Gastroprotective Activity of Fruit Ethanolic Extract of *Tetrapleura tetraptera* on Indomethacin-Induced Ulcer in Rats

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Abstract

***Tetrapleura tetraptera* (Schum. & Thonn.) Taub. is an important fruit that has many ethno-medicinal uses such as anti-ulcer and nutritive agent. The present study investigated the gastro-protective activity of ethanolic extract of *Tetrapleura tetraptera* fruit against indomethacin-induced ulcer in rats. For this study, thirty six rats (150-200 g) were separated into six groups of six rats each. For 14 days before ulcer induction with indomethacin, the animals received once daily oral doses of distilled water (groups 1 and 2), omeprazole 20 mg/kg body weight (group 3), and ethanolic extract of *T. tetraptera* fruit at doses of 50, 100 or 200 mg/kg body weight (groups 4, 5 and 6 respectively). After the last treatment, all the animals except group 1 were fasted for 18 hours with access to water only and treated with 100 mg/kg body weight of indomethacin to induce ulcer. The animals were sacrificed 6 hours after ulcer induction and the stomach was removed for biochemical and histological analysis. *T. tetraptera* fruit extract significantly ($p < 0.05$) decreased gastric secretion volume, mean ulcer index, total acidity, total protein and pepsin secretion relative to indomethacin-induced ulcerated rats. The extract also significantly ($p< 0.05$) increased mucin content relative to the ulcerated untreated rats. These results were similar to those achieved by pretreatment with omeprazole. The activity of glutathione peroxidase and reduced glutathione concentration in the animals treated with 200 mg/kg body weight *T. tetraptera* fruit were significantly increased ($P< 0.05$) compared to the negative control. The fruit extract also significantly reduced ($P< 0.05$) the concentration of malondialdehyde and myeloperoxidase activity over the ulcerated untreated rats. Similarly, the histological analysis showed that *T. tetraptera* fruit extract prevented indomethacin-mediated disruption of the mucosal wall of the stomach. This study shows that *Tetrapleura tetraptera* possesses gastro-protective properties which may be attributed to the presence of flavonoids, phenolics and tannins.**

Keywords: stomach ulcer, gastric juice, omeprazole, pepsin, mucin

1.0 Introduction

Ulcer is one of the common defects of the gastric or intestinal walls, clinically presented as abdominal stress, most often in the upper part of the abdomen and epigastric region. It may manifest as superficial, deep or perforated erosions of the mucosal lining of the stomach (gastric ulcer), or the small intestine (duodenal ulcer). These two types of ulcerations are commonly referred to as peptic ulcer [1]. Major causes of peptic ulcers are infection by a bacterium called *Helicobacter pylori* [2] and Non-Steroidal Anti-inflammatory Drugs (NSAIDs) such as aspirin, indomethacin and ibuprofen, especially those that are classified as cyclooxygenase (COX) inhibitors [3].

Most of the commonly used antiulcer drugs including gastric antisecretory drugs-H_2 blockers, anticholinergic agents, proton pump inhibitors (such as Omeprazole), sucralfate and prostaglandin analogues have been reported to elicit side effects and limitations in clinical practice [4]. On the other hand, medicinal plants have equally contributed tremendously in the treatment of ulcer. These include extracts of *Moringa oleifera*, *Momodica* species *Musa paradisiaca* and *Sesbania* species [5-7].

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Tetrapleura tetraptera (Schaum & Thonn) Taub. is popularly known as *Aridan* in Yoruba, *Uyayak* in Ibibio, *Edeminang* in Efik, *Osakirisa* or *Oshosho* in Igbo and *Dawo* in Hausa [8]. The validity of the nomenclature was verified on http://www.theplantlist.org/tpl1.1/record/ild-176 on 15/12/2017. The fruit of the plant has been reported to have anti-ulcer, anti-microbial, anti-convulsant, emulsifying, contraceptive and nutritive potential [9]. The dry fruit naturally has a pleasant aroma that serves as insect repellant [10]. Chemically, *T. tetraptera* fruit contains flavonoids, tannin and phenol [11]. The ethanolic extract of *T. tetraptera* fruits possesses hydrogen donating capabilities and act as an antioxidant [9]. The efficacy of the fruit extracts of *T. tetraptera* in some of its bioactivity may be attributed to its favourable antioxidant potential. The aim of this research is to evaluate the gastroprotective activity of ethanolic extract of *T. tetraptera* fruit as prevention against indomethacin-induced ulcer in rats.

2.0 Materials and Methods

2.1 Plant Material

Tetrapleura tetraptera fruits were collected from a farm at Igbara Odo, Ekiti State, Nigeria. The fruit was identified and authenticated with voucher number UILH/001/1134 and samples were deposited at the Herbarium of the Department of Plant Biology, University of Ilorin, Nigeria.

