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RESEACH ARTICLE

GASTRO-PROTECTIVE EFFECT OF AQUEOUS EXRTRACT OF *ADANSONIA DIGITATA L.* LEAVES AGAINST INDOMETHACIN-INDUCED GASTRIC ULCER IN WISTAR RATS

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Abstract

Background: Peptic ulcer disease (PUD) poses a significant health risk which occurs due to an imbalance between some endogenous aggressive factors and defensive factors. The study aims to explore the potential effects of *Adansonia digitate l.* (*A. digitata l.*) leaves aqueous extract against indomethacin (IND) induced gastric mucosal damage in Wistar rats. **Methods:** The research was an experimental study design. A total of 30 Wistar rats were randomly distributed into six groups of five Wistar rats each. Group 1(control) receive distilled water only, Group 2 (IND) group receive 50mg/kg of indomethacin (IND), Group 3 (CMD) group receive 100mg/kg cimetidine (CMD) for 14 days before ulcer induction, Group 4, 5 and 6 receive 100mg/kg, 150mg/kg and 200mg/kg aqueous extract *A. digitata l.* (A.D) for 14 days before IND administration respectively. IND (50mg/kg) was administered intraperitoneally to each group after 48h of fasting using raised wire mesh cage to induce gastric ulceration. The gastric tissues harvested were used for histological studies. Data were analyzed using IBM SPSS version 22. **Results:** Pre-treatment with cimetidine and aqueous extract at 150mg/kg AD+IND and 200mg/kg AD+IND significantly decreases ($P<0.05$) the ulcer score and ulcer index compared to IND group. Percentage inhibition of ulcer increases (36.2%, 49.9% and 57.7%) in extract treatment groups compared to percentage inhibition of ulcer in IND (29.0%) group. Histological studies of gastric tissues show damaged and denuded mucosa in the indomethacin group which were reversed by the protective effects of aqueous extract. **Conclusion**: The extract provides the protective effects against the damaging effects of indomethacin shown in the histological studies and gastric ulcer parameters.

Keywords: *Adansonia digitata l.,* Indomethacin-induced gastric ulceration, Wistar Rats.

Introduction

Peptic ulcer is an acid induced lesion of the digestive tract that is usually located in the stomach or proximal duodenum, and is characterized by denuded mucosa with the defect extending into the submucosa or muscularis propria (Narayanan *et al.,* 2018). It occurs due to lack of equilibrium between some endogenous aggressive factors and cytoprotective or defensive factors. The aggressive factors include hydrochloric acid, pepsin, refluxed bile, leukotrienes and reactive oxygen species (ROS), while the protective factors include surface active phospholipids,

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nitric oxide (NO), bicarbonate barrier, mucosal blood flow, prostaglandins (PGs), cell migration and renewal, enzymatic and non- enzymatic antioxidants like catalase, and some growth factors (Alrashdi *et al.,* 2012). The lifetime prevalence of PUD in the general population has been estimated to range between 5 and 10% with an incidence of 0.1-0.3% per year (Kasper, 2015). However, in 2019 the global prevalence of PUD was approximately 8.09 million, reflecting a 25.82% increase since 1990 (Xie *et al.,* 2022). However, in many regions, especially in high-income countries, the prevalence and incidence of PUD have declined, which is most likely secondary to the introduction of new therapies and improved hygiene, which resulted in a decline in *H. pylori* infections (Kuna *et al.,* 2019). Studies from Africa reveal a wide variability in PUD prevalence, ranging from 7.9% in Nigeria (Eniojukan *et al.,* 2017) to 71.3% in Ghana (Tabiri *et al.,* 2016), indicating significant disparities in disease burden across the continent. Risk factors for developing peptic ulcer include *H. pylori* infection, alcohol and tobacco consumption, non-steroidal anti-inflammatory drugs (NSAIDs) mis-use, and Zollinger-Ellison syndrome (Soreide *et al.,* 2015). Indomethacin induces its gastrointestinal toxicity via several mechanisms such as an increase in gastric acid secretion, interfere with mucosal cell regeneration via inhibition of PGE2 synthesis, production of free radicals, reduction of gastric nitric oxide level and invasion of activated neutrophils as well as induction of gastric cells apoptosis (Matsui *et al.,* 2011). Several studies have been conducted regarding the development of a wide spectrum of anti-ulcer drugs (Idowu *et al.,* 2021). However, most of these drugs have adverse drug reactions like arrhythmias, gynecomastia, and haemopoietic changes and are considerably expensive (Bech *et al.,* 2000). Hence, the need to search for alternative and effective agents with fewer side effects, affordability, efficacy and safety (Antonisamy *et al*., 2014), therefore, traditional products show evidence of cost-effectiveness, easier to obtain, none existence of side effects than pharmaceuticals and effective for medicinal purpose (Sam, 2019). Baobab (*Adansonia digitata linn.*), a tree plant belonging to the Malvaceae family, widespread throughout the hot, drier regions of tropical Africa (De Caluwe *et al.,* 2010). Leaves, bark, roots, pulp and seeds are used for multiple medicinal purposes in many parts of Africa and were found to show interesting medicinal properties including antioxidant, pre-biotic-like activity, anti-inflammatory, analgesic, antipyretic activity, anti-diarrhea and anti-dysentery activity (Sanchez *et al.*, 2011).

