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Possible Gastroprotective Mechanisms of *Dacryodes edulis* Extract in Indomethacin-Induced Gastric Ulceration in Male Wistar Rats

E. Nwaonukuru[1], O. O. Olaniyi[1] and F. S. Oluwole[1*]

[1]Gastrointestinal and Inflammatory Research Unit, Department of Physiology, University of Ibadan, Ibadan, Nigeria.

Authors' contributions

This work was carried out in collaboration between all authors. Author EN designed the study and carried out all the experimental procedures. Author OOO assisted in the experimental procedures and wrote the first draft of the manuscript while author FSO developed the protocol for the study and managed the literature searches. All authors read and approved the final manuscript.

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Original Research Article

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ABSTRACT

African bush Pear known as is a well-known plant in West Africa, the fruits are edible while the bark, leaves, stem and roots are employed for a variety of purposes. It has been previously reported to possess high antioxidant properties and has also been used in folkloric medicine to treat ulcer among other ailments. This study therefore investigated the possible anti ulcer mechanisms of action of methanolic leaf extract of *Dacryodes edulis* (ME) in male Wistar rats.

Fifty (50) adult male Wistar rats weighing between 180 and 200g were randomly divided into two experimental groups. Twenty five (25) animals were further sub-divided into 5 groups (n=5). The first subgroup was used for the antiulcer study using indomethacin induced ulceration model. The second experimental group was used to examine the mechanisms of action of ME i.e gastric mucus secretion, antioxidant enzymes and prostaglandins secretion. Each subgroup was divided into; Control, Omeprazole (positive control) and three doses of (ME) *D. edulis* (50 mg/kg, 100 mg/kg and 200 mg/kg) pre-treated for twenty-eight days orally.

D. edulis (200 mg/kg) conferred a significant reduction in the mean ulcer score (P=0.05),

**Corresponding author: E-mail: drtobiolaniyi@gmail.com;*

producing 64.75% ulcer inhibition. Compared with the control, the catalase activity was significantly increased in the 200 mg/kg group of *D. edulis* and in the Omeprazole group, while SOD levels were significantly increased across all test groups and in Omeprazole group. There was significant reduction MDA level of all the pre treated groups when compared with the control. There was dose dependent increase across all the groups pre-treated with *D. edulis* when these were compared with the control.
In conclusion, the anti-ulcer effect of *Dacryodes edulis* is likely mediated via the production of antioxidant enzymes (Catalase, SOD), reduction in lipid peroxidation (MDA concentration), and increase endogenous prostaglandins (PGE_2).

Keywords: Dacryodes edulis; antioxidant enzymes; prostaglandins (PGE_2).

1. INTRODUCTION

Peptic ulcer is a common disease throughout the world [1,2,3]. It represents one of the major health problems, both in terms of morbidity and mortality [4]. The pathogenesis of peptic ulcer disease is traceable to an imbalance between gastric 'offensive factors and gastric 'defensive' factors. The gastric mucosa is continuously exposed to potentially aggressive agents such as acid, pepsin, bile acids, food ingredients, bacterial products (*Helicobacter pylori*) and non-steroidal inflammatory drugs [5]. *Dacryodes edulis* is a versatile plant in African ethno medicine, as its various parts are employed to treat several diseases. The leaves are chewed with kolanut as an antiemetic, leaf sap is used as ear drop to treat ear trouble, while a leaf decoction is prepared to produce vapour that treats fever and headache [6,7]. Furthermore, the leaves are crushed and the juice released to treat generalized skin diseases such as scabies, ringworm, rash and wound [8,9]. Traditionally, the decortion of this plant is used in the treatment of stomach pains by the Igbo's.

In a previous study, *D. edulis* was not among the plants implicated for eventual toxicity evaluation [10,11]. Also lack of toxins in the fruit was reported with indicated values below toxic level for the antinutrient factors such as tannins and cyanide [12]. The study therefore examined the possible anti ulcer effects of *D.edulis* and its possible mechanisms.

2. MATERIALS AND METHODS

The materials used were, Dissecting set, Oral cannula, Dissecting board, Cotton wool, Stop watch, Permanent maker,Organ bottles, EDTA bottles, Plain bottles, Needles and Syringes, Nose cover, Beakers, Conical flask, Measuring cylinder, Methylated spirit, Camera, Spectrophotometer, pH meter Centrifuge, and Homogenizer.

2.1 Drugs and Chemicals

Omeprazole, Ulcertret-20 (*Swiss Pharma Pvt. Ltd. Gujarat, India),* Indomethacin (Sigma) the chemicals used were analytical grade; Sodium acetate, Magnesium chloride, Sucrose, Diethyl ether, Sodium chloride, Distilled water, Hydrochloric acid, Sodium hydroxide, Formalin Biuret reagent, Griesse reagent, Trichloroacetic acid (TCA), Thiobarbituric (TBA).

2.2 Experimental Animals

Fifty (50) adult male Wistar rats weighing between 180 and 200 g were purchased from the Preclinical animal house of the College of Medicine, University of Ibadan, Ibadan, Nigeria. All animals were kept under standard conditions, acclimatized for two weeks and were fed on rats' pellets and water given ad libtium.

