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ANTI-ULCER AND ANTIOXIDANT DEFENSES OF *TARAXACUM OFFICINALE* (DANDELION) LEAF EXTRACTS AGAINST ETHANOL-INDUCED GASTRIC ULCER IN RATS

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ABSTRACT

Objective: One of the common gastrointestinal diseases is ulcer caused by several necrotic agents. Synthetic commercial drugs had been used to cure this damage but with some side effects. The aim of this study is to investigate the antioxidant and ameliorative effects of aqueous extracts of *T. officinale* (T.O) on absolute ethanol - induced ulcer rats. **Methods:** Preliminary acute toxicity test of aqueous leaf extracts of *T. officinale* was performed, on which, two dose levels of 250mg/kgbw and 500mg/kgbw were selected for this study. Omeprazole (20mg/kg) was used as the standard drug. **Results:** Evaluation of rats treated with the extracts showed significant ($p \leq 0.05$) decrease in the ulcer score index and an increase in the percentage inhibition. The catalase and glutathione antioxidant activities were reduced in the ulcer group with respect to the standard drugs and treated rats. **Conclusion:** These results indicate that *T. officinale* showed anti-ulcer and antioxidant defense properties against ethanol-induced gastric injury in a dose dependent manner.

KEYWORDS: *Taraxacum officinale* extract (T.O.E), Omeprazole, Gastrointestinal, Catalase, Glutathione.

INTRODUCTION

A plethora of naturally occurring plants have been identified and used for the treatment of different diseases worldwide. Much focus has been placed on scientific research of traditional

drugs obtained from these plants. Increase in the synthesis of drugs from plant origin has resulted to the emergence of alternative type of medicine called traditional medicine.[1,2] These medicinal plants are capable of synthesizing an overwhelming variety of organic compounds generally referred to as secondary metabolites.[3] Screenings of these metabolites have produced over 100,000 bioactive components that have led to the invention of drugs for use in treatment of various diseases.[4] The generation of reactive oxygen species (ROS) appears to be implicated in the pathogenesis of the toxicity of most human organs.[5,6] These organs/cells have various mechanisms, especially enzymatic and non-enzymatic antioxidants systems such as catalase, gluthathione (GSH), gluthathione s-transferase (GST), gluthathione reductase (GR) and superoxides dismutase (SOD), to scavenge these reactive oxygen species against cellular damage.[7,8,9,10] Ulcer is primarily caused by an imbalance between the endogenous aggressive and protective factors in the stomach.[11] Although ulcer is not a deadly disease but it can lead to other serious medical complications.[12] Medications are used to lessen the pain, alleviate the ulcerations and protect the recurrence of the mucosal erosion. These synthetic drugs include the use to antacids, antibiotics[13] proton pump inhibitors, H2 receptors blockers,[14] cytoprotectants, demulcents, anti-cholinergics sulfhydryl compounds.[15,16,17,18] Some of such drugs have side effects which are damaging to organs of the body.[19,20] Several researches have confirmed the efficacy of medicinal plants for the treatment of diseases with fewer side effects. The observed activity on the use of plants is the fact that they possess protective natural antioxidants that can promote health and alleviate illness.[21] These antioxidants include the presence of flavonoids, alkaloids, terpenoids, tannins, saponins, major lignans and phenolic acids, many of which have been isolated, characterised and their medicinal properties investigated in-vivo and in-vitro.[22,23,24]

Taraxacum Officinale WEBER (Dandelion) for decades has served traditional medicine practitioners as a useful plant in treatment of diseases. Ayurvedic physicians have used it in breast cancer.[25] The root is part of the Lydia E. Pinkham's formula of medicinal concoctions used as diuretic, cholagogue, appetite stimulant, hepatitis remedy or weight loss agent.[26] Castleman (The healing herb) mentioned dandelion for use in premenstrual syndrome, lower high blood pressure congestive heart failure, cancer prevention and digestive aid.[27] Reports on the leaves hepatoprotective activity,[28,29] its effect on the hematology profile of rats[30] and the use as antidote for snake and insect bites[31] have been recorded. The roots have long history with Chinese physicians who have prescribed dandelion for cold, bronchitis, pneumonia, boil, ulcer, itching problems, dental and for internal injuries.[32,33,34] The primary

aim of this research is to investigate the effect of antioxidant components and the anti-ulcer potentials of aqueous extracts of *Taraxacum officinale* (Dandelion) leaves on absolute ethanol- induced gastric mucosal injury.

