



Effects of Ethyl Acetate Fraction of *Dialium guineense* Willd Leaves on the Stomach Architecture of Indomethacin-Intoxicated Albino Wistar Rats: Implication in Ulcer Management

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Abstract

Peptic ulcer disease (PUD) is prevalent in many developing countries like Nigeria mainly due to abuse of alcoholic beverages and excessive use of pain killer drugs. This study aimed to evaluate the effects of ethyl acetate fraction of *Dialium guineense* (DG) leaves on the stomach architecture of indomethacin intoxicated Wistar rats. Methanol extract of the leaves was eluted with ethyl acetate to obtain the ethylacetate fraction (EAF). The fraction was subjected to phytochemical analysis. Thirty six adult Wistar rats were divided into 6 groups of 6 rats per group. Group 1 was normal control, while groups 2 - 6 received indomethacin (40 mg/kg via oral gavage). Group 2 animals were indomethacin control, Group 3 received omeprazole (20 mg/kg), while Groups 4 to 6 received 100, 200 and 400 mg/kg of ethyl acetate fraction respectively. The animals were treated for 14 days after indomethacin administration. On the 15th day blood samples were taken and the animals were sacrificed by cervical dislocation and their stomach isolated for histopathology. Free acidity, total acidity and pH were estimated. Antioxidant activity was investigated using glutathione (GSH), superoxide dismutase (SOD), catalase (CAT), and malondialdehyde (MDA) activity. Phytochemical analysis showed the presence of total phenolics, and tannins in high concentration, flavonoids, alkaloids, terpenoids and steroids in moderate concentration. Antioxidant studies indicated significantly ($P < 0.05$) increased and decreased values of SOD and MDA respectively, CAT and GSH were significantly decreased. Free acidity and total acidity significantly ($P < 0.05$) decreased in the treatment groups, while pH was not significantly ($P > 0.05$) altered. Histopathology demonstrated normal stomach histoarchitecture in the EAF treatment groups with mild shedding of mucosal lining in positive control.

Keywords: Ethyl acetate, *Dialium guineense*, ulcer, stomach, antioxidant, histopathology

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Introduction

Peptic ulcer disease and its complications remain the cause of significant morbidity worldwide, representing a major burden for health care resources (Chime *et al* 2025). Although potent anti-ulcer drugs are available, most of them produce several toxicities, thus emphasizing the need to search for new alternative (Mukheet *et al* 2019). In Nigeria peptic ulcer disease is rife due to abuse of drugs and alcoholic beverages. Peptic ulcer disease (PUD) is the erosion of mucosal lining of the epithelial surface of the stomach or duodenum sometimes extending to the muscularis mucosa. PUD is caused by the action of acid pepsinogen complex on the mucosal layer leading to gaps in the continuity of the mucosal layer (Thabrew and Arawwawala 2016). PUD is reported to be the most common disorder of gastro-intestinal tract resulting mainly because of an imbalance between the gastric defensive and aggressive factors (Bongu and Vijayakumar 2012). Defensive factors against peptic ulcer are adequate blood flow, secretion of prostaglandins, mucin, bicarbonate, mucus bicarbonate layer, cellular regeneration, mucosal barrier, surface mucus secretion and secretion of nitric oxide (Mehta 2016; Thomas *et al* 2017). Aggressive factors were reported to be reactive oxygen species, increased secretion of hydrochloric acid and pepsin, inadequate dietary habits, free oxygen radicals, consumption of non-steroidal anti-inflammatory drugs, alcohol, stress and anxiety (Cuevas *et al.*, 2011).

