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Research Article

Effects of Extracts of *Daucus carota* and *Brassica oleraceae* on Ethanol-induced Gastric Ulcer

Oyinloye O.E[1], Olooto W.E[2], Kosoko A.M[3] Alabi A.A[1], Udeh A.N[1]

[1]*Department of Pharmacology, Olabisi Onabanjo University, Ago-Iwoye, Nigeria*
[2]*Department of Chemical Pathology and Immunology, Olabisi Onabanjo University, Ago-Iwoye, Nigeria*
[3]*Department of Biochemistry, College of Biosciences (COLBIOS). Federal University of Agriculture Abeokuta (FUNAAB), Nigeria*

ABSTRACT

Disruption of gastric mucosal integrity occurs due to imbalance between defensive and offensive factors. This requires treatment using pharmacological agents to reduce the burden. The associated drug adverse effects attract research into crude plant materials and plant products from which active compounds with promising therapeutic results can be obtained. Phytochemical screening of *D. carota* and *B. oleraceae* extract were done. Forty-eight Wistar strain rats, age 8-10 weeks, weighing 100g–152g, were acclimatized for 14 days after which they were fasted for 10-12h and given 1ml of 90% ethanol/100g body weight orally to induce gastric ulceration. Extract of *D. carota* and B. oleraceae were administered orally for fifteen days after which the rats were sacrificed and stomach harvested. Phytochemical screening showed that both *D. carota* and *B. oleraceae* contain tannin, cardiac glycoside. Stomach tissue antioxidant levels showed a non-significant increase in GSH ($p = 0.21$); a significant increase in SOD and CAT ($p = 0.000, 0.000$); and a significant decrease in MDA, GPx, and GPR ($p = 0.000, 0.002, 0.000$) in the treated groups. *B. oleraceae* extract demonstrated a 25.7% cure, *D. carota* extract showed 56.6% cure while combined *B. oleraceae* and *D. carota* extracts showed 70% cure rate. Modifications of gastric mucosal damage by the administered extracts were revealed histopathologically. It could be concluded that extract of *D. carota* and *B. oleraceae* singly or in combination exhibited antiulcer activities in ethanol-induced gastric ulceration and showed some synergism in the management of gastric ulcer.

Keywords: *Daucus carota, Brassica oleraceae, ethanol, antioxidants, gastric ulcer*

*Author for correspondence: *E-mail*: olotoenny@yahooo.com

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INTRODUCTION

Gastric ulcer presents as a superficial erosion or deep perforation of the gastric mucosal lining like other peptic ulcer disease (PUD). Gastric ulceration occurs due to disruption of the maintenance of gastric mucosal integrity caused by imbalance between defensive factors (prostaglandin, mucin, nitric oxide, bicarbonate, surface active phospholipids, endogenous antioxidants, and epidermal growth factors) and offensive factors (gastric acid, pepsin, free radicals, bile, and bacterial infection) (Agbaje and Okpara, 2013; Wasman et al., 2010). The imbalance could be secondary to frequent and indiscriminate use of non-steroidal anti-inflammatory drugs (e.g. aspirin, indomethacin, ibuprofen, etc), stress, cigarette smoking, bacterial infection with Helicobacter pylori, chronic alcoholism and nutritional deficiencies (Kaur et al. 2012; Umamaheswari et al., 2007). In Nigeria, 2.1-6.0% of the population was reported to have gastric ulcer (Nwokediuko et al., 2012).

Generally, the pharmacological treatment of gastric ulcer involves the use of antacids, proton pump inhibitors, histamine H2 receptor antagonist, anticholinergics and antibiotics, through which the morbidity and mortality rate had been reduced. This drug combination serves to reduce gastric acid secretion, prevent gastric mucosal lining erosion, and stimulate gastric epithelial cell proliferation for effective healing promotion.

However, there are various adverse effects obtainable from these drugs and cases of recurrence of the disease despite the use of these drugs. These include gynaecomastia, acute interstitial nephritis, hematopoietic alterations (Ra and Tobe, 2004); thrombocytopenia (Zlabek and Anderson, 2002); anaphylaxis reactions (Gonzalez et al., 2002); and hepato-renal toxicity (Fisher and Le Couteur, 2001). These observations attract research into crude plant materials and plant products from which active compounds with relatively little or no side effects and having promising therapeutic activities are isolated for the treatment of PUD.

