ethanol. Groups C - F were the fraction groups given 97.98 mg/kg of N-hexane, Dichloromethane, Ethyl acetate, and N-butanol fractions, respectively. Group G received Omeprazole, and H with Cimetidine as the positive control groups. The administration lasted for twenty-eight days. To ascertain that ulceration has been established, macroscopic examination was carried out on twelve animals as a pilot study with a hand lens, and the presence of ulcer lesions was scored according to the standard method described by Nwafor et al., (2000).

Table 1: Schedule for the administration of treatment in control and test groups

Groups (n=8)	No. of Rats	Treatment/ Dosage (mg/kg)	Duration (Days)
A	5	10 mL/kg BW of distilled water for	28
B	5	Ulcer induced given 10 mL/kg BW of distilled water for	28
C	5	Ulcer induced given 97.98 mg/kg BW of n-hexane fraction for	28
D	5	Ulcer induced given 97.98 mg/kg BW of DCM fraction for	28
E	5	Ulcer induced given 97.98 mg/kg BW of Ethyl acetate fraction for	28
F	5	Ulcer induced given 97.98 mg/kg BW of n-Butanol fraction for	28
G	5	Ulcer induced given 0.29 mg/kg BW of omeprazole for	28
H	5	Ulcer induced given 5.71 mg/kg BW of cimetidine for	28

Key: BW- Body weight. N – Number of rats. DCM - Dichloromethane MP – *Musa paradisiaca*

Induction of Gastric Ulcer in Laboratory Animals

The laboratory animals were fasted for 24 hours before the experiment but given free access to water four hours before the induction (Simona et al., 2019). Gastric ulcer was experimentally induced, using 0.5 mL of 90 % ethanol, administered orally using a hypodermic syringe attached to an oral cannula. The animals were kept for four hours, and ulceration was determined by a pilot study before the administration of the extract. To ascertain that ulceration has been induced in the laboratory animals before the commencement of the administration, a pilot study was carried out. Twelve Wistar rats of both genders were selected for ulcer induction. The animals were deprived of food and water for 24 hours, weighed, and found to be 164 - 220 g. The rats were injected with 0.5 mL of 90 % ethanol to induce ulceration.

Termination of Experiment / Sample Collection

On the final day of the experiment, the final body weights were taken. The animals were anaesthetized using ketamine hydrochloride 50 mg/kg body weight of the animals (Rosenbaum et al., 2024). The stomach was opened along the greater curvature, fixed in 10 % normal saline for immunohistological, histological studies, and biochemical analysis.

Histological Procedures

The excised organs were collected and weighed, washed in normal saline, and fixed using 10 % formaldehyde to preserve the tissue structure and component from decay. The tissues were dehydrated in graded doses of alcohol to avoid plasmolysis, remove excess

water, and allow for penetration of the paraffin wax; then cleared with xylene as a clearing agent. The tissues were infiltrated with paraffin wax, and embedded in a mould for sectioning through a microtome. They were mounted on a slide for staining.

Hematoxylin and Eosin

The tissues were deparaffinized by putting them in xylene and hydrated in descending grades (100%, 95%, and 70%) of alcohol. The sections were then stained in Hematoxylin for 3 – 5 minutes. Afterwards, they were washed in running tap water until sections turns blue for 5 minutes. The tissues were differentiated in 1% acid alcohol for 5 minutes and washed in running tap water again until the tissue shows blue colour. They were stained in 1% Eosin for 10 minutes. Washed again in running tap water for 1 – 5 minutes. Dehydrated in increasing grades of alcohol, cleared in xylene, and mounted in a mounting medium (Fischer et al. 2008) and (Hermann et al. 2017).

Periodic Acid Schiff

The tissues were stained following the method described by Thonard and Scherp, (1962). Tissue samples were deparaffinized and washed in distilled water. The sections were treated with periodic acid for 5 minutes. Rinsed in distilled water and soaked in Schiff's regent for 10 - 15 minutes. The sections were washed to remove the excess solution with distilled water and counterstained with Hematoxylin for 15 seconds. They were washed again with distilled water and rinsed with alcohol. The sections were cleared using xylene and mounted.