MATERIALS AND METHODS

Plant material

Fresh leaves of *Taraxacum officinale* (TO) were obtained from a bush farm in Kaiama town in Kolokuma/Opokuma Local Govt. Area of Bayelsa State, Nigeria. The plants were identified and authenticated by Dr, Nwosu of the Plant Science and Biothecnolgy Dept. of the University of Port Harcourt, Choba, Port Harcourt, Rivers State, Nigeria.

Extract Preparation

Freshly harvested leaves *Taraxacum officinale* (TO) was sun dried and coarsely powdered with a blender. 100gm of the powdered leaves were boiled in 500ml of distilled water for 15 minutes. The decoction was taken and allowed to cool for 45minutes at room temperature. It was then filtered twice using Whatman No1 filter paper, then evaporated to dryness in an oven at 50^0C, to produce 38.13g of the aqueous extract. Stock solution of the concentrated plant samples were constituted with distilled water at 250mg/ml and different doses (250 and 500mg/kg).

Experimental animals

For this study Wistar rats of both sex weighing between 150-200g body weights were purchased from animal house of the Department of Biochemistry, Federal University of Agriculture, Abeokuta (FUNAAB), Ogun State, Nigeria. The rats were randomly divided into five (5) groups of 4 rats per group, kept in metal cages at room temperature and allowed to acclimatize for one week under standard environmental conditions. The rats were fed with balanced rodent pellet diet and allowed free access to water *ad libitum*.

Acute toxicity test

Preliminary acute toxicity studies of *Taraxacum officinale* (TO) leave extract were performed on the rats in accordance to the OECD guideline no 423 (Acute Toxic Class Method) to determine the safe dose concentration of the extract to be administered. The rats were fasted for 24 hours prior to dosing with the leave extract in increasing dose up to 5000mg/kg body weight. The rats were observed at an interval of 4 hours daily for 3 days for any clinical or

toxicological manifestation. It was observed that at this dose no abnormal behavior was recorded, hence 1/10th (500mg/kg) of this dose was selected for the study.

Absolute ethanol-induced gastric mucosal injury studies

In this study the rats were divided into five groups of four rats each.

Groups	Treatment	Description
A1.	Normal	- rats administered with distilled water only
A2.	Negative Control (Ulcer control)	- rats induced with1ml/100g absolute ethanol
A3.	Positive Control	- rats induced with1ml/100g absolute ethanol + 20mg/kg Omeprazole
A4.	Treated Rats	- rats induced with1ml/100g absolute ethanol + 250mg/kg aqueous extract of *T. officinale*
A5.	Treated Rats	- rats induced with1ml/100g absolute ethanol + 500mg/kg aqueous extract of *T. officinale*

Estimation of gross gastric lesion

Gastric mucosa ulcer appears as dark hemorrhagic lesions of the stomach. The stomach of the experimental rats was dissected along the greater curvature and examined for damage. Each damage was measured using a planimeter (10 x10 mm^2 = ulcer area) by viewing under microscope magnification (1.8X). The length and breadth of the ulcer area was evaluated by counting the number of small squares (2mm x2mm) of the stomach. The total number of these lesions multiplied by 4 x 1.8= ulcer area (UA mm^2).[35]

The gastric lesions were counted and ulcer index (UI) was calculated using the expression;[36]

$$UI = (n + \text{lesion I}) + (n + \text{lesion II}) + (n + \text{lesion III})$$

Where;

I = Presence of edema, hyperaemia and single submucosal, puntiform hemorrhage (petechiae);

II = Presence of submucosal, hemorrhage lesions with small erosions;

III = Presence of deep ulcer with erosions and invasive lesions.[37]

n = Number of ulcer.