Materials and Methods

Leaves Collection, Authentication and Processing

The leaves of the *Adansonia digitata l.* tree were obtained from the farm land on 20th Nov., 2021 located in Chiranchi Tudu (Latitude: 11.9516°N, Longitude: 8.4720°E), under Chiranchi ward, Kumbotso Local Government Area, Kano State. It was submitted to taxonomist Dr. Yusuf Nuhu for authentication at the Department of Plant Biology. The plant was given an herbarium accession number as BUKHAN 0036, and a voucher of the sample was deposited in the Department, then 25 grams of the leaves were washed and cleaned to remove impurities present on them. They were dried under shade for 5 days.

Preparation of the extract

The preparation of the extract was carried out following the method described by (Singh *et al.,* 2014) by macerating 10g of powdered sample in 1L distilled water at normal environmental temperature for 12 h, filtering (Whatman No. 1) and evaporating at 50°C under reduced pressure for 6h. The residue obtained was then used as the aqueous extract. This extraction was carried out at the Department of Pharmacognosy laboratory, Faculty of Pharmaceutical Sciences, Bayero University, Kano.

Phytochemical Analysis

The phytochemical screening of aqueous extract of *A. digitata l.* leaves were tested by the simple and standard qualitative methods described by (Evans 2002), and (Sofowora 2008).

Animals and Environmental Conditions

A total of 30 male Wistar rats 7-8 weeks' old weighed 160-200g were purchased from the animal house of Pharmacology Department, Faculty of Pharmaceutical Sciences, Bayero University Kano. The animals were housed in large cages with a dimension of l=30.1cm, b=19.5cm and h=15.5cm with a total surface area of 2, 711.5cm² in a ventilated animal House with free access to rodent chow and tap water was supplied *ad libitum*. The animals were randomly distributed into different

experimental groups consisted of five rats each. Animals were handled in accordance with the guidelines of the National Institute of Health (NIH) for laboratory animal care and use.

Acute toxicity study

The method of (Lorke, 1983), was used to determine the median lethal dose (LD_{50}) of the extract. The median LD_{50} is calculated using the formula below:

$LD_{50} = \sqrt{D_{100} \times D_0}$

Where D_{100}= least dose that killed a rat, D_0= highest dose that did not killed any rat.

Study Design and Grouping

The research was an experimental study design. After two weeks for acclimatization, the animals were grouped into six experimental groups, containing five Wistar rats each, according to the guidelines of the National Institute of Health (NIH) for laboratory animal care and use.

Group 1 (Control): The animals received distilled water (1ml/kg) orally and served as control.

Group 2 (IND): The animals were fasted for 48h before intraperitoneal injection of a single dose of indomethacin (50mg/kg) (Akpamu *et al.,* 2013).

Group 3 (100mg/kg CMD+ 50mg/kg IND): The animals received 100 mg/kg of cimetidine daily for 14 consecutive days orally and fasted for 48 h before intraperitoneal indomethacin (50mg/kg) injection (Adefisayo *et al.,* 2017).

Group 4 (100mg/kg AD+ 50mg/kg IND): The animals received aqueous extract of A.D leaves (100mg/kg) daily for 14 consecutive days orally and fasted for 48 h before intraperitoneal indomethacin (50mg/kg) injection. Group 5 (150mg/kg AD+ 50mg/kg IND): The animals received aqueous extract of A.D leaves (150mg/kg) daily for 14 consecutive days orally and fasted for 48 h before intraperitoneal indomethacin (50mg/kg) injection. Group 6 (200mg/kg AD+ 50mg/kg IND): The animals received aqueous extract of A.D leaves (200mg/kg) daily for 14 consecutive days orally and fasted for 48h before intraperitoneal indomethacin (50mg/kg) injection (Basipogu *et al*., 2018).

