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Research article

Protective effect of ethanolic leaf extract of myrianthus arboreus on indomethacin induced gastric ulcer in adult male wistar rats

Augustine Agu*, Uriah Dike, Samuel Chime, Augustus Ugwu, Kelechi Duru

Department of Anatomy, Faculty of Basic Medical Sciences, University of Nigeria, Enugu Campus, Nsukka, Enugu State, Nigeria

ABSTRACT

Gastric ulcers are a common gastrointestinal disease with a complex etiology. It manifests with various signs and symptoms, which, in severe cases, could be life-threatening, especially in developing countries. Medicinal plants have been known to exhibit therapeutic potential with minimal adverse effects and thus have been employed in treating various diseases. This study evaluated the effect of ethanolic Myrianthus arboreus leaf extract on indomethacin-induced gastric ulcers in adult male Wistar rats. Twenty-five rats were divided into five groups of five rats each: group A received distilled water; group B received distilled water for 14 days, and 30 mg/kg body weight of indomethacin after 24 hours of fasting. Group C received 20 mg/kg of omeprazole for 14 days and 30 mg/kg of indomethacin after 24 hours of fasting. Groups D and E received 50 mg/kg and 100 mg/kg of *M. arboreus*, respectively, for 14 days and 30 mg/kg of indomethacin each after 24 hours of fasting. The ulcer index, antioxidant parameters, gastric pH, and histopathology of the stomach were evaluated after the laboratory experiment. The results showed a significant increase in ulcer index and malondialdehyde caused by the indomethacin, while there was a reduction in glutathione, superoxide dismutase, and hydrogen ion concentration (pH), as well as extensive damage to the gastric mucosa. In contrast, both the extract and the omeprazole significantly improved these damages. The results revealed that the leaf extract of *M. arboreus* has a significant gastro-protective effect comparable to that of omeprazole on the indomethacin-induced gastric ulcer.

Keywords: Gastric ulcer protection, Myrianthus *arboreus* extract, Indomethacin.

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Correspondence: Augustine Agu ✉ augustine.agu@unn.edu.ng, **Orcid Id**: 0000-0002-8615-1947

Department of Anatomy, Faculty of Basic Medical Sciences, University of Nigeria, Enugu Campus, Nsukka, Enugu State, Nigeria.

INTRODUCTION

Stomach ulceration is a common benign inflammatory disease of the gastrointestinal tract in which a painful sore develops in the mucosal lining of the stomach [1]. An imbalance between cytoprotective factors (mucus bicarbonate barrier, prostaglandins (PGs), surface active phospholipids, cellular regeneration, mucosal blood flow, enzymatic and non-enzymatic antioxidants) and aggressive endogenous factors (pepsin, leukotrienes, bile, reactive oxygen species (ROS)) causes it [2]. Some exogenous factors like non-steroidal anti-inflammatory drugs (NSAIDs), stress, and Helicobacter pylori can also be implicated [3, 4]. The prevalence of the disease is high in developing countries like Nigeria, especially in the elderly [5, 6].

The NSAIDs, such as ibuprofen and indomethacin, are widely used as analgesics and anti-inflammatory drugs in the management of arthritis and musculoskeletal diseases [7]. They exert their effect by inhibiting cyclooxygenase (COX), which in turn inhibits prostaglandin production, and through ROS produced by the recruitment of leukocytes, thereby exposing the gastrointestinal epithelium to erosion [8, 9]. Thus, indomethacin has been used to induce gastroduodenal mucosal lesions.

Uncontrolled oxidative stress causes lipid peroxidation, which results in oxidative damage to cells, tissues, and organs [10]. One of the end products of lipid peroxidation is malondialdehyde (MDA). Superoxide dismutase (SOD) and glutathione (GSH) are antioxidants that play a role in supporting cellular function by fighting against ROS; hence, they form the first line of defense [11]. When there is an imbalance between the antioxidant system of the mucosal epithelium and the level of ROS, cellular damage occurs, resulting in gastric ulceration. Thus, MDA, SOD, and GSH are oxidative stress biomarkers and have been used in assessing the therapeutic potentials of numerous plant extracts [8, 12-14].

Some synthetic drugs, including antacids, antihistamines such as ranitidine, and proton pump inhibitors such as lansoprazole, are used in the management of gastrointestinal ulcerations [15]. Though these drugs exhibit some degree of efficacy, they are not readily available and affordable, especially in rural areas, and are not

without adverse effects [16]. Thus, the need for and increasing interest in natural anti-ulcer agents from medicinal plants.