2.1.1 Extraction

Thoroughly washed *T. tetraptera* fruits were shade-dried for five days and then milled with an electric blender. The resulting powdered plant part was extracted successively with ethanol in a rotary evaporator. The solvent extract was concentrated at 40ºC in a water bath and kept at 4º C in a refrigerator until use.

2.1.2 Phytochemical Screening

Ethanolic extract of *T. tetraptera* was subjected to phytochemical screening which was carried out according to the methods of Harborne [12], Trease and Evans [13] and Wagner [14] to identify its active constituents.

2.2 Experimental Design

Adult Wistar rats with an average weight of 150 g – 200 g were obtained from the animal house, Department of Biochemistry, University of Ilorin, Nigeria. The animals were adequately fed with standard rat pellets and allowed free access to drinking water. They were acclimatized for one week before the commencement of the study.

2.2.1 Induction of Ulcer

Ulcer was induced in the rats via oral administration of indomethacin (100 mg/kg body weight) after the animals were starved of food for 18 hours but with free access to drinking water.

2.2.2 Animal Groupings and Treatment

Thirty six (36) Wistar rats were randomly divided into six (6) groups of six (6) animals each and administered as follows:

- Group 1(control): Received only distilled water.
- Group 2 (Ulcerated untreated): Received distilled water + Indomethacin (100 mg/kg body weight).
- Group 3 (Ulcerated: Received reference drug, Omeprazole (20 mg/kg body weight) + Indomethacin (100 mg/kg body weight)
- Group 4 (Ulcerated: Received extract (50 mg/kg body weight) + Indomethacin (100 mg/kg body weight
- Group 5 (Ulcerated: Received extract (100 mg/kg body weight) + Indomethacin (100 mg/kg body weight.
- Group 6 (Ulcerated: Received extract (100 mg/kg body weight) + Indomethacin (100 mg/kg body weight.

The animals were administered with their respective treatments for two weeks before induction of ulcer.

2.3 Excision of Stomach and Collection of Gastric Juice

After two weeks of treatment, the animals were anaesthetized with diethyl ether and sacrificed by head blow. They were then dissected and the stomach was excised carefully keeping the oesophagus closed but opened along the greater curvature. The gastric contents were carefully collected in plain tubes followed by the addition of 5 ml of distilled water. The mixture was centrifuged at 3000 rpm for 5 min and the volume of the supernatant was expressed as ml/100 g body weight. The mucosa was flushed with saline and observed for gastric lesions using microscope to determine ulcer score. The cleaned stomach was preserved in 0.1 M phosphate saline buffer (1:4 (w/v), pH 7.4) prior to microscopic examination and homogenization.

2.4 Determination of Mean Ulcer Index

The excised stomach was viewed with the aid of microscope (x 400 magnification) to determine the level of ulceration using the method of Raju *et al.* [15]. The ulcerative lesions were counted and scored as follows:

- Normal stomach: 0
- Red colouration: 0.5
- Spot ulceration: 1.0
- Haemorrhagic streaks: 1.5
- Ulcer: 2.0
- Perforations: 3.0

Mean ulcer score for each animal was expressed as ulcer index.

2.5 Determination of Total Acidity

The gastric content was centrifuged at 1000 x *g* for 10 minutes and the volume of gastric juice was recorded. The supernatant (1 mL) was pipetted and diluted to 10 mL with distilled water and the total acidity of the gastric juice was estimated by titration using 0.01 N NaOH and phenolphthalein as the indicator. The result was expressed as free acid output in terms of mEq/L [16].

$$\text{Total acidity} = \frac{\text{Volume of NaOH X Normality}}{0.1} \times 100 \text{ mEq/L/100 g}$$

2.6 Determination of Total Carbohydrate Content

H_2SO_4 (96%, 5 mL was added to test tubes containing 0.15 mL gastric juice or a blank of 0.15 mL of distilled water and thoroughly mixed. After 10 minutes, the test tubes were placed in a water bath and kept at 20ºC for 20 minutes. The optical density of the developed yellow-orange colour was read at 482 nm using a Jenway Visible Spectrophotometer. Several concentrations of a standard glucose solution were run in order to prepare a standard curve. The total liberated carbohydrate was expressed in terms of g/litre gastric juice. The mucoadhesive activity was expressed as the TC:PR ratio [17].

2.7 Determination of Total Protein Concentration

Estimation of the protein content was carried out as described by Lowry *et al.* [18]. Gastric juice (1 mL) was added to 9 mL of 95% alcohol and the mixture centrifuged at 3000 x *g* for 15 minutes and the precipitate obtained was dissolved in 1 mL of 0.1 N NaOH. Then, 0.9 mL of distilled water was added to 0.1 mL of this solution. From this solution, 0.4 mL was taken into another test tube followed by the addition of 4 mL of an alkaline reagent and allowed to react for 10 minutes. Finally, 0.4 mL of phenol reagent was added to the mixture and allowed to react for 10 minutes to allow for colour development. Readings were taken against the blank prepared with distilled water. The protein content was obtained from standard curve prepared using bovine serum albumin. The protein concentrations were expressed in terms of g/L- gastric juice.