Pylorus ligation induced ulcer

Gastric ulceration was induced in the animals according to the procedure described by (Sayanti *et al.,* 2007). The animals were fasted for 48h before pylorus ligation with water *ad libitum* by placing them individually in separate cages with raised wide wire mesh to avoid coprophagia. The study rats were administered with a singles dose of IND (50 mg/kg) intraperitoneally and the abdomen was opened by midline incision below the xiphoid process, under light ketamine hydrochloride (50mg/kg) anaesthesia. The pyloric portion of the stomach was ligated, avoiding damage to its blood supply, the stomach was placed back carefully and the abdominal wall was closed with sutures. After 5 hours, animals were euthanized by decapitation under anaesthesia, stomach removed, opened on greater curvature and spread on filter paper which were examined for ulceration.

Ulcer index determination

The number of ulcers and the length of each ulcer were measured according to the method of (Ohara *et al.,* 1995). Ulcer index was calculated using severity scores and average number of ulcers per length of the tissue. Severity scores assessment were as follows:

Normal stomach (0), Red coloration (0.5), Spot ulcers (1), Haemorrhagic streaks (1.5), Ulcer > 3 mm but <5 mm (2), Ulcers > 5 mm (3).

Ulcer index (UI) and percentage inhibition (PI) of ulcer was calculated using the formula according to (Hano *et al.,* 1976):

$UI = (UN + US + UP) \times 10^{-1}$.

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

Percentage inhibition= $\frac{\boldsymbol{UIcontrol} - UI\ pretreated}{UI\ control} \times 100$

Histological studies

The gastric tissue samples from each group were fixed with 10% formaldehyde. Specimens were embedded in paraffin, sectioned (3-5µm) and stained with haemotoxylin and eosin (H&E) examined under a light

microscope (Leica DM 750 microscope) at a magnification of 100× and photographed with Leica ICC SOHD camera (Auwioro, 2010).

Statistical Analysis

Variables were summarised as Mean ± SEM. Data were compared by one-way analysis of variance (ANOVA), followed by a Tukey's post-hoc to determine the significant difference between the groups using IBM SPSS version 22. The $p<0.05$ indicated a significance difference.

Results

Phytochemical screening

The aqueous extraction of phytochemical constituents of A.D leaves revealed the presence of alkaloids, flavonoids, saponins, steroids, and tannins. The presence or absence of the compound was expressed as positive (+ve) or negative (-ve) respectively, presented in Table 1 below.

Table 1: Phytochemical components of *A. digitata l.* leaves.

Phytochemicals screened	Aqueous extract (inference)
Alkaloids	+
Anthraquinones	-
Flavonoids	+
Saponins	+
Steroids	+
Tannins	+
Terpenoids	-

Keys: (+): present; (-): Absent

Acute oral toxicity (LD_{50}) test of the aqueous extract of *Adansonia digitata l.* leaves

The result of acute toxicity test showed that there was sign of toxicity at 5000mg/kg dose in the second phase of the test. Signs of toxicity such as salivation, stretching of the entire body, weakness, decrease locomotion, writhing, decreased in sensitivity to touch, weight loss were noticed in the first 4 hours and subsequently 24 hours after extract administration and there was no death recorded throughout the study. Therefore, LD_{50} was found to be greater than 5000mg/kg as there was no mortality up to 5000mg/kg dose of the extract.

Effects of aqueous extract of *Adansonia digitata l.* on Ulcer score, Ulcer index and Percentage inhibition of ulcer across experimental groups

Table 2 below shows the result of the effects of aqueous extract of *A. digitata l.* on gastric ulcer parameters. The result shows that there was statistically significant difference in ulcer score and ulcer index (P=0.001, 0.000) respectively, across the groups. There was significant increase in ulcer score in IND group (4.24±0.22) compared to control group (1.20±0.34).

There was significant decrease in ulcer score in CMD+IND and 200mg/kg AD+IND group (1.90±0.70 and 1.60±0.48) respectively compared to IND group (4.24±0.22).

