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Antiulcerogenic effect of the methanolic extract of B*ryophyllum pinnatum* on the indomethacin induced gastric ulceration in male albino rats

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Abstract

Plants which are medicinal used in traditional medicine contain a diverse range of materials that can treat and provide care to many diseases. The aim of this study is to evaluate the antiulcer activities of the methanolic extract of leaves of *Bryophyllum pinnatum* in indomethacin-induced male albino rats. In this experiment, 42 rats were divided into six (6) groups with 7 rats in each group. Group A (Negative control) was given Indomethacin 40mg/kg b.wt, Group B pretreated with 20mg/kg b.wt of Cimetidin (antiulcer drug) and Groups C, D, E and F were pretreated with 10, 20, 30 and 40 mg/kg b.wt of *Bryophyllum pinnatum*, respectively for two weeks. After 2 weeks 40mg/kg indomethacin was administered to induce ulcer in groups A to F after fasting them for 24 hours. At the end of the experiment the ulcer length was measured and percentage ulcer protection were calculated and its effect on oxidative stress parameters was determined. Gross and histopatological examination of the stomach was also done which revealed that the negative control rats exhibited stomach injury. The histological study of the gastric wall showed that negative control rats suffered damage of gastric mucosa compared to rats pretreated with *Bryophyllum pinnatum* extract where there was increase in gastric percentage protection from ulcer. The result showed a significant increase in SOD and Catalase activity and a decrease in malondialdehyde level when compared to the negative control. In conclusion, the result shows that the *Bryophyllum pinnatum* extract possess antiulcer effect in rats. This result confirms the traditional use of *Bryophyllum pinnatum* for treatment of ulcer.

Keywords: *Bryophyllum pinnatum;* Antiulcer; Cimetidin; Indomethacin; Ulcer Length; Histopathology

1 Introduction

Peptic ulcers are open sores that develop on the inside lining of the stomach and the upper portion of the small intestine. They are usually formed as a result of inflammation caused by the bacteria Helicobacter pylori, as well as from erosion from the stomach acids [1]. Pepsin, a catalytic enzyme that assists in protein breakdown, increases the gastric acidity in the stomach and assists in digestion. This production of excessive acid can overwhelm the protective lining of mucus within the stomach and duodenum. The stomach tissue cannot handle the acidity and begins to erode [2].

Several factors are involved in the etiology of gastric ulcers such as imbalance between hydrochloric acid and pepsin secretion, irritant drugs as NSAIDs (aspirin), stress factors, smoking, and *H. pylori* infection [3]. A number of drugs including proton pump inhibitors and histamine (H2) receptor antagonists (Cimetidin) are available for the treatment of peptic ulcer, but these drugs have shown incidence of relapses, side effects, and drug interactions. Thus, the development of new antiulcer drugs and the search for novel molecules has been extended to herbal drugs that offer

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better protection and decreased relapse. The long-term use of chemical drugs for treating gastric ulcer leads to an ineffectiveness of different drug regimens and even resistance to drugs is emerged. Therefore, there is an urgent need to identify more effective and safe antiulcer agents from medicinal plants [4].

Medicinal plants used in folk medicine contain a wide range of substances that can prevent and treat many diseases. The medical value of these plants is due to presence of some bio active constituents such as flavonoids, phytosterols, diterpenes, triterpenes, and polyphenolic compounds [5].

Bryophyllum pinnatum is a fleshy shrub, which grows 2-4 feet tall. The plant, which belongs to the family Crassulaceae, is widely grown in the region for ornamental and medicinal uses [6]. Its common names include air plant, Canterbury bells, Mexican love plant, resurrection plant etc. The plant is native to Madagascar and southern Africa [7]. It is a perennial herb growing widely and used in folkloric medicine in tropical Africa, India, China, Australia and tropical America. A number of active compounds, including flavonoids, glycosides, steroids, bufadienolides and organic acids, have been identified in *Bryophyllum pinnatum*. The leaf of the plant is rich in alkaloids, triterpenes, glycosides, flavonoids, steroids and lipids. It is called "ewe abamoda or odundun" by the Yoruba tribe of South western Nigeria, "odaa opue" among the Igbos. It is referred to as "da bu si" in Chinese Ghasi *et al* [8] and "Karan massallachi" by the Hausa peoples of Nigeria.

The leaves of *Bryophyllum pinnatum* have been reported to possess antimicrobial, antifungal, anti-ulcer, anti-inflammatory and analgesic, and antihypertensive activities. The methanol extract of the leaf of the plant has also been reported to have histamine receptor (H1) antagonism in the ileum, peripheral vasculature and bronchial muscle [9].

