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BIOACTIVE CONSTITUENTS, ACUTE AND SUB-ACUTE EFFECT OF *TELFAIRIA OCCIDENTALIS HOOK F* (FLUTED PUMPKIN) LEAVES EXTRACT ON SOME KIDNEY FUNCTION INDICES IN RAT

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ABSTRACT

This study assessed the renal toxicity potentials of *Telfairia occidentalis Hook f,* a widely consumed vegetable in Nigeria and other parts of the world. Fifty healthy adult Wistar albino rats were randomly selected and divided into two groups A and B. Each group was divided into 5 sub-groups: 1, 2, 3, 4 and 5. Subgroup 1 served as the control group and was fed with standard animal feed only, while sub-groups 2, 3, 4 and 5 were test groups, and in addition to the standard animal feed, 500mg/kg, 1000mg/kg, 2000mg/kg and 4000mg/kg extract of *Telfairia occidentalis* leaves was orally gavaged to the test groups 2, 3, 4 and 5 respectively. Animals in group A were tested for acute effect after 10 days of extract administration. Those in group B were similarly assessed for sub-acute effect after 4 weeks of extract administration. Acute phase of extract administration produced significant increases only in K^+ and urea levels at $P < 0.05$ and $P < 0.01$ respectively. In the sub-acute phase, significant increases in total body weight ($P < 0.01$), kidney weight ($P < 0.01$), kidney to body weight ratio ($P < 0.001$), K^+ ($P < 0.001$), HCO^-_3 ($P < 0.01$) and urea ($P < 0.01$) were obtained. The effect of the extract on renal function indices may be dose-dependent, hence dosage adjustment may be necessary in patients with renal impairment.

Keywords: *Telfairia occidentalis*, renal functions, effects, rats.

INTRODUCTION

There is a widespread use of folk remedies globally especially in the developing countries of sub-Saharan Africa where more people are now seen using natural products derived from herbs, shrubs and trees of great medicinal value.

A similar trend is observed in the metropolitan areas of developed countries where the use of plants and plant products have increased tremendously with about 33% of the population using alternative medicine yearly (Zollman and Vickers, 1999). Apart from the medicinal values, plants have provided food, shelter and clothing for human being and domestic animals ever since the advent of civilization (Afag *et al*., 2011). According to World Health Organization, about 80% of people (mainly in the developing countries) rely on or choose to use medicinal plants to cover all or parts of their health care needs (WHO, 2002; Arukumar and Mutheselvan, 2009). Such upsurge in affinity for herbal remedy is probably due to a number of factors ranging from easy accessibility, non-involvement of expert consultation, safety to use and inadequacy of primary health care services.

One major drawback/limitation in the use of folk medicine is the inability to standardize the practice. Most of the herbal products used have not been subjected to a thorough phytochemical and biochemical analysis to ascertain the active ingredients responsible for the acclaimed numerous therapeutic effects and determine the safe dose and duration of administration. It is common to see practitioners treat their patients without pre-evaluation to determine possible contraindicating symptoms for a particular herbal regimen. To date, patients with end-stage organ damage such as diabetic and hypertensive nephropathy, fulminate hepatitis with imminent renal and hepatic failure are still taking unspecified herbal remedies for treatment of their conditions. Also with the increase use of herbal medicine, a number of idiosyncratic kidney toxic reactions to some of these herbal mixtures have been reported (Smith and Dillon, 2009). In some cases, the risk from the use of this mixture may over shadow potential benefits especially in the already immune and hepato-renal compromised individuals and also such periods as pre-dialysis, dialysis and the post kidney transplant (Combest *et al*., 2005).

The incidence of renal toxicity associated with the ingestion of medicinal herb and leading to kidney failure is increasing day by day and is in literature. In Nigeria, an uncertified herbal preparation is one of the etiologic factors in an estimated 30 million diagnosed kidney problems. In Africa, about 35% of all causes of Acute Renal Failure are associated with the use of traditional remedies (Luyckx *et al*., 2002).