The difference in ulcer index in IND group (5.04±0.41) and control group (2.28±0.11) were also significant (P=0.000). Also, there was a significant decrease in ulcer index in CMD+IND, 150mg/kg AD+IND and 200mg/kg AD+IND groups (2.33±0.56, 1.97±0.70 and 0.94±0.27) respectively compared to IND group (5.04±0.41).

There was decrease in percentage inhibition in IND group (29.0%) compared to control group (100%). Also, percentage inhibition of ulcer increases in all the groups (43.5%, 36.2%, 49.9% and 57.7%) compared to IND group (29.0%).

Table 2: Ulcer score, ulcer index and percentage inhibition among control and study groups. (Mean±SEM, n=5)

Variables	Ulcer score	Ulcer index (mm^2)	Percentage inhibition (%)
Group 1 (control)	1.20±0.34	2.28±0.11	100
Group 2 (IND)	4.24±0.22[a]	5.04±0.41[a]	29.0
Group 3 (CMD+IND)	1.90±0.70[b]	2.33±0.56[b]	43.5
Group 4 (100mg/kg AD+IND)	3.17±0.45	3.16±0.19	36.2
Group 5 (150mg/kg AD+IND)	2.25±0.43	1.97±0.70[b]	49.9
Group 6 (200mg/kg AD+IND)	1.60±0.48[b]	0.94±0.27[bd]	57.7
F-value	6.091	11.656	
P-value	0.001*	0.000*	

*= P<0.05.IND= Indomethacin, CMD= Cimetidine, AD= Adansonia digitate l. a= There is significant diff. with control group, b= significant diff. with indomethacin group, c= significant diff. with cimetidine group, d= significant diff. with the 100mg/kg AD extract, e= significant diff. with the 150mg/kg AD extract, f= significant diff. with the 200mg/kg AD extract. (P<0.05 indicate significance difference).

Histological evaluation

The photomicrograph of the stomach sections of the control and treated groups are shown in Figure 1. The histology of the stomach sections of control rats was structurally normal having the normal epithelial architecture, lamina propria, submucosa and muscularis propria and no histopathological changes such as ulceration and inflammatory changes were observed (Plate I). Gastric tissue histology result of Wistar rats administered with 50mg/kg indomethacin (group 2) revealed damaged gastric mucosal epithelium and glands, also there was degenerative changes in the submucosa (Plate II). Histology result of Wistar rats administered with 100mg/kg cimetidine+ 50mg/kg indomethacin (group 3) revealed significant regeneration of mucosal layer and mucosal integrity was maintained with mild ulceration in the mucosal epithelium (Plate III). Pretreatment with A.D at 100 and 150mg/kg had mild epithelial damage with intact mucosal and muscularis mucosae associated with areas of granulated tissue, new connective tissue around the healed ulcerated area (Plate IV and V) while pretreatment with the 200mg/kg AD showed no observable hemorrhagic necrosis and intact gastric pits was maintained (Plate VI) and these observations were comparable with the normal control.