The percentage ulcerated surface was calculated as the total area covered by all lesions expressed as a proportion of the total corpus mucosa surface area. The percentage of inhibition (I%) was calculated using the formula;[38,39]

$$\text{Percentage ulcer inhibition (\%UI)} = \frac{USc - Ust}{USt} \times 100$$

Where;

USc = Ulcer surface area of control

USt = Ulcer surface area of treated

Measurement of Reduced Glutathione (GSH) Activity

The level of the reduced Glutathione (GSH) was measured using a GSH assay kit (Cayman, Ann Arbor, MI, USA). This process involved an optimized enzymatic recycling method and glutathione reductase (GR). The sulphydryl group of the glutathione reacts with 5,5-dithio-bis-2-nitrobenzoic acid (TNB). A mixture of disulfides, GSTNB was formed between GSH and TNB, which is reduced by GR to recycle GSH, thereby releasing more TNB. The rate of production of TNB is directly proportional to the recycling reaction which in turn is directly proportional to the GSH concentration in the sample. The absorbance of TNB was taken at a wavelength of 410nm which is used to determine the value of GSH and expressed as µmol/mg protein.[40]

Estimation of Catalase (Cat) Activity

The catalase activity was estimated based on the peroxidatic function of catalase using the catalase assay kit (Cayman). This process is based on the reaction of the enzyme with methanol in the presence of hydrogen peroxide.(H_2O_2).

The product of this reaction, formaldehyde is measured at 540nm using the colorimetric calibration with a chromogen (4-amino-3-hydrazino-5-mercapto-1,2,4-triazole (Purpald). The catalase activity is expressed as $^{\mu}/_{mg}$ protein.[41]

Measurement of Mucus Production

Gastric mucus production was estimated in the animals induced by NSAID (Ibuprofen) and absolute ethanol. The glandular part of the stomach was removed weighed and recorded. Each part was transferred into a 1% Alcian blue solution in sucrose acetate at pH 5. The excess dye was washed off with sucrose solution. The gastric wall mucus formed complexes with the dye and this was removed using magnesium chloride solution. A 4ml aliquot of the blue extract was then shaken with an equal volume of diethyl ether. The resultant emulsion was centrifuged and the absorbance at 580nm of the aqueous layer was recorded. The amount of the extracted alcian-blue per gram of glandular tissue was then determined.[42,43]

Statistical Analysis

All values were reported as mean ± standard deviation (SD). The statistical significance of differences between groups was assessed using one-way analysis of variance (ANOVA), followed by Dunnett's test. A value of $P \leq 0.05$ was considered significant difference between the groups. Statistical computations were calculated using Statistical Package for Social Sciences (SPSS) Version 20,(SPSS Inc, Chicago, IL, USA).

RESULTS

Qualitative and quantitative phytochemical composition of *T.officinale* extract

Results of the preliminary phytochemical study of *T.officinale* extract showed (Table 1) the presence of the following secondary metabolites, alkaloids, flavonoids, glycosides, phenolic acid, saponins and tannins. Tables 2, 3 and 4 revealed the quantitative analysis of the saponins, tannins and glycosides content of *T.officinale* leave extract respectively.

Table 1: Qualitative Phytochemical analysis of *T.officinale* leave extracts.

S/No.	Constituents	Aqueous leave extract
1.	Phenolic acid	+
2.	Alkaloids	+
3.	Tannins	+
4.	Glycosides	+
5.	Flavonoids	+
6.	Saponins	+

(**+**) Presence of phytoconstituent in *T.officinale* leave extract.

Table 2: Quantitative Phytochemical analysis of Tannins in *T.officinale* leaves.

S/No.	Constituents	*Taraxacum officinale* Aqueous (mg/100g)
1.	Corilagin	0.00001
2.	Geraniin	0.000008
3.	Acetannin	36.86141
4.	Phylanthusin – D	0.000006
5.	Amariin	0.000001
6.	Tannic acid	381.86998
7.	Amaulone	0.000001
8.	Amarinic acid	0.000008
	Total =	**418.73144**

Table 3: Quantitative Phytochemical analysis of Glycosides in *T.officinale* leaves.

S/No.	Constituents	*Taraxacum officinale* Aqueous (mg/100g)
1.	Taraxacin	12.35131
2.	Taraxaoulide	23.28647
3.	Dihyrlactucin	5.15193
4.	Amygdalin	0.00001
5.	Quabain	0.00650
6.	Taraxacoside	1.65820
7.	Ixerin	2.04674
8.	Digitoxin	0.00889
9.	Stelladerol	0.00564
10.	Digoxin	0.00073
	Total =	**44.51645**

Table 4: Quantitative Phytochemical analysis of Saponins in *T.officinale* leaves.