The discovery of phytochemicals of medicinal values had shown that plant does not only have nutritional values but also exhibits therapeutic benefits which include antimicrobial, antihyperglycemic, antioxidant, hypolipidemic, anticancer, anti-inflammatory, antipyretic, analgesic and many other effects (Al-Snafi, 2016). Daucus carota and Brassica oleraceae had been reported to possess cytotoxic, antioxidant, antidiabetic, antimicrobial, smooth muscle relaxant, hypotensive, decrease intraocular pressure, nephro-protective, hepato-protective, cardio-protective, antidepressant, antiinflammatory, wound healing and gastro-protective activities (Agbaje and Okpara, 2013; Al-Snafi, 2017).

The present study wanted to investigate the synergism of antiulcer activities of both Daucus carota and Brassica oleraceae and also their antioxidant properties in laboratory-induced gastric ulcer using animal model and elucidate the involved mechanisms.

MATERIALS AND METHODS

Plant collection: The fresh root of *Daucus carota* and leaves of *Brassica oleraceae* were bought from Idi-Oro market of Lagos state and was identified and authenticated in the herbarium at the department of Botany and Microbiology, University of Lagos.

Extract preparation: The juice extract of *Daucus carota* root was prepared according to Bishayee et al (1995) with slight modification. One kilogram (1kg) of the fresh roots of *Daucus carota* was peeled, washed, chopped into pieces and homogenized using a blender without adding water. The homogenate roots were squeezed and filtered to yield a residue. The obtained juice was concentrated under reduced pressure at 40°C, using rotary evaporator and stored in a freezer (-2°C) until used for analysis.

Also, three kilogram (3kg) of fresh leaves of *Brassica oleraceae* were chopped into bits and blended to obtain a puree of juice which was filtered, dried in an oven and concentrated under reduced pressure at 40°C, using rotary evaporator and stored in a freezer (-2°C) until used for analysis. Distilled water (0.9L) was added to facilitate blending.

Phytochemical screening: The qualitative and quantitative phytochemical screening of the extracts obtained from the root of *D. carota* and leaves of *B. oleraceae* were done to demonstrate the presence and the amount of the phytochemicals present using standard methods (Trease and Evans, 1989; Sofowora, 1993).

Animals: Forty eight (48) healthy Wistar strain Albino rats (both sexes), age 8-10 weeks, weighing 100g–152g, obtained from the laboratory animal centre, college of medicine, University of Lagos were used for this study. The rats were kept in well-ventilated standard cages, under room temperature of 25±2°C with 12h light and dark cycles, fed with standard rat chow and were given water *ad libitum*. The animals were acclimatized for 14 days before the experiment commenced. The care of the animals was done in accordance with the US Public Health Service Guidelines (NRC, 2011).

The grouping for the antiulcer studies involved six groups of eight animals each. The animals were randomly selected and grouped. Group 1 received 1ml of 90% ethanol only (positive control), group II received 1ml of 90% ethanol + 750mg/kg of *B. oleraceae*, group III received 1ml of 90% ethanol + 400mg/kg of *D. carota* , group IV received 1ml of 90% ethanol + 375mg/kg of *B. oleraceae* +200mg/kg of *D. carota* , group V received 1ml of 90% ethanol + 20mg/kg of Omeprazole, while group VI received 1ml of distilled water only (negative control).

Induction of Gastric Ulcer: The curative antiulcer experimental model using absolute ethanol as ulcer-inducing agent was employed in this study. On day fourteen the rats were fasted overnight (10-12h fast) before the oral administration of 1ml of 90% ethanol/100g body weight into the stomach of the rats (using oral cannula) except those in group VI (negative control group) (Robert et al., 1979).

Different doses of the extracts, extract combination or distilled water were administered respectively into rats in groups II – VI once daily for fifteen days.

Collection of Organs: One hour after the induction, rats in group 1 were anesthetized using diethyl ether and the stomach harvested for physical examination, histopathological studies and antioxidant level measurement.

