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Effect of Aqueous Extract of the Bark of *Entandrophragma utile* in Acute Gastric and Duodenal Ulcer Models

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Abstract

Purpose: The bark of *E. utile* is claimed in Nigerian traditional medicine to have antiulcer properties. We therefore tested its effectiveness in experimental acute gastric and duodenal ulcer models.
Methods: Ulcers generated as lesions, from pin-point craters to larger eruptions, were quantified qualitatively for cold-restraint, immobilization, pylorus ligation, and aspirin induced gastric ulcers and for histamine or cysteamine induced duodenal ulcers. Ethanol or histamine induced hemorrhagic gastric lesions were quantified by planimetry and a dose-related effectiveness of the aqueous extract of *E. utile* was determined. Data were compared using Student's t-test. At 95% confidence interval, any 2-tailed p value <0.05 was considered significant.
Results: Using qualitative evaluation, the extract of *E. utile* or standard drugs (cimetidine, ranitidine, or nocloprost) did not significantly reduce gastric ulcer incidence and/or ulcer severity. *E. utile* was ineffective for duodenal ulcers. Using the quantitative methods, histamine, 5 mg kg^{-1} i.p. in guinea pigs produced 100% incidence of gastric ulcers with a mean ulcer index (UI) of 55.4 ± 8.38. In this model, 100 mg kg^{-1} cimetidine lowered the incidence to 60% and the UI to 17 ± 9.9 ($p<0.0005$) while 5 x 10^{-3}g kg^{-1} *E. utile* lowered the incidence to 80% and the index to 15.88 ± 11.8 ($p<0.01$). Similarly 1 ml absolute ethanol given orally in rats produced 100% incidence and UI of 49.2 ± 12.69. In this model, 100 µg kg^{-1} nocloprost reduced the incidence to 33% and the mean UI to 10.15 ± 0.55 ($p<0.01$); *E. utile* (50 mg kg^{-1}) prevented ethanol induced hemorrhagic gastric mucosal damage ($p<0.005$).
Conclusion: *E. utile* protected the gastric mucosa against acute noxious assault.

Keywords: Peptic ulcer, anti-ulcer, *E. utile*

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Introduction

Peptic ulcer disease is a product of aggressive factors acting on normal or compromised gastrointestinal mucosa. In the last decade, renewed interest in the disease is actually due to the need to remedy the side effects of aspirin, a potent and effective cardiovascular tonic, especially useful for elderly patients. Aspirin causes severe and disturbing gastrointestinal mucosal damage [1-3] in the stomach, duodenum and colon and physicians and biomedical

scientists are keen on finding prophylactic drugs against this dangerous side effect of such a valuable drug. Aspirin, like other non-steroidal anti-inflammatory pain killers such as indomethacin, inhibits the production of cytoprotective prostaglandins [4,5] thereby compromising mucosal defense. Experimental ulcers in rats have been generated with these drugs.

Mucosal defense in people may also be compromised by stress which causes gastric hypersecretion of hydrochloric acid and pepsin. Restraint or immobilization stress and cold-restraint stress have been used to generate ulcers in laboratory animals. Another experimental model uses pylorus ligation to accumulate gastric acid and pepsin in the stomach to simulate hypersecretion. Hypersecretion in disease patients may be induced by secretagogue action such as excessive coffee drinking. Histamine is a secretagogue [6]. It is released from mast cells during stress-induced mast cell degranulation [7] and has been used to differentially generate gastric and duodenal ulcers in rodents. In this report, various models based on these factors were used to test the prophylactic effectiveness of an aqueous bark extract of *Entandrophragma utile* which is used in Nigerian traditional medicine as an antiulcer agent. Traditionally, the aqueous bark extract has been used to treat gastrointestinal ulcers and the dried pulverized bark has been used to treat leg ulcers but any antiulcer effectiveness of the bark was not scientifically published before John and Onabanjo [8]. Further studies testing the aqueous bark extract of *E. utile* in the healing process of established experimental chronic gastric and duodenal ulcers showed that the gastric ulcer incidence and index were reduced by the *E.utile* extract or nocloprost ($p > 0.45$ in either case) [9]. Similar results were obtained for duodenal ulcer with the extract matched against cimetidine [9]. In other studies, gastric antisecretory property of the extract was established with statistical significance indicating the extract could be developed as adjunct therapy to minimize aggravation of mucosal damage by acid-peptic autodigestion [9]. In the present report, this prophylactic potential is further investigated in acute gastric and duodenal ulcer models.

