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Evaluation of nephroprotective effects of *Setariamega phyla* (Steud) T. Durand sphinz (Poaceae) root extract on paracetamol-induced in juryin rats

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Abstract
Setariamega phylla (Steud) T. Dur and Schinz (Poaceae), is apopular medicinal plant used by the indigenes of Nigeria's Niger Delta region to treat malaria, hemorrhoids, urethritis, inflammation, diabetes, fevers and various pains [1]. Due to the claims by the traditional users of this plants' about its effectiveness, it becomes essential to investigate the potential toxic or protective effect of *Setariamega phylla*. This work is therefore designed to investigate the nephroprotective effects of *Setariamega phyla* ethanol root extract.
Setariamega phylla ethanol root extract (150, 300, 450 mg/kg) was investigated for its biochemical and histological effects in rats kidneys using standard procedures. There was decrease in weights of kidneys. Reductions in urea and creatinine levels of animals pretreated with the extract (150 - 450 mg/kg) when compared to the paracetamol group was also seen. Histology showed hepatotoxic and nephrotoxic effects in the paracetamol group which were absent in the extract treated groups. The results of this study revealed that *S. megaphylla* ethanol root extract possesses nephroprotective effect.

Keywords: Hepatoprotective, nephroprotective, *Setaria megaphylla,* medicinal plant

1. Introduction
Setariamega phylla is a perennial broad-leafed bristle grass, with robust roots measuring about 30 cm diameter at the base [2]. It has large leaves that are soft to touch and bluish grey green in colour, usually about 1 m long and 10 cm broad. It has glabrous and scour bridges with compressed and more or less keeled leaf sheaths [2]. It is located along rivers in low lying areas or forests and in areas where there is plenty of moisture, like tropical and subtropical areas of Africa, America [3].
A leaf-decoction is sedative on cough, and is also indicated for oedema [4]. Ijo in South East Nigeria rub leaves crushed with salt on the forehead for headache, and squeeze the sap on to a sore after it has been cleaned. The grass has a reputation for beneficial action on urino-genital troubles. Pressed juice of the leaves of *Setaria Megaphylla* is used for anuria. The plant has anodynal and analgesic properties. Zulus in South Africa apply crushed leaves to bruises. In Republic of the Congo, sap is massaged into areas of pain. For more vigorous action the affected part may be scarified by rubbing with the rough leaf, and ash of the calcined plant applied [4].

2. Materials and Methods
2.1 Collection and Identification of Plant Sample
Setaria Megaphylla roots were collected from Anwa forest in Uruan, Uruan Local Government Area of AkwaIbom 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, Nigeria.

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*.Permission for animal studies was obtained from the Animal Ethics Committee of the College of Health Sciences, University of Uyo, Nigeria..

2.3 Evaluation of Nephroprotective Effect
A total of 36 adult Swiss albino rats of both sexes were weighed and divided into six groups of6 animals each and treated as follows: Groups A consisted of normal animals that were

administered with distilled water (0.2 ml/kg), Group B was administered with vehicle control (distilled water, 0.2 ml/kg), while groups C, D and E were respectively administered p.o with 150, 300 and 450 mg/kg of *S. megaphylla* extract daily for 8 days. Group F was treated with silymarin (100 mg/kg) (standard drug) for the same period of time. Paracetamol, 2 g/kg, was administered to groups B – F on the eighth day. Twenty-four hours after paracetamol administration, the animals were sacrificed under light diethyl ether vapor. Blood was collected by cardiac puncture into sterile centrifuge tubes and centrifuged immediately at 2500 rpm for 15 minutes to separate the serum at room temperature to avoid hemolysis. This was used to assess for effect of the extract on various kidney biochemical parameters. Urea, and creatinine as well as some ions like sodium, potassium, chloride and bicarbonate were used to assess kidney function. The analyses were done using various diagnostic kits such as Randox Laboratory kits, Dialab diagnostic kits, HUMAN diagnostic kits and TECO analytical kits. The kidneys of the animals were fixed in 10% formaldehyde, were processed, sectioned and stained with heamatoxylin and eosin (H&E) according to standard procedures and analyzed at Department of Chemical Pathology, University of Uyo Teaching Hospital, Uyo.

3. Results

3.1 Effect of Extract on the Weight of Kidneys:

There were no significant effects in kidney weights of rats treated with the extract or silymarin (Table 1).