On the fifteenth day of administration of 1ml of the different extracts, extract combination or distilled water into rats in groups II – VI, as the case may be, the rats were anesthetized using diethyl ether and the stomach harvested for physical examination, histopathological studies and antioxidant level measurement. The tissues for histopathological studies were fixed in 10% formalin while tissue for antioxidant screening was washed in phosphate buffer and placed in ice for immediate transportation to the laboratory for antioxidant screening.

Calculation of Ulcer Index and Percentage Cure

The extent of ulceration in the excised stomach was compared to the controls. The extent of ulceration was expressed as an ulcer index obtained by the average of the scores in each treatment group. The ulcer lesion was rated as: 0 = no lesion, 0.5 = hemorrhage, 1 = 1-3 small lesions, 2 = 1-3 large lesions, 3 = 1-3 thickened lesions, 4 = more than 3 small lesions, 5 = more than 3 large lesions, and 6 = more than 3 thickened lesions (Falcao *et al.*, 2008).

Calculation of % cure of ulcer was done using the formula below (Agbaje and Okpara, 2013):

$$\%\ \text{Cure of Ulcer:} \quad \frac{\text{ulcer index of control - ulcer index of test}}{\text{ulcer index of control}}$$

Tissue biochemical analysis: Tissue glutathione (GSH), superoxide dismutase (SOD), catalase (CAT), malondialdehyde (MDA), glutathione peroxidase (GPx), and Glutathione reductase (GPR) were determined by standard methods described by Sedlak and Lindsay (1968), Misra *et al.* (1972), Sinha *et al.* (1971), Moore and Roberts (1998), Wendel (1980), and Fisher *et al.* (2001) respectively.

Histology studies: A portion of the stomach tissue linings were removed and washed in ice-cold 1.15% KCl solution to remove blood stain, dried and weighed. Part of these tissues were fixed in 10% formalin solution and used for histopathology. The remaining tissues were homogenized separately in 50mM phosphate buffer, pH 7.4 and centrifuged at 10,000 × g for 15 min at 4°C to obtain post-mitochondrial fraction (PMF). The fixed stomach tissues were dissected longitudinally, placed in embedding cassettes, embedded in paraffin, cut into 4cm sections, stained with hematoxylin and eosin (H & E) and examined under the microscope for histopathological changes. The changes given consideration are hemorrhagic appearance, edematous appearance, mucosal erosion, degenerative changes, and necrosis.

Statistical analysis: All data were analysed using SPSS version 21 and variables expressed as mean ± standard error of mean (SEM). Differences in mean between groups were compared using analysis of variance (ANOVA) and level of significance was considered at $p < 0.05$.

RESULTS

Results from the phytochemical screening showed that *D. carota* contain alkaloids, saponin, tannin, cardiac glycoside, flavonoids, phenols but lacks terpenoids, phlobatanine, anthraquinone and steroids. *B. oleraceae* on the other hand was observed to contain tannin, cardiac glycoside, flavonoids, and phenols but lacks alkaloid, saponnin, terpenoids, phlobatanine, anthraquinone and steroids (Table 1).

Result of stomach tissue antioxidant levels showed a non-significant increase in GSH ($p = 0.21$); a significant increase in SOD and CAT ($p = 0.000, 0.000$); and a significant decrease in MDA, GPx, and GPR ($p = 0.000, 0.002, 0.000$) levels in extract treated, omeprazole treated and control groups as compared with ethanol group (Table 2).

Table 1:
Qualitative and quantitative phytochemical screening of the *Daucus carota* and *Brassica oleraceae*

Phytochemicals	***Daucus carota***		***Brassica oleraceae***	
	Inferences	Concentration (mg/100g)	Inferences	Concentration (mg/100g)
Alkaloid	+	19.38±0.018	-	
Saponin	+	49.87±0.04	-	
Tannin	+	32.56±0.02	+	21.81±0.013
Cardiac glycosides	+	22.47±0.027	+	28.99±0.105
Flavonoid	+	17.26±0.018	+	11.32±0.10
Terpernoid	-	-	-	-
Phlobatanin	-	-	-	-
Anthraquinone	-	-	-	-
Steroid	-	-	-	-
Phenol	+	14.48±0.014	+	20.57±0.014

Key: + = Present; - = Absent

Table 2:
The effect of aqueous extract of *Daucus carota* and *Brassica oleraceae* on stomach antioxidant enzymes in rats.