Materials and Methods

Preparation of *E. utile* extract

The fresh bark of *E. utile* was collected for us by Chief Felix O Esho, a traditional medicine practitioner, who identified an *E. utile* tree in its natural habitat at Ojokoro, Lagos State of Nigeria. The botanical profile was confirmed at the Forestry Research Institute of Nigeria, Ibadan and the tree was identified by a taxonomist, Dr MO Soladoye. The institute displays herbarium sheets FHI 86848, FHI 50264 and FHI 9155 containing specimen from *E. utile*. The bark was sun-dried to constant weight and the aqueous extract was prepared as previously described following the boiling and decanting method of traditional healers [9].

Animals

Sprague-Dawley rats and guinea-pigs used in these studies were obtained from the Laboratory Animal Center (LAC), College of Medicine, University of Lagos (CMUL) and were utilized according to the ethical approval by the LAC. Test and control animals were acclimatized to the lab conditions simultaneously. They were used in experiments with weight and sex matched for controls and tests. They were starved for 24h before experiments.

Investigation of *E. utile* in the cold-restraint acute gastro-duodenal ulcer model

Rats were fasted for 24h before experiments. Ten rats were used to confirm the gastro-duodenal ulcer-generating effectiveness of the model as follows. The method used was that of Singh [10]. The rats were each put separately in a tightly fitting cylindrical tube of non-flexible medium mesh wire gauze, taking care to prevent respiratory collapse and then placed in a cold room at 4 ^{o}C for 24 h. They were then removed and immediately sacrificed using ether (May and Baker, Dagenham, England). All the animals were opened up by an incision in the left ventral body wall from the mid-abdomen to the rib cage out-line. The stomach was identified below the

liver and carefully excised with 6cm of duodenum. The excised stomach was dissected along the greater curvature after which the luminal environment was examined. The lumen was flushed properly with distilled water and pinned flat along the cut edges on to a dissecting board. Few drops of formalin (BDH, Poole, England) were used to fix the tissue. The degrees of ulcerations were noted for animals in this control ulceration group. The model was then used to test the antiulcer effect of feeding and *E. utile* extract respectively. Ten test rats were given water and food (Pfizer, Nigeria) 30 min before the cold-restraint was applied [10]. In another set, 15 rats were administered orally with 1.0ml of the extract containing 1.0g kg^{-1} 30min before applying cold-restraint as above. The animals were similarly sacrificed and examined.

Investigation of *E. utile* in immobilization induced gastric ulceration

A constructed plastic compartment was used to confine each rat and to prevent movement during 48h after which the rat was sacrificed. Ten animals were used to test the effectiveness of the model in generating gastric ulcers. Then six rats were given 100mg kg^{-1} cimetidine (Smith, Kline and French, Nigeria) orally in 1 ml distilled water [11] 30 min before they were immobilized. Similarly, ten rats were administered 1.0ml of 1.0g kg^{-1} of the extract orally 30 min before immobilization. The rats were sacrificed and examined after 48 hr.

Investigation of *E. utile* in pylorus ligation gastric ulcer

The pylorus of each animal used was ligated under ether anesthesia according to the method of Shay *et al.*, 1954 [12]. Each rat was given 5ml physiological saline (0.9% NaCl, BDH, Poole, England) subcutaneously (s.c.) post-operation [13]. The saline given was to counteract the effect of blood loss during operation. The animal was left for 8h and thereafter sacrificed and the stomach examined as above. To confirm the effectiveness of the model, three rats were used. The model was then used to test the antiulcer effect of anti-ulcer drug ranitidine (Glaxo Nigeria) or *E. utile* extract. After ligating the animals at the pylorus, they were given a dose as they recovered from anesthesia according to the procedure of Prino *et al* [14]. Eight rats were each given 8.0mg kg^{-1} ranitidine in 0.5ml s.c. plus 0.5ml 0.9% NaCl by oral cannulation. Each of the ten rats in a group was administered 10 x 10^{-3} g kg^{-1} extract orally in 0.5ml. The animals were sacrificed 8 h post ligation.