Immunohistochemical Procedure

Immunohistochemistry staining is used to identify the presence of specific proteins and antigens in a tissue sample. In the stomach, it detects the presence of *Helicobacter pylori*, which causes gastritis and peptic ulcer disease. An immunohistochemical study was conducted to assess the level of apoptosis in gastric cells using B-cell lymphoma 2 (BCL-2) proteins as an antibody. These proteins are the major regulators of apoptosis, regulates and mediates the intrinsic apoptosis pathway whereby the mitochondria contribute to cell death (Hardwick and Soane, 2013). BCL-2 inhibits apoptosis by preserving mitochondrial membrane integrity. The immunohistochemistry for gastric mucosa was conducted using the non-biotin, enzymatic, one-step detection kit, ImmPRESS™ HRP Polymerized Reporter Enzyme Staining System (Vector® Labs, USA), which provides very high sensitivity staining with very minimal background interference in immunohistochemical applications.

Reagents used includes:

i. ImmPRESS™ (Peroxidase) Polymer Anti-Rabbit IgG Reagent made in horse, ready-to-use). This requires no mixing or tittering to obtain optimal immunohistochemical staining. The staining was applied at room temperature. For optimal performance, the ImmPRESSTM Reagent was equilibrated to room temperature before use. Phosphate buffered saline (PBS) was used as buffer.

ii. 2.5 Normal Animal (Horse) Serum for blocking (ready-to-use). The staining protocol was performed following the guiding principles described by Ijomone et al. (2018) and Erukainure et al. (2019). The paraffin embedded tissues were put on positively charged glass slides, deparaffinized in xylene, rehydrated in descending grades of alcohol (100%, 95%, 70% ethanol), and taken to water. Heat-mediated antigen retrieval was performed using a citrate-based antigen unmasking solution, pH 6.0 (Vector®, Burlingame, CA, USA; #3300) in a steamer for 30 minutes. Sections were washed in PBS for 2 minutes. Endogenous peroxidase blocking in 0.3% hydrogen peroxide solution in PBS for 10 minutes. Sections were washed in PBS for two minutes. Sections were then incubated at room temperature for two hours in primary rabbit antibodies diluted in a universal diluent and blocking reagent, UltraCruz® Blocking Reagent (Santa Cruz, USA). Primary antibodies B-Cell Lymphoma 2 (BCL-2 Novus Biologicals, USA) NB100-56098 at 1:2500. Sections were washed in PBS for 2 minutes. Sections were incubated in ImmPRESS™ HRP Anti-Rabbit IgG (Peroxidase) Polymer Reagent, made in horse for 30 minutes. Sections were washed again in PBS for 5 minutes, 2 times. Color was developed with Diaminobenzidine (DAB) Peroxidase Substrate Kit (Vector® Labs, USA). Sections were rinsed well in tap water. Sections were counterstained with Hematoxylin. Sections were dehydrated in ascending grades of ethanol (70 %, 95 %, 100 %), cleared in xylene, and mounted with Permount (Fischer Scientific, USA). The positive cellular reaction appeared as a cytoplasmic blue color (Ma and Wallace, 2000). Sections without primary antibodies were similarly processed to control for immunohistochemistry procedures. No specific immunoreactivity was detected in control sections.

Biochemical Analysis

The tissues are homogenised in a Teflon glass homogeniser with a buffer containing 1.5% potassium chloride to obtain 1:10 (w/v) whole homogenate for oxidative stress analysis (Moldovan and Moldovan, 2004).

Total Antioxidant Capacity (TAC)

Total antioxidant capacity (TAC) in serum was determined by colorimetric method using a commercially available kit following previously outlined procedures (Koracevic et al., 2001). The anti-oxidative capacity in rat serum was measured by the reaction of antioxidants in the sample with a known amount of exogenously supplied hydrogen peroxide (H_2O_2), resulting in the removal of a specific amount of H_2O_2. The remaining H_2O_2 was estimated colorimetrically by an enzymatic reaction, which involves the conversion of 3, 5, dichloro–2–hydroxyl benzensulphonate to a coloured product.

Malondialdehyde (MDA)

The level of serum malondialdehyde (MDA), a major lipid peroxidation product was measured colorimetrically using a commercially available kit following previously outlined instructions (Ohkawa et al., 1979., Placer et al., 1996). This assay is based on the principle of reaction of thiobarbituric acid (TBA) with MDA in an acidic medium at a temperature of 95° C for 30 minutes to form a thiobarbituric acid reactive product with a pink color, with its absorbance measured at 534 nm. Malondialdehyde was measured using the thiobarbituric acid test to determine the concentration of lipid peroxidation. One volume of the test sample and two volumes of stock reagent which is trichloroacetic acid and thiobarbituric acid was mixed in a centrifuge tube. The solution formed was incubated in boiling water for 20 minutes. On cooling, the solution was centrifuged at 810 g for 5 minutes to remove precipitate, and the absorbance of the supernatant was spectrophotometrically measured at 532 nm against a blank containing all the reagents except the test sample on a spectrophotometer. Thus, the results were expressed in nmol/g.