The plants have considerable attention for their medicinal properties and find application in folk medicine, as well as in contemporary medicine. It is used in ethno medicine for the treatment of diarrhoea, vomiting, earache, burns, abscesses, gastric ulcer, insect bites, and lithiasis. The juice from the fresh leaves is used to treat small pox, otitis, cough, asthma, palpitations, headache, jaundice, gout infection, convulsion etc. In Sierra Leone, a cough medicine is made from the roots while in Ivory Coast; the root sap is taken for attacks of epilepsy. In Ghana, the leaves of the plant are rubbed on the head and inserted in the nostrils to relieve headache. It has been reported that the leaves are taken in West India for the treatment of arthritis and to clean the bladder [10]. Among the Igbos of Nigeria, *Bryophyllum pinnatum* is believed to have antihypertensive activity. Decoctions of the leaf are usually taken to lower the blood pressure. Some people also chew the raw leaves of the plant for this purpose (Ghasi *et al.*, 2011). In South-eastern Nigeria, this herb is used to facilitate the dropping of the umbilical cord of new borne [11]. The plant leaf is mildly exposed to heat and the juice extracted and applied to the baby's umbilical cord on daily basis. The crushed leaves as well as the extracted juice are mixed with shear butter or palm oil and rubbed on abscesses or other swellings. Topical application of the plant extract is used for the treatment of external ulcers and burns [12]. Several plants and herbs are used in folkoric medicine to treat gastrointestinal disorders including peptic ulcers. Hence this study aims to investigate the antiulcerogenic activity of the methanolic extract of bryophyllum pinattum on indomethacin-induced gastric ulceration in rats.

2 Materials and methods

2.1 Plant Materials and Extraction Procedure

Fresh leaves of *Bryophyllum pinnatum* were gotten by the side of the postgraduate building in Crawford university, Faith city, Igbesa, Ogun state, Nigeria. The plant was washed and dried in oven at 40ºc for 21 days. The leaves were then chopped and pulverized. This was done to make the leaf sample enter the Soxhlet apparatus and allow a large surface area for the extraction. The sample was extracted using methanol. A condenser and a round bottom flask were fitted at the top and bottom of the Soxhlet, respectively. A water pump was available that provides water for cooling the condenser. As the extract was collected in the round bottom flask with the solvent, the water bath heated it and the solvent evaporated and condensed. The cycle continued until the extract obtained from the sample was about 20g yield.

2.2 Experimental animals

Male adult albino rats of the Wistar strain weighing between 120g- 150g were used for the study. They were obtained from Crawford animal laboratory. All procedures for maintenance and sacrifice were done in line with the criteria given by National Academy of Science published by the National Institute of Health (NIH, 1985).

The animals were acclimatized for a period of two weeks and housed in a plastic cage with good ventilation. The rats were kept at room temperature of 28±2ºc with 12 hours natural light and dark cycle. The rats were allowed free access to standard feeds from Mobat Feeds Ltd, Lusada, Ogun State and portable water ad libitum.

2.3 Experimental design

42 male rats weighing about 120- 150g were selected for the study. The rats were divided into Six groups with seven animals in each (n=7). Group A (Negative control) were given Indomethacin (40mg/kg b.wt), Group B (positive control) were given Cimetidin (20mg/kg b.wt), Groups C, D, E and F were given 10mg/kg, 20mg/kg, 30mg/kg and 40mg/kg of *Bryophyllum pinnatum* extract respectively for two weeks. The rats were fasted for 24 hours but allowed free access to drinking water, until 4 hours to the experiment.

On the day of sacrifice, group B was given 20mg/kg of cimetidin while groups (C, D, E and F) were given 10mg/kg, 20mg/kg, 30mg/kg and 40mg/kg of the *Bryophyllum pinnatum* extract. After 2 hours, groups (A, B, C, D, E and F) were given 40mg/kg b.wt of indomethacin dissolved in 2% sodium carbonate in water was administered orally to each rat. The rats were euthanized and the stomach was excised immediately and each stomach was opened along the greater curvature, washed with distilled water and grossly examined for gastric lesions. Ulceration in the stomach was accessed by means of a scoring technique whereby microscopic examination of the stomach was made using a hand lens. The length of ulcer was measured and percentages of protection from ulcer were calculated.