2.8 Assay of Pepsin Activity

The centrifuged (5000 g for 10 minutes) gastric juice (0.1 mL) was added to 1 mL bovine albumin (0.5% w/v in 0.01 N HCl; pH 2) and incubated for 20 minutes at 37ºC. A duplicate background control tube (gastric juice blank), in which 1 mL albumin was replaced with 1 mL of 0.01 N HCl, was run simultaneously. Hydrolysis was stopped by adding 2 mL of 10% TCA. The tubes were heated in boiling water for 5 minutes, then cooled and the precipitate was removed by centrifugation (9000 *g* for 10 minutes). The supernatant (1 mL) was mixed with 0.4 mL of 2.5 N NaOH and 0.1 mL of

the Folin-Ciocalteu reagent, and then the volume was made up to 10 mL using distilled water. Absorbance was measured at 700 nm. The peptic activity was calculated in terms of micrograms of tyrosine liberated per milliliter of gastric juice [19].

2.9 Determination of Reduced Glutathione Concentration

Aliquots of the homogenates (5 mL) were mixed with 4 mL distilled water and 1 mL of 50% TCA. The mixture was intermittently shaken for 10-15 minutes, and then centrifuged for 15 minutes at 3000 rpm. Supernatant (2 mL) was mixed with 4 mL of 0.4 M Tris buffer (pH 8.9) and 0.1 mL 5, 5'-Dithio-Bis-2-Nitrobenzoic-Acid (DTNB). The absorbance was read within 5 minutes of the addition of DTNB at 412 nm against a blank reagent blank without the homogenate [19].

2.10 Assay of Glutathione Peroxidase Activity

Glutathione Peroxidase (GPx) activity was determined according to the method of Lawrence and Burk [20]. The absorbance at 340 nm was recorded for 5 min. The activity was determined by measuring the amount of oxidised NADPH as mol per minute per mg tissue (mol min^{-1} mg $tissue^{-1}$).

2.11 Assay of Myeloperoxidase Activity

Myeloperoxidase (MPO) activity was determined according to the modified method of Bradley *et al*. [21]. The homogenized samples were frozen and thawed three times, before centrifuging at 1500 × *g* for 10 min at 4ºC. MPO activity in the supernatant was determined by adding 1 mL of the supernatant to 1.9 mL of 10 mmol/L phosphate buffer (pH 6.0) and 1 mL of 1.5 mmol/L *o*-dianisidine hydrochloride containing 0.0005% (w/v) hydrogen peroxide. The changes in absorbance at 450 nm of each sample were recorded on a UV–Vis spectrophotometer. The myeloperoxidase activity was calculated as change in absorbance per gram (g) of wet tissue. Results were expressed as U/g.

2.12 Determination of Malondialdehyde (MDA) Concentration

The concentration of MDA was determined according to the method described by Ohkawa *et al*. [22]. The stomach homogenate was prepared in a ratio of 1 g of wet tissue: 9 mL of 1.15% KCl using a glass Potter-Elvehjem homogenizer. A reaction mixture containing 0.1 mL of the sample, 0.2 mL of 8.1% sodium dodecyl sulfate, 1.5 mL of 20% acetic acid solution and 1.5 mL of a 0.8% aqueous solution of thiobarbituric acid (the pH of the 20% acetic acid solution previously corrected to 3.1) was finally diluted to 4 mL with distilled water and heated at 95ºC for 60 minutes. After cooling with tap water, 1 mL of distilled water and 5 mL of the mixture of n-butanol and pyridine (15:1, v/v) were added and the mixtures were vigorously shaken and centrifuged at 3000 rpm for 15 minutes. The absorbance of the supernatant was then measured at 532 nm.

2.13 Histopathological Examination of the Stomach

A portion of the stomach was preserved in 10% formalin solution for histopathological examination (x 100 magnification). The central part of damaged or ulcerated tissue (if present) was cut off along the long diameter. If the stomach was protected from the damage then the section was taken from the basal part, thickness of about 5 µm were cut and stained with haemotoxylin and eosin. The sections were examined under the microscope for histopathological changes such as congestion, hemorrhage, necrosis, inflammation, infiltration, erosion and ulcers.

2.14 Statistical Analysis

Data were expressed as mean ± standard error of mean (n = 6). Comparative analysis was performed between the various groups using analysis of variance (ANOVA) and Duncan multiple range test for the post hoc. Differences were considered significant at $p<0.05$.

3.0 Results

The secondary metabolites present in the extract are total phenolic (2,730 mg/100 g), flavonoid (4.795 mg/kg QAE) and tannin (162.188 mg/kg).