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Luyckx *et al*. (2005) in their study of acute renal failure in 78 patients associated with recent folk remedy use reported a mortality of 41%, worse in adults (45.5%) and patients with both renal and liver dysfunctions (62.5%) than those with renal dysfunction only (22.6%). Similar nephrotoxic effect has been recorded in over 100 people in Belgium who ingested a Chinese weight loss/slimming remedy containing aristolochic acid (Vanherweghem *et al*., 1993; Combest *et al*., 2005), and in the Balkans, a similar type of nephropathy was recorded and termed "Balkan Endemic Nephropathy" (Tatu *et al*., 1998).

Luyckx *et al*. (2005), also reported metabolic acidosis in 80.8% and volume depletion in 62.8% of patients with renal failure after a recent folk remedy use. Again, plasma electrolytes alteration (K^+, Na^+, Ca^{2+}, HCO^-_3, Cl^-, PO^-_4) have been associated with the effect of some herbal remedies, thus altering the acid/base balance required for normal homeostatic processes in the body.

However, the use of folk remedies should not be completely condemned to extinction, as there are growing amount of evidences that showed that some folk remedies possessed a remarkable nephro protective effect (Combest *et al*., 2005). A study demonstrated that Silibinin protected renal tubular cells from oxidative damage from cisplatin (Gaedeke *et al*., 1996). Extract of roots and rhizomes of *Picrorhiza kurrooa* offers protection against various renal toxins. Picroliv protects the kidney in a renal ischemia-reperfusion induced injury model in rats (Seth *et al*., 2000). In the light of these, this study was set to evaluate the renal toxicity/protective potentials of acute and sub-acute administration of leaf extract of *Telfairia occidentalis Hook f*, a common and widely used vegetable in Nigeria, most parts of sub-Saharan Africa and other countries of the world.

Telfairia occidentalis Hook f is a vegetable from the tribe of Joliffieae of the sub-family Cucurbitaceae. The leaves are nutritious and are used in preparing soup, salad, in baked goods and other confections (Axtell, 1992). Documented evidence showed that the herb is used in the treatment of anemia, convulsion, atherosclerotic cardiovascular disorders, high blood pressure, hyperglycemia, dyslipidemia, arthritis, liver problems and inflammatory conditions (Ajayi *et al*., 2000; Alada, 2000; Oluwole *et al*., 2003; Eseyin *et al*., 2007; Eseyin *et al*., 2010). Because of these wide nutritive and therapeutic spectra, it has been extensively studied and found to contain some bioactive substances such as: tannins, hence its purgative (Adeniyi *et al.*, 2010), anti asthmatic, antitussive and anti hay fever effect (Gills, 1992). Others include terpenoid, an antifeedant with insecticidal property. Flavonoids and Saponins are also present (Khalid *et al*., 1989; Adeniyi *et al*., 2010). Flavonoid compounds are found to possess antimicrobial, antifungal, antiviral, hypoglycemic, anti parasitic and anti-inflammatory while saponin containing compounds are found to possess antimicrobial, immune stimulating, hypo-cholesterolemic, anti-carcinogenic, anti protozoan, anti oxidant, hypoglycemic and antifungal effects (George *et al*., 2002, Wallace *et al*., 2004; Pinarosa *et al*., 2006).

Despite these extensive nutritive and therapeutic uses, there exist paucity of information about the effect of this herb on some vital organs (e.g. kidney) involved in biotransformation and excretion of drugs, chemicals and other xenobiotics. This organ is also involved in maintenance of water and electrolytes, synthesis and metabolism of proteins and waste products of metabolism. Compelling evidences have shown that some drugs, chemicals, toxins and herbal remedies directly or indirectly interfere with the kidney functions causing some levels of functional derangement, and could reflect on performing routine renal function tests.

In clinical practice, plasma enzymes, proteins, urea, creatinine and electrolytes usually use for this purpose. This study was therefore set to assess the acute and sub-acute effects on the renal biochemical status in rats fed with aqueous extract of *Telfairia occidentalis* leaves using the above-mentioned parameters.