2.4 Determination of ulcer index (UI)

The mean score of ulcers is expressed as ulcer index. The stomach of each animal was washed with distilled water to view the ulcer in the stomach. The total number of ulcers was taken and the severity score of the ulcer was checked microscopically with a hand lens and scoring were done as per Kulkarni [13]. The scoring was based on the following observations and assigned values: Normal stomach = 0, Red coloration= 0.5, Spot ulcer= 1.0, Haemorrhagic streak= 1.5, Deep ulcer= 2.0 and Perforations= 3.0. It can be calculated as;

$$\text{Ulcer index} = (UN + US + UP) \times 10^{-1}$$

Where;
UN= Average number of ulcers per animal
US= Average severity score
UP= Percentage of animal with ulcer

$$\%\text{Inhibition of ulceration} = \frac{\text{Ulcer index in control} - \text{Ulcer index in test}}{\text{Ulcer index in control}} \times 100$$

The stomach was preserved in 10% formalin solution till processed for histological examination.

2.5 Oxidative stress assay

2.5.1 Estimation of Catalase (CAT)

Catalase is a common enzyme found in living organisms (such as bacteria, animals and plants) exposed to oxygen. The Catalase enzyme catalyses the decomposition of hydrogen peroxide to water and oxygen. Reactive oxygen species is used by the enzyme to protect the cell from oxidative damage. Moreover, Catalase has one of the highest turnover numbers of all enzymes. One Catalase molecule can convert millions of hydrogen peroxide molecules to water and oxygen.

2.5.2 Procedure

The Catalase activity was determined in tissue homogenate. 50µl of the homogenate was added in all test tubes using a micropipette with 2ml of phosphate buffer (pH 7.0) and 1ml of 30mM H_2O_2. Catalase activity was measured at 240nm at 1 minute interval using spectrophotometer. The molar extinction coefficient of H_2O_2, 43.6M/cm was used to determine the Catalase activity. One unit of activity is equal to one millimoles of H_2O_2 degraded per minute and expressed as units per milligram (units/mg) of protein [14].

2.5.3 Estimation of Superoxide Dismutase (SOD)

Superoxide dismutase was estimated in tissue homogenate in which 50µl of the homogenate is kept in test tubes, 75mM of Tris-Hcl buffer (pH 8.2), 30Mm of EDTA and 2Mm of Pyrogallol were added. An increase in absorbance was recorded at 420nm for 30 seconds by a spectrophotometer. One unit of enzyme activity is 50% inhibition of the rate of auto

oxidation of Pyrogallol as determined by change in absorbance/min at 420nm. The activity of SOD is expressed as units/mg protein [15].

2.6 Determination of Malonaldehyde (Lipid Peroxidation)

MDA is a product of lipid peroxidation. When heated with Thiobarbituric acid (TBA) under alkaline condition, it forms a pink coloured product which has absorption maximum at 540nm.

2.6.1 Procedure

To 1ml of the homogenate, 2ml of Thiobarbituric acid, Trichloroacetic acid and hydrochloric acid reagent (1:1:1) (Ph 8.2) is added in the test tubes and incubated at 95ºC for 15 minutes, kept in ice-cold water to cool. The samples were centrifuged at 3000rpm for 10 minutes, the supernatant was collected and absorbance was read at 532 using a spectrophotometer [16].

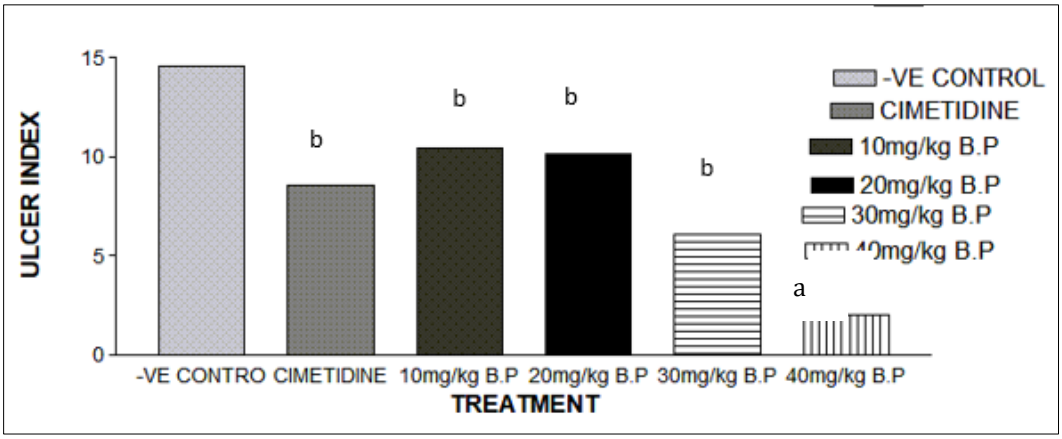
2.6.2 Histological Procedure

Stomachs of the sacrificed rats were preserved in 10% neutral formalin solution. The fixed specimens were trimmed, washed and dehydrated in ascending grades of alcohol. The specimens were then cleared in xylene, embedded in paraffin boxes, sectioned at 4-6 microns thickness, stained with Haematoxylin and Eosin and examined under microscope as described by [17].