2.3 Experimental Design

After the period of acclimatization, the fifty experimental Wistar rats were divided into two major groups, each containing twenty five animals and each group was sub divided into five groups containing five animals each. Treatments are as shown in Table 1.

The first experimental group was used to study the possible mechanisms of action of ME; mean ulcer score, Catalase, Superoxide Dismutase, lipid peroxidation (MDA) and Prostaglandins E (PGE_2), while the second major group was used for the gastric mucous study.

Table 1. Treatments of the various groups of animals

Grouping	Treatment
Group 1	Had access to clean water
Group 2	Pre-treated with 20mg/kg body weight Omeprazole.
Group 3	Pre-treated with 50mg/kg body weight of (ME) of the leaf of *Dacryodes edulis*
Group 4	Pre-treated with 100mg/kg body weight of (ME) of the leaf of *Dacryodes edulis*
Group 5	Pre -treated with 200mg/kg body weight of (ME) of the leaf of *Dacryodes edulis*

2.4 Collection, Identification and Extraction of *Dacryodes edulis*

Dacryodes edulis leaves were purchased from Omoku, Rivers state, Nigeria. The plant was botanically identified and authenticated by Dr Esimekuai D.P.O; Department of Botany, University of Ibadan, Ibadan, Nigeria. A specimen was deposited at the herbarium of the department of Botany in University of Ibadan, Ibadan, Nigeria. The voucher number is UIH – 22525.

It was washed (to remove dust and other impurities) and air dried for two weeks to ensure proper removal of the moisture content while reserving the important constituents of the leave. It was weighed with electronic balance and was found to be about 3 kg. The dried plants were grinded with electric blender. 2 kg of the *D. edulis* was measured out and macerated in an airtight glass jar for 72 hours. The plant was macerated and 10 litres of solvent added with (80% methanol and 20% distilled water). After maceration it was carefully filtered with the Watman filter paper of pore size 25 mm. The filtrate was concentrated using a rotatory evaporator at an optimum temperature of 40–50ºC. The filtrate was then kept in a water bath to allow for evaporation of water at a very low temperature of 40ºC at a high pressure above atmospheric pressure. At the end 1230 g of the extract was obtained with a percentage yield of 67.48%.

The extracts obtained were kept in a desiccator after every administration to avoid hydration of the extract.

2.5 Indomethacin Gastric Ulcer Induction

Indomethacin (sigma) was used to induce ulcer at a dosage of 40 mg/kg body weight. The stock solution of indomethacin was made and was further dissolved in 0.5 ml of 1.25% sodium bicarbonate for perfect solution. The required dose was administered 4 hours prior to sacrifice. The animals were sacrificed by cervical dislocation 4 hours after the induction of ulcer. Then, the stomachs were removed and cut open along the lesser curvature for the counting of ulcer spots.

2.6 Assessment of Ulcer Spots

Examination of the stomach was done with a hand lens at X2 magnification. The method used was that reported by [13] modified by [1]. Ulcer scores were assessed by two independent observers using these criteria:

2.7 Determination of Percentage Inhibition (%)

Percentage Inhibition (P.I %) was later calculated as follows:

$$\text{P.I \%} = \left(\frac{Ulcer\ index\ of\ Control - Ulcer\ Index\ of\ treated}{Ulceer\ Index\ of\ Control}\right) \times 100$$

2.8 Histological Assessment

Sections were prepared from strips removed from the fundic area of the stomach and stained using the method of Drysdale and Marks [14] as modified by Oluwole et al. [15], using the Hematoxylin and Eosin stain.

2.9 Preparations of the Stomachs for the Determination of Total Proteins, Antioxidant Enzymes and lipid Peroxidation

Each stomach was cut into smaller pieces, placed in a universal bottle and 0.1 M phosphate buffer was added. The homogenate of the stomach pieces was made using a homogenizer this was poured into a test tube, centrifuged at 1000 rpm for 15 minutes. The supernatant was then used for the estimation of superoxide dismutase, and catalase level in the stomach tissues. Also, the supernatant was equally used to determine lipid peroxidation (MDA).

Table 2. Gastric ulcer score criteria

Scoring	Nature of ulcer spots
0	Normal stomach (No Ulcer)
0.5	Punctuated hemorrhage/pin-point ulcer
1.0	Two or more small hemorrhage ulcer (approximately 2 mm)
2.0	Ulcer greater than 3mm in diameter

2.10 Determination of Antioxidant Activity

2.10.1 Assay of catalase

Catalase activity was determined according to according to the method of Sinha et al. [16]. This was done by measuring the absorbance of H_2O_2 at 480 nm. Absorbance was read and expressed in µmol/mg protein.

2.10.2 Assay of superoxide dismutase (SOD)

The principle of the assay method involves the inhibition of auto oxidation of adrenaline to adrenochrome as described by Misra et al. [17].

2.11 Determination of Lipid Peroxidation

MDA assessment was done according to the method of [18].