Statistical Analysis

The data obtained were subjected to statistical analysis of variance (ANOVA) and analysed using graph pad prism 7 (Graphpad Software Inc., California Corporation, USA).

3. RESULTS

Total Antioxidant Capacity and Malondialdehyde

The results of malondialdehyde (MDA) showed no significant ($p<0.05$) change in groups A, B, E, and G when compared to group F respectively. In addition, group F showed a significant ($p<0.05$) decrease in MDA when compared to groups B, respectively (Table 2). Total antioxidant capacity (TAC) showed significant ($p<0.05$) decrease in group B when compared to groups A. The fraction groups, C – F showed a significant increase ($p<0.05$) in TAC compared to groups A and B.

Table 2: Effect of *Musa paradisiaca*, omeprazole and cimetidine on total antioxidant capacity and malondialdehyde

Groups	Treatment	MDA (µmol/L)	TAC (mmol/TE/L)
A	10 mL/kg distilled water	0.570 ± 0.0307	1.172 ± 0.025
B	Induced ulcer / 10 ml/kg distilled water	0.576 ± 0.0287	1.052 ± 0.085
C	Induced ulcer / 97.98 mg/kg n-hexane	0.614 ± 0.0495	1.150 ± 0.103
D	Induced with ulcer / 97.98 mg/kg dichloromethane	0.476 ± 0.0275	1.466 ± 0.031 *b
E	Induced with ulcer / 97.98 mg/kg ethyl acetate	0.574 ± 0.0246	1.566 ± 0.043 **b*c
F	Induced with ulcer / 97.98 mg/kg n-butanol	0.456 ± 0.0370*c	1.282 ± 0.050
G	Induced with ulcer / 0.29 mg/kg omeprazole	0.550 ± 0.0358	1.324 ± 0.034
H	Induced with ulcer / 97.98 mg/kg cimetidine	0.546 ± 0.0232	1.184 ± 0.088
		P= 0.0016	P<0.0001
		F= 3.375	F= 5.300