S/No.	Constituents	*Taraxacum officinale* Aqueous (mg/100g)
1.	Hispgenin	0.32400
2.	Solagenin	0.00204
3.	Diosgenin	0.00020
4.	Tigogenin	0.00068
5.	Neochlorogenin	4.22792
6.	Hecogenin	0.00013
7.	Sapogenin	37.85117
8.	Tribuloin	0.00040
9.	Yanogenin	0.00059
10.	Conyzorgin	0.00005
11.	Saponine	20.43711
	Total =	**62.84433**

Ruling-out ulcerogenicity

Rats pre-treated with aqueous *T.officinale* leaves using the highest concentration of 500mg/kg the stomach were cut open by the greater curvature for examination. The linings of the stomach were observed to be normal and no form of ulcer or any lesion was seen on the mucosa. This can be inferred that *T.officinale* is non-ulcerogenic to the gastric mucosa of experimental rats. This result agrees with previous researches on *Phyllantus niruri* leaf,[44] *Jasminum sambac* leaf,[45] *Rumex Bequaertii* leaf[46] etc.

Ulcer Scoring

Table 5 show the ulcer score on stomach of experimental rats.

Table 5: Ulcer scoring.

Observation on stomach	Range	Ulcer score
No ulcer. Normal color		0
Pink to red colored stomach	US < 0.5mm^2	1
Hemorrhage streak	0.5 mm^2 < US <2.5 mm^2	2
No of ulcer less than 5	2.5 mm^2 < US < 5 mm^2	3
No of ulcer equal or more than 5	5 mm^2 < US <10 mm^2	4
Ulcer with bleeding	10 mm^2 < US <20 mm^2	5
Perforation of gastric wall	25 mm^2 < US <35 mm^2	6

Data for the confirmation of the presence of ulceration is as presented in Table 6. The rats in the ulcer control group recorded an ulcer area as high as 109.27 $\pm$ 0.86(mm^2) and 98.10 $\pm$ 4.30(mm^2) on the day 7 and day 14 respectively, showing severity of ulcer. Treatment with the reference drug, Omeprazole [17.17 $\pm$1.07(mm^2)] and the leave extracts (250 and 500mg/kgbw) significantly ($p \leq 0.05$) reduced the ulceration compared to the ulcer control group which. This same trend was observed in the ulcer index results as presented in Table 7.

Table 6: Effect of *T.officinale* extract (T.O.E) on Ethanol - induced Ulcer on Ulcer Area.

Group	Treatment	Ulcer Area (mm^2) Day 7	Ulcer Area(mm^2) Day 14
1	Normal control	0.00 $\pm$ 0.00^b	0.00 $\pm$ 0.00^b
2	Ulcer control	109.27 $\pm$ 0.86^a	98.10 $\pm$ 4.30^a
3	Omeprazole	36.53 $\pm$ 0.83$^{a\,b}$	17.17 $\pm$ 1.07$^{a\,b}$
4	T.O.E 250mg/kg bw	59.70 $\pm$ 0.60$^{a\,b}$	42.30 $\pm$ 1.78$^{a\,b}$
5	T.O.E 500mg/kg bw	54.33 $\pm$ 1.09$^{a\,b}$	38.10 $\pm$ 0.62$^{a\,b}$

Values are mean ± S.D of triplicate determination. Values with the same column with superscripts alphabets ‘a’ and ‘b’ are significantly different at $P \leq 0.05$ when group 1 and group 2 are compared with other groups respectively.

Table 7: Effect of *T.officinale* extract (T.O.E) on Ethanol - induced Ulcer on Ulcer Index.

Group	Treatment	Ulcer Index Day 7	Ulcer Index Day 14
1	Normal control	0.00 $\pm$ 0.00^b	0.00 $\pm$ 0.00^b
2	Ulcer control	5.16 $\pm$ 0.11^a	4.93 $\pm$ 0.05^a
3	Omeprazole	2.00 $\pm$ 0.00$^{a\,b}$	1.86 $\pm$ 0.15$^{a\,b}$
4	T.O.E 250mg/kg bw	4.23 $\pm$ 0.11$^{a\,b}$	3.73 $\pm$ 0.05$^{a\,b}$
5	T.O.E 500mg/kg bw	3.13 $\pm$ 0.15$^{a\,b}$	3.03 $\pm$ 0.05$^{a\,b}$

Values are mean ± S.D of triplicate determination. Values with the same column with superscripts alphabets 'a' and 'b' are significantly different at P≤0.05 when group 1 and group 2 are compared with other groups respectively. Table 8 show results of the percentage inhibition.