3 Results

3.1 Effect of methanolic extract of *Bryophyllum pinnatum* on ulcer index in Indomethacin induced gastric lesions in rat models

Figure 1 indicated that there was a significant increase in the degree of ulceration of the Indomethacin-treated group (negative control). However, administration of the methanolic extract of *Bryophyllum pinnatum* significantly ($p < 0.05$) reduces the ulcer index in group C, and D and highly significant ($p < 0.05$) reduction in groups E and F as compared to the negative control.

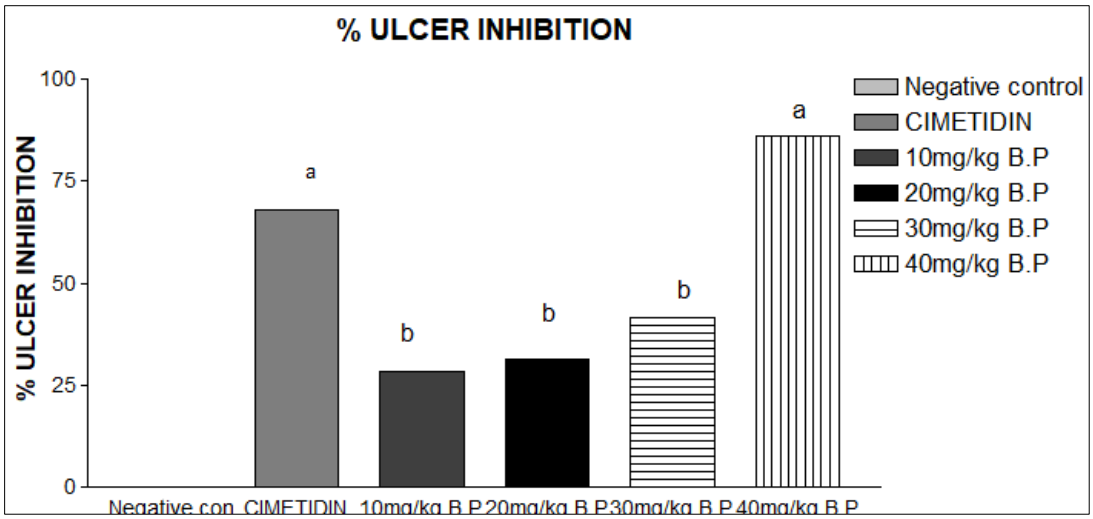


Bars with different superscripts are significantly different ($p<0.05$)

Figure 1 Effect of methanolic extract of *Bryophyllum pinnatum* on ulcer index in Indomethacin-induced gastric lesions in rat models

3.2 Effect of methanolic extract of *Bryophyllum pinnatum* on degree of protection against ulceration in indomethacin ulcerated rats

There was a significant ($p <0.05$) increase in the percentage inhibition of ulceration in the 40mg/kg b.w extract group as compared to the positive control, while the 10mg/kg B.P, 20mg/kg B.P and 30mg/kg B.P has 28%, 40% and 49% percentage inhibition respectively as compared to the positive control as shown in Figure 2



Bars with different superscripts are significantly different ($p<0.05$)

Figure 2 Effect of methanolic extract of *Bryophyllum pinnatum* on the degree of protection against ulceration in indomethacin ulcerated rats

3.3 Effect of methanolic extract of *Bryophyllum pinnatum* on gastric Malondialdehyde (MDA) level of indomethacin induced rats

Figure 3 indicated that there was a significant increase ($p < 0.05$) in malondialdehyde level as seen in the negative control group. However, administration of Cimetidin and the methanolic extract of *Bryophyllum pinnatum* significantly ($p < 0.05$) reduces the malondialdehyde level in the Cimetidin group (B) and all the extract groups (C, D, E and F) respectively when compared to the negative control group.