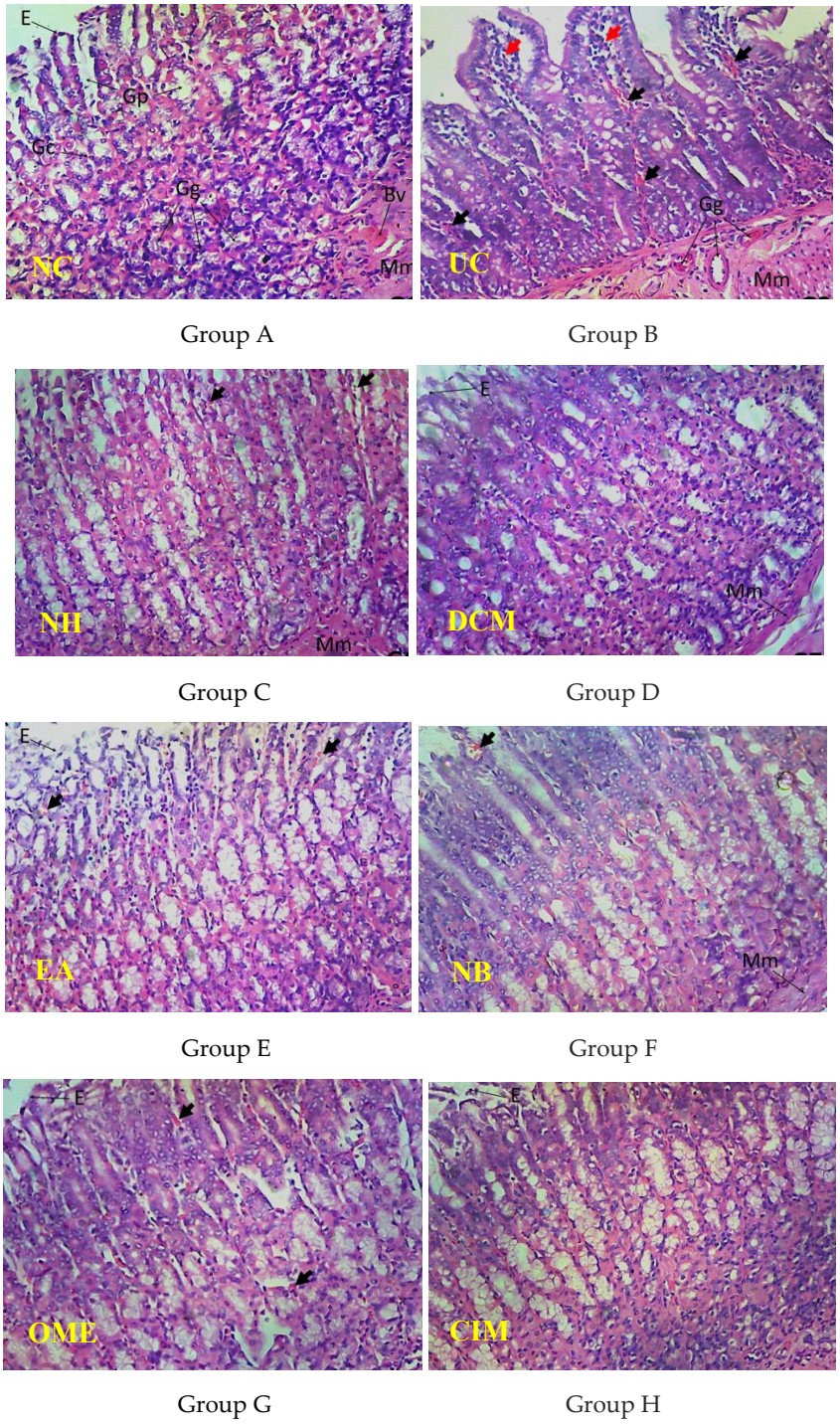

Figure 1: Photomicrograph of the longitudinal section of the stomach of normal control (Group A) showing well-defined gastric mucosa with thickened epithelial wall, and numerous gastric cells; Group B showed ulcerated gastric mucosa with haemorrhagic blood vessels (black arrow), numerous inflammatory cells (red arrow) and few gastric cells; Groups C and D showed no ulceration; Groups E and F showed mild ulceration with few inflammatory cells and reepithelization; Group G showed ulcerated gastric mucosa with the presence of inflammatory cells; Group H showed no ulceration with thickened mucosal wall and absence of inflammatory cells, H & E. Mag × 100.
NC = normal control; UC = Ulcerated control NH = n-hexane; DCM = dichloromethane; EA = Ethyl acetate; NB = n-butanol; OME = Omeprazole; CIM = Cimetidine