Table 8: Effect of *T.officinale* extract (T.O.E) on Ethanol - induced Ulcer on Percentage Inhibition.

Group	Treatment	Percentage Inhibition(%) Day 7	Percentage Inhibition(%) Day 14
1	Normal control	0.00 ± 0.00[b]	0.00 ± 0.00 [b]
2	Ulcer control	9.96 ± 0.89[a]	17.13 ± 2.70 [a]
3	Omeprazole	69.89 ± 0.82 [a b]	85.48 ± 1.13 [a b]
4	T.O.E 250mg/kg bw	50.80 ± 0.68 [a b]	64.67 ±1.32 [a b]
5	T.O.E 500mg/kg bw	55.22 ± 1.10 [a b]	67.79 ± 1.03 [a b]

Values are mean ± S.D of triplicate determination. Values with the same column with superscripts alphabets 'a' and 'b' are significantly different at P≤0.05 when group 1 and group 2 are compared with other groups respectively.

Table 9: Effect of *T.officinale* extract (T.O.E) on Ethanol - induced Ulcer on Mucus Weight.

Group	Treatment	Mucus Weight (mg) Day 7	Mucus Weight (mg) Day 14
1	Normal control	178.90 ± 1.30[b]	189.93 ± 1.65.00 [b]
2	Ulcer control	46.90 ± 1.30[a]	54.46 ± 1.01 [a]
3	Omeprazole	181.10 ± 0.88 [a b]	195.67 ± 0.61 [a b]
4	T.O.E 250mg/kg bw	121.13 ± 0.75 [a b]	134.63 ±1.19 [a b]
5	T.O.E 500mg/kg bw	124.40 ± 0.98 [a b]	178.47 ± 0.75 [a b]

Values are mean ± S.D of triplicate determination. Values with the same column with superscripts alphabets 'a' and 'b' are significantly different at P≤0.05 when group 1 and group 2 are compared with other groups respectively.

Enzymatic antioxidant activity

Both endogenous Glutathione (GSH) and Ccatalase (CAT) activities were significantly (p≤0.05) increased from 30.93 ± 0.25(U/mg protein) for glutathione and 149.23 ± 0.30(U/mg protein) for catalase in the ulcer control group respectively to 45.60 ± 0.40(U/mg protein) and 300.10 ±1.95 (U/mg protein) in the Omeprazole group. The rats administered with aqueous extracts of T.officinale at 500mg/kgbw recorded 42.97 ± 0.15(U/mg protein) and 275.93 ± 1.36(U/mg protein) for GSH and CAT levels respectively as presented in Table10. GSH is an

endogenous antioxidant whose activity is related to the thiol group of cysteine in its structure. GSH reacts with peroxides and ROS radicals to protect the cells from injury[47]. The role of glutathione redox cycle and endogeneous catalase.

Table 10: Effect of *T.officinale* extract on enzymatic antioxidant.

Group	Treatment	Glutathione (GSH) (U/mg protein)	Catalase (CAT) (U/mg protein)
1	Normal control	55.03 ± 0.15 [b]	341.00 ± 1.22[b]
2	Ulcer control	30.93 ± 0.25 [a]	149.23 ± 0.30[a]
3	Omeprazole	45.60 ± 0.40 [a,b]	300.10 ±1.95[a,b]
4	T.O.E 250mg/kg bw	39.50 ± 0.40 [a,b]	221.07 ± 0.98 [a,b]
5	T.O.E 500mg/kg bw	42.97 ± 0.15 [a,b]	275.93 ± 1.36 [a,b]

Values are mean ± S.D of triplicate determination. Values with the same column with superscripts alphabets ‘a’ and ‘b’ are significantly different at P≤0.05 when group 1 and group 2 are compared with other groups respectively.

Histological evaluation of gastric lesions

The rats in the ulcer control group showed marked extensive damage to the gastric mucosa, leucocytes infiltration and edema. Rats that were treated with the reference drug Omeprazole and extracts of *T. officinale* revealed a restructuring of the mucosa and absence of leucocytes infiltration (Fig 1a, 1b, 2a, 2b, 3a and 3b).