Investigation of *E. utile* in aspirin-induced gastric ulceration

In this experiment, rats were surgically prepared as described by Konturek *et al* [15]. After the surgery, each animal was left for 15 min and then given a constant infusion of 40mg kg^{-1} h^{-1} of aspirin (Sigma, St. Louis, U.S.A.) for 1h through the superior vena cava. Gastric perfusion with 0.15 M HCl (BDH, Poole, England) through the inserted polyethylene tube was carried out at a rate of 4ml h^{-1}. At the end of 3h, each animal was sacrificed and examined as above. Groups of six fasted rats were operated on as described [15]. In one group, nocloprost was perfused s.c. at a rate of 100 ng kg^{-1} h^{-1} and this was continued throughout the 3 h aspirin infusion period. In the second group the extract at a rate of 2.0 x 10^{-3}g kg^{-1} h^{-1} was perfused orally for 30min before giving aspirin and HCl. The animals were then sacrificed and examined.

Investigation of *E. utile* extract in necrotizing substances-induced gastric ulceration

In a preliminary study, male rats were used in groups of ten. The method of Robert (1979) [16] was used. A constant volume (1 ml) of each of the test substances, absolute ethanol (May and Baker, UK), 0.2 N NaOH (Merck, Darmstadt, Germany), 25% NaCl or 0.6N HCl was given separately, all orally to each group of the animals. They were sacrificed an hour later and the stomachs were examined for ulcer. The ethanol model was chosen to test the effect of *E. utile* extract because it produced 100% incidence and accurately quantifiable ulceration and was suitable for a dose-effect evaluation of the *E. utile* extract. Rats were fasted and dosed orally in groups of N = 6 - 10. The animals each received 100 μg kg^{-1} nocloprost in 0.6ml respectively 30min before ethanol administration or 0.5 x 10^{-3}

g kg^{-1}, 1 x 10^{-3} g kg^{-1} or 50 x 10^{-3} g kg^{-1} of *E. utile* respectively in 0.5ml 2h prior to ethanol administration and all were sacrificed 2h after being given ethanol and examined.

Investigation of *E. utile* in histamine-induced gastric ulceration model

The method used for induction of ulcer was that reported by Eagleton and Watt [17]. Male fasted guinea-pigs (5) were used, one serving as the control. Histamine acid phosphate (BDH, U.K) in aqueous solution of 1mg ml^{-1} was injected i.p. in doses of 5mg kg^{-1}. The guinea-pigs were killed 1 hour after dosing and examined as before. Two groups of five fasted guinea-pigs were given 1.0ml 100mg kg^{-1} cimetidine or 5 x10^{-3}g kg^{-1} extract at 1h and 0.5h respectively orally prior to histamine administration [17].

Investigation of *E. utile* in histamine-induced duodenal ulceration

In the control ulceration group, five fasted male guinea-pigs were used and the experiment was carried out as described [17]. A dose of 0.25mg kg^{-1} of histamine acid phosphate in solution was given intramuscularly (i.m.) every 0.5h for 4h (8 times). The animals were sacrificed 0.5h after the last administered dose and examined as above. Two groups of four and five fasted guinea-pigs were respectively given 40mg kg^{-1} ranitidine in 1.0 ml saline i.p. and 50 x 10^{-3}g kg^{-1} extract orally in 1.0ml, 0.5h and 1h prior to histamine administration [17]

Investigation of *E. utile* in cysteamine-induced duodenal ulceration.

In accordance with the method of Szabo *et al* [18], oral lavage of 280 mg kg^{-1} cysteamine (BDH, England) in 0.5 ml deionized water was done every 3h in divided doses. Groups of ten fasted rats were used. In one group, 50mg kg^{-1} cimetidine suspended in 0.5ml water was administered by oral cannulation 1h before the doses of cysteamine were given [18]. In another group, a single dose of 50 x 10^{-3} g kg^{-1} extract in 0.5ml was similarly given orally. In another group, 50 x 10^{-3} g kg^{-1} extract in 1ml was given in three divided doses through the same route 30 min prior to each dose of cysteamine. The experiments were completed by sacrifice of the animals and examination of the duodenums.

Qualitative evaluation of ulcer index

From the preliminary investigation carried out, it was observed that not all ulcerations obtained could be assessed quantitatively especially duodenal ulcer in which patches or tiny craters were seen. In such cases, the degree of ulceration was determined visually as previously described [19]. A scoring of 1 to 10 was applied. Zero (0) denotes no ulcer formation. Superficial ulcer or erosion was scored 1 for each formed. Transmucosal necrosis was scored 2 and perforated or penetrated ulcer was scored 10 for each formed. Total scores were calculated per animal.