MDA (units/mg protein) =

$$\frac{Absorbance\ x\ volume\ of\ mixture}{E532nm\ x\ volume\ of\ sample\ x\ mg\ protein}$$

2.12 Determination of Prostaglandin E Level

The ELISA KIT (Enzyme Linked Immunosorbent Assay kit) was used for the assaying of Prostaglandin E_2. This was ordered from Elab Science official website (elabscience.com). The ELISA Kit uses a Competitive-ELISA as the method. The concentration of PGE_2 in the samples was extrapolated from the standard curve.

2.13 Gastric Mucus Secretion Study

This study was carried out using the spectrophotometry method described by Corney et al. [19].

Gastric mucus secretion (mg/g tissue) = Weight of dye (mg) / Weight of stomach (g)

2.14 Statistical Analysis

Statistical analysis was done using Graph Pad Prism 7.0 and One-way Analysis of Variance (ANOVA). Data were expressed as Mean ± Standard Error of Mean (SEM). *P*=0.05 was considered significant.

3. RESULTS

3.1 Effect of *D. edulis* on Mean Ulcer Score, Ulcer Index and Percentage Inhibition

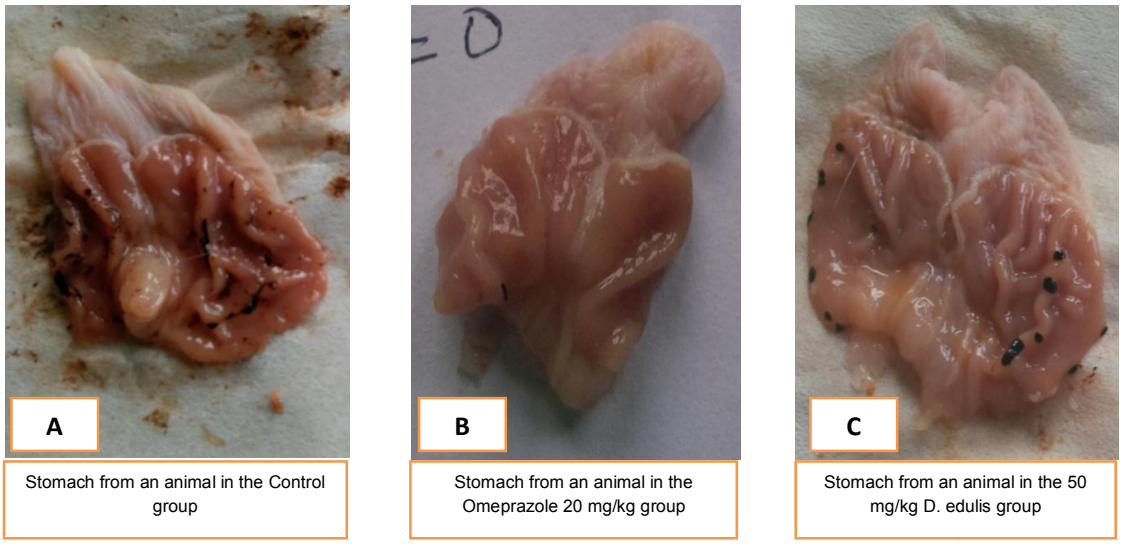
The gross mean ulcer score of the pre-treated rats following the induction of gastric ulcer using indomethacin is presented in the Table 1.

The Ulcer Index was significantly reduced in the *D. edulis* 200 mg/kg group (9.13±1.88) and the Omeprazole 20 mg/kg pre-treated groups (5.20±1.06) when compared with the control group (27.60±1.85 mm) (P=0.05). The percentage inhibition for the *D. edulis* groups and Omeprazole group were 37.14%, 59.06%, 64.75%, and 78.99% respectively.

Table 3. Effect of *D. edulis* on mean ulcer score in indomethacin induced gastric ulcer

Grouping	Treatment (28 DAYS)	Mean ulcer score (MEAN ± SEM)	% protection
I	Control	27.60±1.85	0
II	Omeprazole (20 mg/kg)	5.20±1.06^{a*}	78.99
III	*D. edulis* (50 mg/kg)	16.75±3.19^{NS}	37.14
IV	*D. edulis (*100 mg/kg)	10.70±1.21^{NS}	59.06
V	*D. edulis (*200 mg/kg)	9.13±1.88^{a*}	64.75

Data expressed as Mean ± SEM; n=5;
a = Significant P = 0.05 (When compared with control).*
NS = Not significant (When compared with control).



Stomach from an animal in the Control group

Stomach from an animal in the Omeprazole 20 mg/kg group

Stomach from an animal in the 50 mg/kg D. edulis group

Stomach from an animal in the 200 mgkg *D. edulis* group

Stomach from an animal in the 100 mg/kg *D. edulis* group

Plate 1. Macroscopic views of stomach samples of various pre-treatment groups
A Control group (distilled water + vehicle) – very severe ulcer of more than 3 mm
B Omeprazole group (distilled water 20 mg/kg omeprazole) – lesser or no ulcer
C 50mg/kg group (D. edulis + DW + vehicle) – less severe ulcer of more than 3 mm
D 100 mg/kg group (D. edulis + DW + vehicle) – mild ulcer
E 200 mg/kg group (D. edulis + DW + vehicle) – lesser or no ulcer

3.2 Effect of *Dacryodes edulis* Pre-Treatment on Histological Changes in the Gastric Mucosa

Histological observations in the control group showed extensive damage to the gastric mucosa. The epithelial cells layer showed focal areas of moderate ulcer and necrosis. The submucosal layer showed moderate infiltration of inflammatory cells involving polymorphs majorly (Plate 2A).