PUD is treated with drugs such as antacids, proton pump inhibitors, antihistamines, anticholinergics and prostaglandin analogues. These drugs have associated adverse reactions that limit their adherence. As an alternative, there is increasing patronage of ethnomedicine which is not only accessible and affordable, but also believed to be safe (Chime *et al* 2025a). Siddiqui and Moid (2022) posited that nearly 80% of the world's populace makes use of natural medicine in primary health care. Many plants show anti-ulcer potential due to the presence of various phytochemicals that have demonstrated antioxidant and antimicrobial activities. They could improve mucosal defense, reduce acid production, and combat *Helicobacter pylori* (Agu *et al.*, 2023). Phytochemicals that have antiulcerative properties are alkaloids, tannins, flavonoids, terpenoids, glycosides, carotenoids and saponins (Ghosh *et al.*, 2020). The plant *Dialium guineense* (DG) Wild (Fabaceae), grows in dense savannah forests, shadowy canyons and gallery forests. It is native to Nigeria, Benin Republic, Burkina Faso and other West African countries. It is called "icheku" (Ibo, Eastern Nigeria), "awin" (Yoruba, Western Nigeria), "tsayirarkurm" (Hausa, Northern Nigeria), velvet termarind or black tamarind (English) and tamarinier noir (French). The

leaves and stem bark are used as folklore remedies for the treatment of infections and other ailments such as diarrhea, severe cough, bronchitis, wound, stomachache, malaria fever, jaundice, peptic ulcer disease (PUD), hemorrhoids and prevention of cancer (Bero *et al.*, 2009; Gideon *et al.*, 2013). The leaves, also known as velvet tamarind leaves, possess significant nutritional potential. They are a source of various vitamins and minerals, including vitamins C and E, and are also rich in phytochemicals like alkaloids, tannins, phenols, and flavonoids. These components contribute to the plant's antioxidant and antimicrobial properties, potentially offering health benefits (Saxen *et al.*, 2013; Ginovyan *et al.*, 2017; Bubonji-Sonje *et al.*, 2020). They are a source of iron, magnesium and copper (Agu *et al.*, 2023).

The aim of this study was to evaluate the antiulcer effects of ethyl acetate fraction of *Dialium guineense* leaves by examining the stomach architecture of indomethacin intoxicated Wistar rats.

Materials and Methods

Plant material

The leaves of *Dialium guineense* were collected from Agu Ibagwa Forest in Nsukka LGA of Enugu State, Nigeria and identified by Isaac Ossai, a taxonomist at the Biodiversity and Conservation Programme (BDGP) Nsukka, Nigeria, where a voucher specimen with number BDGP/C24/002 is preserved.

Extraction and fractionation of the plant material

Extraction of plant leaves was done according to with some modifications. The leaves were shaded, dried and pulverized. The pulverized leaves (100 g) were macerated in 1000 ml of methanol for 48 hr and filtered with Whatman filter paper No 1. The filtrate was concentrated using rotary evaporator. The concentrated crude methanol extract was eluted with ethyl acetate using column chromatography technique to afford the ethylacetate fraction (EAF) (Girma *et al.*, 2015). The fraction was used in this study.

Qualitative and Quantitative Phytochemical Analysis

The methods of Harbone (1973) and Trease and Evans (1989) were used to qualitatively and quantitatively determine phytochemical constituents in EAF.

Animal

Thirty six adult Wistar rats (150 ± 20 g) were purchased from the Animal House of the Department of Pharmacology and Toxicology, University of

Nigeria, Nsukka. The rats were housed in cages in the Animal House of Anatomy Department, University of Nigeria, Enugu Campus under standard environmental condition. The animals were fed with laboratory chow (Chikun feeds PLC) and drinking water ad libitum for a period of two weeks for them to acclimatize to the new laboratory environment prior to the study. Natural light and dark cycles were maintained, and temperature was kept between 27°C and 30°C.

Experimental Design

Thirty six adult Wistar rats were divided into 6 groups of 6 rats per group. Group 1 was normal control, while groups 2 - 6 received indomethacin (40 mg/kg via oral gavage), and treated as follows;

Group 2 animals were indomethacin control,

Group 3 received Omeprazole (20 mg/kg),

Groups 4 received EAF 100 mg/kg,

Group 5 received EAF 200 mg/kg

Group 6 received RAF 400 mg/kg

The animals were treated for 14 days after indomethacin administration. On the 15th day the animals were fasted for 8 hr, and blood samples were collected for antioxidant assays, and the animals were sacrificed by cervical dislocation and their stomach isolated, fixed in 10 % phosphate-buffered formalin for the histopathological examinations.