We hope the results of this research work will help to produce additional information about this widely consumed herb to its consumers in our communities and similar communities worldwide.

MATERIALS AND METHODS

Collection and identification of plant samples

Telfairia occidentalis leaves were obtained from the agricultural farm in Uyo Local Government Area in Akwa Ibom State, and authenticated by a Taxonomist in the Department of Botany, University of Uyo, Nigeria. Two (2) kg weight of the leaves was measured using OHAUS electronic weighing balance. The leaves were washed, oven dried and pulverized into powder. This powder was macerated with 200ml of water, then stored in the refrigerator at 4^oC for 48 hours, and sieved with a white clean cloth.

The filtrate was evaporated by heating in water bath at 40^oC to obtain a solid extract, and the extract reconstituted with normal saline for use in the study.

Collection and maintenance of animals

Fifty adults healthy Wistar albino rats weighing 150-200g were obtained from the animal house of the Faculty of Basic Medical Sciences, University of Uyo, Nigeria, and randomly divided into two groups A and B; each group consisting of twenty-five rats of 5 sub-groups; 1, 2, 3, 4 and 5 with five rats per sub-group. Subgroup 1 in each group served as the control and fed with standard animal

feed (Bendel Feed and Flour Mill Ltd, Benin) only, while sub-groups 2, 3, 4 and 5 were the test groups and in addition to the standard animal feed, they were orally gavaged with 500mg/kg, 1000mg/kg, 2000mg/kg and 4000mg/kg body weight of the extract respectively. Lethality studies put the LD_{50} of *Telfairia occidentalis* extract at about 5244.04mg/kg, from which convenience doses were chosen to preclude the lethal range.

The experimental animals were weighed before treatment commenced and housed in a standard wooden cage with wooden shavings as their beddings, kept and maintained in the animal house of the Faculty of Basic Medical Sciences, University of Uyo for one week prior to the study to allow for acclimatization. They had free access to water adlibitum, good light and maintained in room temperature. After 10 days of extract administration, all the experimental rats' in group A were weighed again and then sacrificed after being anaesthetized. They were dissected to expose the heart and blood was obtained through cardiac puncture into specimen bottles with no anticoagulant and sent to a chemical pathology unit of the University of Uyo Teaching Hospital for the analysis. The kidney of each rat was removed and the weight measured and recorded.

Similar procedures were repeated for the experimental animals in group B after 4 weeks of extract administration. The research protocols were carried out the University of Uyo, according to the rules in Nigeria (Revised Helsinki Declaration, 2008) governing the use of laboratory animals as acceptable internationally.

Biochemical Assays

U-boat 5ml of blood was obtained, stored for 1 hour in the plain specimen bottle and later centrifuged to obtain the plasma which was used for the analysis. Serum urea was determined by a simple direct method of Marsh *et al*. (1965) Creatinine by Hinegard and Tiderstrom method (1973). Bicarbonate and chloride were estimated using the modified titrimetric method of Van Slyke stated by Varley (1969). Potassium and sodium were determined by flame emission photometer using Lithium as internal standard.

STATISTICAL ANALYSIS

The mean and its corresponding standard errors were calculated for each of the indices. Differences in renal indices in relation to research groups were compared using one-way analysis of variance (ANOVA). Probability values less than 0.05 were considered statistically significant. Statistical analysis was performed using the statistical package for social sciences (SPSS 17.0).

RESULTS

Table 1 results showed that acute administration of *Telfairia occidentalis* leaves extract on experimental animals caused a non-significant difference in sodium ($P = 0.052$), calcium ($P = 0.055$), bicarbonate ($P = 0.366$), chloride ($P = 0.101$), creatinine ($P = 0.440$), kidney weight ($P = 0.660$), kidney weight/body weight ratio ($P = 0.513$) and uric acid ($P = 0.707$) between test and control groups. Although sodium, body weight, kidney weight/body weight ratio were higher in group 3, bicarbonate in group 2, calcium, chloride, creatinine, uric acid, kidney weight in group 4 respectively.