3.2 Effect of Extract on Kidney Function of Rats with Paracetamol-induced Nephrotoxic-I-city:

Administration of paracetamol (2 g/kg) produced significant (p<0-01 - 0.001) increases in the levels of urea and creatinine but none in Na^+, K^+, Cl^-, and HCO_3^- when compared to the control group (Table 2). There were significant (p<0.05 - 0.001) reductions in urea level of animals pretreated with the extract (150 - 450 mg/kg) when compared to the paracetamol group. Also, while there was significant (p<0.05 - 0.01) increases in creatinine levels of the extract treated groups when compared to control, significant (p<0.01) reductions were observed in creatinine levels of rats treated with the highest dose (450 mg/kg) of extract when compared to the paracetamol group. There were significant (p<0.05) decreases in the levels of Na^+ and K^+ of extract treated groups when compared to control and of Cl^-, (p<0.05 – 0.001) when compared to the paracetamol group. There was no significant effect on the level of H_{CO3}^- and the various effect of the extract were not comparable to that of silymarin 100 mg/kg (Table 3).

3.3 Histology

The kidneys of rats in the paracetamol groups revealed mild to moderate vascular related (acute and *subacute* extra-renal) injuries that depicted mild to moderate nephrotoxicity. The extract and silymarin treated groups showed kidneys with just mild to moderate vascular related (acute and *subacute* extra-renal) injuries and negligible nephrotoxicity. The kidneys of rats in control group had negligible to mild toxic tissue effect as evidenced by absence of glomerular necrosis/ thickening, and tubular necrosis (Plates I to VI). Thus, nephrotoxicity is restricted to the vascular system while the renal parenchymal tissues are spared. The results therefore shows a nephron protective effect by the extract at the doses administered.

Table 1: Effect of extract on weight of kidneys of rat with paracetamol-induced nephrotoxicity

Treatments mg/kg	Weight Of kidneys
Distilled water	0.59 ± 0.50
Distilled water/ Paracetamol	0.60 ± 0.01
Extract 150	0.52 ± 0.02
Extract 300	0.57 ± 0.02
Extract 450	0.57 ± 0.01
Silymarin 100	0.58 ± 0.01

Data are expressed as mean ± SEM. Significant at $^a p$<0.05, When compared to control, $^e p$<0.01, $^f p$<0.001 when Compared to paracetamol, n = 6.

Table 2: Effect of extract on indices of kidney function with paracetamol-induced nephrotoxicity in mice.

Treatments mg/kg	Na^+	K^+	Cl^-	HCO_3^-	Urea	Creatinine
Distilled Water	147.83 ± 0.40	8.58 ± 0.72	99.66 ± 0.21	23.5 ± 0.56	5.81 ± 0.33	50.5 ± 2.88
Distilled Water/ Paracetamol	146.33 ± 0.61	7.00 ± 0.37	103.66 ± 0.21	24.0 ± 0.36	7.78 ± 0.15^b	86.83 ± 5.67^c
Extract 150	146.33 ± 0.61	6.66 ± 0.13^a	99.33 ± 1.44	24.5 ± 0.56	5.65 ± 0.56^e	76.5 ± 2.88^b
Extract 300	141.16 ± 3.00	6.56 ± 0.11^a	99.00 ± 1.09^d	23.5 ± 0.22	4.18 ± 0.41^{af}	72.66 ± 8.17^a
Extract 450	140.83± 2.21^a	7.43 ± 0.26	94.33 ± 1.74^{af}	24.1 ± 0.74	4.5 ± 0.23^f	60.0 ± 4.74^e
Silymarin 100	147.83 ± 0.74	7.33 ± 0.49	104 ± 0.36	21.5 ± 0.56	4.88 ± 0.29^f	53.33 ± 2.15^f

Data are expressed as mean ± SEM. significant at $^a p$<0.05, $^b p$<0.01, $^c p$<0.001 when compared to control, $^d p$<0.05, $^e p$< 0.01, $^f p$<0.001 when compared to paracetamol, n = 6.