In vivo Antioxidant studies

For antioxidants assay, catalase activity was assayed using the method of Aebi (1984). The product of lipid peroxidation (MDA) was assayed using the method of Wallin *et al.*, (1993). The superoxide dismutase activities were determined as described by Xin *et al.*, (1991) while the reduced glutathione (GSH) was determined by the method of Floreani *et al.*, (1997).

Determination of pH

Gastric acid was obtained by ligation of the pylorus and carefully aspirating the stomach gastric juice with a syringe. An aliquot of 1ml of gastric juice was diluted with 1ml of distilled water, and the pH of the solution was measured using a pH meter (Adwa AD8000) (Abebaw *et al* 2017)

Determination of total acidity and free acidity

This is based on simple acid base titration. Gastric juice (1mL) was pipetted into a 100 mL conical flask and diluted with 9 mL distilled water. Two or three drops of Topfer's reagent then added and titrated with 0.01 N sodium hydroxide until all traces of red color disappeared and the color of the solution was

yellowish orange. The volume of alkali added was noted. This volume corresponds to free acidity. Two or three drops of phenolphthalein were then added, and the titration was continued until a definite red ting appeared; the volume of alkali added was noted. The volume corresponds to total acidity. Acidity was expressed in terms of mEq/L (Albertus *et al* 2001)

Histopathological Examinations

The histopathological examinations of the stomachs were done using the method of Drury *et al.*, (1967). It involved fixing and washing the tissues. Dehydration was achieved using alcohol and the embedment was done in paraffin. They were subsequently cleared, infiltrated with paraffin wax, sectioned, mounted on slides and stained with eosin and haematoxylin. The slides prepared were mounted on photomicroscope one after the other and viewed at x 400 magnification power of the microscope. Qualitative histological interpretations of the different photomicrographs were made and reported.

Statistical Analysis

Data was reported as means $\pm$ SD. One way analysis of variance (ANOVA) was used to analyze the experimental data. Duncan multiple test range was used to separate the means and differences were considered significant at $P < 0.05$ using statistical package for service solution (SPSS) version 23.

Results

Results for qualitative and quantitative analysis

The result of quantitative and qualitative phytochemical analysis indicated that tannins and total phenolics were in high concentration, while flavonoids, alkaloids, steroids and terpenoids were in moderate concentration, Glycosides were in mild concentration but saponins were not detected (Table 1).

Antioxidants Effect of EAF

The fraction caused a significant ($p < 0.05$) increase in the level of SOD, whereas the levels of GSH and CAT were significantly ($P < 0.05$). The lipid peroxidation marker malondialdehyde (MDA) demonstrated a significant ($P < 0.05$) reduction (Table 2).

Effect EAF on Free acidity, Total acidity and PH

The fraction did not significantly ($P > 0.05$) affect the pH and free acidity, however there was a non-

significant ($P < 0.05$) decrease in values of total acidity (Table 3).

Table 1: Qualitative and quantitative phytochemical results analyses

Phytochemicals	Bioavailability	Amount (mg/100g)
Saponin	ND	0.00
Glycosides	+	16.80±72
Reducing sugar	++	1137.68±73.4
Alkaloids	++	509±88.62 ^b
Flavonoids	++	1697.09±425.23
Tannins	+++	57.89±1.23
Total phenolics	+++	111021.51±232.80
Steroids	++	9.03±06
Terpenoids	++	266.63±8.48

Table 2: Antioxidants activities of EAF

Groups	GSH (mg/dl)	MDA (mg/dl)	SOD (IU/L)	CAT IU/L
NC	0.88±0.42	0.74±0.16	11.42±0.07	1.05±0.34
Indo	1.50±0.30 ^b	2.05±0.98 ^b	10.71±0.44 ^a	2.69±0.45 ^b
Omepe	0.58±0.11 ^a	0.77±0.13 ^a	11.41±0.06 ^b	0.92±0.10 ^a
EAF 100	1.04±0.28 ^{ab}	0.74±0.15 ^a	11.47±0.01 ^b	0.73±0.23 ^a
EAF 200	0.77±0.11 ^{ab}	0.71±0.04 ^a	11.44±0.04 ^b	0.92±0.60 ^a
EAF 400	1.28±0.60 ^{ab}	0.81±0.17 ^a	11.47±0.01 ^b	0.87±0.09 ^a

NC- Normal control, Indo- Indomethacin 40 mg/kg, Omepe- (omeprazole 20 mg/kg EAF-Ethyl acetate fraction of *D. guineenses* (mg/kg) Superscripts that are different were considered significant ($P < 0.05$).

