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Antiulcer activities of the ethanol root extract of *Setaria megaphylla* (Steud) T. Dur and schinz in rat

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Abstract
Setaria megaphylla (Steud) T. Dur and Schinz (Poaceae), is a medicinal plant used in South-South Nigeria to treat malaria, hemorrhoids, urethritis, inflammation, diabetes, fevers and various pains [1]. While some researches have been carried out to authenticate the uses of the leaves of the plant, very little research has been done on the root extract and its fractions.
This work is therefore designed to investigate the antiulcer potential of *Setaria megaphylla* ethanol root extract. The ethanol root extract (150, 300, 450 mg/kg) was investigated for indomethacin, ethanol and histamine- induced ulcers in rats using standard procedures. The extract caused a progressive, dose-dependent and statistically significant ($p<0.05$ - 0.001) decline in ulcer index of the rats pretreated with the extract and a dose-dependent progressive preventive ratio. The observed effect of the extract (150 - 450 mg/kg) was weak compared to the standard drugs, cimetidine 100 mg/kg and propranolol 40mg/kg respectively used in the indomethacin and ethanol models, but the 450 mg/kg dose of the histamine model had a higher effect than the standard drug, cimetidine 100 mg/kg. The results of this study revealed that the ethanol root extract of *S. megaphylla* possesses anti-ulcer effects from its phytochemical components.

Keywords: Antiulcer, *Setaria megaphylla,* medicinal plant

1. Introduction

Setaria megaphylla is a perennial broad-leafed bristle grass, with robust roots 30 cm diameter at the base [1] with leaves that are soft to touch and bluish grey green in colour, usually about 1 m long and 10 cm broad. It has glabrous but scarbrid edges with compressed and more or less keeled leaf sheaths [2]. It is locate along rivers in low lying areas or forests and in areas where there is plenty of moisture, like tropical and subtropical areas of Africa and America [3]. Leaf-decoction is put into a bath or given by mouth in Ivory Coast to babies suffering convulsions or fits of epilepsy. Used to treat blennorhoea, given to a pregnant woman to ease delivery and is abortifacient [5]. Pressed juice of the leaves of *Setaria megaphylla* is used for anuria and the ashes of the leaves with kaolin face makeup is used for psychosomatic disorders [5]. It is also used for psychosis, debility, psychological problems, neurasthenia and insanity [5]. The plant possesses antiplasmodial [6], anti-inflammatory [7], anti-nociceptive effects [8], hypolipidaemic effects [9], significant anticancer and moderate antileishmanial activity [10].

2. Materials and Method
2.1 Collection and Identification of Plant Sample
Setaria megaphylla roots were collected from Anwa forest in Uruan, Uruan Local Government Area of Akwa Ibom State, Nigeria. It was Identified and authenticated in the Department of Botany and Ecological Studies, University of Uyo and a voucher specimen (FPHUU 221) deposited in the Faculty of Pharmacy Herbarium, University of Uyo.

2.2 Animal Stock
Adult Swiss albino rats were obtained from the Animal House of the University of Uyo, Uyo, Akwa Ibom State and were maintained in the University of Uyo Animal House and fed with growers pellet feed with water given *ad libitum*.

2.3 Extraction
The roots of the plant were washed and air-dried to get a constant weight, cut into small pieces and pulverized to powder using pestle and mortar. The powder (1.5 kg) was macerated in 70 % ethanol for 72 hours. The liquid filtrate of the extract was concentrated and evaporated to dryness in a vacuo at 40 °C using rotary evaporator, and then weighed and stored in a refrigerator at -4 °C until used for the proposed experiments.

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2.4 Acute Toxicological Study

Acute toxicity study was carried out to determine the median lethal dose (LD$_{50}$) of the root extract using the method [11]. as reported by Udobang *et al* [7]. The mice were treated with various doses (1000 - 5000 mg/kg) of the ethanol extract and observed for 24 hours. Physical signs of toxicity such as writhing, decreased motor activity, decreased body/limb tone, decreased respiration and deaths were recorded.