Parameters	**Ethanol (90%)**	***B oleraceae* (750mg/kg)**	***D. carota* (400mg/kg)**	***B.oleraceae* & *D. carota***	**Omeprazole (20mg/kg)**	**Water (1ml/kg)**
GSH µmol/g tissue	23.00±0.14	24.42±0.11	25.44±0.16	24.85±0.13	25.05±0.17	24.18±0.10
SOD units/mg tissue	4.25±0.07	8.24±0.01[a]	7.06±0.03[a]	8.95±0.02[a]	8.11±0.23[a]	7.10±0.11[a]
CAT µmol/mg tissue	43.56±1.03	70.23±0.22[a]	74.20±0.49[a]	87.99±0.81[a]	74.33±0.87[a]	84.39±1.13[a]
MDA µmol/g tissue	6.04±0.09	3.83±0.12[b]	3.43±0.03[b]	1.90±0.04[b]	1.75±0.09[b]	2.79±0.03[b]
GPx µmol/g tissue	2.49±0.02	0.80±0.00[b]	1.11±0.01[b]	1.13±0.01[b]	2.22±0.06	1.92±0.03
GPR µmol/g tissue	3.25±0.024	1.04±0.00[b]	1.40±0.01[b]	1.49±0.01[b]	1.83±0.08[b]	1.50±0.04[b]

Data is represented as Mean ± SEM (n=8). a = statistically significant increase at p<0.05 b = statistically significant decrease at p<0.05. KEY: GSH = Glutathione, SOD = superoxide dismutase, CAT = Catalase, MDA = Malondialdehyde, GPx = Glutathione peroxidase, GPR = Glutathione reductase

Table 3:
The curative effect of aqueous extract of *Brassica oleraceae* and *Daucus carota* on an alcohol-induced gastric ulcer in rat

Groups	Ulcer index	% cure
Ethanol (90%)	5.83±0.44	-
B. oleraceae (750mg/kg)	4.333±0.67	25.7
D. carota (400mg/kg)	5.50±0.50	56.6
B. oleraceae (375mg/kg) & *D. carota* (200mg/kg)	1.75±0.75	70.0
Omeprazole (50mg/kg)	2.33±1.20	60.0
Control (1ml/kg of H_2O)	0.00±0.00	100

Data represented as mean ± SEM (n=8).

Result of the curative effect of the extract of both *Brassica oleraceae* and *Daucus carota* on the induced ulcer showed a 25.7% cure in *B. oleraceae* extract treated group, 56.6% cure in *D. carota* treated group, 70% cure in both *B.* oleraceae and *D. carota* treated group and a 60% cure in omeprazole treated group (Table 3). There was no lesion observed in the group given distilled water.

The result of histopathologic studies showed that administration of absolute ethanol causes extensive foci of erosions of the covering epithelium of the gastric mucosa, necrosis of the mucous glands at the tips of the mucosa, moderate congestion of the mucosal blood vessels, and mild expansion of the tunica submucosa with increased loose connective tissue in rat giver ethanol only (Plate 1).

Administration of the extract of *B. oleraceae* (750mg/kg), *D. carota* (400mg/kg), and a mixture of *B. oleraceae* (375mg/kg) and *D. carota* (200mg/kg) resulted in presence of multiple foci of mild erosions of the covering epithelium of the gastric mucosa, moderate hyperplasia of the mucous glands of the mucosa, necrosis of the mucous glands at the tips of the mucosa, moderate congestion of the mucosal blood vessels, mild aggregates of inflammatory cells at the base of the tunic mucosa, and moderate expansion of the tunica submucosa with edema fluid and loose connective tissue (Plates 2 - 4).

