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ORIGINAL ARTICLE

# Gastroprotective effects of polyphenol rich extract of *Anacardium occidentale* L. leaf

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## SUMMARY

The leaves of *Anacardium occidentale* are used in folkloric medicine for the management of gastrointestinal disorders. This study evaluated the gastroprotective properties of methanol extract of *A. occidentale* leaf against ethanol- and indomethacin-induced gastric ulcers. Cold maceration method was used in the preparation of methanol extract of *A. occidentale* leaf. The extract was concentrated under reduced pressure using a rotary evaporator. The gastroprotective effects of the methanol extract of *A. occidentale* was tested at 100, 200 and 400 mg/kg against ethanol and indomethacin-induced gastric ulcer. Omeprazole and misoprostol were used as the positive controls for the ethanol and indomethacin-induced gastric ulcer models respectively while distilled water was used as the negative control. The effects of the extract on histamine receptor were also evaluated on isolated rabbit jejunum. The extract significantly ($p < 0.05$) reduced ulcer index in the treated rats relative to the negative control. The effects of the extract were comparable with the effects of the reference drugs. The extract relaxed spontaneously contracting rabbit jejunum and inhibited histamine induced contraction of rabbit jejunum. This study suggests a pharmacological basis for the folkloric use of *Anacardium occidentale* in the management of gastric ulcer.

**Key words:** *Anacardium occidentale*; ulcer; ethanol; indomethacin; misoprotol; omeprazole

## INTRODUCTION

Peptic ulcer is a discontinuity in the mucosa of stomach and/or duodenum which often penetrate into the muscularis layer of the digestive tract (Singh *et al*., 2018). It is caused by impaired mucosal defense against the offensive factors of the gastrointestinal tract (Huang *et al*., 2018). It affects about 10% of the global population and about 4 million new cases are reported annually worldwide (Khushtar *et al*., 2016; Thabrew and

Arawwawala, 2016). Peptic ulcer is conventionally treated with $H_2$-receptor antagonist, prostaglandin and its analogues, antacid, proton-pump inhibitors, antibiotics etc (Khushtar *et al*., 2016). The use of these drugs are associated with a range of side-effects such as dry mouth, headache, vomiting, diarrhoea, constipation, renal disorder, blurred vision and many more (Khushtar *et al*., 2016). The difficulties in treating ulcer have been compounded by *Helicobacter pylori* resistance to some antibiotics (Megraud *et al*., 2013). The aforementioned limitations and side-effects of conventional ulcer drugs have made it exigent to search for more efficacious and safer alternatives for the management of gastrointestinal ulcers (Li *et al*., 2018; Singh *et al*., 2018). The most widely used alternatives are plant based products, especially those rich in polyphenols (Farzaei *et al*., 2015; Li *et al*., 2018).

*Anacardium occidentale* L. commonly called cashew belongs to the family anacardiaceae. It is well distributed in the tropics; Africa, India and Brazil (da Silva *et al*., 2018). The leaf decoction or infusion as well as the hydroalcoholic extract, rich in polyphenols, are used in the ethnomedical management of gastrointestinal tract disorder and hypertension in West Africa and South America (Konan *et al*., 2007; Razali *et al*., 2008). The antimicrobial (Kudi *et al*., 1999), antihypertensive (Tchikaya *et al*., 2003), antiviral (Goncalves *et al*., 2005), antioxidant (Razali *et al*., 2008), anti-inflammatory (Olajide *et al*., 2013) and antidiabetic (Kamtchouing *et al*., 1998) activities of *A. occidentale* have been documented. The antiulcerogenic potential of cloned *A. occidentale* in city of Fortaleza, Brazil has been reported, but there is no information on the antiulcerogenic activities of the wild varieties of *A. occidentale* in West Africa, especially South-Eastern Nigeria (Konan and Bacchi, 2007; Morais *et al*., 2010). This study investigated the antiulcerogenic and antihistamine activities of *A. occidentale* leaf harvested from South-Eastern Nigeria.