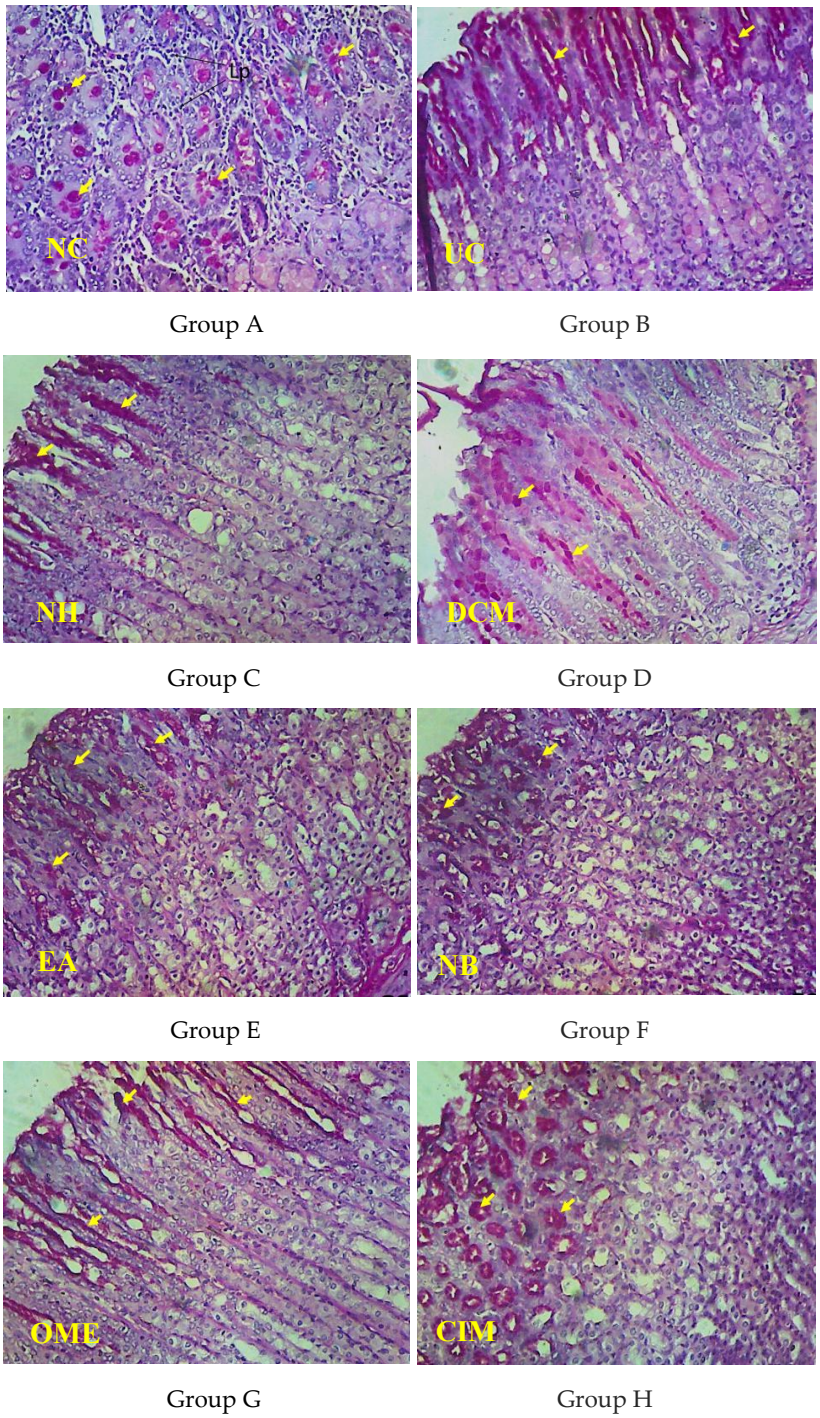

Figure 2: Photomicrograph of the longitudinal section of the stomach of normal control (Group A) showing deeply stained mucosa with high glycogen deposits, and glandular mucin (yellow arrow); Group B showed lightly stained gastric mucosa with irregular gastric epithelium (black arrow) and sparse glycogen deposits; Group C showed less glycogen deposits and mucin from the lightly stained PAS; Group D showed presence of glycogen and glandular mucins yellow arrow); Groups E and F showed less glycogen deposit and mucins; Group G showed light PAS stain with presence of less glandular mucin and less glycogen stores; Group H showed deeply stained PAS, rich glycogen deposits and wide glandular mucins, PAS. Mag × 100. NC = normal control; UC = Ulcerated control NH = n-hexane; DCM = dichloromethane; EA = Ethyl acetate; NB = n-butanol; OME = omeprazole; CIM = cimetidine