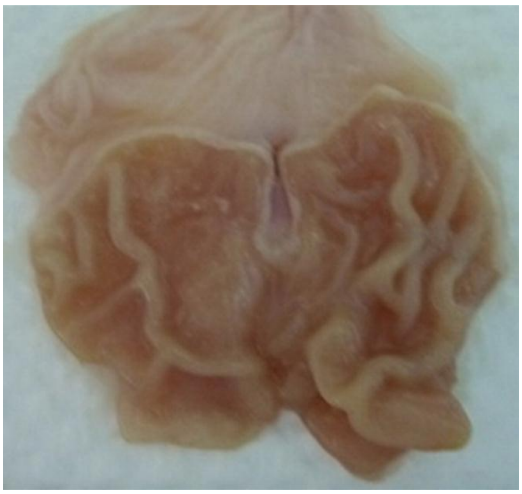

Figure 1a: Normal group rats. No injuries to the gastric mucosa are seen. X200.

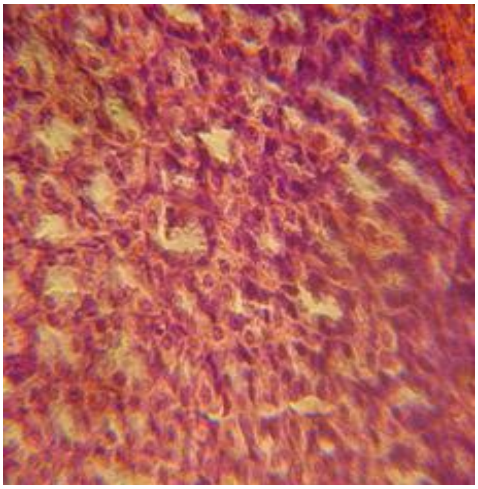

Figure 1b: Normal group rats showed normal gastric mucosa with normal glands, Nucleus appears distinct. X100.

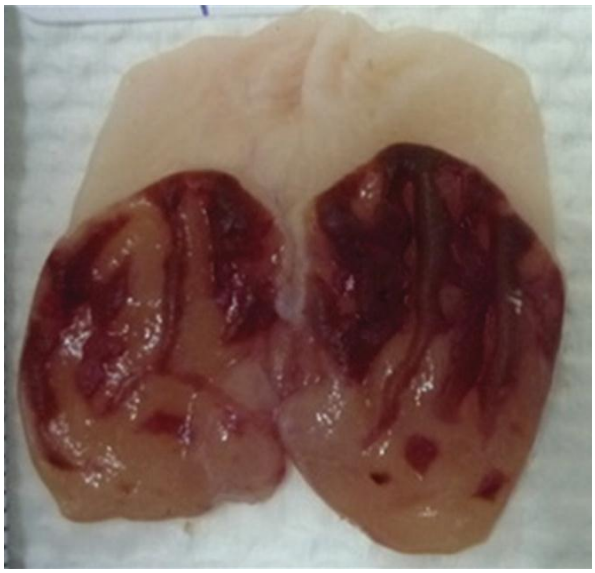

Figure 2a: Ulcer group rats (ulcer control). Severe injuries are seen in the gastricmucosa. Absolute ethanol produced extensive visible hemorrhagic necrosis of gastric mucosa. X200

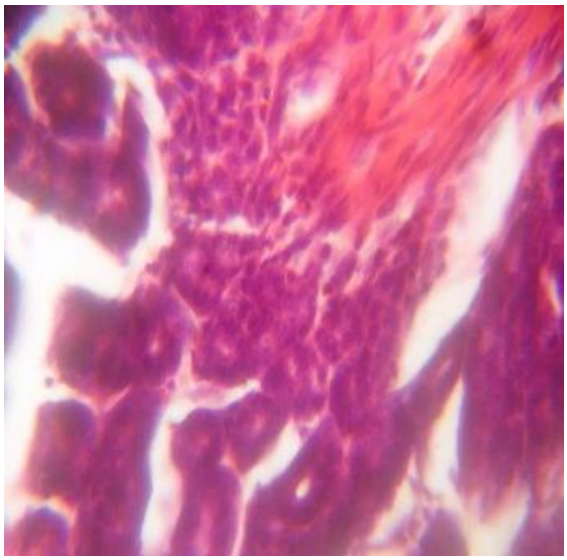

Figure 2b: Ulcer group showed mucosal ulceration with sub mucosal edema, inflammation and polymorphonuclear infiltrate at the ulcer site as well as in the oedematous submucosa. X100.