## MATERIALS AND METHODS

### Plant Identification/Collection

Fresh leaves of *Anacardium occidentale* were obtained from Umudike, Abia state and authenticated by a taxonomist, and a voucher specimen (MOUAU/CVM/VPP/2017/1) was kept in the Department of Veterinary Physiology and Pharmacology, Michael Okpara University of Agriculture Umudike herbarium for reference.

### Extract Preparation

The leaves of *Anacardium occidentale* were collected,washed and air-dried to constant weight and then pulverized into fine powder using a contact mill. The quantity of the fine powder was weighed with a balance scale. The leaf powder was macerated in 1:4 w/v analytical grade methanol (MeOH) for 48 hours and was vigorously agitated every 3 hours. The mixture was filtered through Whatmann filter paper into an already measured beaker at room temperature. The filtrate obtained was concentrated under reduced pressure using a rotary evaporator (Cole-Parmer type N-1110, China). The *Anacardium occidentale* extract (AOE) was refrigerated at 4 °C till use.

### Experimental Animals

Sixty (60) albino Wistar rats of both sexes (110 - 115 g) and one rabbit (2.2 kg) were used for the study. The animals were housed in wire-mesh rodent cages and fed *ad libitum* with pelleted feed (Vital Feed®) and water except when fasting were required. The experimental protocol was approved by the institutional Animal Ethics Committee, and the animals were handled with reference to the Guide for the Care and Use of Laboratory Animals of National Research Council (National Research Council, 2010).

Acute toxicity test

The toxicity study of AOE was conducted as per 425 guideline of OECD (Organization of Economic Co-operation and Development) and limit dose of 2000 mg/kg in rats (OECD, 2008).

Ethanol Induced gastric ulcer in Rats

The effect of AOE on ethanol induced gastric ulcer was evaluated in 25 rats (n = 5) fasted for 48

hours as described by Sahoo *et al.* (2016). The AOE was tested at 100, 200 and 400 mg/kg while distilled water and omeprazole 20 mg/kg were used as the negative and positive controls, respectively. After 1 hour of the treatments, 1 ml of absolute ethanol was orally administered to each rat and 2 hour later, the rats were sacrificed by cervical dislocation and stomach was opened along the greater curvature, washed with running tap water and the mucosa was examined for lesion. The severity of ulceration, ulcer index and percentage ulcer protection were calculated.

Ulcer index ($U_I$) = ($U_N$ + $U_S$ + $U_P$) × 1/10

Where, $U_N$ = average number of ulcer per animal, $U_S$ = average severity score, $U_P$ = percentage of animal with ulcer and $U_I$ = ulcer index.

The percentage ulcer inhibition (PUI), was determined using the formula:

$$PUI = \frac{UI\ (control) - UI\ (Treatment)}{UI\ (control)} \times \frac{100}{1}$$

Indomethacin induced gastric ulcer in rats

The effects of AOE on indomethacin induced gastric ulcer were evaluated in 25 rats (n = 5) fasted for 48 hours as described by Adinortey *et al*. (2013). The AOE was tested at 100, 200 and 400 mg/kg while distilled water and misoprostol 50 µg/kg were used as the negative and positive controls, respectively. One hour post treatments, indomethacin 25 mg/kg was orally administered to each rat and 4 hour later, the rats were sacrificed by cervical dislocation. The stomach was ligated both end and inflated with 2 ml of 1% formalin and preserved in same overnight. Later stomach was opened along the greater curvature, washed tap water and the mucosa was examined for lesions. The severity of ulceration, ulcer index and percentage ulcer protection were calculated as aforementioned.

**Histopathological Evaluation**

The stomach tissues were harvested from rats and fixed in 10% formal saline, embedded in paraffin, sectioned and stained with hematoxylin and eosin. The histological slides were evaluated by light microscopy (Yu *et al*., 2015).

**Effects of AOE on Isolated Rabbit Jejunum**

The effects of AOE on the rhythmic contraction of isolated rabbit jejunum was tested at final bath concentration (FBC) of 0.10 – 0.80 mg/mL. The inhibitory effects of AOE on histamine induced contraction of the isolated jejunum were also evaluated. The Tyrode solution was prepared as described by Vadivel *et al*. (2017) while the rabbit jejunum isolation as well as setting up of the physiography recorder (Medicaid Physiopac, India) were as reported by Ibeh *et al.* (2017).