Myrianthus arboreus, also known as giant yellow mulberry or bush pineapple, is a dioecious Cecropiaceae shrub found in tropical African rainforests, including Nigeria [17]. It is a common leaf in the Delta and Edo States of Nigeria, and as such, it is classified among the most popular indigenous vegetables of the people [18]. Its leaves and stems are used for the treatment of various ailments such as diarrhea, dysentery, fever, pains, and coughs [19, 20]. The leaves are traditionally used as a remedy in cases of amenorrhea, female infertility, and to improve lactation [21]. It has also been reported to possess antibacterial, antioxidant, and wound-healing properties [22, 23].

The aim of the study was to evaluate the protective effects of an ethanolic leaf extract of *M. arboreus* on indomethacin-induced gastric ulcers in adult male Wistar rats.

MATERIALS AND METHODS

Plant collection and authentication

The *M. arboreus* leaves were obtained from a farm at Kwale in Ndokwa West Local Government Area of Delta State. The identification and authentication of the leaves was done by a botanist in the Plant Science Department of the University of Nigeria, Nsukka, with voucher number UNH606.

Extraction preparation

The ethanolic leaf extract of the *M. arboreus* preparation was done using the technique described by Agwa et al. (2011) with little modification [24]. The fresh leaves were washed with distilled water and dried at room temperature for seven days. Thereafter, they were ground into a fine powder, and 700.53 g of it was added to 2.4 liters of 70% ethanol in a plastic container at room temperature (28±2ºC). The mixture was stirred for 2 hours and allowed to settle for 2 days (48 hours). The solution was filtered with a sterile muslin cloth and then with filter paper. The filtrate was concentrated and made to evaporate to dryness with the help of an evaporator (rotary) at 550C. The crude extract weighed 16.30 g and had a percentage yield of 2.3268%.

Procurement of drugs

Indomethacin (manufactured by Yangzhou No. 3 Pharmaceutical Co., Ltd., Yiling, Jiangdu, Jiangsu, China) and Omeprazole (manufactured by Surmount Laboratory PVT LTD, Gujarat, India) were purchased from Joephina Pharmacy Limited, Ugwuaji Road, Maryland, Enugu.

Ethical clearance

Ethical clearance was obtained from the College of Medicine Research Ethics Committee, University of Nigeria, Enugu Campus, protocol no. 0127/11/2021.

M. Arboreus Qualitative Phytochemical Screening

The qualitative phytochemical analysis of the extract was done using standard phytochemical methods as described by Harborne (1998) [25].

Experimental Animals

Twenty-five adults male Wistar rats were purchased from the Animal House of the Department of Pharmacology and Toxicology, University of Nigeria, Nsukka. The rats were sheltered in cages in the Animal House of the Anatomy Department, University of Nigeria, Enugu Campus, under standard environmental conditions. They were provided with easy access to laboratory chaw and drinking water ad libitum and were acclimatized for a period of two weeks.

Experimental design

After acclimatization, the rats were divided into five groups of five rats each.

Group A (normal control): received 2 ml of distilled water by oral gavage for 14 days.

Group B (negative control): was given 2 ml of distilled water for 14 days, and an ulcer was induced with 30 mg/kg body weight of indomethacin (dissolved in 2 ml of distilled water) after 24 hours of fasting.

Group C (positive control) received omeprazole 20 mg/kg for 14 days and indomethacin 30 mg/kg (to induce ulcer) after 24 hours of fasting.

Groups D and E (extract pretreated) received 50 mg/kg and 100 mg/kg of *M. arboreus*, respectively, for 14 days and 30 mg/kg of indomethacin each after 24 hours of fasting.

Sacrifice of animals

The animals were anesthetized with chloroform and sacrificed seven (7) hours after the ulcer was induced with indomethacin. Their stomachs were harvested and excised along the greater curvature. The gastric content was emptied into a centrifuge tube, diluted with distilled water, and centrifuged for 10 minutes at 3000 rpm. The supernatant was used for the measurement of pH using a pH meter.

Macroscopic examination of mucosal lesions and ulcer scoring

The methods used by Suheryani et al. (2019) and Fahmy et al. (2015) were employed [26,27]. The excised stomachs were washed with saline to remove blood clots. The lesions in the mucosa were examined under a 10X magnifying glass to assess the ulcer formation, the number, and the severity of the ulcers per stomach. Ulcer scoring was determined using the following:

Normal-colored stomach = 0.

Red coloration = 0.5

Spot ulcers = 1

Hemorrhagic streaks = 1.5

Deep ulcers = 2

Perforations = 3

The sum of the scores from the parameters in each stomach was taken as the ulcer score for that stomach.

The mean ulcer score was calculated as follows:

$$\text{The mean ulcer score} = \frac{\text{the total ulcer score of the group.}}{\text{Number of animals in the group}}$$

Ulcer index (UI) and percentage (%) inhibition were calculated using the:

Ulcer Index (UI)

$$UI = \frac{\text{Total number of ulcer scores in the group}}{\text{Number of ulcerated animals in the group}}$$ [28].