The gastric volume and total acidity of the ulcerated untreated animals were significantly increased ($P< 0.05$) when compared with the control. However, upon treatment with *T. tetraptera* fruit extract at 200 mg/kg body weight, the gastric volume was significantly reduced. The result also showed that there was no significant difference ($P< 0.05$) in the gastric volume and total acidity of the rats pretreated with the extract at 200 mg/kg body weight and omeprazole treated group (Figures 1 and 2). Furthermore, the mean ulcer index was significantly reduced ($P < 0.05$) following

pretreatment with the *Tetrapleura tetraptera* fruit extract at all the studied doses when compared with the ulcerated untreated animals. However, the index was significantly increased ($P < 0.05$) in the group pretreated with the extract at 200 mg/kg body weight when compared with the group pretreated with Omeprazole (Figure 3).

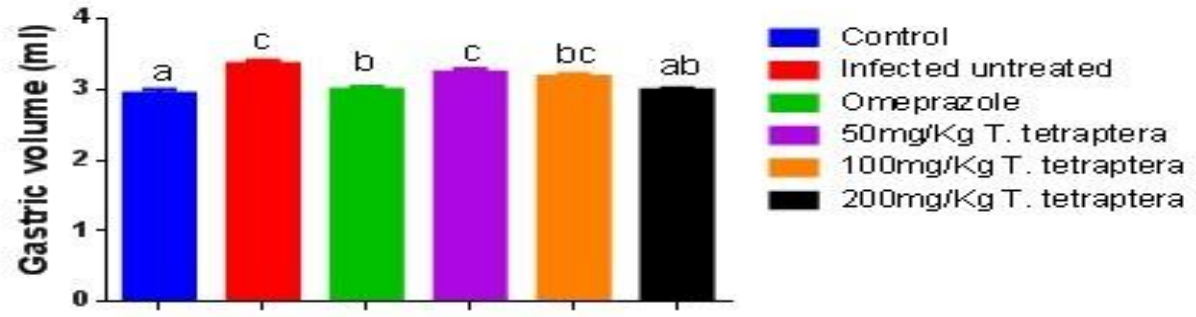


Fig. 1: Effect of *T. tetraptera* fruit on gastric volume of indomethacin-induced ulcer in rats. Values are Mean ± SEM of 6 determinations. Bars carrying different alphabets are significantly different (p<0.05).

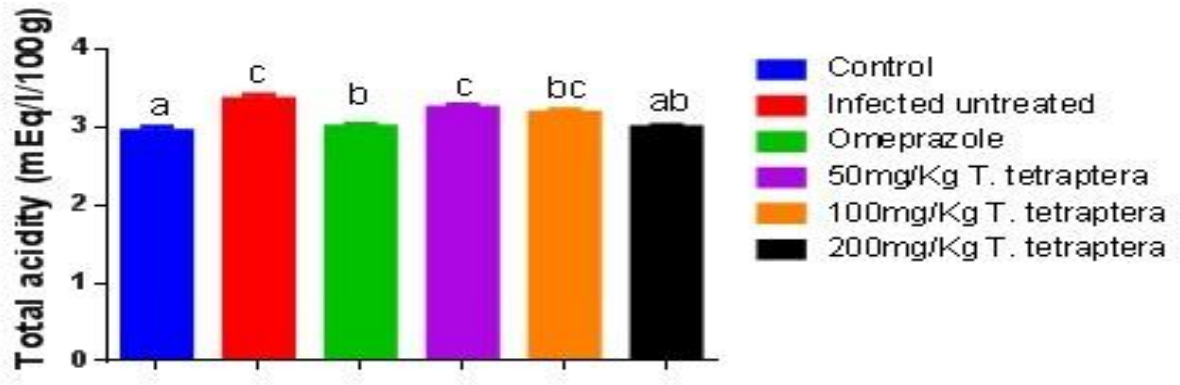


Fig. 2: Effect of *T. tetraptera* fruit on total acidity of indomethacin-induced ulcer in rats. Values are Mean ± SEM of 6 determinations. Bars carrying different alphabets are significantly different (p<0.05).

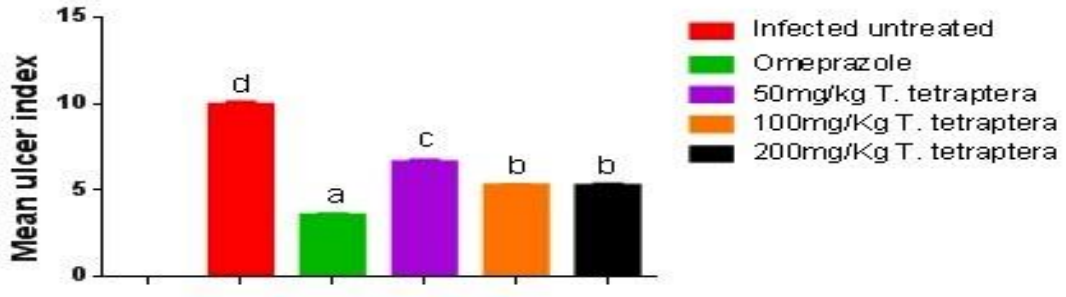


Fig. 3: Effect of *T. tetraptera* fruit on mean ulcer index of indomethacin-induced ulcer in rats. Values are Mean ± SEM of 6 determinations. Bars carrying different alphabets are significantly different (p<0.05).