**Statistical Analysis**

Data obtained were presented as mean ± SEM and analysed using one-way-analysis of variance (ANOVA) and post-hoc comparisons were carried out using either Dunnett's t-test or the Kruskal-Wallis test (where appropriate) on SPSS version 4.05. Values of $P < 0.05$ were considered significant in the study.

## RESULT

**Acute toxicity test**

The extract was well tolerated by the rats up to 2000 mg/kg. The $LD_{50}$ of AOE was therefore greater than 2000 mg/kg.

**Antiulcer Activity**

The extract produced significant ($p < 0.05$) dose-dependent decrease in ulcer score and index in treated rats in both ethanol-induced (Table I) and indomethacin-induced (Table II) ulcer models relative to the distilled water treated group. The AOE produced its optimum activity at 400 mg/kg dose. The activities of AOE were comparable to the activities of the reference drugs used in both models.

The effects of AOE on the histopathological lesions induced by ethanol and indomethacin in the stomach

The histopathological sections of ethanol-induced gastric ulcer is presented in Plate 1. The distilled water treated group (A) showed large and deep ulcer that reached the submucosa while the AOE 100 and 200 mg/kg treated group (C

**TABLE I: Effects of AOE on ethanol-induced gastric ulcer**

| Treatment | Number of ulcers | ulcer score | ulcer index | % protection |
|---|---|---|---|---|
| Distilled water, 5 ml/kg | 14.25 ± 2.06 | 23.75 ± 3.47 | 13.80 ± 0.53 | - |
| Omeprazole, 20 mg/kg | 1.25 ± 1.25* | 1.25 ± 1.25* | 2.75 ± 0.25* | 80.07 |
| AOE, 100 mg/kg | 3.25 ± 1.89* | 3.50 ± 2.02* | 5.68 ± 0.39* | 58.84 |
| AOE, 200 mg/kg | 0.25 ± 0.25* | 0.25 ± 0.25* | 2.55 ± 0.05* | 81.52 |
| AOE, 400 mg/kg | 0.00 ± 0.00* | 0.00 ± 0.00* | 0.00 ± 0.00* | 100 |

*p < 0.05 relative to the distilled water treated group; AOE = *Anacardium occidentale* extract

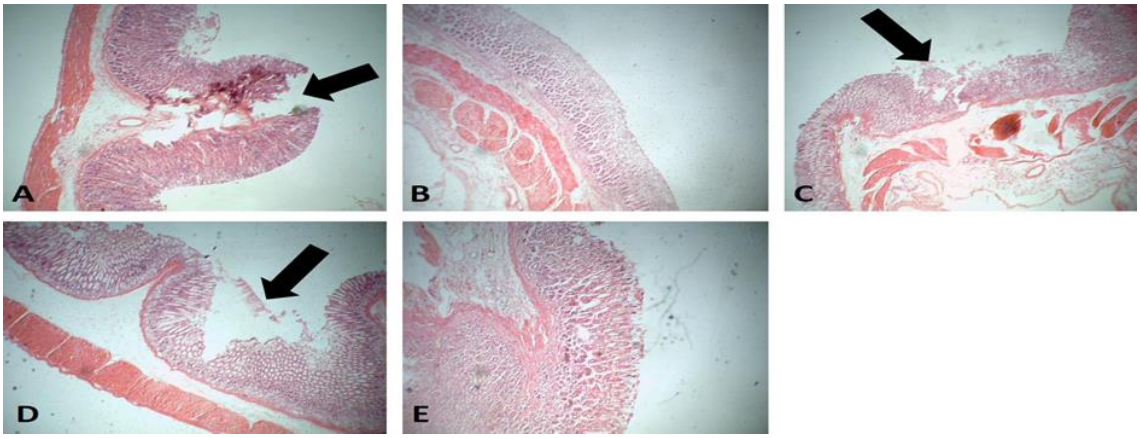


**Plate 1: Histological sections (H & E, x40) of stomachs of ethanol-induced gastric ulcer in rats**
Legend: The arrow shows area of ulceration; A = distilled water treated group; B = omeprazole, 20 mg/kg treated group; C = AOE 100 mg/kg treated group; D = AOE 200 mg/kg treated group; E = AOE 400 mg/kg treated group.