Percentage (%) inhibition

$$\text{Percentage (\%) inhibition} = \frac{\text{UI control} - \text{UI treated}}{\text{UI control}} \times 100$$

Determination of biochemical parameters

Preparation of tissue homogenate

The frozen stomach tissue was homogenized with 5 mL of phosphate buffer at pH 7.4 and centrifuged at 4000 rpm for 20 minutes at 40 °C.The supernatant was separated and used for the determination of biochemical parameters: malondialdehyde (MDA) in mmol MDA/g of wet tissue, superoxide dismutase (SOD) in U/mg of protein, and glutathione (GSH) in mM.

Evaluation of MDA

The level of lipid peroxides was estimated by the thiobarbituric acid reaction method described by Walin et al. (1993) [29]. It was based on the reaction of thiobarbituric acid (TBA) with MDA, a lipid peroxidation product. To 0.2 ml of the test sample, 0.2 ml of 8.1% Sodium Dodecyl Sulfate (SDS), 1.5 ml of 20% acetic acid (pH 3.5), and 1.5 ml of 0.8% TBA were added. The mixture was made up to 4 mL with water and then heated in a water bath at 95 ^{o}C for 60 minutes. As it cooled, 5 ml of the n-butanol and pyridine mixture was added to 1 ml of water, and the two were vigorously shaken. The mixture was centrifuged for 10 minutes at 4000 rpm, and then the organic layer was obtained while its absorbance was calculated at 532 nm wavelength. The MDA was measured as milimoles of MDA per gram of wet tissue.

Evaluation of SOD

This was done using Arthur and Boyne's (1985) technique [30]. To the 100 ul of epinephrine (3 mM) and 0.800 ml of carbonated buffer (100 mM, pH 10.2), 500 ul of the supernatant were added. The samples' absorbance changes were measured using a spectrophotometer set to 480 nm. This was repeated at 15-second intervals for 2 minutes. Parallel and standard tests were performed to determine SOD activity. One in ten (1/10) dilutions of the reaction mixture were done before recording the spectrophotometer reading. A unit of SOD is the amount of enzyme that produces 50% epinephrine inhibition.

Evaluation of reduced glutathione

The reduced glutathione level was obtained through Exner et al.'s (2000) method [31]. This method was based on the development of a yellow colour when 5, 5'-dithio-bis-2-nitrobenzoic acid (DTNB) is added to the compound containing sulfhydryl groups. In a nutshell, 0.2 mL of sample was combined with 1.8 mL of EDTA solution. Three milliliters of precipitating reagent were added to it. The thorough mixture was kept for 5 minutes prior to centrifugation. Four milliliters of 0.3 M disodium hydrogen phosphate and 1 ml of DTNB reagent were added to 2 ml of the filtrate. The colour change was recorded at 412 nm in a spectrophotometer. The values were expressed as mmol/g of wet tissue.

Histopathological examination

The fixed tissue samples from all the groups were collected for histological analysis. The tissues were processed and cut into thin sections with a rotary microtome, stained with haematoxylin and eosin, and mounted on slides for microscopic examination under a light microscope.

Statistical analysis

The statistical analysis was done using the statistical package for social sciences (SPSS), 23rd version. The data was presented as a mean with a standard deviation. Statistical differences in the mean between groups were obtained using one-way ANOVA (analysis of variance). Then a Bonferroni posthoc test was used to determine where the difference was. The significance level was set at $p<0.05$.

RESULTS AND DISCUSSION

The therapeutic potencies of medicinal plants are due to their phytochemical constituents [32]. The phytochemical contents of *M. arboreus* leaf extract in this study show that steroids, flavonoids, and terpenoids appeared in moderate concentration while saponins, glycosides, and alkaloids were in trace concentration and tannins and phenols were absent (table 1). These concentrations of phytochemicals slightly differed from those of other studies, which reported trace concentrations of flavonoids, saponins, tannins, and terpenoids and the absence of steroids [20, 23, 33]. These variations may be due to the fact that the leaves were obtained from different locations with different soil textures as well as different methods and conditions of extraction.

We noted a significant difference ($p<0.05$) in the mean ulcer scores across the groups: The mean ulcer score of Wister rats in group B (5.85±0.35) was significantly higher than that of group A (0.00±0.00). Those of groups C, D, and E (2.15±0.35, 2.35.00±1.41, and 2.25±0.35 respectively) were significantly lower than that of group B (5.85±0.35) (table 2). There was no significant difference

among the mean ulcer scores of groups C, D, and E. However, the percentage inhibition was higher in group C (60.0%) than in groups D and E (47.0% and 51.0%, respectively).