Potassium and urea were significantly higher in group 4 than other groups at ($F = 2.78$, $P = 0.025$), and ($F = 6.37$, $P = 0.008$) respectively (Fig. 1).

Table 2 results showed that sub-acute administration of extract caused significant differences in potassium ($F = 10.23$, $P = 0.00$), bicarbonate ($F = 5.40$, $P = 0.004$), urea ($F = 6.71$, $P = 0.001$), body weight ($F = 38.03$, $P = 0.00$), kidney weight ($F = 24.09$, $P = 0.00$), kidney to body weight ratio between test and control groups (Fig. 2).

DISCUSSION

This study has shown that acute administration of aqueous extract of *Telfairia occidentalis* leaves did not cause significant changes in tested renal function parameters except K^+ and Urea, which significantly increased in the experimental groups at higher extract concentrations than control. In contradistinction, significant increase in total body weight, kidney weight, kidney to body weight ratio, K^+, HCO^-_3 and Urea levels were observed in all experimental groups in the sub-acute phase of the extract administration.

The results as obtained in the acute phase may imply the absence of a significant renal adverse effect of the extract when consumed at a low dosage and for a short period. This assertion lends credence to a recent research findings which showed that acute and sub-chronic administration of the extract of *T. occidentalis* leaves on rat do not result in any severe toxicological consequences (Akpan *et al*., 2011). However, it is worthy of note that the concentrations of the extract used in this study were higher than the above mentioned and could provide an explanation for the observed disparities on some of the parameters noted.

Table 1. Acute Effect of Administration of *T. occidentalis* Leaves Extract on Renal Function Indices in Rats.

Indices	Group – 1 (Control) (n=5)	Acute				F-Value	P-Value
		Group - 2 (500mg/kg)	Group - 3 (1000mg/kg)	Group - 4 (2000mg/kg)	Group - 5 (4000mg/kg)		
Na+ (mmol/L)	141.19±0.57	140.75 ± 0.48	140.25 ± 0.250	143.75 ± 1.75	140.0 ± 0.40	3.43	0.052^{NS}
K^+ (mmol/L)	4.12 ± 0.20	4.28 ± 0.41	4.13 ± 0.41	5.07 ± 0.13	5.48 ± 0.13	4.46	0.025^{*}
Ca^{2+} (mmol/L)	1.69 ± 0.005	1.69 ± 0.103	1.68 ± 0.014	1.74 ± 0.025	1.77 ± 0.047	2.78	0.055^{NS}
HCO^-_3 (mmol/L)	21.03 ± 0.39	21.75 ± 0.85	23.75 ± 0.48	22.75 ± 1.11	23.00 ± 0.41	1.16	0.366^{NS}
Urea (mmol/L)	4.20 ± 0.20	4.61 ± 0.13	4.67 ± 0.24	4.68 ± 0.24	5.25 ± 0.16	6.37	0.008^{**}
Chloride (mmol/L)	99.81 ± 0.42	98.75 ± 0.75	99.50 ± 0.65	99.50 ± 0.87	101.50 ± 0.65	2.59	0.101^{NS}
Creatinine (µmol/L)	63.25 ± 4.71	63.50 ± 7.94	67.50 ± 2.84	68.00 ± 3.24	75.25 ± 5.85	0.968	0.440^{NS}
Uric acid (mmol/L)	0.25±0.0003	0.252 ± 0.004	0.254 ± 0.002	0.252 ± 0.002	0.256 ± 0.006	0.54	0.707^{NS}
Body weight g	153.80±3.06	157.84 ± 2.36	158.36 ± 2.16	162.20 ± 5.59	160.20 ± 4.97	0.610	0.660^{NS}
Kidney Weight g	0.79 ± 0.015	0.80 ± 0.012	0.79 ± 0.014	0.79 ± 0.014	0.83 ± 0.041	0.531	0.715^{NS}
Kidney Weight/ Body weight Ratio	0.0050 ± 0.0002	0.00491 ± 0.0001	0.00502 ±	0.00506 ± 0.00009	0.00541 ± 0.00036	0.843	0.513^{NS}

Values are represented as means ± standard error of means (means ± SEM)
NS P > 0.05 not significant at 5%, *P < 0.05 significant at 5% and **P < 0.01 significant at 1%.