The carbohydrates and mucin concentrations in the stomach of the experimental animals are presented in Figures 4 and 5. The concentrations of the two parameters were significantly increased ($P < 0.05$) in the animals pretreated with the extract when compared with the ulcerated untreated rats. However, there was no significant difference in the mucin concentration between the animals pretreated with the extract and those administered with Omeprazole (Figure 5).

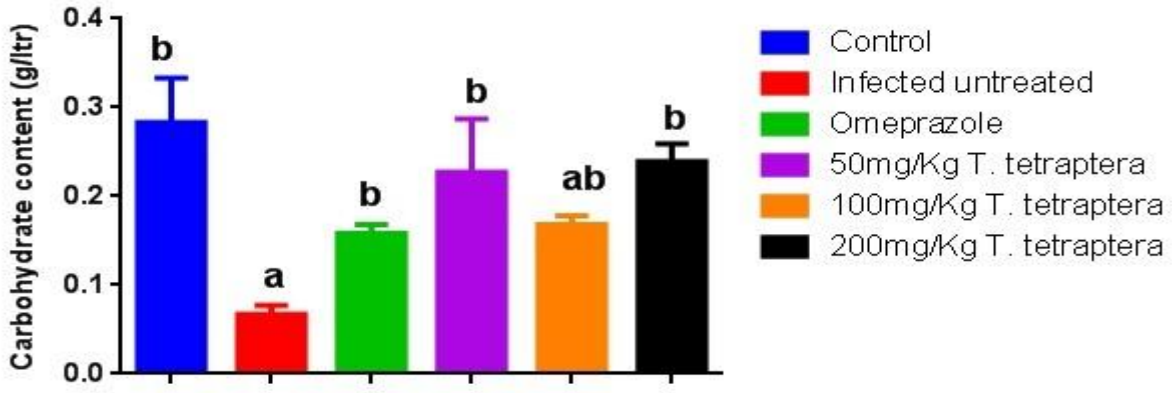


Fig. 4: Effect of *T. tetraptera* fruit on carbohydrate content of indomethacin-induced ulcer in rats. Values are Mean ± SEM of 6 determinations. Bars carrying different alphabets are significantly different (p<0.05).

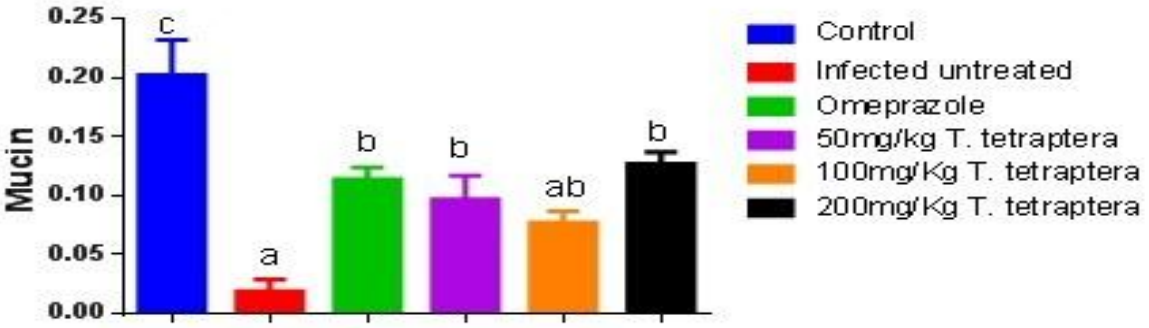


Fig. 5: Effect of *T. tetraptera* fruit on mucin content of indomethacin-induced ulcer in rats. Values are Mean ± SEM of 6 determinations. Bars carrying different alphabets are significantly different (p<0.05).

In this study, pretreatment with extract of *T. tetraptera* fruit was able to attenuate total protein concentration as well as the activities of pepsin and myeloperoxidase in the ulcerated untreated rats (Figures 6, 7 and 8). The effect of the extract compared favorably with that of the omeprazole pretreated group particularly at 200 mg/kg bw (Figures 6 and 8). However, there was a significant increase ($P < 0.05$) in the activity of pepsin following pretreatment with the extract when compared with the Omeprazole pretreated group (Figure 7).

Induction of ulcer led to a significant increase ($P < 0.05$) in the level of malondialdehyde in the experimental animals (Figure 9). However, pretreatment with extract of *T. tetraptera* fruit significantly reduced ($P < 0.05$) the concentration of malondialdehyde; and the effect compared favourably with that of Omeprazole. With respect to the activity of glutathione peroxidase, pretreatment with the extract brought about a significant increase ($P < 0.05$) in the activity of this enzyme in a manner that is comparable to Omeprazole particularly at 200 mg/kg body weight (Figure 10). Finally, the information obtained in respect of the histopathological examination of the stomach of experimental animals is presented in Figure 11.