2.5 Phytochemical Studies

The ethanol root extract of *Setaria megaphylla* was subjected to phytochemical screening to reveal the presence of chemical constituents in the plant such as saponins, alkaloids, tannins, flavonoids, terpenes and cardiac glycosides using the methods described by Odebiyi and Sofowora (1978) [12]. and Trease and Evans (2002) [13].

2.6 Evaluation of Antiulcer Activity

2.6.1 Indomethacin-induced Ulcer

Male adult Swiss albino rats (150 -170 g) were randomly divided into five groups of six rats each. The animals were starved from food and water for 24 hours and 2 hours respectively, before the commencement of experiment [14]. They were treated as follows: group 1 (control) received only indomethacin (Sigma, 60 mg/kg dissolved in 5 % Na$_2$CO3) p.o; groups 2, 3 and 4 were respectively pretreated with *S. megaphylla* extract 150, 300 and 450 mg/kg p.o; group 5 received cimetidine (100 mg/kg dissolved in 50 % Tween 80) p.o. One hour later, groups 2, 3, 4 and 5 were administered with indomethacin. The drugs were administered with an orogastric cannula. Animals were killed by cervical dislocation 4 hours after indomethacin administration. The stomachs were removed and opened along the greater curvature. The tissues were fixed with 10 % formaldehyde in saline. Macroscopic examination was carried out with a hand lens and the presence of ulcer lesions were scored [14]. Ulcer index (UI) and preventive ratio (PR) of each of the groups pretreated with extract were calculated using standard methods [14, 15].

Ulcer	Scoring System Criteria
0.0	Normal
0.5	Punctate or pinpoint hemorrhagic ulcers
1.0	Two or more small hemorrhagic ulcers less than 3 mm in diameter
2.0	Ulcers greater than 3 mm in diameter.
3.0	Several ulcers

2.6.2 Ethanol-induced Gastric Ulceration:

The procedure was similar to that used in indomethacin-induced ulceration except that the negative control group (group 1) received only ethanol (2.5 mL/kg p.o.), groups 2, 3 and 4 were respectively pretreated with *Setaria megaphylla* extract 150, 300 and 450 mg/kg p.o. and positive control group (group 5) received propranolol (40 mg/kg. dissolved in distilled water) p.o. The drugs were administered with an orogastric cannula. Animals were sacrificed by cervical dislocation 4 hours after ethanol administration. The stomachs were removed and opened along the greater curvature. The tissues were fixed with 10 % formaldehyde in saline. Macroscopic examination was carried out with a hand lens and the presence of ulcer lesions were scored [14]. Ulcer index

(UI) and preventive ratio (PR) of each of the groups pretreated with extract were calculated using standard methods [14, 15].

Ulcer scores	Scoring system criteria
5	Multiple ulcers along entire length of the gastric fold.
4	Lesions which followed approximately 80 % of the fold.
3	Ulcers 1 - 4 mm in length of 80 % of the fold.
2	At least 2 ulcers of approximately 2 mm in length
1	The presence of 1 ulcer and generalized erythema
0	no visible ulcer.

2.6.3 Histamine-induced Gastric Ulceration in Rats:

The procedure was similar to that used in indomethacin-induced ulceration except that the negative control group (group 1) received only histamine acid phosphate i.p (Sigma, 100 mg/kg dissolved in distilled water), and positive control group (group 5) received cimetidine (100 mg/kg dissolved in 50 % Tween 80) p.o, groups 2, 3 and 4 were pretreated with *S. megaphylla* extract 150, 300 and 450 mg/kg p.o., respectively. The drugs were administered with an orogastric cannula. Animals were sacrificed by cervical dislocation 18 hours after histamine acid phosphate, (100 mg/kg, i.p.) administration. The stomachs were removed and opened along the greater curvature. The tissues were fixed with 10 % formaldehyde in saline. Macroscopic examination was carried out with a hand lens and the presence of ulcer lesions were scored [14]. Ulcer index (UI) and preventive ratio (PR) of each of the groups pretreated with extract were calculated using standard methods [14] 15].

3. Results

3.1 Indomethacin - induced Ulcer in Rats: The results of the effect of *Setaria megaphylla* root extract on indomethacin - induced ulcer in rats is as shown in Table: 1. The extract caused a progressive reduction in ulcer index of the rats pretreated with the extract. The reduction was dose-dependent and statistically significant ($p<0.05 – 0.001$) relative to control. The extract also showed a dose-dependent progressive preventive ratio. The observed effect of the extract was weak compared to the standard drug, cimetidine 100 mg/kg.