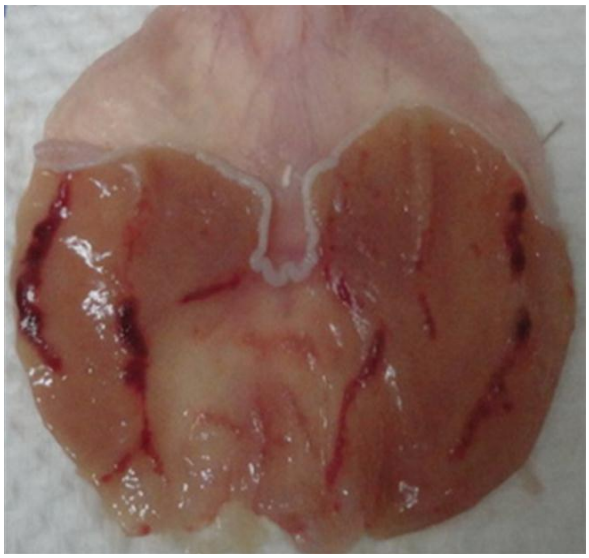

Figure 3a: Rats treated with Aqueous Extract. Injuries to the gastric mucosa are milder compared to the injuries seen in the ulcer control rats.

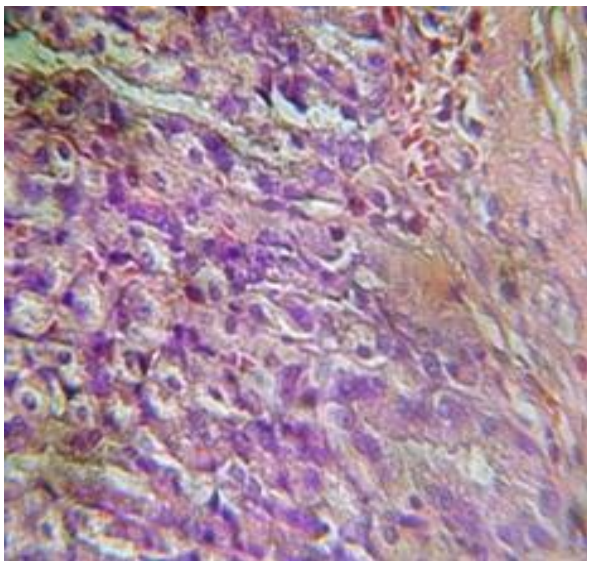

Figure 3b: Aqueous Extract treated group: There is a mild disruption to the surface epithelium and mild infiltration and haemorrhages to the submucosal layer.

DISCUSSION

Absolute ethanol causes severe damage to the mucosa by its direct necrotic action which in turn reduces the secretion of bicarbonate and mucus.[47] These actions are due to the activities of free radicals, oxidative stress and changes in the mucosal permeability.[48] Furthermore absolute alcohol injury produces extensive submucosal edema, linear hemorrhage,

inflammatory cells infiltration, mucosal friability and epithelial cell loss.[49] Results from this study showed that the extract did not indicate any form of toxicity, no mortality and no abnormal behavioral changes on the rats during the period of the experiment. This is an indication that *T.officinale* is safe and can be orally administered at the prescribed dose of 250 and 500mg/kgbw. The experimental results showed that *T.officinale* extract displayed an antiulcer and antisecretory effect against absolute ethanol –induced gastric mucosal damage. This antiulcer and antisecretory potential of *T.officinale* can be attributed to the activities of the variety of phytochemicals present in the plant, these include alkanoids, flavonoids, glycosides, phenols, saponins and tannins. These secondary metabolites are scavengers of free radicals and reactive oxygen species (ROS) which are usually implicated in the toxicity of cells, such as the injury caused by ethanol- induced gastric mucosa. These components in the plant improve the secretion of mucus through their vasoconstricting effects.[6] Results from this study agreed with the findings of previous researchers using *Jasminun sambac,*[45] *Acanthopanax trifollatus*[50] and *Ocimum basilicum*[51] seed extract.

CONCLUSION

The present study showed that treatment of absolute ethanol-induced gastric ulcer with aqueous extract of *T.officinale* ameliorated the damage in a dose dependent manner as evidenced in the reduction of ulcer area, ulcer index and increase in percentage inhibition and mucus weight. The endogenous enzymatic antioxidants, glutathione (GSH) and catalase (CAT) were restored almost to the normal.

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