Quantitative determination of ulcer index

The induced ulcerations in the excised stomachs were compared with stomachs of controls for each of the investigations made and the indices were calculated by planimetry as reported earlier [9]. Plastic transparencies graduated in mm^2 were made by photocopying of graph sheets onto transparencies. Small graduated transparency sheets of about 2 square inches (Figure 1) were used to trace the surface area of the stomach as well as the damaged area. The ulcer index (UI) was calculated as area of mucosal damage (DA)

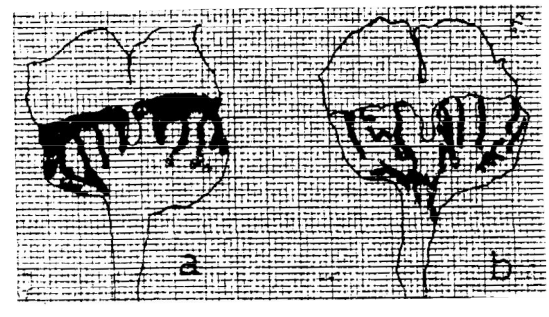

Figure 1: Graduated transparent film used to calculated ulcer index (UI). In this case UI was 40.4% for (a) and 30.6% for (b).

over total area of glandular mucosa (TA) times 100% (i.e. (DA/TA) x 100%). This quantification

was used for necrotizing agents and histamine-induced gastric ulcers.

Histopathological examinations

Small pieces of tissues taken at autopsy were fixed in 10% formol saline. The tissues were dehydrated through alcohol series, cleared in chloroform and finally embedded in paraffin wax (m.p. 56^0C). They were sectioned on a rotary microtome (R. Jung, Heidelberg, Germany) and dried in an oven for 12h at 56^0C. Sections were deparaffinised by placing them in xylene for 2min, taking them through haematoxylin for 10min and they were finally washed and blued in tap water. Counter-staining was carried out with 1% aqueous eosin, and the specimen were dehydrated in alcohol, cleared in xylene and mounted in xam. Sections were examined and compared for any evidence of histopathological changes.

Results

Effects of standard drugs and *E. utile* extract on ulceration

Table 1 shows the ulcer incidences and the ulcer indices of control animals and animals given standard treatments or the test extract of *E. utile* bark for various ulcer models as described in the Methods above. The experiments testing different models for producing gastric and duodenal ulcers show two types of damage. One type manifests as a few or many small areas of damage which generally were as small as pin-point craters seen with the aid of a magnifying glass to lesions of about 3mm.[2] These were produced by cold-restraint, immobilization, pylorus ligation, and aspirin. The photomicro-graphs of normal rat stomach and a severe gastric ulcer crater following aspirin dosage are provided in Figure 2 (A and B). Morphological examinations revealed a protective effect of *E. utile.* Figure 2 (C and D) shows the stomach of a rat protected by the extract with similar morphology to a control. In these qualitative models, where the *E.utile* extract reduced ulceration, the effects were not statistically significant. The other type of ulceration manifests as wide transmucosal hemorrhagic gastric lesions that were traced and measured quantitatively. These were produced by all necrotizing agents: absolute ethanol, 0.2 N NaOH, 25% NaCl or 0.6N HCl as well as by histamine. Figure 3 shows both incidences and ulcer indices for the ethanol model. *E. utile* extract produced a dose-dependent anti ulcer effect. The composite Figure 4 shows a superficial ethanol-induced erosion and leucocytes infiltration of the mucosa and submucosa (lower left). Figure 4 compares normal glandular mucosa (upper left) with identical regions in an ethanol assaulted stomach (middle) and in a stomach protected by *E. utile* extract before ethanol assault (right). *E. utile* prevented the extravasation of erythrocytes and damaged glandular structure seen in the stomachs administered with ethanol alone (middle). Stomachs of rats pretreated with *E. utile* extract did not develop hemorrhagic lesions but were

Table 1: Effects of standard drugs or *E. utile* extract on experimental gastro-duodenal ulcers of various etiologies. Values depict ulcer incidences as percentages and ulcer indices as means.