Table 3: Effect of the fraction on Free acidity, Total acidity and PH

Groups	Free acidity (μM/μl)	Total acidity (μM/μl)	pH
NC	0.03±0.01	0.05±0.01	3.83±0.44
Indo	0.15±0.02 ^{b,c,d}	0.24±0.07 ^{cb}	4.08±0.15 ^{a,b}
Omepe	0.14±0.04 ^{a,b,c,d}	0.22±0.05 ^{cd}	3.47±0.105 ^a
EAF 100	0.15±0.11 ^{abcd}	0.19 ±0.16 ^{bc}	3.57±0.91 ^a
EAF 200	0.15±0.09 ^{bcd}	0.17 ±0.09 ^{abcd}	4.100±0.854 ^{ab}
EAF 400	0.12±0.09 ^{abcd}	0.14±0.09 ^{ab}	4.53±0.58 ^{ab}

NC-Normal control, Indo-Indomethacin 40 mg/kg, Omepe-Omeprazole 20 mg/kg, EAF-Ethyl acetate fraction of *D. guineenses* (mg/kg). Superscripts that are different were considered significant ($P < 0.05$).

Histopathological Results of Stomach of Albino Wistar Rats Treated with Ethyl acetate Fraction of Dialium guineense

Photomicrography of normal control showed stomach architecture with intact gastric mucosa (M), sub-mucosal (SM) and muscularis externa (ME) layer. The mucosa had intact columnar epithelium (E), well-defined gastric pits (GP) and glands (GG). Submucosa contains connective tissue, while the muscularis externa displays distinct inner circular and outer longitudinal muscle layer. No pathological changes such as inflammation or ulceration are observed. (Figure 1). Administration of indomethacin resulted in shedding and ulceration in gastric epithelium and gastric pit. Sub-mucosal and muscularis externa layers were intact. Submucosa contained connective tissue, blood vessels, and nerve fibers, while the muscularis externa displayed distinct inner circular and outer longitudinal muscle layer. Epithelium (E), Gastric pit (GP), Blood vessel (BV) and Gastric glands (GG). (Figure 2). Photomicrography of the stomach treated with omeprazole demonstrated mild shedding and lesions in gastric epithelium. Sub-mucosal and muscularis externa layers were intact. Submucosa had connective tissue while the muscularis externa displayed distinct inner circular and outer longitudinal muscle layer. Epithelium (E), Gastric pit (GP), Blood vessel (BV) and Gastric glands (GG). (Figure 3). The section of albino rat stomach treated with 100 mg/kg of ethyl acetate (Figure 4) showed normal

stomach architecture with intact gastric mucosa (M), sub-mucosal (SM) and muscularis externa (ME) layer. Mucosa showed intact columnar epithelium (E), well-defined gastric pits (GP) and glands (GG). Submucosa had connective tissue, while the muscularis externa displayed distinct inner circular and outer longitudinal muscle layer. No pathological changes such as inflammation or ulceration are observed. The section of albino rat stomach treated with 200 mg/kg of ethyl acetate (Figure 5) showed normal stomach architecture with intact gastric mucosa (M), sub-mucosal (SM) and muscularis externa (ME) layer. Mucosa shows intact columnar epithelium (E), well-defined gastric pits (GP) and glands (GG). Submucosa contains connective tissue, while the muscularis externa displays distinct inner circular and outer longitudinal muscle layer. No pathological changes such as inflammation or ulceration were observed. The section of albino rat stomach treated with 400 mg/kg of ethyl acetate fracture (Figure 6) showed normal stomach architecture with intact gastric mucosa (M), sub-mucosal (SM) and muscularis externa (ME) layer. Mucosa showed intact columnar epithelium (E), well-defined gastric pits (GP) and glands (GG). Submucosa contained connective tissue, while the muscularis externa displayed distinct inner circular and outer longitudinal muscle layer. There were no pathological changes such as inflammation or ulceration.