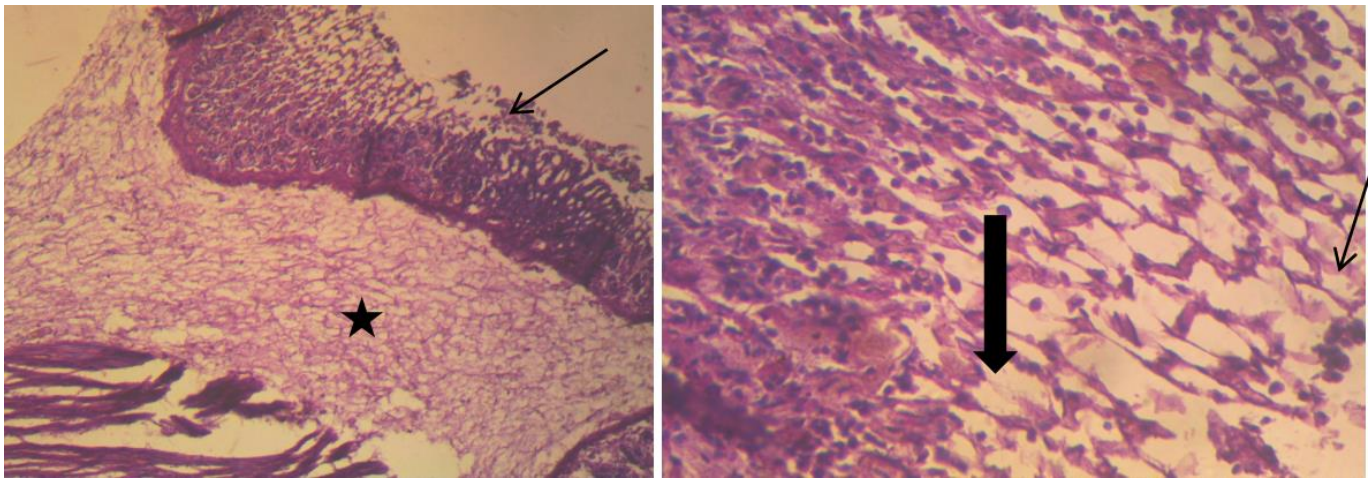

Plate 1: Ethanol-induced gastric ulcer. Thin arrows show necrosis of the mucous glands at the tips of the mucosa, thick arrow shows moderate congestion of the mucosal blood vessels and star shows mild expansion of the tunic submucosa (Mag: Left: x100, Right: x400).

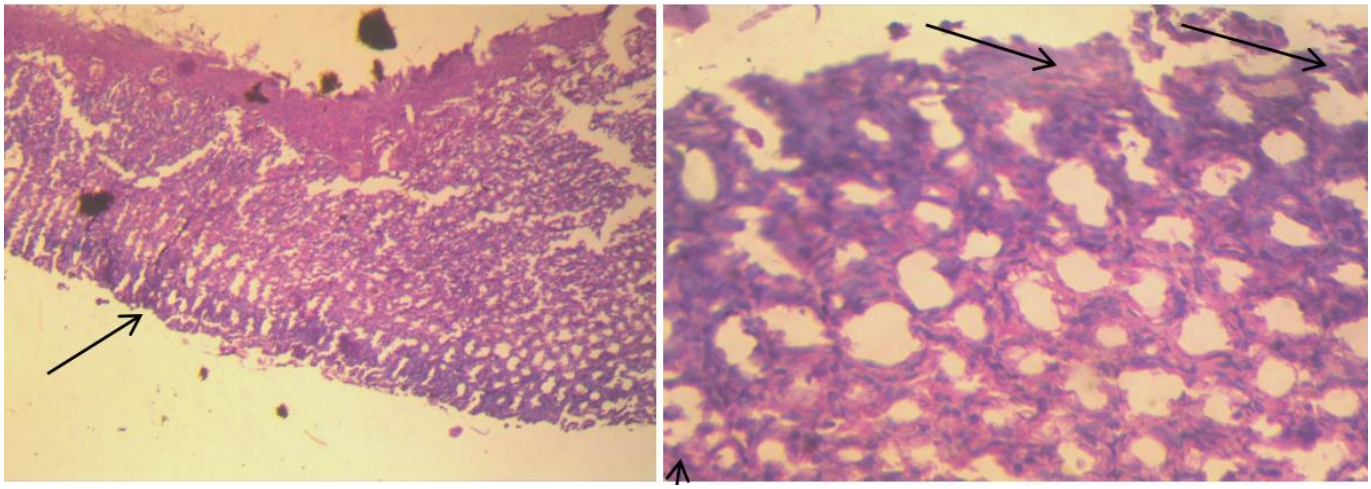

Plate 2:
Changes in gastric erosion by *B. oleraceae*. The arrows indicate multiple foci of mild erosions of the covering epithelium of the gastric mucosa.