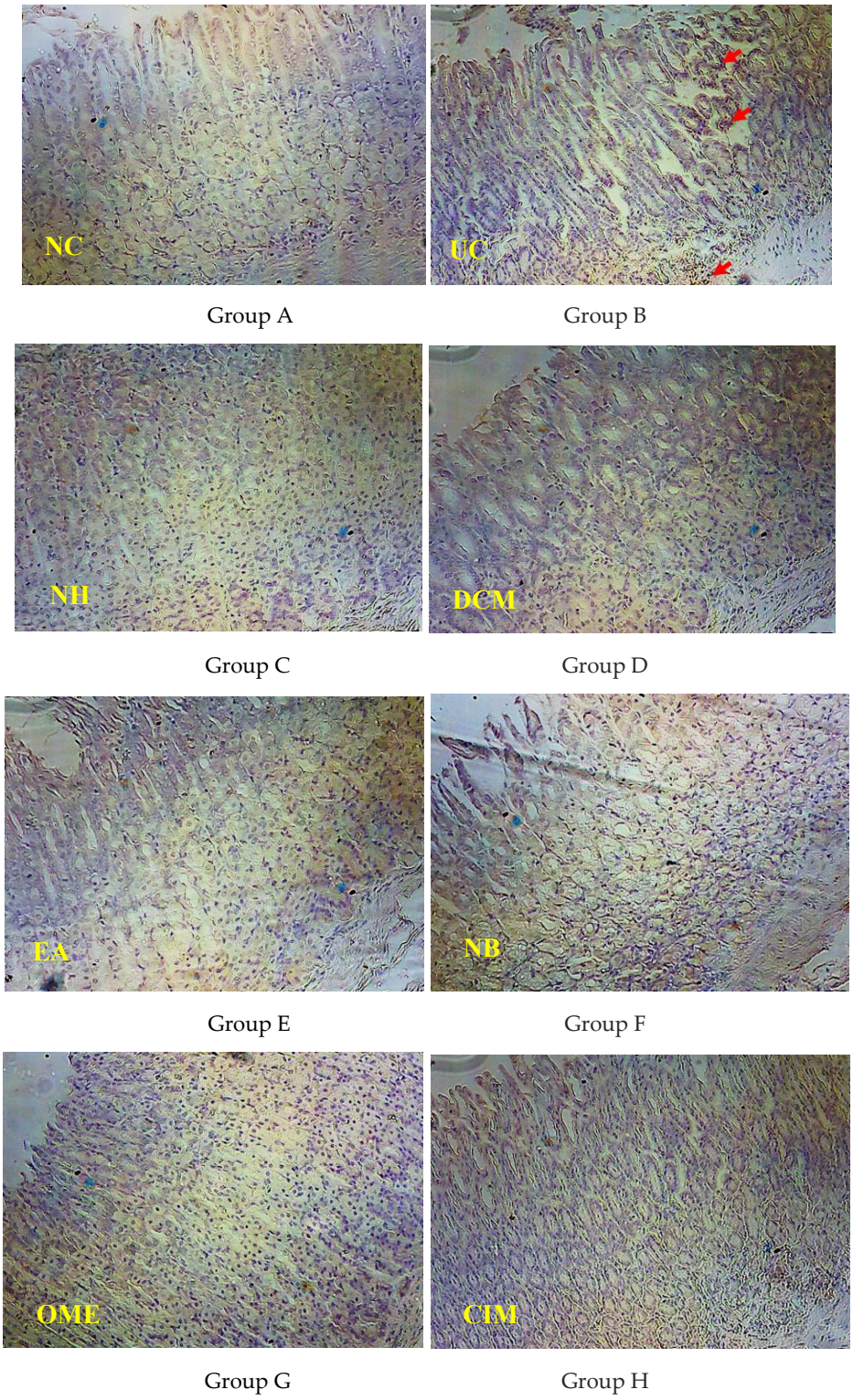

Figure 3: Photomicrograph of the longitudinal section of the stomach of normal control (Group A) showing normal gastric mucosa with no detectable anti-apoptotic activity; Group B showed increased BCL-2 overexpression suggesting active anti-apoptotic response in damaged mucosa preventing normal cell turnover and healing; Group C showed potential healing effect without promoting abnormal cell survival. Group D showed effective mucosal recovery; Groups E and F showed no abnormal anti-apoptotic signal; Group G maintained normal apoptotic balance in gastric mucosa; Group H showed no BCL-2 overexpression, consistent with mucosal protection, BCL-2. Mag × 100.
NC = normal control; UC = Ulcerated control NH = n-hexane; DCM = dichloromethane; EA = Ethyl acetate; NB = n-butanol; OME = omeprazole; CIM = cimetidine

4. DISCUSSION

Gastric ulcer exacerbates mucosal injury by consistent overproduction of reactive oxygen species linking it directly to oxidative stress. Malondialdehyde and total antioxidant capacity are oxidative biomarkers that indicates lipid peroxidation and measures overall antioxidant defense. The results for malondialdehyde (MDA) showed no significant increase difference in Group B induced with ulcer using ethanol and administered with 10 mL/kg body weight of distilled water. This slight increase reflects lipid peroxidation caused by accumulation of reactive oxygen species and altered antioxidant defenses. However, the result showed a significant increase $p(<0.05)$ in MDA in Group C receiving n-hexane fraction and slight increase in Group E receiving ethyl acetate as shown in Table 2, suggesting a mild improvement and presence of few antioxidant constituents that were not sufficient enough to perform a strong antioxidant effect but gave progressive antioxidant recovery. Groups E, G, and H showed no significant change in the level of malondialdehyde portraying little to no improvement in the reduction of oxidative damage. Groups D and F given dichloromethane and n-Butanol fraction, respectively showed significant decrease in the level of malondialdehyde signifying strong reduction in oxidative damage, having the most effective antioxidant to offer effective protection against lipid peroxidation and suppression of MDA when compared with control group A and Group C treated with n-hexane fraction. The level of total antioxidant capacity (TAC) was significantly decreased in Group B compared to Group A, suggesting the depletion of endogenous antioxidants caused by the presence of ulcer, and failure of the body's defense mechanism to counteract oxidative injury. The fraction Groups C – F showed a significant increase in TAC compared to Groups A and B, revealing excellent antioxidant status and recovery. Group J showed similar increase in TAC to Group F exhibiting moderate boost of antioxidants when compared to Group G. This proves that the fraction possesses anti-inflammatory properties that reduces inflammation and lowers the production of malondialdehyde. It not only neutralizes reactive oxygen species but further reinforces that dichloromethane fraction of *Musa paradisiaca* therapeutically suppresses lipid peroxidation and enhances antioxidant reserves to protect gastric tissues and cells from oxidative damage and supports mucosal regeneration. Group H administered with cimetidine showed moderate reduction in malondialdehyde and a noticeable increase in TAC signifying the presence of cytoprotective and anti-inflammatory properties that attenuates oxidative stress but its effects cannot be compared to that exhibited by dichloromethane.