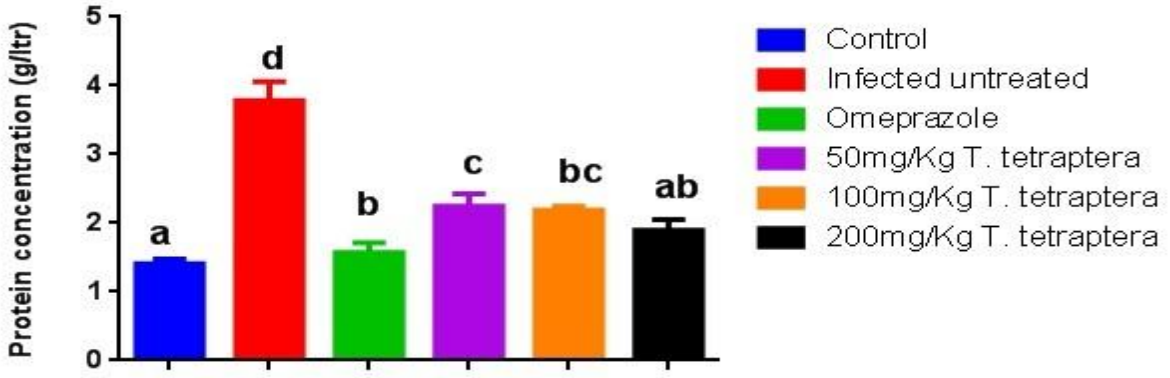


Fig. 6: Effect of *T. tetraptera* fruit on protein concentration of indomethacin-induced ulcer in rats. Values are Mean ±SEM of 6 determinations. Bars carrying different alphabets are significantly different (p<0.05).

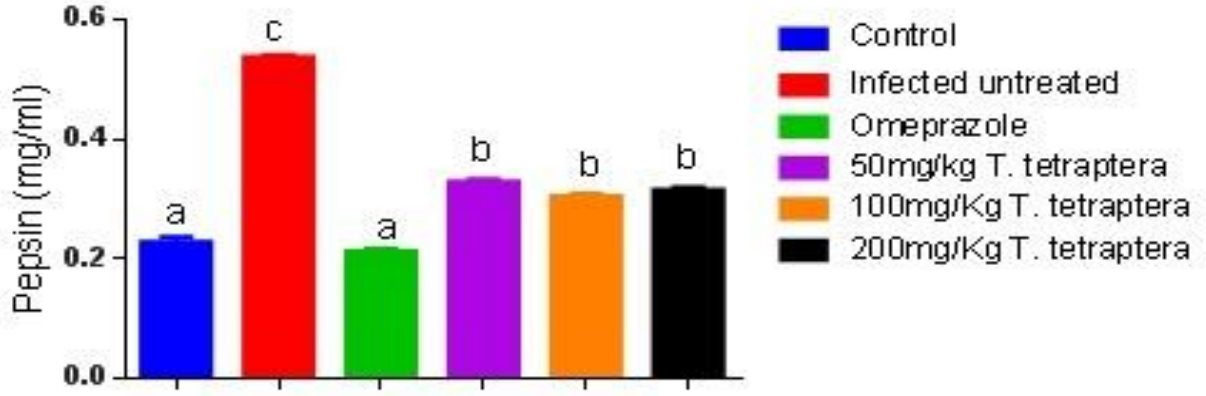


Fig. 7: Effect of *T. tetraptera* fruit on pepsin activity of indomethacin-induced ulcer in rats. Values are Mean ± SEM of 6 determinations. Bars carrying different alphabets are significantly different (p<0.05).

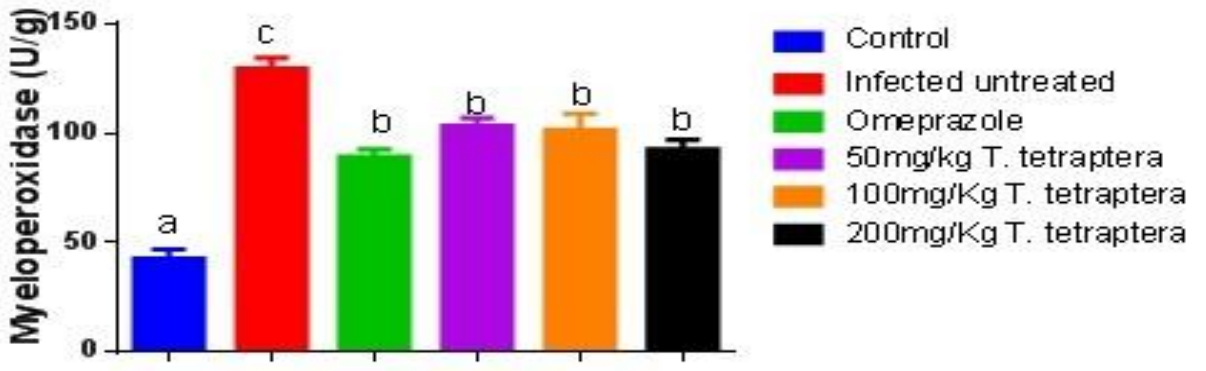


Fig. 8: Effect of *T. tetraptera* fruit on myeloperoxidase activity of indomethacin-induced ulcer in rats. Values are Mean ± SEM of 6 determinations. Bars carrying different alphabets are significantly different (p<0.05).