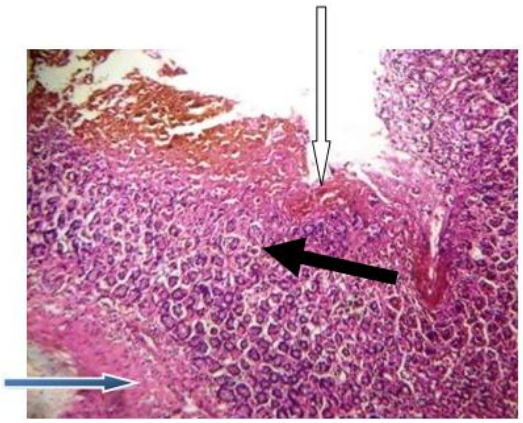
The stomachs of rats pre-treated with *Dacryodes edulis* and Omeprazole were observed to show better protection in their gastric mucosa as seen in the reduction of ulceration, reduced or absence of necrosis and leukocyte infiltration (Plates 2B-E).

3.3 Catalase Activities on *D. edulis* Pretreated Animals

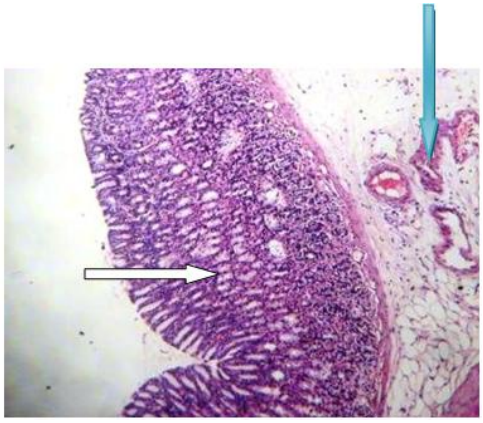
There was a significant increase in CAT activity in 200 mg/kg *D. edulis* and Omeprazole compared with animals in the control group (Fig. 1).

3.4 Superoxide Dismutase Activities on *D. edulis* Pretreated Animals

The activities of SOD were significantly higher in all the groups pretreated with *D. edulis* (50, 100 and 200) mg/kg and in Omeprazole group when compared with animals in the control group as shown in Fig. 2.

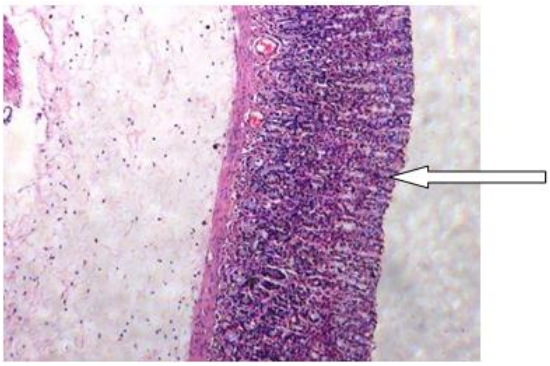


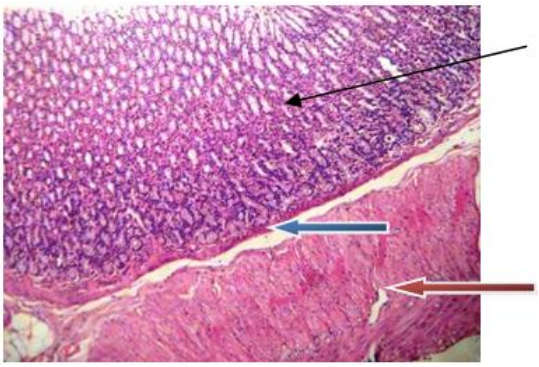
A (Control):
Photomicrograph Showing Poor Architecture, The Mucosa Epithelial Cells Layer are Poorly Preserved, Showing Focal Areas of Moderate Ulcer (White Arrow) and Necrosis (Black Arrow), the Mucosa Layer Shows No Infiltration of the Gastric Glands and Lamina Propria. The Submucosal Layer Shows Moderate Infiltration of Inflammatory Cells Involving Polymorphs Majorly **X100 (H&E)**



B (Omeprazole 20 mg/kg):
Photomicrograph Showing Normal Architecture, the Mucosa Epithelial Cells Layer are Preserved (White Arrow), the Mucosa Layer Shows No Infiltration of the Gastric Glands and Lamina Propria. The Submucosal Layer Shows Scanty Infiltration of Inflammatory Cells Involving Polymorphs Majorly (Blue Arrow).
X100 (H&E)

C (200 mg/kg *D. edulis*)