These effects of *M. arboreus* on the indomethacin-induced gastric ulcerations (seen as a reduction in the number of hemorrhagic streaks, spot ulcers, and ulcer scores) were probably due to the anti-inflammatory properties of the flavonoids and the ability of *M. arboreus* to significantly increase the pH values (table 3) by neutralizing or inhibiting the acid production, thus causing a reduction in the ulcer scoring parameters. This explains why most of the conventional gastric ulcer drugs are either acid neutralizers (antacids) or production inhibitors (proton pump inhibitors and H2 antagonists). Our result corroborates with the previous study, which noted an increase in pH values, a reduction in ulcer scores, and fewer hemorrhagic streaks due to the administration of their study extract [15, 34].

The mean values of the antioxidant biomarkers were statistically significant across the groups ($p<0.05$). The value of MDA in group B (5.99±0.02) was significantly higher than those of groups A, C, D, and E (3.50±0.16, 3.41±0.21, 3.06±0.04, and 3.04±0.03 respectively). The mean values of GSH and SOD in group B (5.91±0.13 and 8.19± 0.01) significantly differed from those of groups A (8.41±0.44 and 11.48±0.56), C (8.80±0.57 and 11.55±0.09), D (8.70±0.14 and 11.57±0.22), and E (8.87±0.19 and 11.57±0.22) (table 3). The biomarker of lipid peroxidation is elevated levels of MDA, which is one of its end products [35]. This increase in the level of MDA following the administration of indomethacin was significantly reduced by pretreatment with *M. arboreus*. This suggests that *M. arboreus* has the ability to reduce lipid peroxidation and MDA levels, thereby protecting against reactive oxygen species. This is in consonance with other studies that showed elevated levels of MDA in the gastric tissue following administration of an NSAID and a significant decrease due to pretreatment with their extracts [26, 27, 36]. The significant increase in GSH and SOD levels in *M. arboreus* pretreated groups compared to the decrease caused by indometacin is consistent with previous studies [15, 34]. These antioxidant effects (reduction in MDA and increase in SOD levels) demonstrated by *M. arboreus* could be because of its free radical scavenging activity from the flavonoids, terpenoids, and saponins, which are the major phytochemical constituents of the plant. Flavonoids are known to possess free radical scavenging potential and anti-inflammatory properties [37]. They are also said to increase the production of prostaglandins in the gastric mucosa [38].

The histological section of the Wistar rats' stomach in group A (Figure 1) showed normal stomach histoarchitecture, with normal mucosa thickness and well-outlined mucosal epithelial lining (yellow arrow), and narrow, tightly packed gastric glands (black circles), normal submucosa, and normal musclaris external. In group B (Figure 2), there was severe tissue damage as evidenced by loss of epithelial lining with necrotic debris (white arrows), decreased mucosal thickness, distorted (dilated) gastric glands (red lines), and inflamed cells within the glands. As shown in Figure 3, there was very little tissue damage, with an epithelial lining (yellow arrows) almost identical to Group A; normal blood vessels (black arrows) are present in the lamina propria; and there was increased mucosal thickness and slightly dilated gastric glands (black circles) compared to Group A.

Similarly, groups D and E, which received low and high doses of the extract, respectively, also showed minimal tissue damage, mild erosive changes of the epithelial lining, and aggregates of inflammatory cells (AIC) within the mucosa and the submucosa (Figures 4 and 5). There was an increased mucosa thickness and number of gastric glands (black circles) that were more closely compared to those of group A.

Table 1: Phytochemical contents of *M. arboreus* ethanolic leaf extract

Phytochemicals	Degree of occurrence
Saponins	+
Glycoside	+
Tannin	-
Flavonoids	++
Steroids	++
Terpenoids	++
Phenol	-
Alkaloids	+

(-) = absent; (+) = trace concentration; (++) = moderate concentration; (+++) = high concentration.

Table 2: Mean ulcer scores or indices and percentage inhibition of the groups

Experimental groups	Mean ulcer score	% inhibition
Group A	0.00±0.00	-
Group B	5.85±0.35[a]	-
Group C	2.15±0.35[b]	60
Group D	2.35±0.41[b]	47
Group E	2.25±0.35[b]	51
P-value	0.002	0.013

Groups A (normal control), B (negative control), C (positive control), D (low dose treated group), and E (high dose treated group) were studied.
Key: [a] = significant when compared to group A; [b] = significant when compared to group B