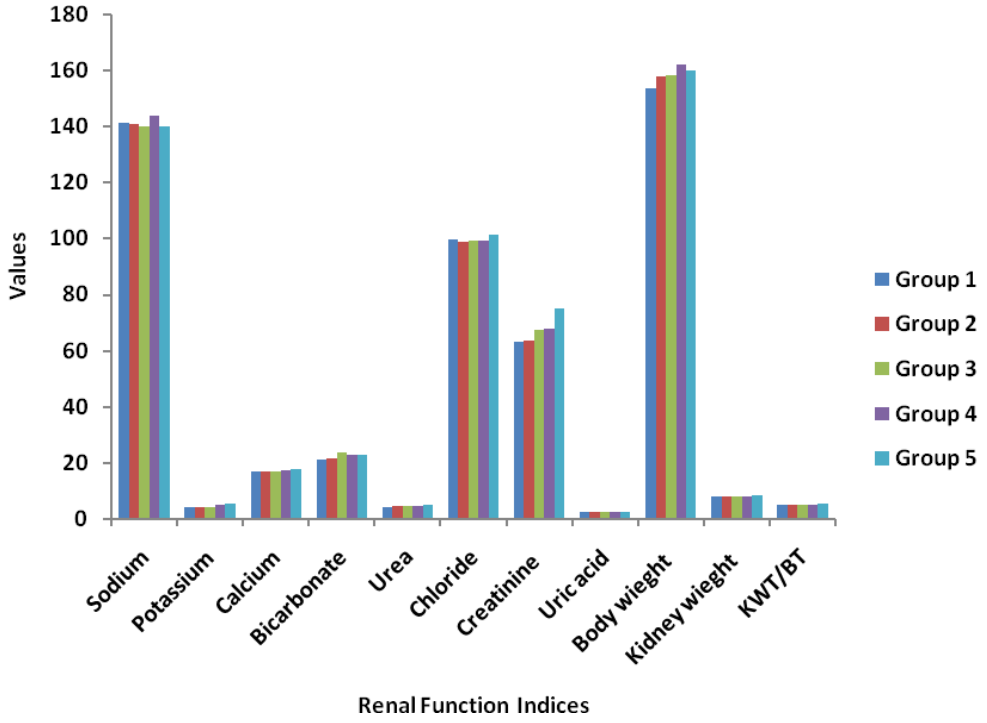

Fig. 1. Cluster bar chart showing acute effect of *T. occidentalis leaves* on renal function indices.
Note: 10, 100, 10 and 100 multiplied Values of calcium, uric acid, kidney weight, ratio of kidney weight to body weight plotted respectively. KWT= Kidney weight and BT = Body weight

Also, of great significance is the dose dependent increase in body weight of the animals in the test groups, which occurred exponentially up to the dose of 2000mg/kg body weight in both acute and sub-acute phases of the extract administration. This may be due to the presence of some rich nutrients in the extract, with the concentration of such nutrients being proportional to the quantity of the extract consumed at a given time. The peak nourishing effect of the nutrients could have reached at a maximum dose of 2000mg/kg body weight. Beyond this, the extract may become toxic to the animals. Such effect could also offer a possible explanation for the significant changes in the levels of K^+ and urea at higher doses of the extract observed in the acute and sub-acute phases of the administration. These assertions are consistent with studies that showed that *Telfairia occidentalis* contain

Table 2. Sub-acute Effect of Administration of *T. occidentalis* Leaves Extract (aqueous) on Renal Function Indices in Rats.