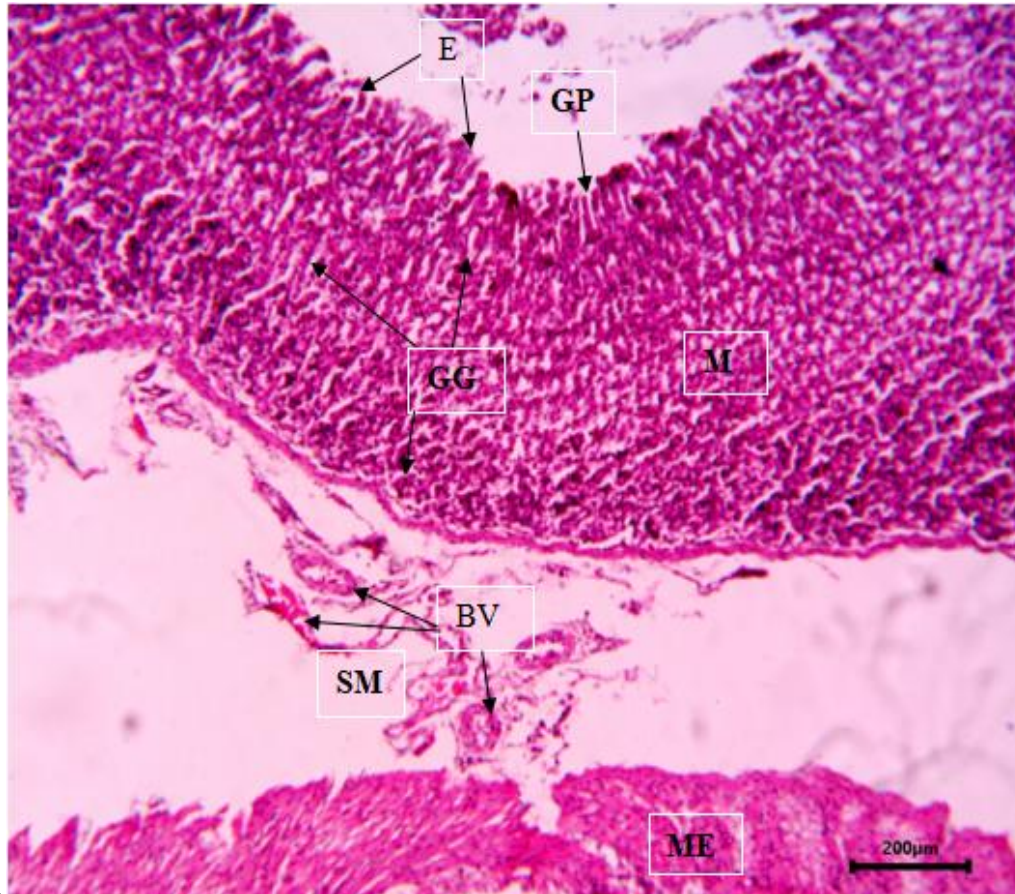


Figure 1: Photomicrograph of the stomach of the Normal control rats H&E, x100

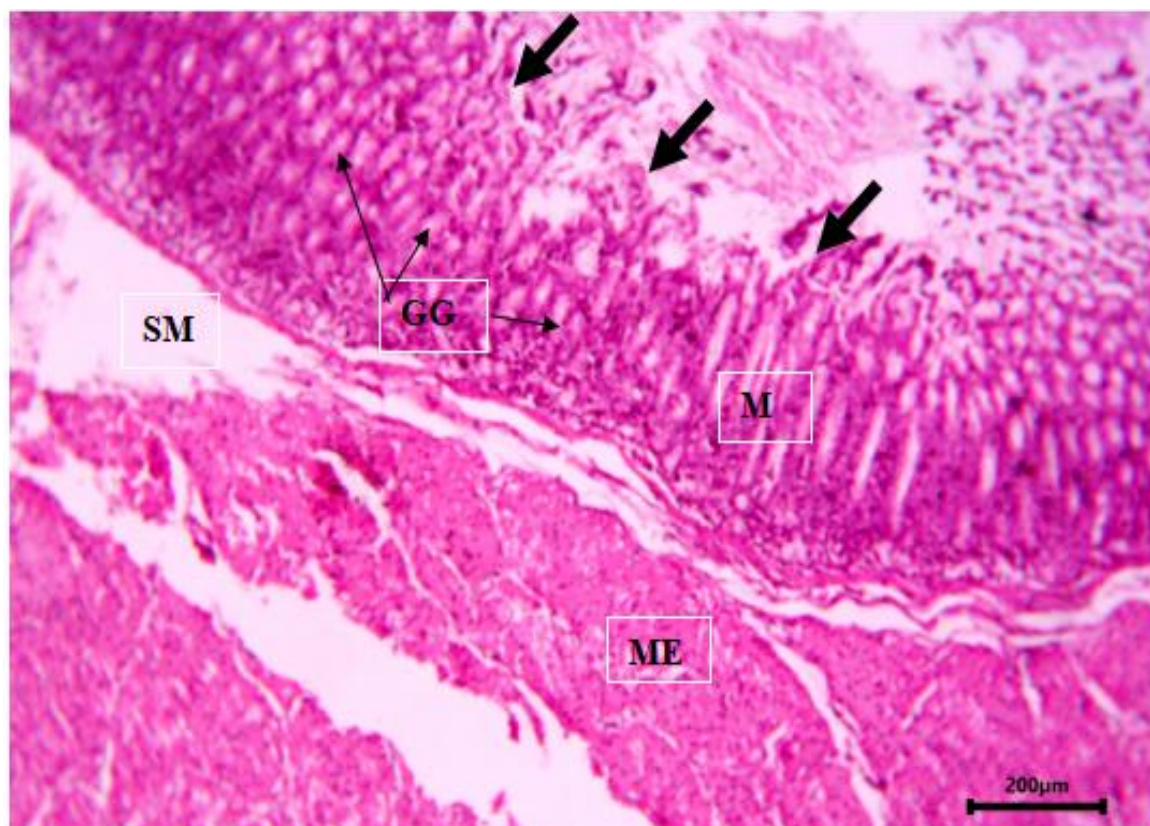


Figure 2: Photomicrograph of the stomach of the Indomethacin (40 mg/kg) only treated rats
H&E, x100



Figure 3: Photomicrograph of the stomach of the rats treated with Omeprazole (20 mg/kg) H&E, x100