Table 3: Mean SD of the antioxidant biomarkers and pH in the various groups

Antioxidants	MDA	GSH	SOD	pH
Group A	3.50±0.16	8.41±0.44	11.48±0.56	5.90±0.28
Group B	5.99±0.02[a]	5.91±0.13 [a]	8.19±0.01[a]	4.00±0.28 [a]
Group C	3.41±0.21[b]	8.80±0.57[b]	11.55±0.09[b]	5.70±0.14[b]
Group D	3.06±0.04[b]	8.70±0.14 [b]	11.28±0.03[b]	5.55±0.49 [b]
Group E	3.04±0.03[b]	8.87±0.19[b]	11.57±0.22[b]	5.65±0.21[b]
P-value	0.000	0.000	0.000	0.032

Group A (normal control), B (negative control), C (positive control), D (low dose treated group), and E (high dose treated group)
Key: [a] = significant when compared to group A; [b] = significant when compared to group B

Thus, the anti-ulcerative potential of *M. arboreus* extract was further substantiated by these histological results, which showed increased mucosal thickness with more closed gastric glands and just mild erosive changes in the epithelial lining as against the marked damage caused by the indomethacin. This implied that *M. arboreus* possessed bioactive compounds that protected the cells responsible for the secretion of cytoprotective substances from the destructive effect of free radicals, thereby reducing the damage to the gastric mucosa. This confirms the findings of other studies [39, 40].

Figure 1: Photomicrograph of the stomach of rats in group A (normal control).H & E, X 150.
Mucosa (M); Lamina propria (LP); Muscularis mucosa (MM); Submucosa (SM); Musclaris externa (ME); Lumina surface (L).

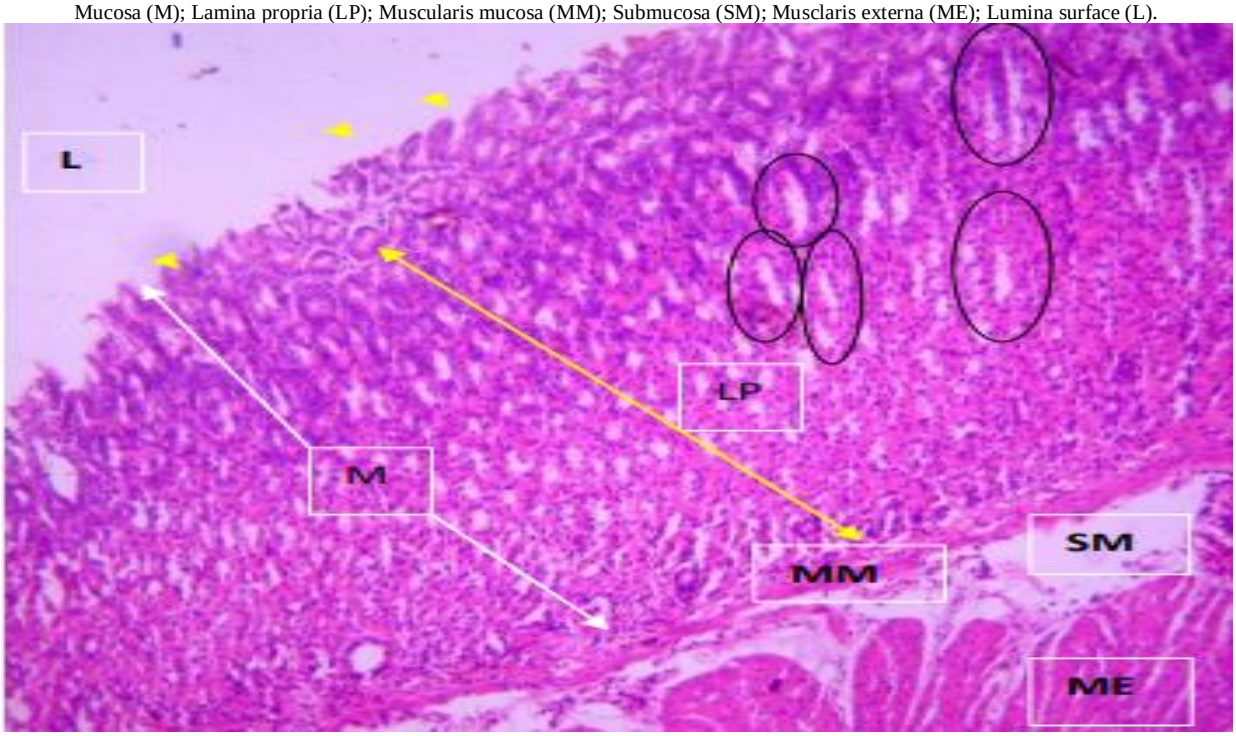


Figure 2: Photomicrograph of the stomach of rats in group B (indomethacin only). H & E, X 150.
Lamina propria (LP); Muscularis mucosa (MM); Submucosa (SM); Musclaris externa (ME)