In this study, histological photomicrographs focused on the level of ulceration, mucosal integrity, apoptosis, and glycogen storage as well as the level of staining expressed in the gastric mucosa after treatment for 28 days. Hematoxylin and Eosin staining results demonstrated stark contrast between the treated and untreated groups. Group B which was induced with 0.5 mL/kg body weight of ethanol for ulceration exhibited a 5-degree ulceration represented by numerous ulcers across the gastric mucosal layer of the stomach degrading the gastric cells and causing haemorrhagic blood vessels (Figure 1). The red arrows showed immune response by the body system to ameliorate the disorder by sending infiltrating inflammatory cells, which signifies the presence of injuries in the mucosa to stave off infection, clear bacteria and debris to prepare the wound bed for new tissue growth. In contrast, it was observed that Group C given n-Hexane fraction showed decreased level of ulceration and few inflammatory cells in the gastric mucosa, a well-defined gastric epithelium and the presence of numerous gastric cells, glands, and pits. Group D given Dichloromethane fraction and Group H contain certain organic compounds that are highly purified and potent in eliminating gastric ulcers as no gastric lesions were observed, the epithelial lining was intact, gastric cells and glands were preserved. The inflammatory cells were absent in the gastric mucosa. Meanwhile, when compared to Groups C administered with n-hexane and Group D administered with dichloromethane fraction, Group E administered with ethyl acetate, Group F receiving n-butanol and Group G given Omeprazole, mild to moderate ulceration and epithelial distortion (Figure 1) was observed suggesting partial protection to an extent lesser than dichloromethane and Cimetidine. This proves that Cimetidine is more potent and therapeutic as a curative agent for gastric ulcers than Omeprazole. Periodic Acid Schiff stain (PAS) further elucidated the protective mechanism of the test substances by presenting mucopolysaccharide content, such as mucin and glycogen. The level of magenta expression was lightly stained and limited to the apical region of the gastric mucosa, which has been eroded by inflammation caused by gastric wounds in Group B induced with ulcer and administered with 10 mL/kg body weight of distilled water compared to control Group A where glycogen storage was pronounced and scattered along the entire surface of the gastric mucosa (Figure 2). Groups D administered with dichloromethane and Group H receiving Cimetidine exhibited rich PAS-positive reaction characterized by deep magenta staining which indicates robust glandular mucins secretion and accumulation of rich glycogen. This suggests that *Musa paradisiaca* and Cimetidine enhance mucosal defense through increased mucin production and glycogen reserves caused by glycosides and alkaloids, which are essential for epithelial regeneration and protection against harsh gastric acid, causing gastric lesions. Other fraction groups and Group G receiving Omeprazole (Figure 2) was observed to exhibit weak glycogen stores in the gastric mucosa, and sparse mucin presence as expressed by the lightly stained PAS expression