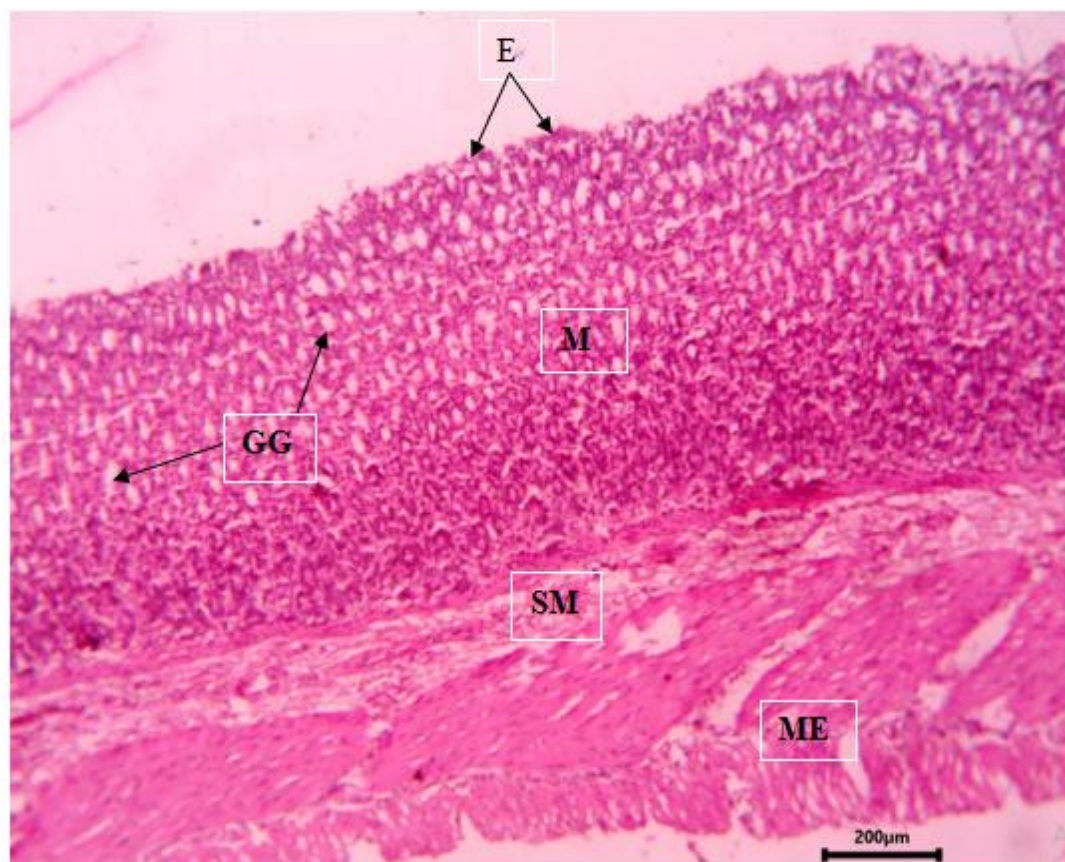


Figure 4: Photomicrograph of the stomach of the rats treated with Ethyl acetate fraction of *D. guineenses* (100 mg/kg). H&E, x100