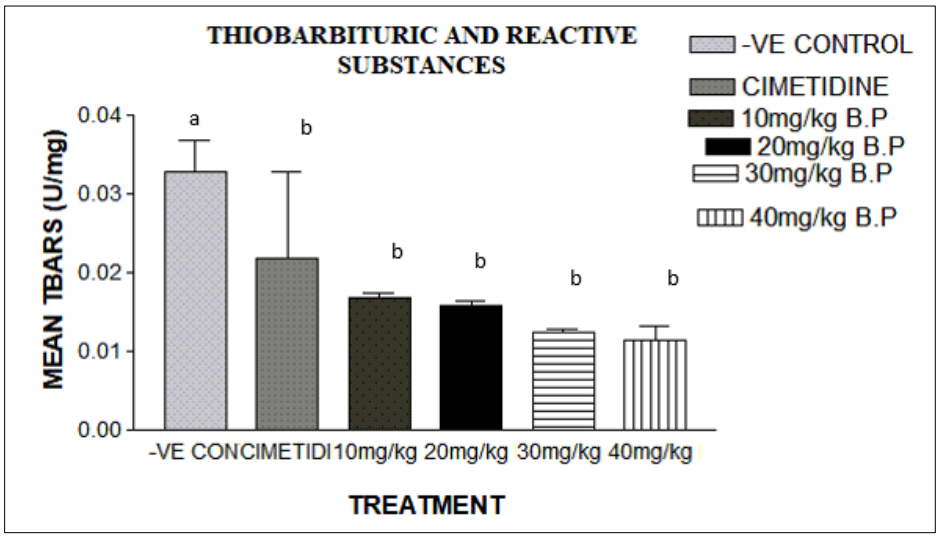
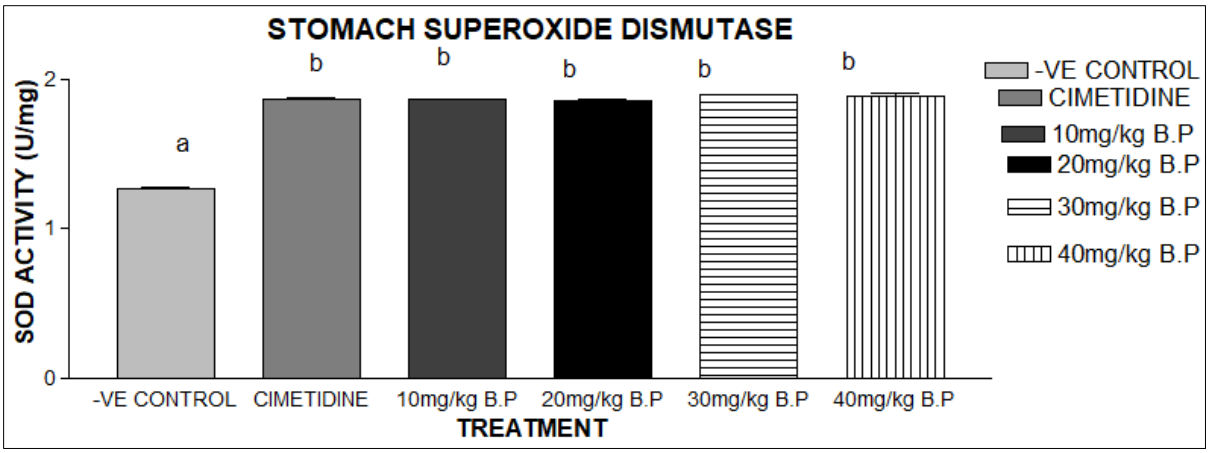


Figure 3 Effect of methanolic extract of *Bryophyllum pinnatum* on gastric Malondialdehyde (MDA) level of indomethacin induced rats

3.4 Effect of methanolic extract of *Bryophyllum pinnatum* on gastric superoxide dismutase (SOD) activity of indomethacin ulcerated rats

There was a significant decrease in the stomach superoxide dismutase (SOD) activity in the negative control group. Pretreatment with the methanolic extract of *Bryophyllum pinnatum* was able to increase the activity of SOD significantly in all the extract groups as compared to the negative group as shown in fig. 4.



Bars with different superscripts are significantly different ($p<0.05$).

Figure 4 Effect of methanolic extract of *Bryophyllum pinnatum* on gastric superoxide dismutase (SOD) activity of indomethacin ulcerated rats

3.5 Effect of methanolic extract of *Bryophyllum pinnatum* on Catalase activity of indomethacin induced rats

The indomethacin-induced group (negative control) shows a decrease in Catalase activity. Administration of the methanolic extract of *B. pinnatum* significantly increases ($p < 0.05$) Catalase activity in all the extract groups when compared to the negative control. There was also a significant increase in Catalase activity in the Cimetidin group (group B) when compared to the negative control as shown in fig 5.