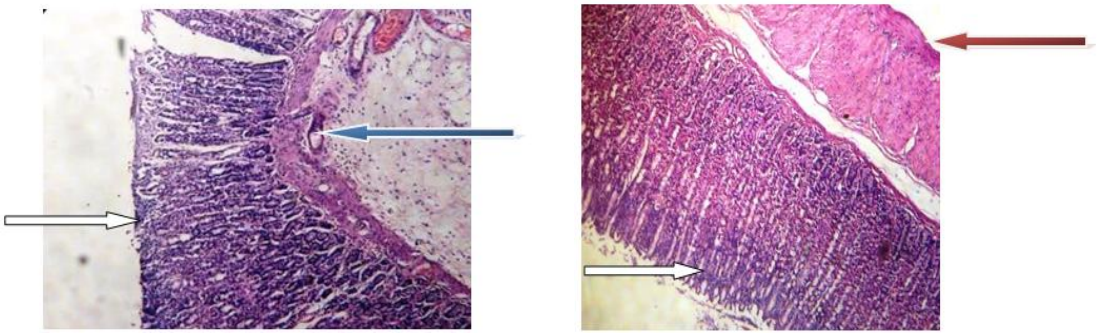




C (200 mg/kg D. edulis):

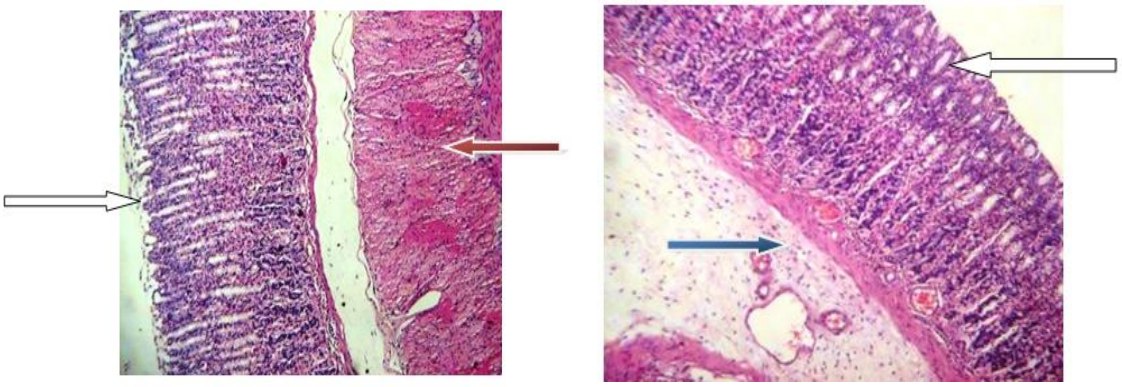
Photomicrograph Showing Normal Architecture. The Mucosa Epithelial Cells Layer are Preserved, (White Arrow), the Mucosa Layer Shows No Infiltration of the Gastric Glands and Lamina Propria (Slender Arrow). The Submucosal Layer Show Mild Infiltration Of Inflammatory Cells Involving Polymorphs Majorly (Blue Arrow). The Crcular Muscle Layer Appears Normal (Red Arrow)
X100 (H&E)

D (100 mg/kg *D. edulis*)



Photomicrograph Showing Normal Architecture,the Mucosa Epithelial Cells Layer are Moderately Preserved (White Arrow), The Mucosa Layer Shows No Infiltration of the Gastric Glands and Lamina Propria. The Submucosal Layer Shows Mild Infiltration of Inflammatory Cells Involving Polymorphs Majorly. **X100 (H&E)**

E (50 mg/kg *D. edulis*)



Photomicrograph Showing Moderate Architecture. The Mucosa Epithelial Cells Layer are Moderately Preserved (White Arrow). The Mucosa Layer Shows No Infiltration of the Gastric Glands and Lamina Propria. The Submucosal Layer Show Very Mild Infiltration of Inflammatory Cells (Blue Arrow). The Circular Muscle Layer Appears Normal (Red Arrow)
X100 (H&E)

Plate 2. Histology of the stomach sections of the various pretreatment groups stained using the hematoxylin and eosin stain (H&E Stain)

3.5 Malondialdehyde (MDA) Concentration in *D. edulis* Pretreated Rats

MDA level was significantly reduced in all the *D. edulis* pre treated groups (50, 100 and 200 mg/kg) and in Omeprazole when compared with animals in the control group (Fig. 3).

3.6 Prostaglandin E_2 (PGE_2) Concentration in *D. edulis* pre Treated Animals

PGE_2 was significantly increased in all the groups pre treated with *D. edulis* (50, 100 and 200 mg/kg). PGE_2 was equally elevated in the Omeprazole pre treated groups as compared with the control group (Fig. 4).

3.7 Gastric Mucous Content in *D. edulis* Pretreated Animals

There was no significant difference in the gastric content of all animals pretreated with D edulis (50 mg/kg, 100 mg/kg and 200 mg/kg) when compared with those in control groups (Fig. 5). Treatment of rats with Omeprazole (Group II) caused significant increase in gastric mucous content as compared to the control group.