3.2 Ethanol - induced Ulcer in Rats: The result of the investigation into effect of *Setaria megaphylla* root extract on ethanol - induced ulcer in rats (Table 2.) showed a decline in ulcer index of the rats pretreated with the extract. This effect was significant ($p<0.05 – 0.001$) relative to control and showed a raised dose-dependent preventive ratio. The effect of the extract was weak compared to that of the standard drug, propranolol 40 mg/kg.

3.3 Histamine - induced Ulcer in Rats: Table: 3 shows the result of the effect of *Setaria megaph*ylla root extract (150 - 450 mg/kg) on histamine - induced ulcer in rats. The extract exerted a progressive reduction in ulcer index of the rats pretreated with the extract in a dose-dependent manner. This reduction was statistically significant ($p<0.001$) relative to control. The extract also showed a dose-dependent progressive preventive ratio. The extract (450 mg/kg) exhibited an effect higher than that of the standard drug cimetidine 100 mg/kg.

Table 1: Effect of extract on indomethacin-induced ulcer in rats.

Treatment	Dose (mg/kg)	Ulcer Indices	Preventive Ratio
Control	60	16.50± 1.58	---
Extract.	150	9.00 ± 1. 32ᵃ	45.45
Extract	300	5.75 ± 1.36ᶜ	65.15
Extract	450	5.12 ± 1.71ᶜ	68.96
Cimetidine	100	2.62 ± 1.71ᶜ	84.12

Data were expressed as mean ± SEM. Significant at ᵃp<0.05,
ᶜp<0.001 when compared to control, n = 6.

Table 2: Effect of extract on ethanol-induced ulcer in rats

Treatment	Dose (mg/kg)	Ulcer indices	Preventive ratio
Control	-	4.52 ± 0.68	---
Extract	150	2.50 ± 0.28ᵃ	44.69
Extract	300	2.25 ± 0.62ᵃ	50.33
Extract	450	1.25 ± 0.25ᶜ	72.23
Propranolol	40	0.25 ± 0.25ᶜ	94.46

Data were expressed as mean ± SEM. significant at
ᵃp<0.05; ᶜp<0.001 when compared to control, n = 6

Table 3: Effect of extract on histamine- induced ulceration in rats

Treatment	Dose (mg/kg)	Ulcer index	Preventive ratio
Control	---	8.62 ± 0.51	---
Extract	150	3.25 ± 0.75ᶜ	62.22
Extract	300	2.87 ± 0.72ᶜ	67.48
Extract	450	0.37 ± 0.12ᶜ	94.54
Cimetidine	100	1.50 ± 0.16ᶜ	83.56

Data were expressed as mean ± SEM. significant at ᶜp<0.001
when compared to control, n = 6

4. Discussion

The results of antiulcer activity of *Setaria megaphylla* extract against indomethacin, ethanol and histamine-induced ulcers showed a statistically significant ($p<0.05$ - 0.001) dose-dependent progressive decline in the ulcer indices and progressive preventive ratio. Peptic ulcers result from an imbalance between protective and aggressive factors [16, 17]. The gastroprotective factors include mucus, mucosal antioxidants, prostaglandins, growth factors and gastric blood flow, while the aggressive factors, such as increased gastric secretion, increased generation of reactive oxygen species and pro-inflammatory cytokines, and infection with *Helicobacter pylori*, can cause mucosal ulcers [18].