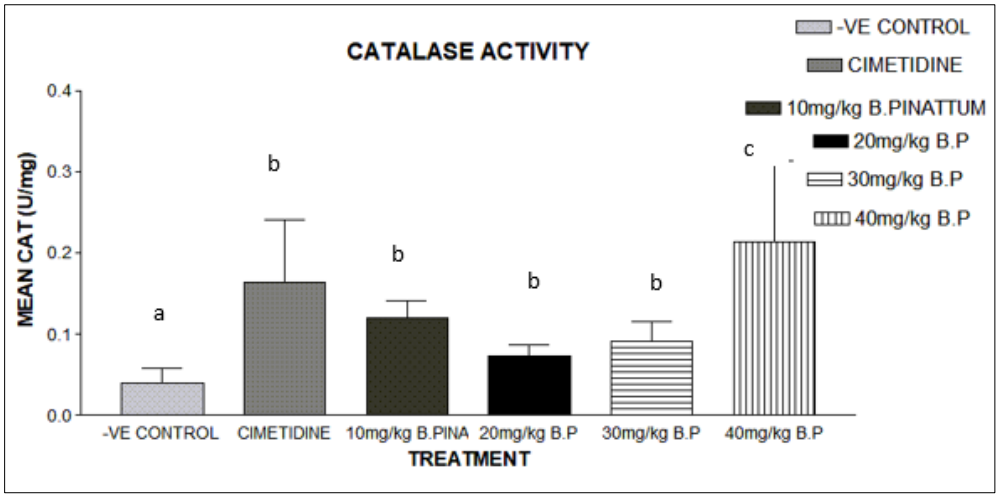
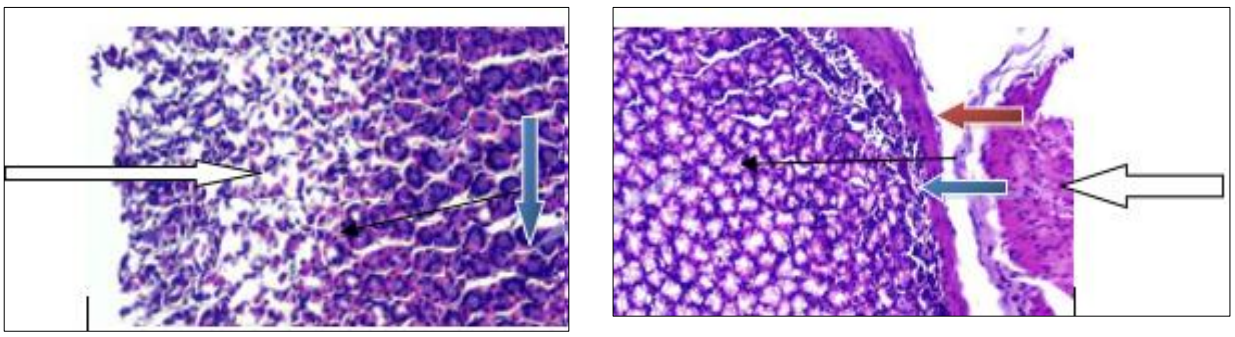


Figure 5 Effect of methanolic extract of *Bryophyllum pinnatum* on Catalase activity of indomethacin induced rats