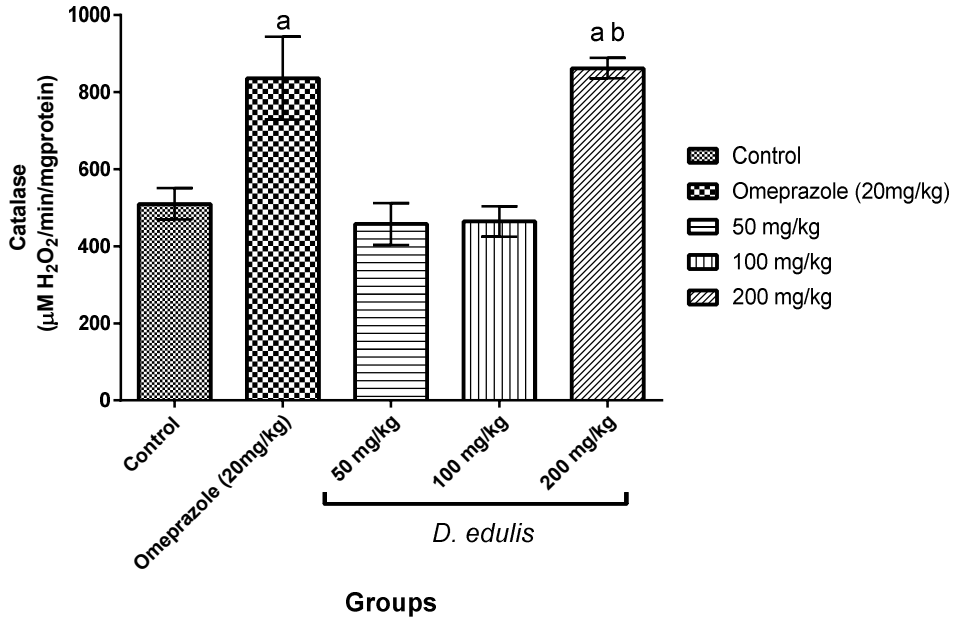


Fig. 1. Catalase activities on *D. edulis* pre treated animals

Data expressed as Mean SEM; n = 5
a = statistically significant compared with control
b = statistically significant compared with Omeprazole
c = statistically significant compared with smaller doses of D. edulis

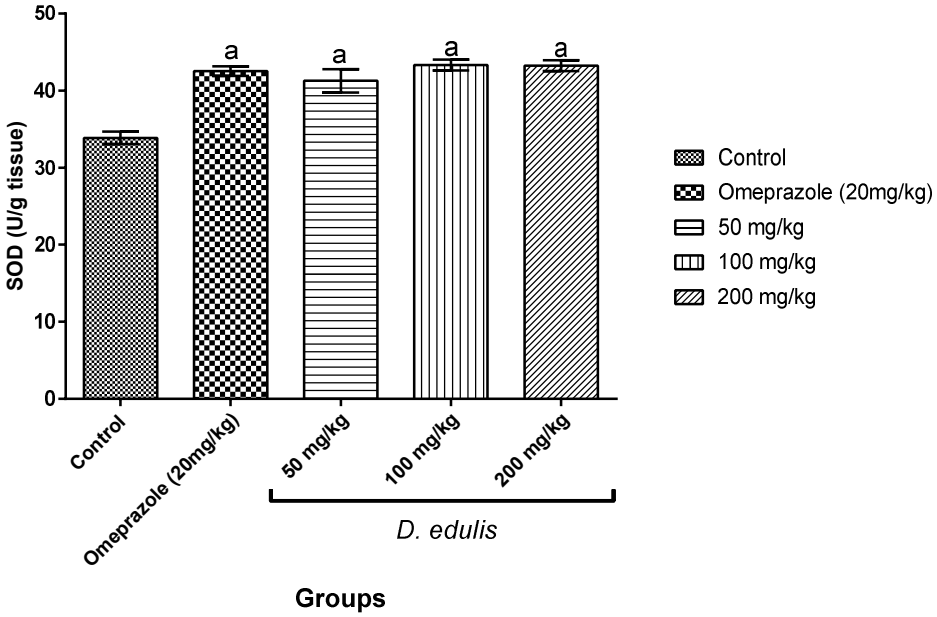


Fig. 2. Superoxide Dismutase activities on *D. edulis* pretreated animals.