Indomethacin is known to cause ulcer especially in an empty stomach and mostly on the glandular (mucosal) part of the stomach by inhibiting prostaglandin synthetase through the cycloxygenase pathway [14]. Prostaglandins protect the stomach from injury by stimulating the secretion of bicarbonate and mucus, maintaining mucosal blood flow and regulating mucosal turn over and repair [19]. Suppression of prostaglandins synthesis by indomethacin results in increased susceptibility of the stomach to mucosal injury and gastroduodenal ulceration. Gastric acid is also involved in the indomethacin-induced gastric mucosal lesion formation and Gerkens *et al.*, 1977 [20] suggested that the reduction of gastric mucosal blood flow contributes to the lesion formation induced by indomethacin. The main drugs used currently to treat ulcers, are histamine H_2 receptor antagonists and proton pump inhibitors, which act by inhibition of the secretion of gastric acid. However, Souza *et al,* 2011 [21] showed that gastric volume, pH, and proton concentration values were not altered by α-terpineol, thus suggesting that the gastroprotective action of α-terpineol does not involve gastric

acid secretion inhibition but occurs by cytoprotective mechanisms. The extract was observed to significantly reduce mucosal damage in the indomethacin-induced ulcer model, suggesting that any of the above mechanism of actions could have been responsible for the anti-ulcer effect of the extract.

Free radicals are a major aggressive factor in the pathogenesis of ethanol - induced gastric ulcers [22], indomethacin - induced gastric ulcers [23] and histamine - induced gastric ulcers[24], which is supported by the facts that lipid peroxide levels are increased [25, 26, 27] and the major antioxidants (including reduced glutathione; vitamins A, C, and E; and enzymes such as superoxide dismutase, catalase, and glutathione peroxidase) are depleted in the insulted gastric tissues [25, 28].

Administration of ethanol has been reported to cause disturbances in gastric secretion, damage to the mucosa, alterations in the permeability and gastric mucus depletion [14]. α-terpineol, an *S. megaphylla* component, showed gastroprotective activity against ethanol-induced and indomethacin-induced ulcers which did not involve an increase in the synthesis of endogenous prostaglandin but could possibly be by stimulation of defense (cytoprotective) mechanisms,, such as alterations of gastric secretion and blood flow [21]. Free radical production has also been implicated as an ulcer causative factor due to ethanol administration [14]. The monoterpenes constituents of this extract such as borneol, astaxanthin, cervacrol and menthone are all reported to possess antioxidant properties and could have contributed to its cytoprotective antiulcer effect [29, 30, 31, 32]. This antioxidant property is supported by the finding that the extract also expressed high free radical scavenging activity with 1, 1-diphenyl-2picrylhydrazyl (DPPH) and could yet be another mechanism of its antiulcer activity. Ethanol is also reported to cause gastric mucosal damage by stimulating the formation of leukotriene C4 (LTC4) [19], so the gastroprotective effect of the extract may in part be due to the suppression of lipoxygenase activity by the extract. Antiulcerogenic effects have been shown by alcohol terpenes [33], with monoterpene terpinen-4-ol and the sesquiterpene elemol isolated from the essential oil of the leaves of *Cryptomeria japonica* showing gastroprotective action in the ethanol and indomethacin ulcer models [34]. Agents that present gastroprotection against ethanol-induced gastric lesions act mainly by stimulation of defense mechanisms (cytoprotective effect) rather than inhibition of aggressive factor production or release (antisecretory effect). Souza *et al,* 2011 [21] posited that the gastroprotection presented by α-terpineol occurs through one or more mechanisms responsible for gastric defense. The phytochemical constituents of this extract may be responsible for its antiulcer effect through one or a combination of the mechanisms mentioned above.

Histamine is known to enhance gastric acid secretion thereby leading to ulceration. Inhibition of histamine-induced ulcer by the extract may be due to its suppression of histamine-induced vasospastic effect and gastric secretion [35]. The root extract has been found to contain flavonoids, terpenes, saponins,

alkaloids and cardiac glycosides among others. Flavonoids have been reported to protect the gastric mucosa from damage by increasing the mucosal prostaglandin content, inhibiting histamine secretion from mast cells, inhibiting histidine decarboxylase and free radical scavenging ability [36, 14]. The results of this study demonstrated that *S. megaphylla* possesses activities which could have resulted from any or all of the above mechanisms.

5. Conclusion
The results of this research work reveals that *Setaria megaphylla* ethanol root extract through its phytochemical constituents possess significant anti-ulcer activity and also validates its ethnomedicinal use in the treatment of peptic ulcer diseases. Further investigation to identify, elucidate and isolate the active components with their possible mechanisms of actions in order to standardize them is recommended to be carried out.

6. Acknowledgement

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