Indices	Group – 1 (Control) (n=5)	Groups				F-Value	P-Value
		Group - 2 (500mg/kg)	Group - 3 (1000mg/kg)	Group - 4 (2000mg/kg)	Group - 5 (4000mg/kg)		
Na+ (mmol/L)	142.8 ± 1.07	145.40 ± 1.02	147.80 ± 2.08	148.0 ± 1.70	148.80 ± 1.39	2.65	0.064^{NS}
K^+ (mmol/L)	4.70 ± 0.19	4.72 ± 0.17	5.15 ± 0.165	5.76 ± 0.14	5.64 ± 0.68	10.23	$< 0.001^{***}$
Ca^{2+} (mmol/L)	1.950±0.005	2.14 ± 0.103	2.15 ± 0.103	2.20 ± 0.025	2.23 ± 0.047	2.78	0.055^{NS}
HCO^-_3 (mmol/L)	23.09 ± 0.30	21.86 ± 0.21	22.03 ± 0.73	23.54 ± 0.86	24.90 ± 0.031	5.40	0.004^{**}
Urea (mmol/L)	4.54 ± 0.21	4.66 ± 0.102	4.80 ± 0.21	4.79 ± 0.10	5.32 ± 0.124	6.71	0.001^{**}
Chloride (mmol/L)	97.29 ± 0.73	98.07 ± 0.55	98.64 ± 0.24	98.60 ± 0.24	98.87± 0.1196	2.10	0.132^{NS}
Creatinine (µmol/L)	68.00 ± 336	70.60 ± 2.58	69.54 v 1.35	76.25 ± 2.24	77.80 ± 4.51	1.92	0.146^{NS}
Uric acid (mmol/L)	0.280±0.0023	0.281± 0.0002	0.283 ± 0.002	0.282± 0.0002	0.282± 0.0002	1.38	0.278^{NS}
Body weight g	153.04±0.32	155.68 ± 0.10	158.72 ± 0.04	166.84 ± 0.33	159.88 ± 1.83	38.03	$< 0.001^{***}$
Kidney weight g	0.788 ± 0.003	0.739 ± 0.002	0.836 ± 0.023	0.730 ± 0.033	0.949 ± 0.004	24.09	$< 0.001^{**}$
Kidney weight/ Body weight	0.0052 ± 0.000001	0.0047 ± 0.00002	0.0053 ± 0.00015	0.0044 ± 0.002	0.0059 ± 0.00008	25.09	$< 0.001^{***}$

Values are reported as means ± SEM.
NS P>0.05 not significant at 5%, $^{*}P < 0.05$ significant 5%, $^{**}P < 0.01$ significant at 1%, $^{***}P < 0.001$ significant at 0.1%.