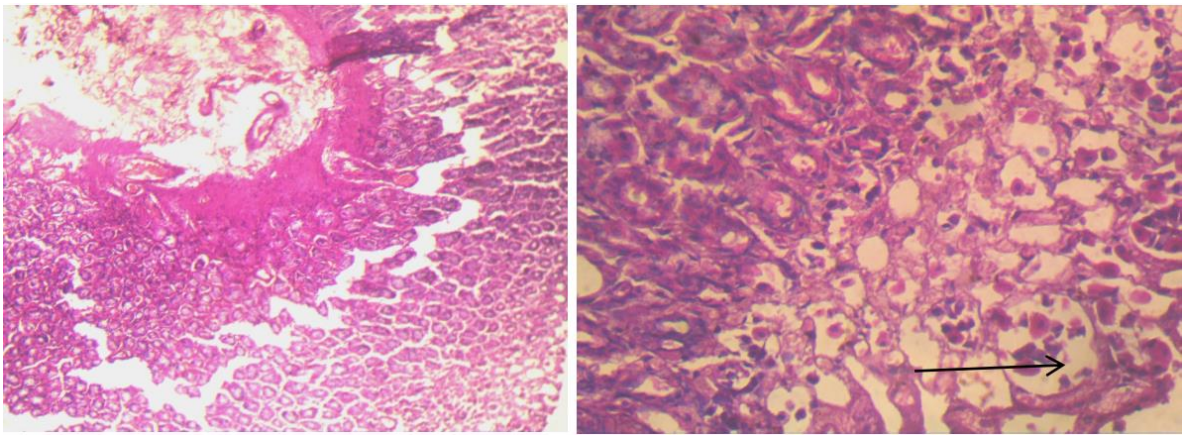

Plate 3:
Changes in gastric erosion by *D. carota* . The arrows indicate necrosis of the mucous glands

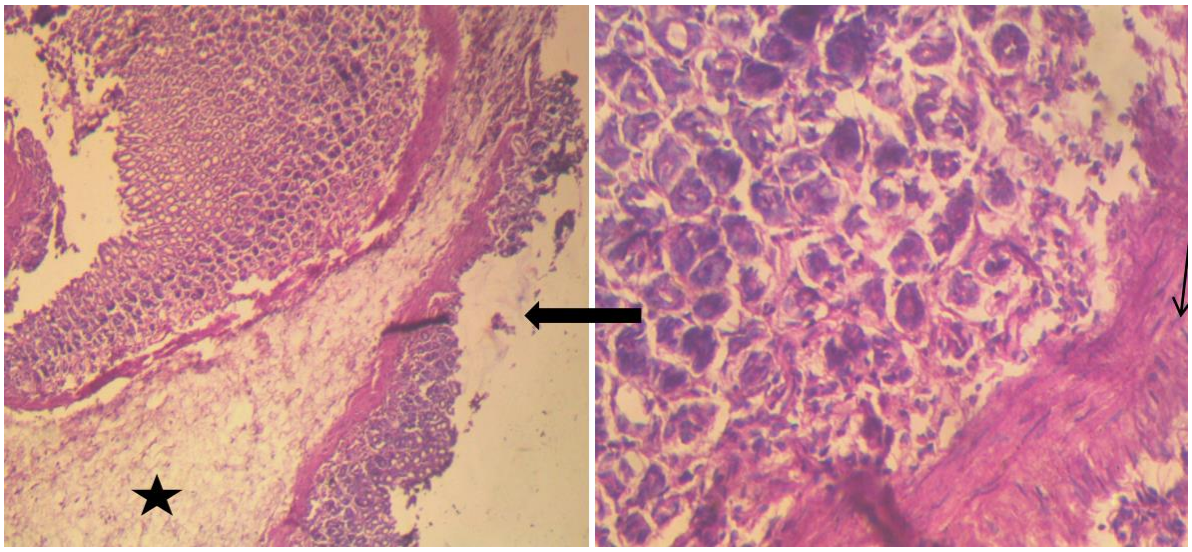

Plate 4:
Changes in gastric erosion by *D. carota and B. oleraceae.* The thick arrow indicate foci of moderate erosions of the mucosa, the thin arrow indicate aggregates of inflammatory cells at the base of the tunic mucosa and star indicate moderate expansion of the tunic submucosa