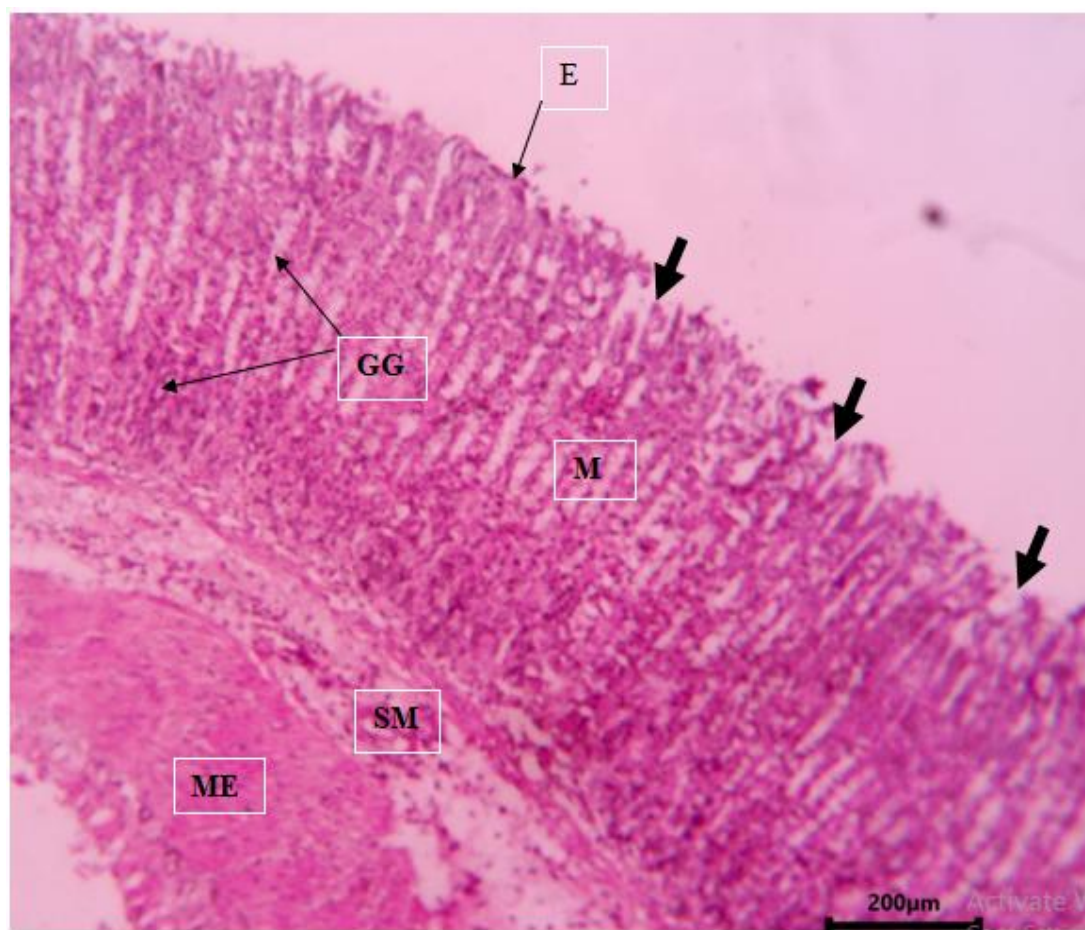


Figure 5: Photomicrograph of the stomach of the rats treated with Ethyl acetate fraction of *D. guineenses* (200 mg/kg). H&E, x100



Figure 6: Photomicrograph of the stomach of the rats treated with Ethyl acetate fraction of *D. guineenses* (400 mg/kg). H&E, x100

Discussion

This study investigated the effects of ethyl acetate fraction of *Dialium guineense* leaves on the stomach architecture of Wistar rats intoxicated with indomethacin. Chime *et al* (2025b) posited that the methanol crude leaf extract of *Dialium guineense* had LD₅₀ of more than 5000 mg/kg using extract. The anti-ulcer activity of its methanol leaf extract had been reported (Chime *et al* 2025a). However, ethyl acetate fraction of *Dialium guineense* leaves was employed in this study. Ethyl acetate is a versatile solvent widely used, due to its low cost, low toxicity, and fast evaporation rate (Hartwig and MAK Commission, 2025). It is highly miscible with most organic solvents like alcohols and ethers, though it is only slightly soluble in water. Ethyl acetate can extract terpenoids, total phenolics, alkaloids, flavonoids, tannins as was evidenced in this study. Thus, it is useful in the extraction of phytoconstituents with antioxidant and anti-inflammatory activity (Agu *et al.*, 2023)

The *in vitro* antioxidant results that revealed decrease in the in GSH and CAT was at variance with previous reports (Agu *et al.*, 2023). The variation seen in CAT activity seems to

suggest that iron-mediated-redox process may not be involved in the antioxidant-mediated anti-ulcerogenic potential of *Dialium guineense*. Indomethacin creates oxidative stress with rampaging free radicals altering the oxidative balance leading to ulcers. *Dialium guineense* has high amounts of total phenolics, terpenoids, flavonoids and other phytochemicals which is a strong indication of its antioxidant capacity (Agu *et al.