3.6 Histopathological Examination of Gastric Tissue



A B

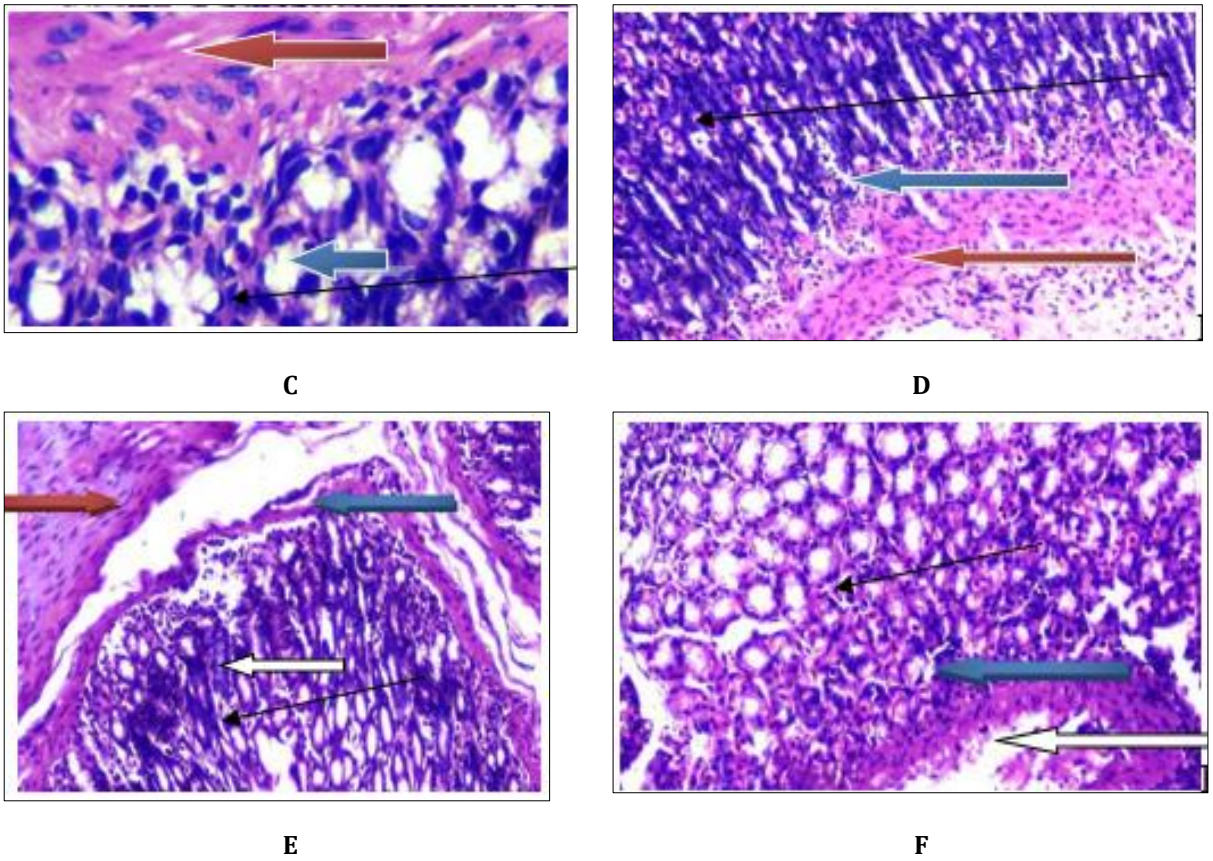


Figure 6 Photomicrograph of stomach sections stained by haematoxylin and eosin from control and treated groups (H & E) x 400. A =control; B = treated with 100 mg/kg cimetidine; C = treated with 10mg/kg of the methanolic extract of *B. pinnatum*; D = treated with 20 mg/kg of the methanolic extract of *B. pinnatum;* E = treated with 30 mg/kg of the methanolic extract of *B. pinnatum*; F = treated with 40 mg/kg of the methanolic extract of *B. pinnatum*

4 Discussion

Indomethacin inhibitory action on prostaglandins synthesis linked with free radicals' formation has been stated as critical biochemical event in the pathogenesis of gastric ulceration [18]. A clear understanding of these events might be of importance in formulating new antiulcer drugs. With the natural antagonistic side effect of and the high cost of synthetic drugs, usage of natural plant source product which are believed to be non-toxic, effective and affordable would be much more appropriate in the treatment of gastric ulcer [19]. Phytotherapy is rapidly growing fast in maintaining human health and prevention of certain diseases[18]. Cells or tissues are in a stable state if the rates of free radical formation and scavenging capacity are essentially constant and in equilibrium. However, an imbalance between them results in oxidative stress which further deregulates cellular functions leading to different pathological conditions. Free radical's thwart antioxidant enzymes activities and initiate lipid peroxidation which is an important event in the toxicity mechanism of indomethacin [20]. Indomethacin has previously been reported to decrease antioxidant enzymes (SOD, CAT and GST) activity in rat stomach thereby inducing gastric ulceration. This is associated with overpowering of the cellular antioxidant defense systems by free radicals ravaging influence that subsequently results in stomach oxidative injury.

This study is aimed to check the antiulcer properties of *Bryophyllum pinnatum* extract (B.P) in rats inflicted with indomethacin-induced gastric ulcer. It also investigates the degree of ulceration and the percentage Inhibition of ulcer in albino rats. Significant increase in the degree of ulceration of the Indomethacin-treated group (negative control) was observed. However, administration of the methanolic extract of *Bryophyllum pinnatum* significantly ($p < 0.05$) reduces the ulcer index in group C, and D and highly significant ($p < 0.05$) reduction in groups E and F as compared to the negative control as shown in fig. 1. So also, there was a significant ($p < 0.05$) increase in the percentage inhibition of ulceration in the 40mg/kg b.w extract group as compared to the positive control, while the 10mg/kg B.P, 20mg/kg B.P and 30mg/kg B.P has 28%, 40% and 49% percentage inhibition respectively as compared to the positive control as

shown in Fig 2. This suggests that, *Bryophyllum pinnatum* extract (B.P) exhibited a significant protective effect on gastric ulcer against indomethacin-induced ulceration.