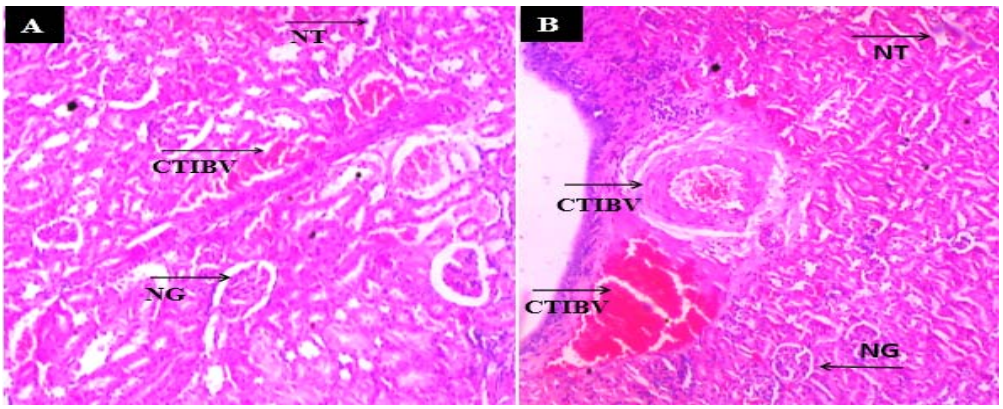

Plate I: Photomicrograph of rats kidney administered with distilled water showed preserved architecture with normal glomeruli (NG), normal tubules (NT) and congested to thrombosed interstitial blood vessels (CTIBV), H & E x 10 (A) and x 40 (B) magnification

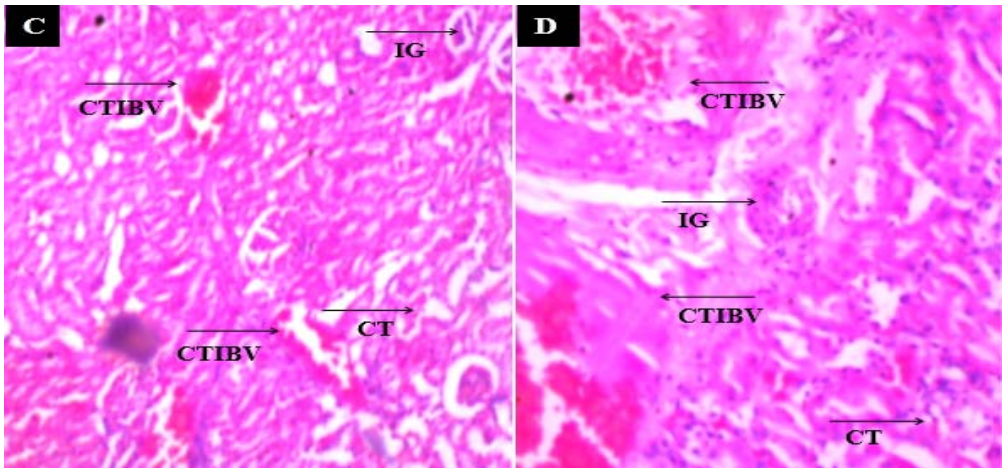

Plate II: Photomicrograph of rat's kidney administered with distilled water and paracetamol, (2000 mg/kg), showed distorted architecture with congested tubules (CT), inflamed glomerulus (IG) and congested to thrombosed interstitial blood vessels (CTIBV), 10 (C) and x 40 (D) magnification.

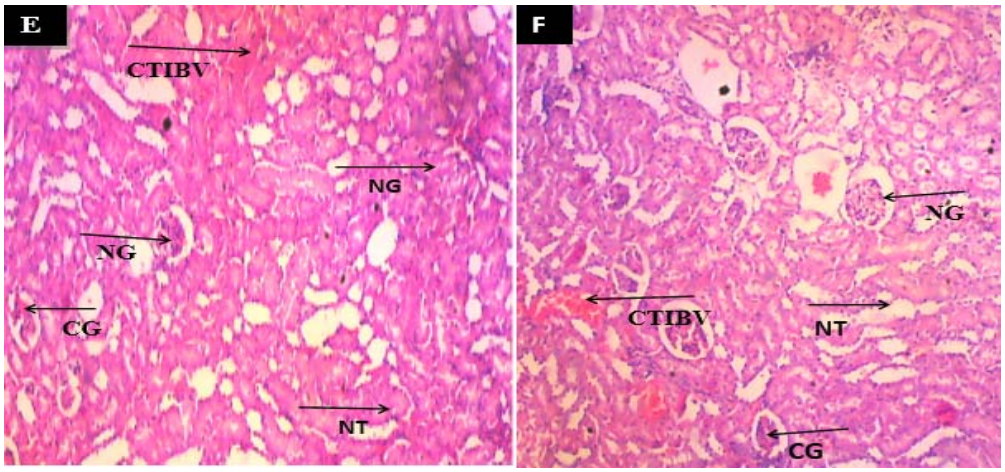

Plate III: Photomicrograph of rat's kidney administered with extract, (150 mg/kg),showed preservedarchitecture with normal glomeruli (NG), congested glomerulus (CG), normal tubules (NT), mild hemorrhage (MH) and congested to thrombosed interstitial blood vessels (CTIBV), H & E x 10 (E) and x 40 (F) magnification.