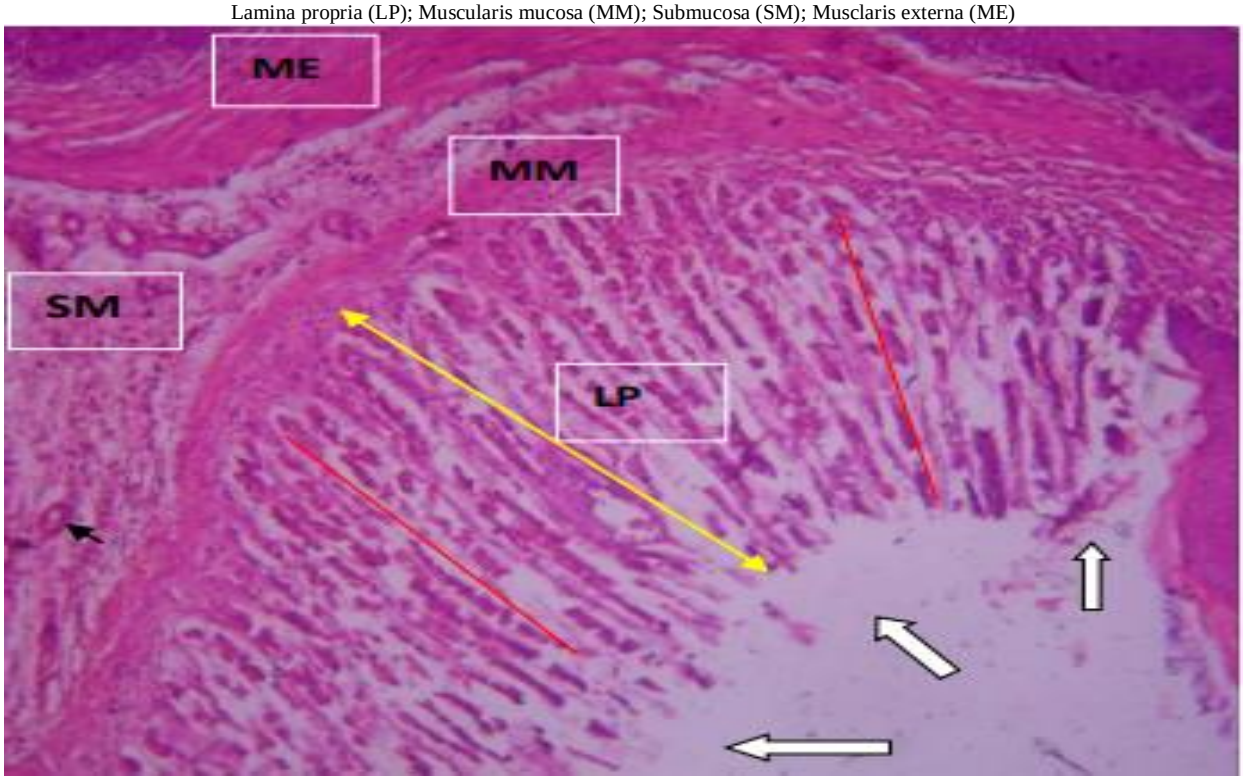


Figure 3: Photomicrograph of the stomach of rats in group C (indomethacin plus omeprazole). H & E, X 150.
Mucosa (M); lamina propria (LP); muscularis mucosa (MM); submucosa (SM); musclaris externa (ME); luminal surface (L).