Ulcer model	Treatment		
	Control	Standard	*E.utile*
Qualitative			
Cold-resistant, gastroduodenal in rat	50%, 2.23.2	Feeding, 40%, 1.9±3.6, p>0.05	21.6%, 2.8±13, p>0.35
Immobilasation, gastric in rat	50%, 1±0.2	Cimetidine: 0%, 0, p>0.49	0%, 0, p>0.35
Pylorus ligation, gastric in rat	90%, 2.15±1.53	Ranitidine: 0%, 0, p<0.01	30%, 1.3±2.48, p>0.035
Aspirin, gastric in rat	80%, 5.38±4.32	Nocloprost: 20%, 0.31±0.67, p>0.25	40%, 1.08±1.62, p>0.02
Histamine, duodenal in guinea-pig	100%, 2.0±0.43	Ranitidine: 20%, 0.2±0.4, p>0.35	40%, 2.0, p>0.3
Cysteamine, duodenal in rat	80%, 1.8±1.2	Cimetidine: 79%, 1.4±1.02, p>0.1	100%, 1.6±0.46, p>0.35
Quantitative			
Ethanol, gastric in rat	100%, 49.2±12.69	Nocloprost: 33%, 10.15±0.55, p<0.01	0%, 0, p<0.005
Histamine, gastric in guinea-pig	100%, 55.4±8.38	Cimetidine: 60%, 17±9.9, p<0.0005	80%, 15.88±11.8, p<0.01

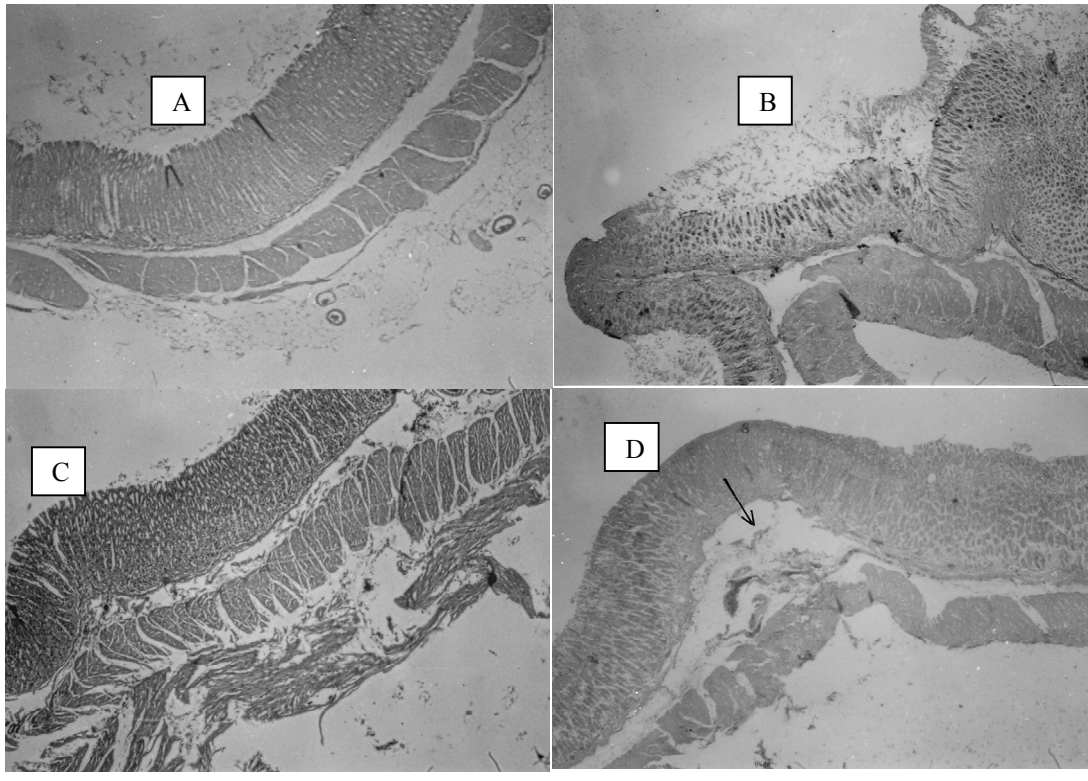

Figure 2: Photomicrographs (x100) of normal rat stomach (A) and severe gastric pathology following aspirin dosage (B) as well as transverse section through ruggae of rat stomachs showing control stomach (C) and stomach protected by administration of *E. utile* extract before ulcerogenic aspirin treatment indicating slight edema (arrow) and no severe damage (D).