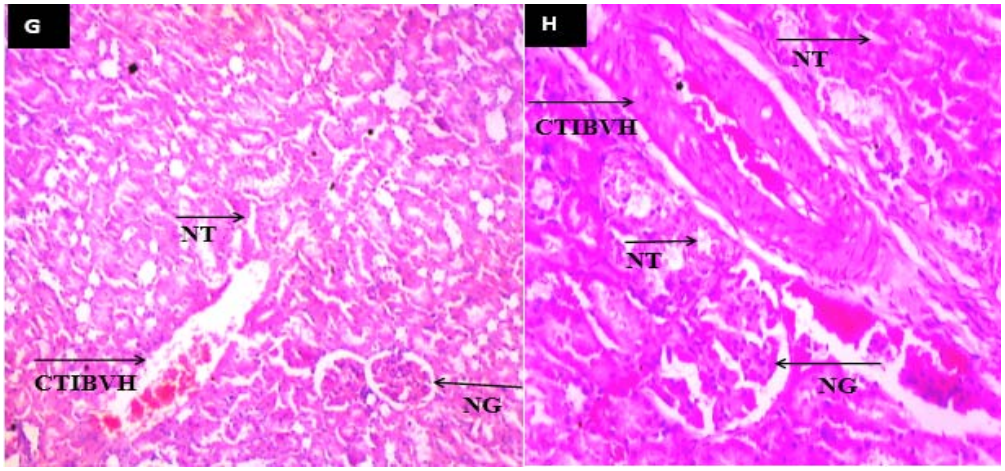

Plate IV: Photomicrograph of rat's kidney administered with extract, (300 mg/kg), showed preserved architecture with normal glomeruli (NG), normal tubules (NT) and congested to thrombosed interstitial blood vessels with haemorrhage (CTIBVH), H and E x 10 (G) and 40 (H) magnification.

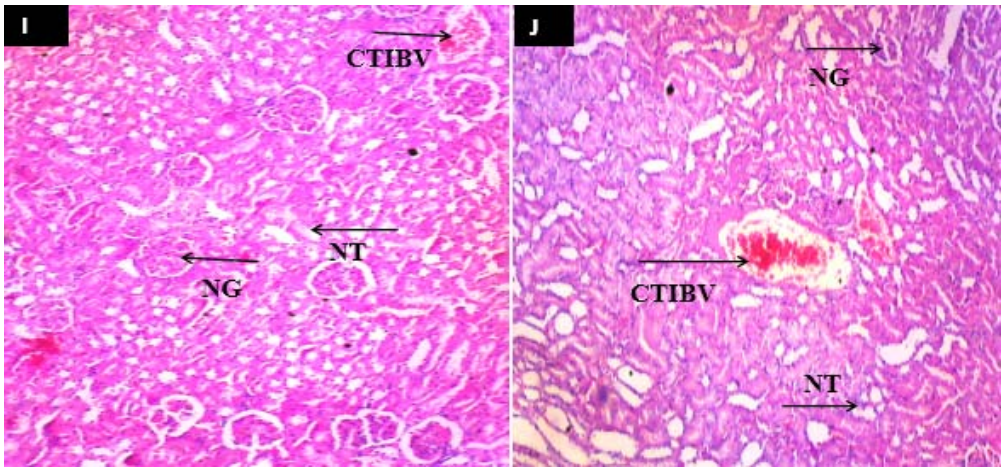

Plate V: Photomicrograph of rat's kidney administered with extract, (450 mg/kg), showed preservedarchitecture with normal glomeruli (NG), normal tubules (NT) and andcongested to thrombosed interstitial blood vessels (CTIBV), H & E x 10 (I) and 40 (J) magnification