(magenta colour). This light stained PAS expression signifies diminished protective activity at the surface of the mucosa, depleted mucosal defense mechanisms and compromised epithelial integrity. These histological and ulcer score index affirm the potency and antiulcer efficacy of *Musa paradisiaca* dichloromethane fraction in preserving gastric mucosal structures, stimulating mucin production, and promoting glycogen accumulation while healing the gastric injuries that were present. This healing is attributed to the rich phytochemical contents contained in the plant's peels like flavonoid, alkaloids, tannins, glycosides that present antioxidant, anti-inflammatory and cytoprotective effects to heal the gastric mucosa. Existing literature agrees with the comparative effectiveness of Cimetidine over Omeprazole observed in both Hematoxylin and Eosin stain, and PAS stain as Cimetidine creates a more rapid histamine H2-receptor blockage in the presence of gastric ulcer (Alese *et al*., 2017). *Musa paradisiaca* possesses superiority to both standard drugs as observed in its reduced ulcer index and histological findings, serving as an effective, potent therapeutic alternative in the treatment of gastric ulcers. Immunohistological staining expressed the presence of apoptotic cells with brown coloration, and its absence with a blue colouration signifying a normal cell structure and type in the gastric mucosa after a 28-day treatment for gastric ulceration using fractions of *Musa paradisiaca*, Omeprazole and Cimetidine by the utilization of B-cell lymphoma 2 (BCL-2) an anti-apoptotic protein which regulates apoptosis at the mitochondrial membrane by inhibiting the release of cytochrome C, to maintain cell vitality under stress conditions. The gastric mucosal in Group B was observed to have a numerous number of apoptotic cells (Figure 3) as a result of the positive overexpression of BCL-2 protein on the gastric cell nuclei which gave a brown colouration signifying programmed cell death cause by toxicity and inflammation from gastric injuries arising from ethanol administration to induce ulcers. This observation is consistent with previous reports that tissue injury and oxidative stress can trigger anti-apoptotic expression as a defense response to prolong the survival of damaged gastric epithelial cells and possibly delay regeneration. This result agrees with the work of Rahman et al. (2019), whose immunohistological studies expressed a significant increase (TUNEL-positive) in apoptotic cells in the control group induced with ulcer using ethanol as compared to the control group administered with distilled water. Rahman et al. (2019), argued that intervention using effective herbal remedies reduces the number of apoptotic cells in comparison to the ethanol-induced gastric ulcer group. In contrast, all treated groups portrayed a negative reaction to BCL-2, comparable to the normal group. The absence of BCL-2 overexpression and normal gastric cell nuclei observed suggest restoration of normal apoptotic balance allowing the clearance of injured cells and promoting gastric healing, this is solely dependent on the treatment given. Thus, the therapeutic action of Omeprazole and Cimetidine in ameliorating gastric ulcers is similar to that of *Musa paradisiaca* fractions, which contain bioactive components that suppress anti-apoptotic signaling in ulcerated mucosa. Its phytochemical compounds that possesses antioxidative and cytoprotective properties modulates apoptotic pathway, supporting tissue recovery without promoting pathological cell survival. The uniform negative BCL-2 overexpression in groups treated with *Musa paradisiaca* fraction also points to the plant's anti-inflammatory activity as it enhances mucus production by combined antioxidant function to give gastroprotective and ulcer-healing effects.

5. CONCLUSION

This study has demonstrated that *Musa paradisiaca* (plantain) peels possess significant gastroprotective, antioxidant, and anti-inflammatory properties, affirming its therapeutic potential in the management of experimentally ethanol-induced gastric ulcers. The phytochemical composition of the plant, particularly its high levels of flavonoids, phenols, and other bioactive compounds, contributes to its cytoprotective efficacy. Among the different treatment groups studied, n-hexane and dichloromethane fractions were found to be the most potent in promoting ulcer healing among other fraction groups. These fractions, particularly dichloromethane demonstrates higher efficacy compared to standard antiulcer drugs, Omeprazole and Cimetidine as it showed to enhanced mucosal regeneration, preserved glandular architecture, reduced inflammatory cell infiltration, no ulceration and, maintained oxidative balance by neutralizing free radicals, as seen in the histological photomicrographs. Dichloromethane closely relates to the actions of Cimetidine but superiorly outperforms Omeprazole and other fraction groups, which had mild ulcerations and offered limited protection from oxidative stress. Dichloromethane fraction offers structural and biochemical protection against gastric ulceration and is therefore presented as a safe, effective, natural phytotherapeutic alternative for the treatment of gastric ulcers.

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Author Contributions:
The manuscript, design of the study, discussion, and research was written by Mfonobong E Sampson, the data analysis and interpretation of result was curated by Kingsley A Okon and proofreading by Eno-Obong I Bassey.

Ethical Approval
The study was approved by the Faculty of Basic Medical Sciences Research and Ethical Committee (Ethical approval number: UU_FBMSREC_2024_005). Regarding animal regulations in the Department of Human Anatomy, the Faculty of Basic Medical Sciences and Faculty of Pharmacy's Animal House, University of Uyo, Uyo, Nigeria, the Animal ethical guidelines were strictly followed during the entire course of this research.

Informed Consent
Not applicable.

Conflicts of interests
The authors declare that they have no conflicts of interest, competing financial interests or personal relationships that could have influenced the work reported in this paper.

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Data and materials availability
The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

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