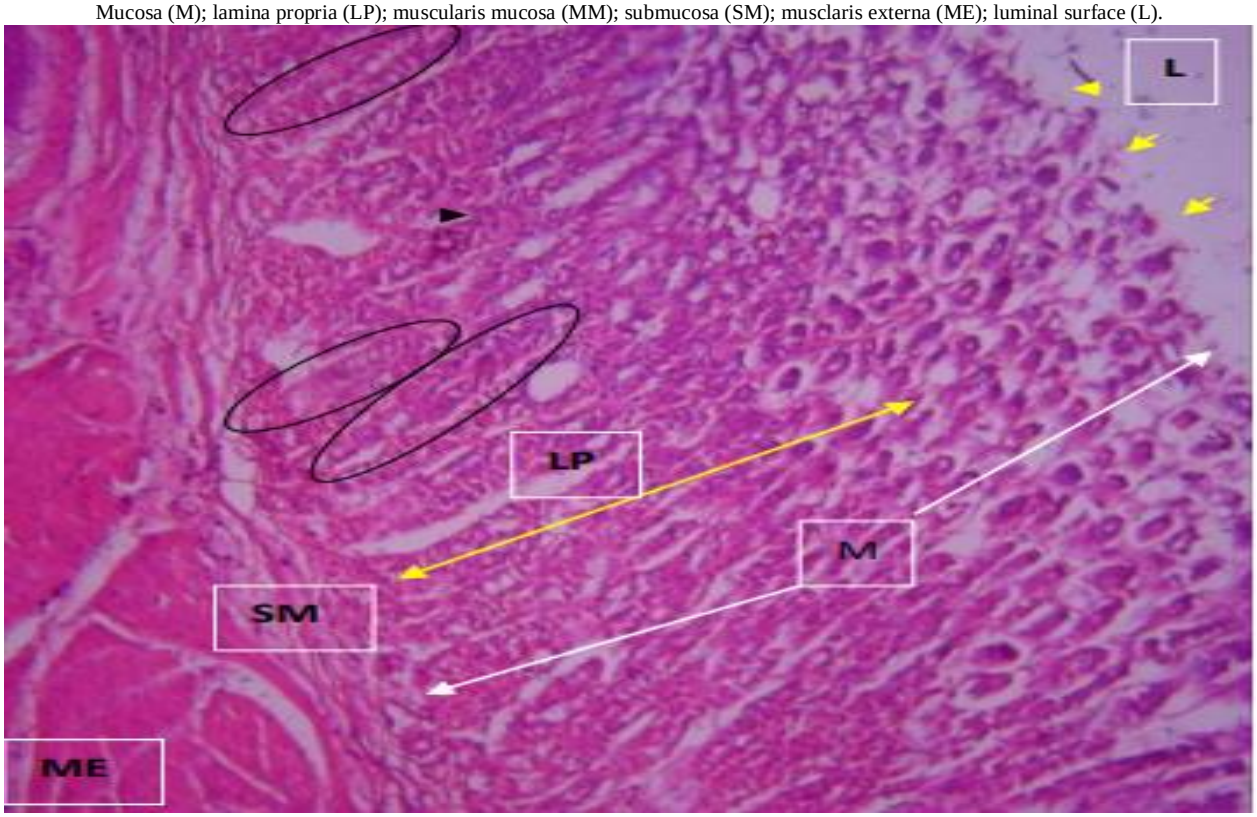


Figure 4. Photomicrograph of the stomach of rats in group D (indomethacin plus low-dose extract). H & E, X 150.
Mucosa (M); lamina propria (LP); muscularis mucosa (MM); submucosa (SM); musclaris externa (ME); luminal surface (L).