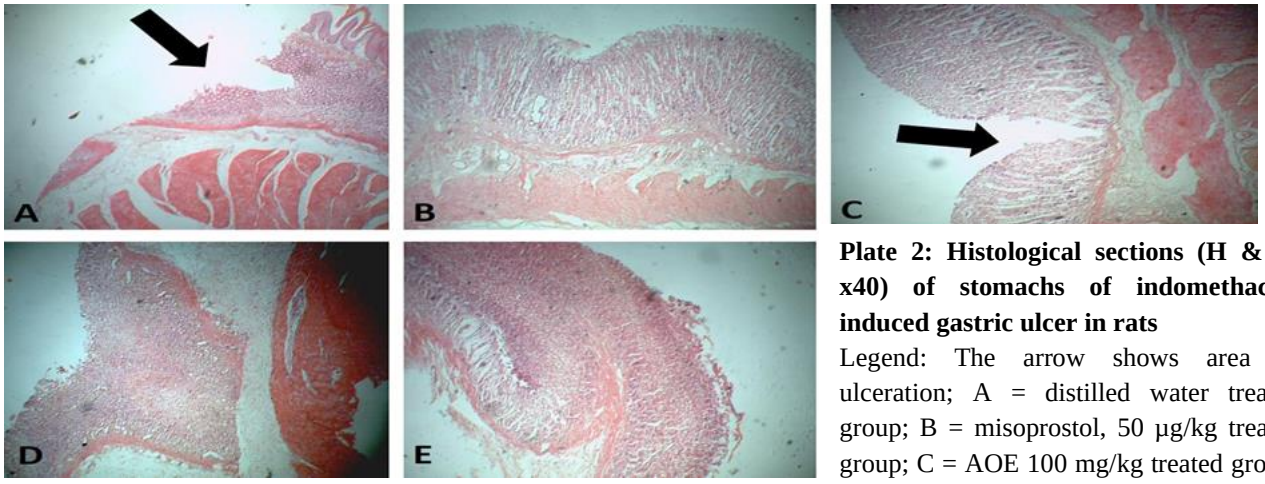


**Plate 2: Histological sections (H & E, x40) of stomachs of indomethacin-induced gastric ulcer in rats**
Legend: The arrow shows area of ulceration; A = distilled water treated group; B = misoprostol, 50 µg/kg treated group; C = AOE 100 mg/kg treated group; D = AOE 200 mg/kg treated group; E = AOE 400 mg/kg treated group.

**TABLE II: Effects of AOE on indomethacin-induced gastric ulcer**

| Treatment | Number of ulcers | ulcer score | ulcer index | % protection |
|---|---|---|---|---|
| Distilled water, 5 ml/kg | 6.75 ± 1.31 | 15.00 ± 4.26 | 12.18 ± 0.54 | - |
| Misoprostol, 50 µg/kg | 3.25 ± 1.25* | 5.25 ± 2.78* | 5.85 ± 0.40* | 51.97 |
| AOE, 100 mg/kg | 1.50 ± 0.96* | 3.00 ± 1.91* | 5.45 ± 0.29* | 55.25 |
| AOE, 200 mg/kg | 1.50 ± 1.19* | 2.25 ± 1.65* | 5.38 ± 0.28* | 55.83 |
| AOE, 400 mg/kg | 1.00 ± 0.58* | 1.50 ± 0.87* | 5.25 ± 0.14* | 56.89 |

*$p < 0.05$ relative to the distilled water treated group; AOE = *Anacardium occidentale* extract

and D) showed shallow area of ulceration that is within the mucosa layer. The omeprazole 20 mg/kg (B) and AOE 400 mg/kg (E) treated groups showed no ulcer lesion.