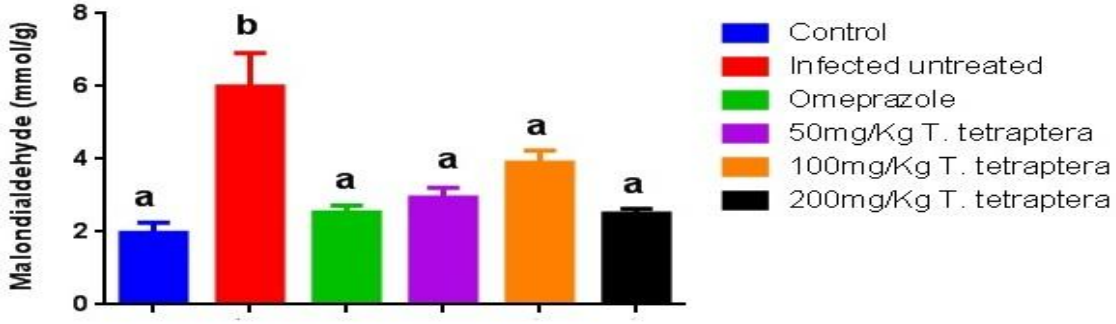


Fig. 9: Effect of *T. tetraptera* fruit on the level of malondialdehyde in indomethacin-induced ulcer in rats. Values are Mean ± SEM of 6 determinations. Bars carrying different alphabets are significantly different (p<0.05).

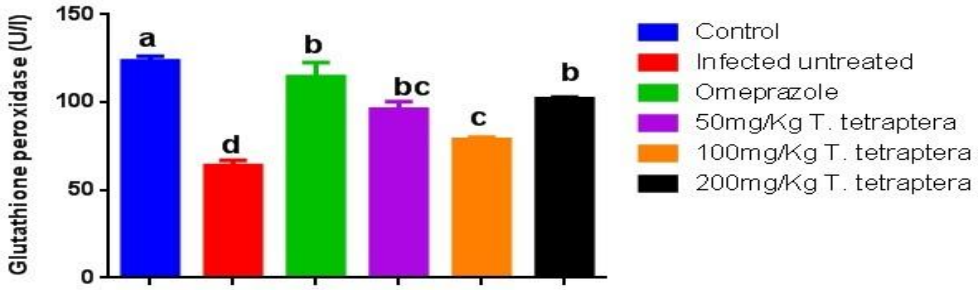
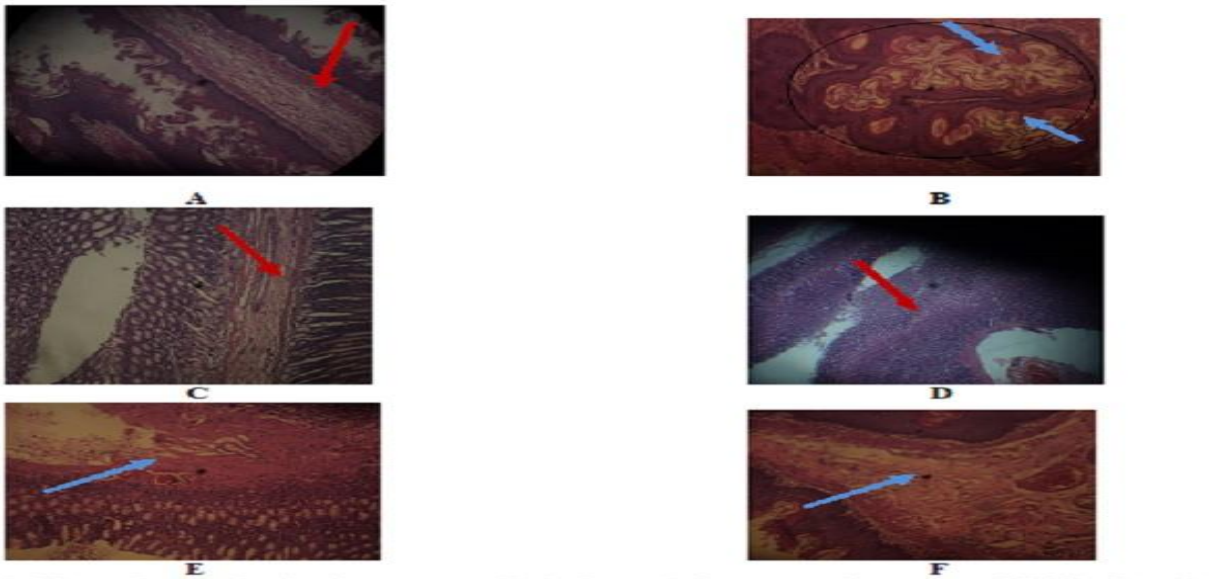


Fig. 10: Effect of *T. tetraptera* fruit on the activity of glutathione peroxidase in indomethacin-induced ulcer in rats. Values are Mean ± SEM of 6 determinations. Bars carrying different alphabets are significantly different (p<0.05).