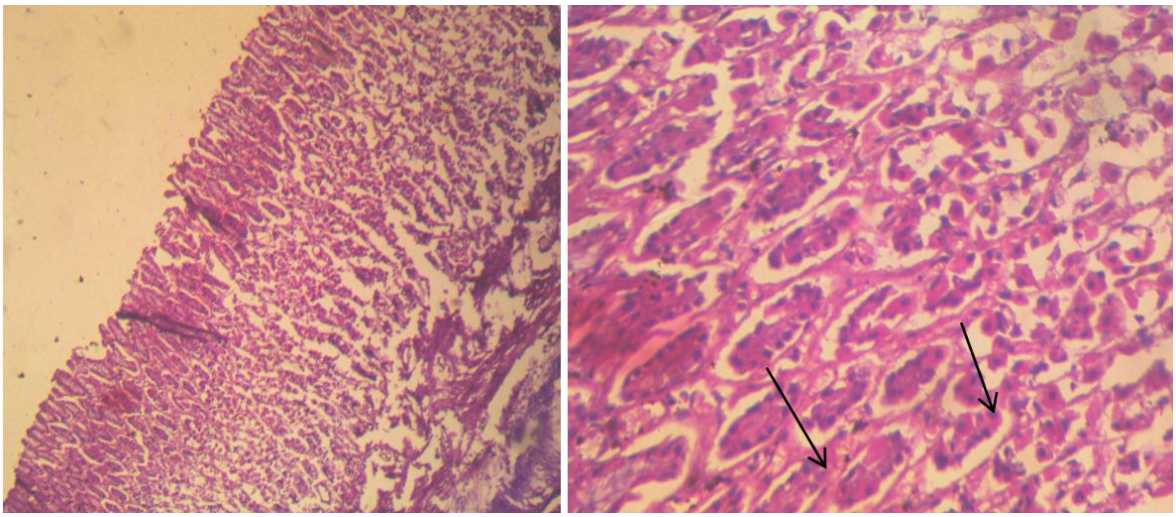

Plate 5:
Changes in gastric erosion by Omeprazole. The arrows indicate degenerate glands in the mucosa.