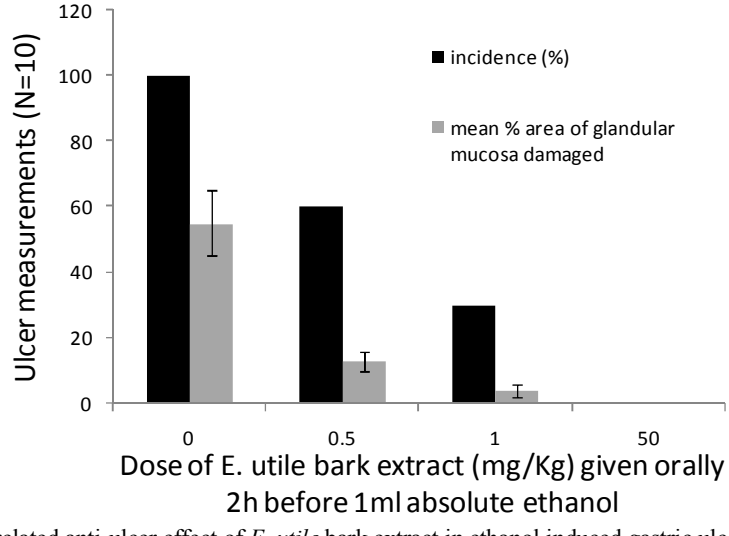

Figure 3: Dose related anti-ulcer effect of *E. utile* bark extract in ethanol induced gastric ulceration.

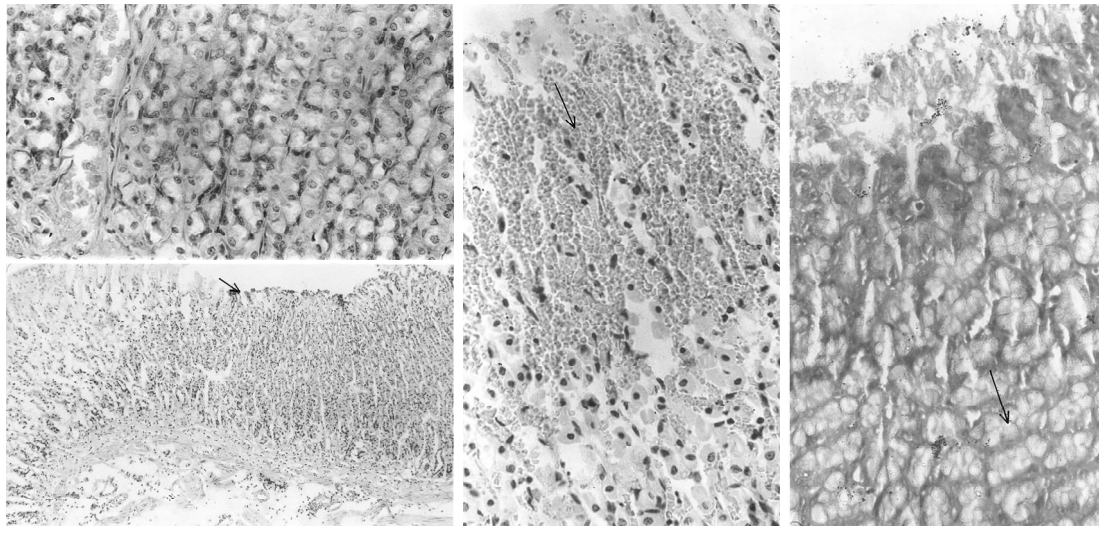

Figure 4: Photomicrographs of surface mucus glands of rat stomach sections showing: normal glandular structure of control rat (upper left); an ethanol induced lesion penetrated to the surface glands with massive leucocytes infiltration of the submucosa (x400) (lower left);hemorrhagic lesion of ethanol treated rat with extravasation of erythrocytes and glandular damage (middle); *E. utile* pretreated rat stomach that was resistant to ethanol damage, had a supra-epithelial covering of precipitated mucus and debris and subepithelial dilated mucus loaded glands (right).

stained brown by the extract. Enhanced production of mucus was observed in the swollen glands of *E.utile* treated rat stomachs and a supraepithelial mucus-debris film was deposited (Figure 4, right).