Data expressed as Mean SEM; n = 5
a = statistically significant compared with control
b = statistically significant compared with Omeprazole
c = statistically significant compared with smaller doses of *D. edulis*

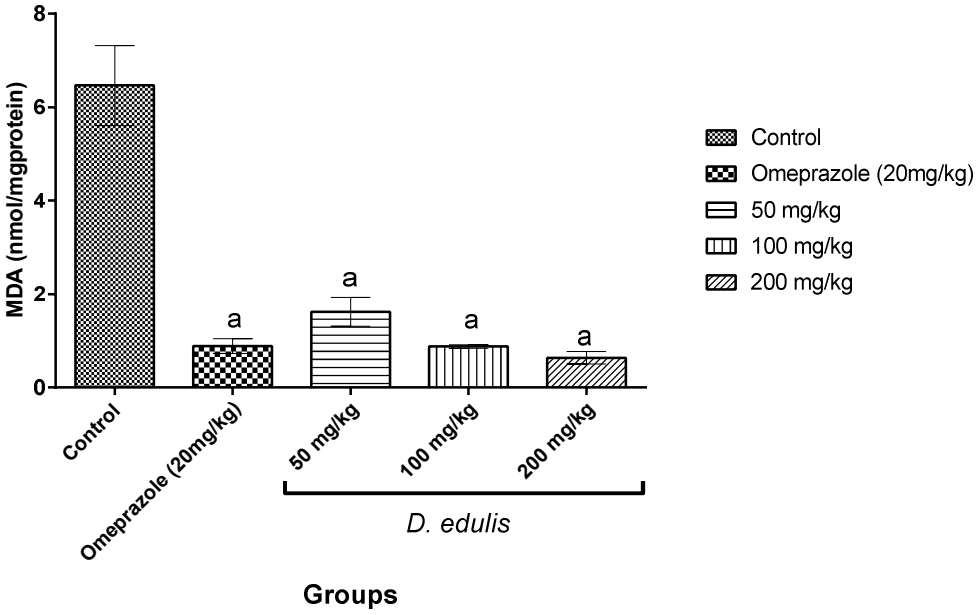


Fig. 3. Malondialdehyde (MDA) Concentration in *D. edulis* pretreated rats

Data expressed as Mean SEM; n = 5
a = statistically significant compared with control
b = statistically significant compared with Omeprazole
c = statistically significant compared with smaller doses of D. edulis

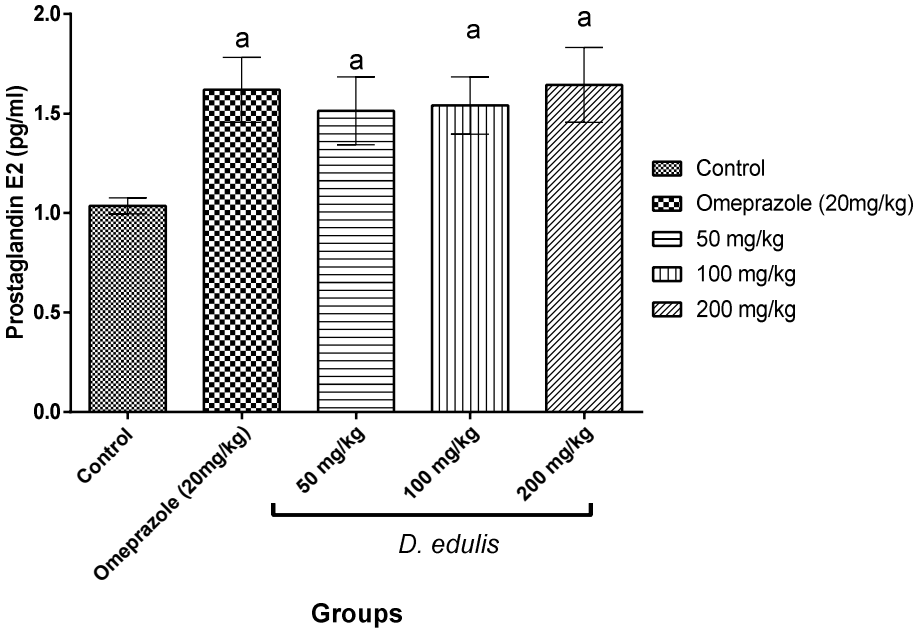


Fig. 4. Prostaglandin E_2 (PGE_2) Concentration in *D Edulis* pre treated animals

Data expressed as Mean SEM; n = 5
a = statistically significant compared with control
b = statistically significant compared with Omeprazole
c = statistically significant compared with smaller doses of D. edulis