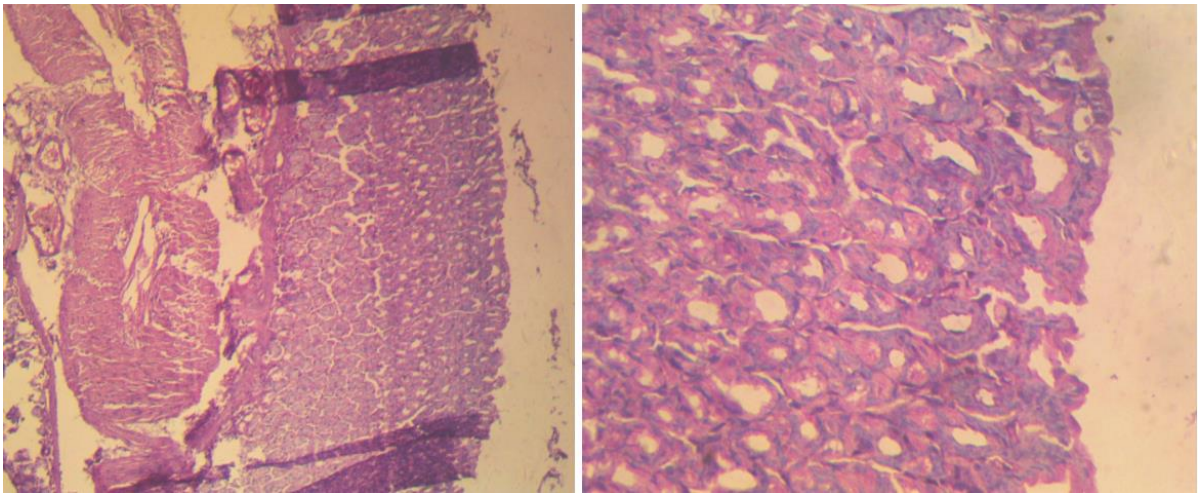

Plate 6:
Shows no changes in gastric erosion by distilled water

Also, administration of 20mg omeprazole (a standard drug) per kilogram body weight revealed the presence of multiple foci of mild erosions in the covering epithelium of the gastric mucosa, large gastric ruggae, and presence of some degenerate glands in the mucosa (Plate 5). On the other hand distilled water showed no lesion (Plate 6)**.**

DISCUSSION

Tannin had been reported to have vasoconstriction and protein precipitation activities which allows for microprotein precipitation on the ulcer site thereby forming an impervious protective layer over gastric mucosa (*Onwuchekwa* and *Oluwole*, 2010). The presence of tannin in *D. carota* and *B. oleraceae* has been observed in this study and this explains the anti-ulcer activities of the extracts of both *D. carota* and *B. oleraceae*.

Gastric mucosal erosion can be induced using NSAIDs, pylorus ligation, and ethanol. Ethanol produces mucosal damage by multifactorial factors which include gastric hemorrhagic erosions. gastric or mucus content depletion, mucosal leukotriene release, modulation of mucosal blood flow by PG, submucosal venular constriction, superficial mucosal cells perturbation, free radicals production, and activation of neutrophils in the gastric mucosa (Nayeem *et al.*, 2010).

On one hand, the administered alcohol enhanced lipid peroxidation which increases glutathione consumption. On the other hand, the administered extracts confer protection on the gastric mucosa against further ethanol injury by decreasing their susceptibility to free radicals as evident by low level of gastric tissue lipid peroxidation (MDA); glutathione peroxidase, and glutathione reductase activities; increasing gastric tissue glutathione level, superoxide dismutase and catalase activities among extract and omeprazole treated groups. The synergism exhibited by *Daucus carota* and *Brassica oleraceae* is revealed in this study by the pronounced differences observed in the above indices of oxidative status

The result of histopathologic studies showed that administration of absolute ethanol causes extensive foci of erosions of the covering epithelium of the gastric mucosa, necrosis of the mucous glands at the tips of the mucosa, moderate congestion of the mucosal blood vessels, and mild expansion of the tunica submucosa with increased loose connective tissue in rat given ethanol only (Figure 1). On the other hand, administration of the extract of *B. oleraceae* (750mg/kg), *D. carota* (400mg/kg), and a mixture of *B. oleraceae* (375mg/kg) and *D. carota* (200mg/kg) and omeprazole (20mg/kg) moderated the observed histopathologic changes in ethanol–induced gastric ulceration. These include presence of mild erosions of the covering epithelium of the gastric mucosa, moderate hyperplasia of the mucous glands of the mucosa, moderate congestion of the mucosal blood vessels, mild aggregates of inflammatory cells, and moderate expansion of the tunica submucosa (Figure 2-6). This observation indicates anti-ulcer potentials of *Daucus carota* and *Brassica oleraceae* as earlier reported by Chandra *et al.* (2015); and Agbaje and Okpara (2013) respectively. The observed improvement in the histopathologic appearances following administration of these extracts further confirms demonstration of therapeutic synergism by *Daucus carota* and *Brassica oleraceae* in the management of gastric ulcer.

The mechanism of anti-ulceration activity of both *Daucus carota* and *Brassica oleraceae* may be antioxidant free radical scavenging, cytoprotection, gastric acid anti-secretory activity, increasing luminal prostaglandin secretion, increasing mucus secretory activity, increased gastric alkaline secretion, and antimicrobial activity among others.

From the result obtained from this study, it is worthy of note that oral administration of either *Daucus carota* or *Brassica oleraceae* singly exhibited anti-ulcer activities in ethanol-induced gastric ulceration. A therapeutic synergism was observed to occur when combined extract of both plant materials were administered orally

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