A: Photomicrograph showing mucus cells (red arrow) from stomach sections (X 100) of rats in the control group. B: Photomicrograph showing ulceration and disruption (blue arrow) of stomach sections (X 100) of infected untreated rats. C: Photomicrograph showing mucus cells (red arrow) from stomach sections (X 100) of Omeprazole group. D: Photomicrograph showing mucus cells (red arrow) from stomach sections (X 100) of group administered with 50mg/Kg *T. tetrapleura*. E: Photomicrograph showing mucus cells (blue arrow) from stomach sections (X 100) of group administered with 100mg/Kg *T. tetrapleura*. F: Photomicrograph showing mucus cells (blue arrow) from stomach sections (X 100) of group administered with 200mg/Kg *T. tetrapleura*.

Figure 11: Effect of *Tetrapleura tetraptera* on the Histopathology of the stomach of rats

4.0 Discussion

Although the etiology of ulcer is usually unknown, it is generally believed that it occurs as a result of an imbalance between offensive and defensive factors that protects the mucosal integrity. To avoid the imbalance, different therapeutic agents including plant extracts may be used. *T. tetraptera* fruit extract is one of such herbal preparations, which is used in this study to assess its gastroprotective activity in indomethacin-induced ulcerated rats.

Phytochemicals detected in the fruit extract of *T. tetraptera* include flavonoids, total phenol and tannins, which may be responsible for its gastroprotective activity as revealed in this study. Flavonoids are among the cytoprotective materials for which antiulcerogenic efficacy has been extensively confirmed. It has been reported that flavonoids stimulate mucus and counteract the deteriorating effects of reactive oxidants species in the gastrointestinal lumen [23]. Recently, it was also reported that high molecular weight phenolics such as tannins, have greater ability to scavenge or reduce free radicals [24].

The increased mucin secretion in pretreated rats indicates protection of the gastrointestinal mucosa by the extract. The decrease in protein content in the gastric juice of the animals pretreated with the extract of *T. tetrapera* fruit suggests a reduction in the leakage of plasma proteins into the gastric juice [25]. The increased pepsin activity coupled with decrease in mucin secretion in the untreated rats indicated altered hydrophobicity and reduced protective ability of the mucosal membrane against hemorrhagic erosion, thus, resulting in tissue damage [26]. Pretreatment with extract of *T. tetraptera* fruit however, facilitated gastro-protective process, which was manifested by decreased pepsin activity and elevated mucin level in the gastric mucosa. This in turn may encourage speedy wound healing of the ulcerated areas of the mucosal epithelia and shield the gastrointestinal membrane, thus abrogating the catastrophic influence of indomethacin in the ulcerated rats.

The observed increase in GPx activity in *T. tetraptera* pretreated indomethacin-induced ulcerogenic rats agreed with the findings of La Casa *et al.* [27]. These researchers suggested that increased GPx activity might be one of the mechanisms underlying the protective and antioxidant properties of rutin against gastric lesions. Previous study further revealed that myeloperoxidase activity increases in non-steroidal anti-inflammatory drugs-damaged stomach tissue [28], in addition to catalyzing the production of reactive oxygen species which damage cell membranes. A high level of myeloperoxidase enzyme activity in gastric tissue indicates increased neutrophil secretion [29]. Neutrophil activation causes excessive secretions of radicals such as O_2^-, H_2O_2 and OH^-. These cytotoxic radicals react to release products such as hypochlorous acid and N-chloramine that cause tissue damage [30].

MDA is the final product of lipid peroxidation which is used to determine the lipid peroxidation levels [30]. The significantly high levels of MDA in the stomach of ulcerated untreated rats lend credence to previous reports that free radicals generated by neutrophils cause excessive secretions of radicals and may be an important factor causing an increase in the level of gastric ulcer injury [31]. The significant reduction in MDA levels in the extract treated animals suggests its protective action against free radical damage. This is also indicative of the fact that the gastroprotective potential of *T. tetraptera* may be connected with the reduction in lipid peroxidation.

5.0 Conclusion

Among all the doses of *T. tetraptera* used in this study, 200 mg/kg body weight produced significant gastroprotective activity comparable to the reference drug, Omeprazole. This dose also produced significant antioxidant activity.

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