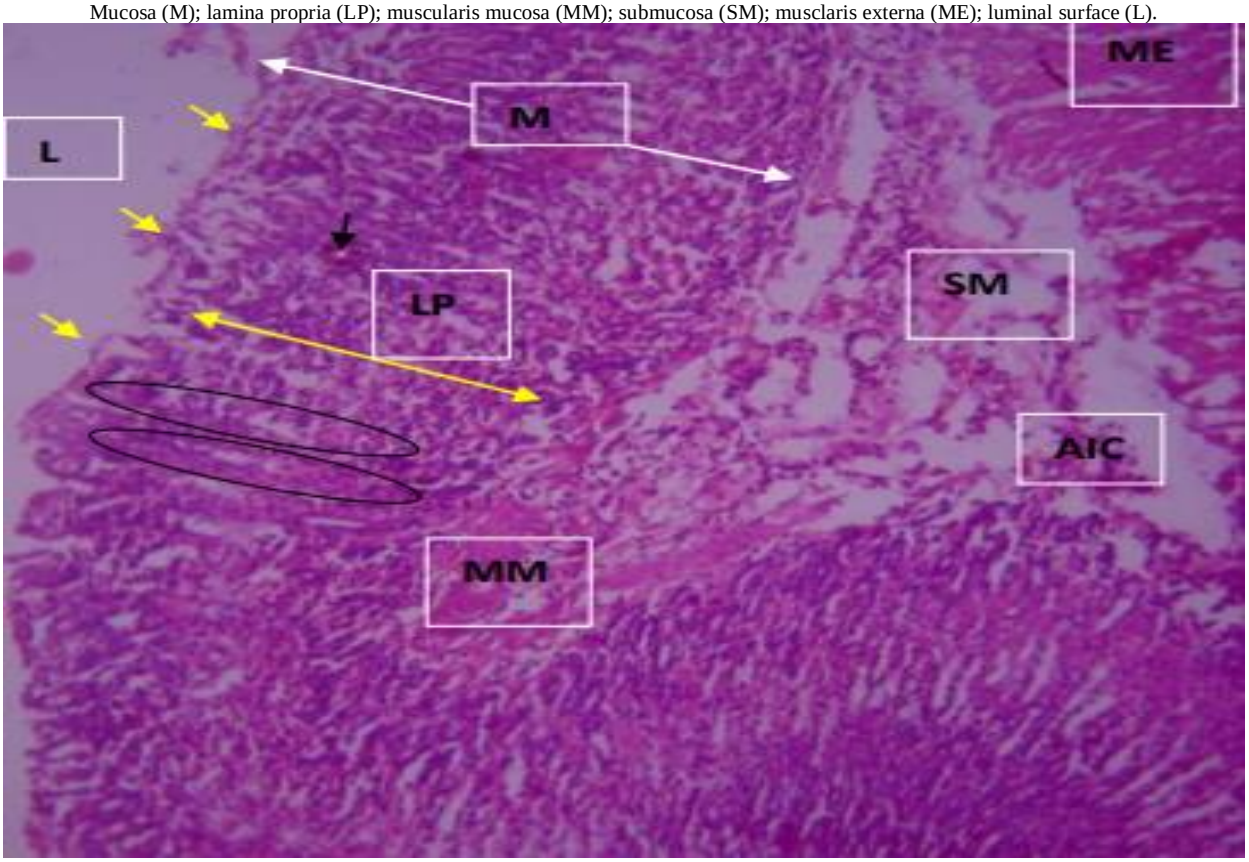
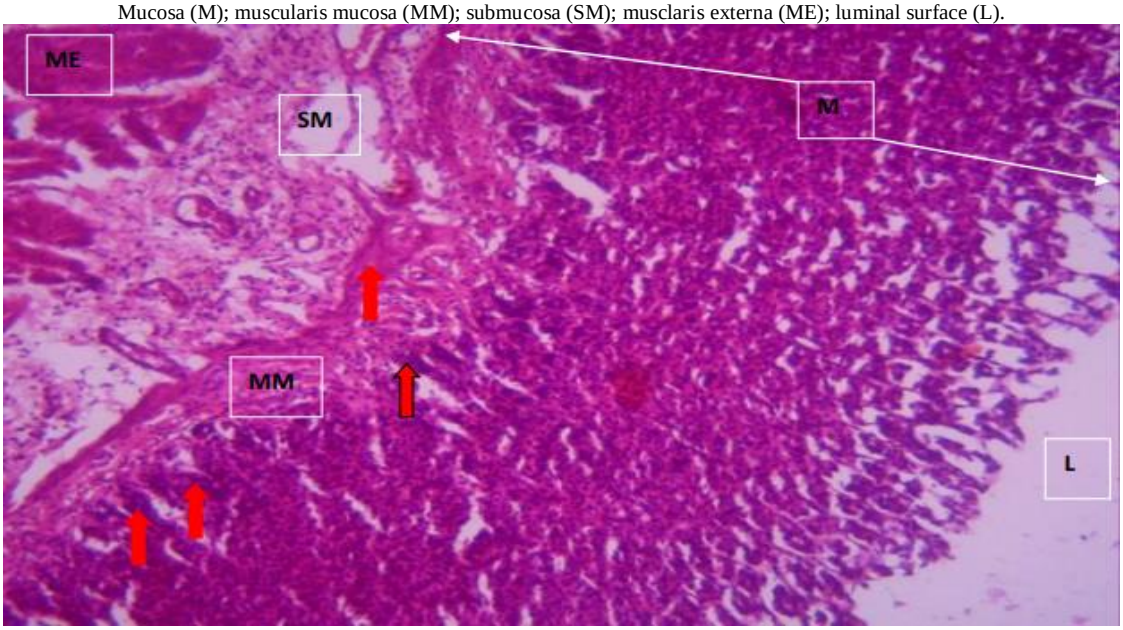


Figure 5: Photomicrograph of the stomach of rats in group E (indomethacin plus high-dose extract)**.** H & E, X 150. Mucosa (M); muscularis mucosa (MM); submucosa (SM); musclaris externa (ME); luminal surface (L).



CONCLUSION

This study demonstrated that the major phytochemicals in the ethanol leaf extract of *M. arboreus* were flavonoids, steroids, and terpenoids. The ethanol leaf extract of *M. arboreus* showed a significant protective effect on the indomethacin-induced gastric ulceration by reducing the number of hemorrhagic streaks, spot ulcers, and ulcer scores in the stomach mucosa of the Wister rats. It was also able to reduce the level of MDA and increase the levels of the antioxidant enzymes GSH and SOD, thereby possessing a protective effect against reactive oxygen species.

Histological evidence showed that it protected the rats from severe tissue damage such as loss of epithelial lining with necrotic debris, decreased mucosal thickness with distorted gastric glands, and inflammatory changes. Therefore, *M. arboreus* could serve as an easily available and affordable anti-ulcerative natural agent.

Conflict of interest:

There is no conflict of interest.

Authors' declaration:

We hereby declare that this article is original and that we will bear any liability relating to the content of the article.

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