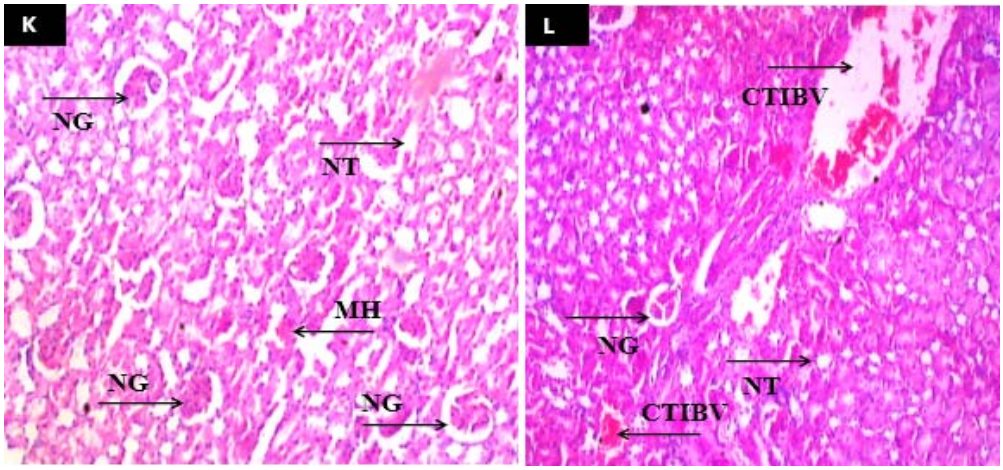

Plate VI: Photomicrograph rat's kidney administered with silymarin, (100 mg/kg), showed preserved architecture with normal glomeruli (NG), normal tubules (NT) congested throm thrombosed bosed interstitial blood vessels (CTIBV), H & E x 10 (K) x 40 (L) magnification.

4. Discussion

In this study to assess *S. megaphylla* extract nephroprotective activity against paracetamol-induced nephrotoxicity in rats, biochemical markers of kidney function such as blood urea, serum creatinine and electrolytes levels were considered. Administration of paracetamol 2 g/kg produced significant (p<0-01 - 0.001) increases in the levels of urea and creatinine when compared to the control group, depicting nephrotoxic effect. The urea and creatinine levels were significantly (p<0.05 - 0.001) reduced in the extract-treated (150 - 450 mg/kg) groups when compared to the paracetamol group. This reversal shows the nephroprotective effect of the extract on the nephrotoxic effect of paracetamol. There was no effect in Na^+, K^+, Cl^-, and HCO_3^- on administration of paracetamol.

Kidneys are involved in the excretion of various xenobiotics, pollutants, toxins and are exposed to high quantities of free radicals which contribute to high oxidative stress which are responsible for the pathogenesis of kidney damage. Large quantities of oxidative free radicals such as superoxide anions and derivatives, especially the highly reactive and damaging hydroxyl radical which induces peroxidation of cell membrane lipids [5], are generated in living cells causing tissue damage [6].The production of reactive oxygen species (ROS) causes cell damage from the cytotoxic action of oxygen and nitrogen derived free radical species [7]. While antioxidants act as cells defense against free radicals, natural antioxidant systems are inactivated by lipid peroxidation and reactive oxygen species **(**ROS**)** [8]. The oxidation of unsaturated fatty acids in biological membranes by free radicals lead to decrease in membrane fluidity and disruption of membrane structure and function [9].

Paracetamol suppresses the activities of enzymatic antioxidants and renders the cells more susceptible to free radical induced injury, though non enzymatic antioxidants such as glutathione (GSH), Vitamin C and E considered as second line of defense against free radicals play a significant role in protecting the cells from oxidative damage [10]. GSH, a major non-protein thiol is considered an important endogenous defense against peroxidative destruction of cellular membranes. In the kidney, p-amino phenol is normally formed from paracetamol by deacetylation and excreted in urine. This exposes the kidney to damage and plays a major role in the pathogenesis of paracetamol induced renal damage [11, 12]. Hepatically derived glutathione conjugates are also involved in paracetamol induced renal injury [13].

Setariamega phylla root fractions have been shown to contain several components with antioxidant and free radical scavenging activities [1]. Astaxanthin provides cell membranes with potent protection against free radical or other oxidative attack and mediates inflammation biomarkers [14]. Borneolshows antioxidant activity by reducing intracellular reactive oxygen species (ROS) generation, attenuating the elevation of nitric oxide (NO), increasing inducible nitric

oxide synthase (iNOS) enzymatic activity and upregulating NOS expression [15]. The chemical pathology findings which shows increase in urea and creatinine on administration of paracetamol (nephrotoxicity) and a reversal of these parameters (nephroprotection) by the extract administration confirms the nephroprotective potential of the root extract. This is further supported by the histolo pathological findings that the groups treated with the extract and silymarin showed just mild to moderate vascular related (acute and *subacute* extra-renal) injuries with negligible nephrotoxicity.

5. Conclusion

The results of this research work reveals that *Setaria megaphylla* ethanol root extract through its phytochemical constituents possess significant nephroprotective activity and also validates its ethnomedicinal use. 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.

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