The histopathological section of indomethacin-induced gastric ulcer is presented in Plate 2. The distilled water treated group (A) showed large and deep ulcer that reached the muscularis layer while the AOE 100 mg/kg treated group (C) showed shallow area of ulceration that is within the mucosa layer. The misoprostol 50 µg/kg (B), AOE 200 and 400 mg/kg (D and E) treated groups showed no ulcer lesion

Effects of AOE on isolated rabbit jejunum

The AOE relaxed rhythmically contracting isolated rabbit jejunum in a concentration dependent manner (Plate 3). It also inhibited histamine induced contraction of the smooth muscle in a concentration dependent manner. The histamine induced contraction was totally blocked at higher concentration of AOE, 0.80 mg/mL (Plate 4).

## DISCUSSION

The methanol extract of *Anacardium occidentale* leaf elicited gastroprotective effects against ethanol and indomethacin induced gastric injury in rats. It also relaxed spontaneously contracting isolated rabbit jejunum and blocked histamine induced contraction of intestinal smooth muscles. Ethanol causes cell death and exfoliation of gastric mucosa via increased membrane permeability to sodium and water as well as intracellular accumulation of calcium (Khare *et al*., 2008). It stimulates gastric acid secretion, enhance free radical release, down-regulate bicarbonate secretion and deplete the protective mucus and makes the gastric mucosa prone to the destructive effects of pepsin and hydrochloric acid leading to gastric ulceration (Adinortey *et al*., 2013). The reduced ulcer lesion in the AOE treated groups implies that, it may have impaired any of the processes through which ethanol produced gastric ulceration and it possess gastroprotective properties. The antiulcer activities of AOE might be via the inhibition of proton pump or scavenging of free radicals (Cuevas *et al*., 2011). Antioxidants scavenge free radicals and enhance membrane stability, thus protecting against cellular injury (Morais *et al*., 2010). The antioxidant activities of *A. occidentale* leaf has been reported (Ajileye *et al*., 2015). Proton pump inhibitors, omeprazole, impairs $H^+$ ion release by the parietal cell, thus reducing gastric acidity and mucosa damage (Jackson *et al*., 2015).

Indomethacin induced ulcer is linked to the inhibition of cyclooxygenase activities which leads to reduced prostaglandin, mucus and bicarbonate production as well as impaired blood flow and platelet aggregation (Adinortey *et al*., 2013). Indomethacin can also cause direct death of epithelial cells via osmotic lysis and/or uncoupling of oxidative phosphorylation (Djahanguiri, 1969). The AOE treated groups had reduced ulcer lesion which indicates that it may have impaired the processes through which

indomethacin produced gastric ulceration and it possess gastroprotective properties. Another possible mechanisms of the gastroprotective activity of AOE are; stimulation of prostaglandin, mucus and bicarbonate production (Amang *et al*., 2014). Misoprostol, synthetic prostaglandin, drastically inhibit gastric acid secretion, and stimulate mucus and bicarbonate secretion and the extract might have acted in similar manner (Konan and Bacchi (2007) and Morais *et al*. (2010). Our findings were in agreement with the reports of Konan and Bacchi (2007) and Morais *et al*. (2010) on the antiulcer activity of *Anacardium occidentale* leaf.

The extract inhibited histamine induced contraction of the rabbit jejunum smooth muscle. This suggests that the extract could be a $H_2$-receptor antagonist. The $H_2$-receptor antagonist, cimetidine, inhibit gastric acid production from the parietal cell and are used as antiulcer drugs (Konan and Bacchi, 2007).

The antiulcerogenic activity of AOE reported in this study is in agreement with previous report on the antiulcerogenic activity of ethanol extract of cloned *A. occidentale* leaf in Brazil (Konan and Bacchi, 2007; Morais *et al*., 2010). This suggests that cloning and the environmental conditions did not affect the composition of the phytoconstituent responsible for the antiulcerogenic activity. The gene and environmental interplay influence the phytochemical composition and biological activities of plant products (Kalt *et al*., 2001).

In conclusion, *A. occidentale* leaf demonstrated appreciable gastroprotective activity and the study authenticates the folkloric use of cashew leaf in the management of ulcer. The possible mechanisms of the gastroprotective activity are the inhibition of $H_2$-receptor and proton pump as well as the stimulation of prostaglandin production and scavenging of free radicals.

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