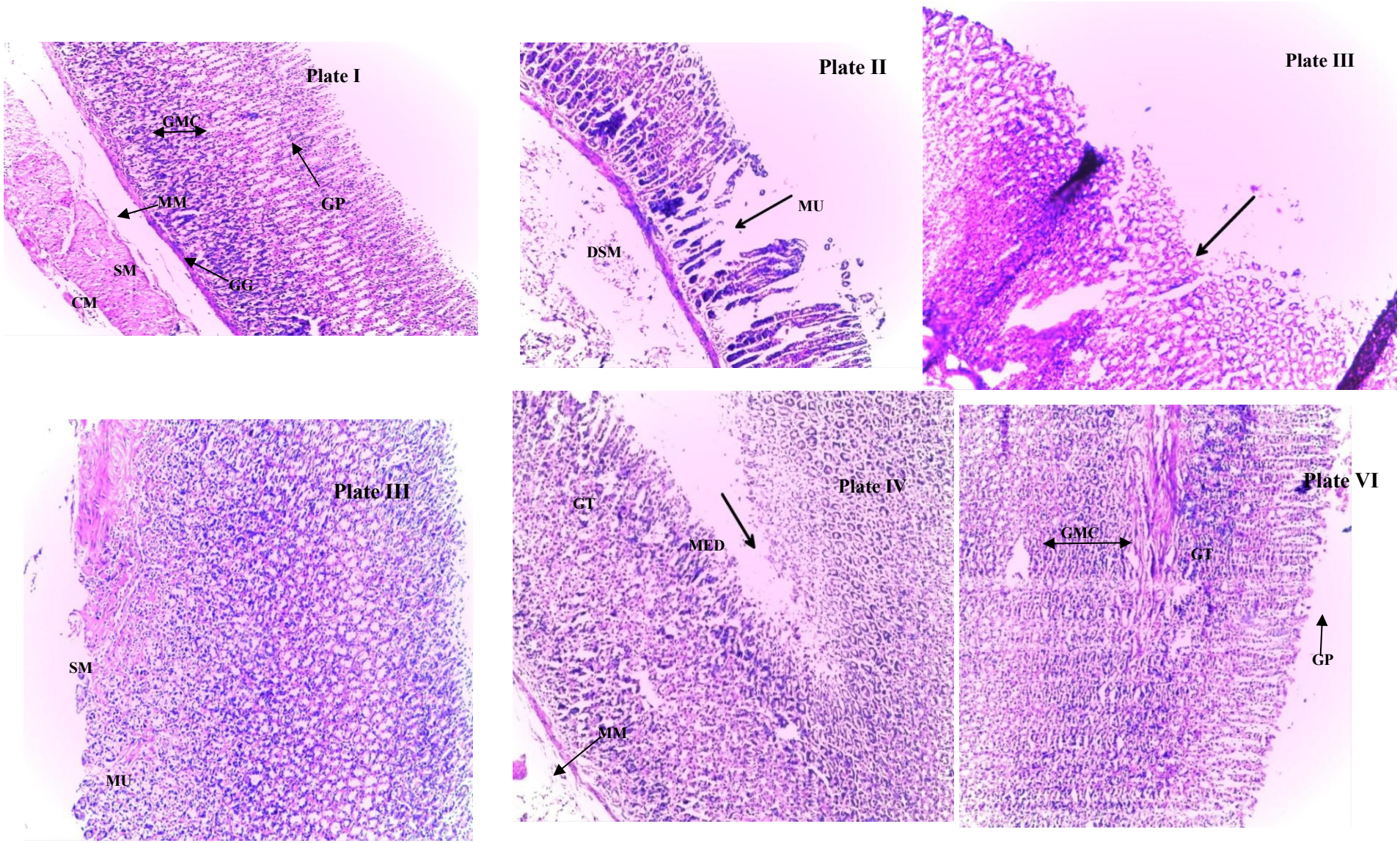

Figure I: Histological gastric tissue preparation of control and experimental group

Discussion

The phytochemical screening of aqueous extract of *A. digitata l.* leaves revealed the presence of tannins, flavonoids, saponins, alkaloids and steroids while terpenoids and anthraquinones were absent. The finding conforms with the study of (Zagga *et al.,* 2018) who reported the presence of saponins, flavonoids, alkaloids, tannins, cardiac glycosides, total phenols and absence of terpenoids, triterpenes and gelatin.

This study investigated the acute oral toxicity test of aqueous extract of *A. digitata l.* leaves and the median lethal dose (LD_{50}) was found to be greater than 5000mg/kg which conforms to the study of (Christian *et al.,* 2012). According to toxicity classes of (Hodge and Sterner, 2005), any compound with oral LD_{50} (rat) of 5000mg/kg or more should be considered as practically harmless. Hence, oral administration of aqueous extract at a dose of less than or equal to 5000mg/kg could be safe.