Furthermore, Administration of indomethacin caused a significant increase ($p < 0.05$) in malondialdehyde level as seen in the negative control group. This increase suggests enhanced lipid peroxidation leading to failure of antioxidant defense mechanism to prevent formation of excessive free radicals. This is in accordance with the work of Oloyede et al, 2015 [21]. However, administration of Cimetidin and the methanolic extract of *Bryophyllum pinnatum* significantly ($p < 0.05$) reduces the malondialdehyde level in the Cimetidin group (B) and all the extract groups(C, D,E and F) respectively when compared to the negative control as shown in fig 3. This suggests that *Bryophyllum pinnatum* has a protective effect against oxidative damage. This is in accordance with the work of De Araújo *et al*., 2021 [22]. which showed a significant decrease (0.01) in the MDA level when pretreated with 5mg/kg of *Bryophyllum pinnatum.*

Moreover, the significant decrease in the stomach superoxide dismutase (SOD) activity in the negative control group may indicate oxidative stress. Pretreatment with the methanolic extract of *Bryophyllum pinnatum* was able to increase the activity of SOD significantly in all the extract groups as compared to the negative group as shown in fig. 4. This result correlates with the findings of De Araújo *et al.,* 2021 [22].

In addition, Catalase converts harmful hydrogen peroxide into water and oxygen and protects the tissues from highly reactive hydroxyl radicals. However, the indomethacin-induced group (negative control) shows a decrease in Catalase activity which may be as a result of a number of deleterious effects in the stomach due to the assimilation of superoxide radical and hydrogen peroxide. However, administration of the methanolic extract of *B. pinnatum* significantly increased ($p < 0.05$) Catalase activity in all the extract groups when compared to the negative control. There was also a significant increase in Catalase activity in the Cimetidin group (group B) when compared to the negative control as shown in fig 5. The results are in accordance with earlier antiulcer and gastric anti-secretory reports of Olaleye *et al.,* 2008 [23].

Finally, the photomicrograph of stomachs of the negative control group (A) showed poorly preserved mucosa epithelial cells layer (white arrow), with infiltration of the gastric glands and lamina propria (slender arrow). The submucosal layers are infiltrated by inflammatory cell (blue arrow) compared to the photomicrograph of stomach of the group treated with cimetidine (B) which showed well preserved mucosa epithelial cells layer (white arrow) and no infiltration of the gastric glands and lamina propria (slender arrow). The submucosal layers is mildly infiltrated by inflammatory cells (blue arrow), The circular muscle layer (red arrow) appears normal when compared to the negative control group.

Also, the photomicrograph of stomach of the group treated with 10 $mg.kg^{-1}$ (C), 20 $mg.kg^{-1}$ (D), 30 $mg.\ kg^{-1}$ (E), showed preserved mucosa epithelial cells layer (white arrow), the mucosa layer showed mild infiltration of the gastric glands and lamina propria (slender arrow) The submucosal layers appear moderately normal and are mildly infiltrated by inflammatory cells (blue arrow), the circular muscle layer (red arrow) appears normal as compared with the negative control group. However, the group treated with 40 $mg.kg^{-1}$ B. *pinnatum* extract (F) showed well preserved mucosa epithelial cells layer (white arrow), no infiltration of the gastric glands and lamina propria (slender arrow). The submucosal layers appear normal and are not infiltrated by inflammatory cells (blue arrow), the circular muscle layer (red arrow) appears normal as shown in fig. 6.

Generally, the protection offered by the methanolic leaf extracts of *Bryophyllum pinnatum* against indomethacin-induced gastric ulceration may be linked to their beneficial medicinal attributes occasioned by phytometabolite constituents. These include ability to scavenge free radicals and regulate mucosal membrane permeability thereby countering the effect of indomethacin on gastric ulceration.

5 Conclusion

In conclusion, this study reveals that, the reduction in indomethacin induced gastric ulceration by administration of methanolic leaf extracts of *Bryophyllum pinnatum* indicates an excellent gastro protective and antioxidative potentials in rats. Hence, this plant could be beneficial for patients suffering from gastric ulcer.

Compliance with ethical standards

Acknowledgment

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Disclosure of conflict of interest

The authors declare no competing interests. This manuscript has not been submitted to, nor is under review at another journal or other publishing venue.

Statement of ethical approval

All animal experiments were conducted in accordance with institutional guidelines for the care and use of laboratory animals.

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