*, 2023). Flavonoids can activate the mucosal defense system by stimulating gastric mucus secretion, scavenging the ROS and free radicals produced by ethanol (Abdelwahab *et al.*, 2011). Different authorities have posited the ability of phenolic compounds to donate proton which leads to the scavenging of free radicals, reactive oxygen, inhibition of lipid peroxidation and its cytoprotective potential (Edeoga and Eriata 2001). The findings in this study are in consonance with those earlier reports (Fahmy *et al.*, 2015; Suheryani *et al.*, 2019) of elevated levels of MDA in the gastric tissue following administration of indomethacin. The significant decrease in total and free acidity for the treatment groups implies that ethyl acetate fraction has a neutralization effect

probably due to the presence of terpenoids and steroids. This study agrees with the results of Obidike *et al.*, (2024) who reported a significant decrease in free acidity by methanol extract and ethyl acetate fraction *Dialium guineense* leaves. The photomicrographs of the stomach specimens of the treatment groups showed normal stomach architecture. There was intact gastric mucosa, sub-mucosa and muscularis externa layer. The mucosa had intact columnar epithelium, well-defined gastric pits and glands with submucosa containing connective tissue, while the muscularis externa displayed distinct inner circular and outer longitudinal muscle layer. No pathological changes such as inflammation or ulceration were observed. The treatment groups compared favorably with the standard drug group which showed mild shedding and ulcer in gastric epithelium but with sub-mucosa and muscularis externa layers intact.

Conclusion

Ethyl acetate fraction of *Dialium guineense* demonstrated curative potentials in ulcer maintaining normal histomorphology of the stomach. Its antioxidant effects may likely contribute to the anti-ulcer activity.

Conflict of Interest

The authors declared no conflict of interest

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