Gastric ulcer parameters among the experimental groups which include ulcer score, ulcer index and percentage inhibition of ulcer. There was a significant increase ($P<0.01$) in ulcer score and ulcer index in the IND group compared with control group. This is closely similar to the study conducted by (Saleh *et al.,* 2015), (Oluwabunmi and Abiola 2015), (Idowu *et al.,* 2021). The ulcer index measures the level of excavation or lesion on the gastric mucosa. The increase in ulcer score and ulcer index of ulcerated rats is an indication of assault on the gastric mucosa which may have resulted from an imbalance between the aggressive factors and defensive factors of the mucosal caused by indomethacin (Soreide *et al.,* 2015). It has been reported that NSAIDs like indomethacin are capable of causing an imbalance between gastric offensive factor and defensive factors (Soreide *et al.,* 2015). Also, there was a significant decrease ($P<0.05$) in ulcer score and ulcer index in (CMD+IND) group compared with IND group which is in line with the findings of (Oluwabunmi and Abiola 2015). Pre-treatment with the cimetidine gave cyto-protective effects which is associated with decreased pepsin activity and elevated mucus level in the gastric mucosa. Thus, the drug shielded the gastrointestinal membrane by reducing the catastrophic influence of indomethacin in ulcerative rats (Bech *et al.,* 2000). This indicates enhanced mucus secretory potential of the drug and suggestive of its significant role in cyto-protection against gastric acid damage to the mucosal epithelium (Nworgu *et al.,* 2019). In the extract treatment groups, there was significant decrease ($P<0.01$) in ulcer score at 200mg/kg AD+IND group compared with (IND) group. Also, there was a significant decrease ($P<0.01$) in ulcer index in 150mg/kg AD+IND and 200mg/kg AD+IND groups compared with (IND) group. This finding is similar to the study conducted by (Basipogu *et al.,* 2018), whom found that *A. digitata l.* leaves aqueous extract significantly decreases the ulcer index at high doses compared to the ulcer group. These observations also suggest that the aqueous extract of *A. digitata l.* can be used as antiulcer agent. This anti-ulcer effect may be due to presence of tannin presents in the aqueous leaves extract which reacts with proteins of the stomach tissues layers by precipitating micro proteins at the site of the ulcer, forming a protective pellicle (thin film) that prevent gastric mucosa from irritation and damage (Vasconcelos *et al.,* 2010). In addition, the extract possibly prevented gastric mucosal lesions through its flavonoid content as explained by (Alanko *et al.,* 1999). Flavonoids could scavenge free radicals, inhibit lipid peroxidation, and increase prostaglandins and mucosal content of the gastric mucosa showing cytoprotective effects (Mota *et al.,* 2009). Flavonoids show gastric cyto-protective activities by increasing mucosal prostaglandins (PG) content, reduction in histamine secretion (Kaur *et al.,* 2014). Saponins may stimulate mucous membrane protective factors, and tannins render the outermost layer of the mucosa less permeable, for instance to chemical irritation. In addition, alkaloids compounds are also reported to have potent activity against gastric ulcers (Kaur *et al.,* 2014).

Moreover, percentage inhibition of ulcer increases in CMD and extract treated groups compared to the IND group. Percentage inhibition of ulcer increases as the dosage of plant extract increases which conforms with the study of (Basipogu *et al.,* 2018) who found a dose dependent percentage inhibition of ulcer mostly at the dose of 200mg/kg aqueous extract of *A. digitata l.* leaves. Healing of mucosa epithelia cells was prominently displayed by the aqueous extract at 200mg/kg dose depicting a better ulcer inhibition compared favorably with cimetidine standard anti-ulcer drug. This is indicative of enhanced mucus secretory potential of the extracts and suggestive of their significant role in ulcer healing process.

The histological slides of gastric mucosa of control group showed normal mucus-secreting surface columnar epithelial cells and gastric pits and no histopathological

changes were observed. This finding agrees with study of (Jambi and Khattab 2019). In comparison to the indomethacin group there were different grades of mucosal injuries observed, resulting in severe epithelial erosion, necrotic and distorted glands accompanied by degenerative changes in the mucosal layers, because indomethacin encourages direct adherence of neutrophils to the gastric endothelium leading to inflammatory reactions which results in mucosal damage and this agrees with the findings of (Shim and Kim 2016). The observed histology of 100mg/kg CMD+IND group shows diminished ulceration of surface epithelium and subsequently restored the normal histological structure due combination of events including released preformed mucus, wound retraction and epithelization which are involved in ulcer protective process by cimetidine after injury by indomethacin (Modirat *et al.,* 2018).

The observed histology of extract pre-treatment groups showed a protection of gastric mucosal epithelium against the catastrophic influence of indomethacin. This could be due to saponins which may stimulate mucous membrane protective factors, and tannins render the outermost layer of the mucosa less permeable to chemical irritation (Kaur *et al.,* 2014).

Based on the research findings it can be recommended that *A. digitata l.* leaves that is used in making soup can be consumed at high concentration to increase gastric mucosal integrity.

Conclusion

The *A. digitata l.* leaves aqueous extract without any apparent toxicological effects conferred a dose dependent protective effect against indomethacin induced gastric mucosal damage. The protective effect of the extract was evident in the histological photomicrograph.

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Conflict of interest

The authors have declared no conflict of interest exists**.**

Authors' contributions

AAI; Funding and conducted the research as it is my MSc research work, MI: Statistical data analysis, MME: Standardized the methodology of the research work, YNW: Review of the work, ASI: Conceptualization and actualization of the research work as my MSc superviso.

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