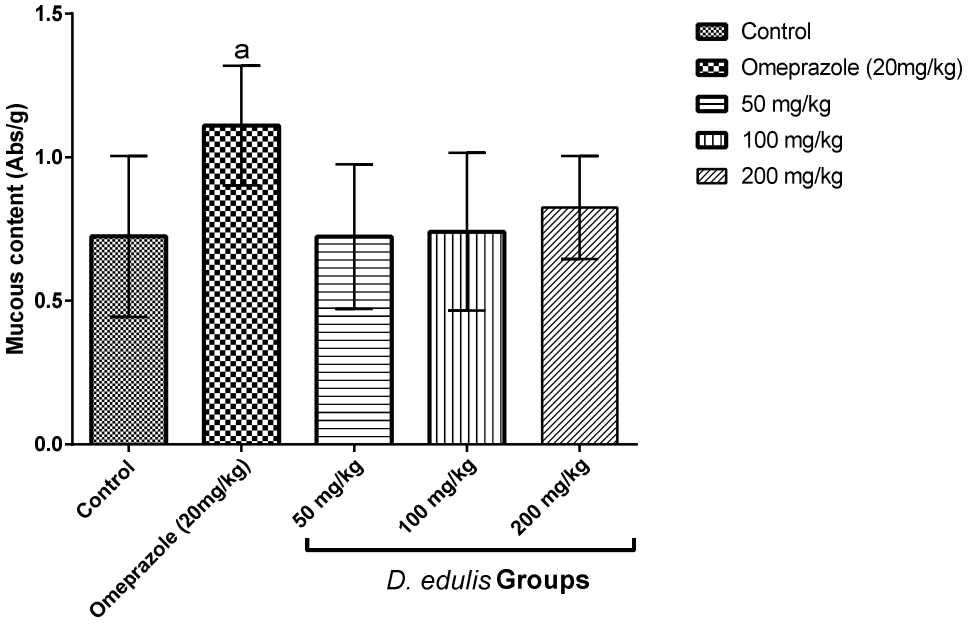


Fig. 5. Effect of *D. edulis* pre-treatment on mucous secretion in indomethacin induced gastric ulcerated rats

Data expressed as Mean SEM; n = 5
a = statistically significant compared with control
b = statistically significant compared with Omeprazole
c = statistically significant compared with smaller doses of D. edulis

4. DISCUSSION

In the study of the effect of the pre-treatments on experimental ulcer induction (Table 3), the animals in the control group which were not pretreated with *D edulis* showed profound gastric injury. In contrast, the animals pre treated with 200 mg/kg of D edulis exhibited significant reduction in gastric mucosa injury. Though the two groups of *D. edulis* with lowe concentration (50 mg/kg and 100 mg/kg) showed little or no ulcer inhibition of the gastric mucosa, This study represents the first report on the anti-ulcer mechanisms of *D. edulis*. This antiulcer effect of the plant was noticed at higher concentration of *D. edulis* pretreatment *(*200 mg/kg), this report is in agreement with the folkloric medicine for treatment of ulcer when boiled singly or in combination with lemon grass and pulp oil from the fruit has been used also for treating ulcer as reported in an ethnobotanical study [20].

Omeprazole similarly demonstrated its antiulcer effect by reducing the degree of ulceration by 78.99% inhibition which agrees with the report of Tuorkey and Abdul-Aziz [21] that, Omeprazole significantly reduced the incidence of NSAID-induced gastric ulceration.

In the catalase activity study, the 200mg/kg *D. edulis* and Omeprazole groups showed significant increase in catalase activity compared to the control (P=0.05) as seen in figure 1. The superoxide dismutase level (SOD) in Omeprazole group was equally elevated when compared with the control group as earlier reported by Popovic et al. [22] and Selvamathy et al. [23], Catalase and SOD may therefore be responsible for the high antioxidant effect by *Dacryodes edulis* leaves reported by Agbor et al. [24].

ROS, especially OH, plays a major role in oxidative damage of gastric mucosa in almost all forms of gastric ulcer [25]. The damage caused by superoxide anions is counteracted by dismutation with SOD [26]. SOD in turn converts the reactive hydrogen peroxide to water, which, if not scavenged by catalase, can cause lipid

peroxidation by increasing generation of hydroxyl radicals [25].

The study on oxidative activity (lipid peroxidation) using malondialdehyde as its indicator (Fig. 3) showed that the control group had the highest level of TBAR activity, while pretreatment with three doses of *D. edulis* significantly reduced the MDA levels (P=0.05). Pre treatment with Omeprazole showed significant decrease in the MDA level compared to the control group. The observation of the result indicates that *D. edulis* and Omeprazole conferred protection to the stomach better than the Control group.

The study on the pretreatment of animals with D. edulis on the Prostaglandin E_2 content showed a significant increase in all groups when compared with the control animals (figure 4). Animals pre treated with Omeprazole had a significant increase in Prostaglandin E_2 content as compared with the animals in the control group. This effect of omeprazole agrees with an earlier report on the effect of Omeprazole on prostaglandin synthesis [27]. Prostaglandin is known to confer cytoprotection against indomethacin induced ulceration [28].

The effect of *D edulis* pretreatments on gastric mucous contents did not show any significant difference amongst the groups as compared to the control (Fig. 5). Omeprazole, a proton pump inhibitor is known to increase mucous secretion as part of its protective mechanism; this is further confirmed by the significant increase in mucous secretion in the Omeprazole pretreated group when compared to the control.

In this study using indomethacin-induced gastric ulceration in Wistar rats, the higher dose of *D. edulis* pre-treatment were effective in the prevention of ulcer formation and the mean ulcer score. Its potency was further supported by the study of its effect on the significant increase in SOD, Catalase, Prostaglandins E (PGE_2), and significant decrease in MDA but with relatively no effect in gastric mucous content.

5. CONCLUSION

The results from this study indicate that the possible mechanisms of action of methanolic extract (ME) of the leaf of *Dacryodes edulis* in male Wistar rats might be associated with its ability to increase the production of antioxidant enzymes; (Catalase and Superoxide Dismutase), Prostaglandins E (PGE_2), and reduction of MDA level thus protecting the gastric mucosa.

CONSENT

It is not applicable.

ETHICAL APPROVAL

We declare that all experiments have been examined and approved by the ethics committee.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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