Discussion

The data above shows that *E.utile* extract protected rat stomachs from acute assault by the noxious agent absolute ethanol and its effectiveness was statistically comparable to that of the cytoprotective prostaglandin nocloprost, significance level being $p<0.01$ in both cases (Table 1). In this model, neither cimetidine (antisecretory agent) nor carbenoxolone (mucogenic agent) prevented damage caused by ethanol assault (data not shown). Figure 4 shows that the extract enhanced mucus secretion and produced a covering made of precipitated mucus on the mucosa. In contrast to carbenoxolone, the effect of *E. utile* appears to be "murogenic" (producing a wall or barrier) rather than simply "mucogenic" producing mucus.

Duodenal and gastric ulcers appear to have different predisposing factors and in this investigation *E. utile* extract appears not to be effective in acute duodenal ulceration models (cold-restraint induced in rats, histamine induced in guinea-pigs, or cysteamine induced in rats). However in the cold-restraint and cysteamine models standard treatments also did not have any effect (Table 1). In the histamine acute duodenal ulcer model, ranitidine (antisecretory agent) protected the rats by both a fall in incidence and a fall in mean ulcer index but the data lacked statistical significance. In a separate study using a chronic duodenal model induced by cysteamine, either *E.utile* extract or cimetidine gave reduction of ulcer index without statistical significance ($p>0.45$) [20]. What can be drawn from these data is that these models are not reliable for testing an unknown agent when used in populations of N = 10 or lower. The high variation of pathology from animal to animal requires that a very large N be used which means sacrificing many animals (hypervivisection). To avoid this, for duodenal ulcers, perhaps antisecretory studies would be more useful in determining the effectiveness of an unknown anti-ulcer agent, acid autodigestion being a recognized predominant component of the pathological process.

For the gastric ulcers, clearly the quantitative determinations were more testable by statistics than the qualitative determinations. This investigation revealed that the immobilization, pylorus ligation, and aspirin models which require qualitative measurement also need a high N for statistical testing. Even when the standard treatments or the extract gave obviously large falls in scores, these had no statistical significance. Because of large individual variations (and high standard errors of means), the qualitative acute models could not be reliably used to test any dose related effect of the *E. utile* extract. A similar result was obtained for chronic gastric ulcers induced by local injection of acetic acid in rat stomachs; reduction either by *E. utile* or nocloprost was not statistically significant ($p>0.45$) [20].

The quantitative methods, using ethanol or histamine in groups of N=10 or less, gave statistically reliable results and indicated that the *E. utile* extract had protective function. The experiments with necrotizing agents was continued with ethanol as the most consistent and reproducible model. For both the ethanol and histamine models, the degrees of ulceration were generally similar between animals in the same group and this was reflected in the low standard errors of means. Because of the predictability of ulceration seen as 100% incidence and a control ulcer index of 49.2±12.69 mucosal damage, the ethanol model was used to investigate a dose dependency of the antiulcer effect of *E. utile*. In the ethanol model, complete protection against formation of hemorrhagic lesions was observed; both the incidence and the mean ulcer index were zero. In the histamine model, *E. utile* extract, similar to the standard drug cimetidine, did not completely remove the incidence of ulceration but gave a significantly drastic fall in mean ulcer index ($p<0.01$).

Histological findings revealed that the extract may stimulate endogenous mucosal defense mechanisms because, in rats pretreated with the extract, the mucous glands were dilated (Figure 4) and excess mucus was found in stomach lumen, some of it being precipitated by natural chemicals in the extract to form a protective coat on the epithelial surface of the mucosa (Figure 4, right). This was considered a "murogenic" (wall or barrier forming) defense property and is in consonance with the claim of Nigerian traditional healers that the aqueous bark extract of *E. utile* has anti-ulcer property. While these observed mucogenic and murogenic effects of *E.utile* extract are intriguing, there appears to be an additional anti-ulcer property of *E. utile*. The aqueous bark extract of *E.utile* appears to have gastric acid antisecretory properties [21,22].

Conclusion

The aqueous bark extract of *Entandrophragma utile* shows gastric protective property against acute noxious attack to the mammalian gastric mucosa.

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Contribution of Authors

We declare that this work was done by the author(s) named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. AOO conceived and supervised the study, TAJ designed the study, collected, analyzed the data, and prepared the manuscript while HA reviewed the manuscript. All authors mentioned in the article approved the manuscript.

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