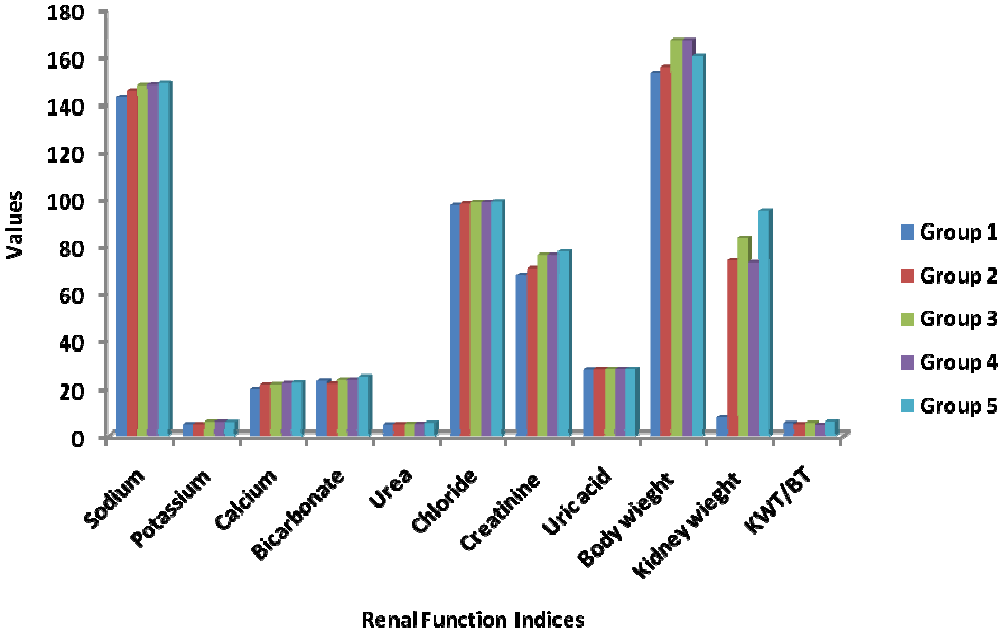

Fig. 2. Cluster bar chart showing sub acute effect of *T. occidentalis leaves* on renal function indices.
Note: Values of calcium, uric acid, kidney weight, ratio of kidney weight to body weight plotted were multiplied by 10, 100, 10 and 1000 respectively. KWT= Kidney weight and BT = body weight.

unique nutritional and phytochemical constituents, which can exert varied physiological and biochemical effects (Longe *et al*., 1983). In addition, *T. occidentalis* extract may contain some growth stimulating factors, which could be due to its well-balanced amino acid profile (Leung *et al*., 1968).

Akoroda (1990), in his study showed that *T. occidentalis* leaf extract is highly nutritive and very rich in protein (21-37%), ash (14%), fat (13%) and fiber (13%). Kayode and Kayode (2010) demonstrated the rich mineral content of *T. occidentalis* extract to include iron, potassium, sodium, phosphorus, calcium and magnesium. High levels of antioxidants and vitamins such as thiamine, riboflavin, nicotinamide and ascorbic acid were also present.

Again, several other studies have shown that the extract of *T. occidentalis* constitute a rich source of an array of amino acids such as alanine, aspartate, glycine, glutamine, histidine, lysine, methionine, tryptophan, cysteine, leucine etc (Tindall, 1968; Fasuyi, 2006; Kayode and Kayode, 2010). The growth stimulating and enhancing the effect of

the above-mentioned nutrients is well understood and documented. Thus, this result stands in clear support with findings by Fasuyi and Nonyerem (2007) who observed that birds kept on 15% *T. occidentalis* leaves meal dietary inclusion level had the highest weight gain with subsequent weight reduction, at doses greater than the 15% extract concentration. Another study by Iweala and Obidoa (2009) showed that if the dose of extract is kept low at a tolerable level, it could be administered or consumed for a longer period without weight loss and hence toxic effects since changes in body weight could be seen as an indicator of adverse effect of drugs and other chemicals (Raza *et al*., 2002). In the same vein, Saalu *et al*. (2010) demonstrated evidence of testicular protective effect in rats treated with dose of *T. occidentalis* extract < 400mg/kg body weight and testicular toxic effect at concentrations > 400mg/kg body weight. These observations lend validity to the testicular protective and spermatogenic enhancing effects observed previously (Nwangwa *et al*., 2007).

The toxicity potentials of the *T. occidentalis* observed at higher doses of the extract may be due in part to the presence of some anti-nutrients found in the extract. Fasuyi and Nonyerem (2007) detected the presence of hydrogen cyanide (HCN), tannic and oxalic acids at levels of 61.2 ± 0.02, 43 ± 0.07 and 80.7 ± 5.01mg/100g of *T. occidentalis* leaves extract respectively. Akwaowo *et al*. (2000) in a similar study detected very high levels of cyanide (60.1mg/100g), and tannin (40.6mg/100g) in young leaves of *T. occidentalis*. Oxalate (10.0mg/100g) and phytate (48.8mg/100g) were also present but at higher concentrations in the older leaves. Generally, these anti-nutrients are usually present in very low and nontoxic concentrations, but at high doses of the extract or if the extract is administered for prolonged period, they accumulate to a toxic levels. For example, several studies have indicated that, chronic cyanide exposure or exposure to high concentrations for a short time may be deleterious to renal functions such as alteration in electrolyte balance, acid/base disturbances, metabolism and excretion of metabolic by-products such as urea and xenobiotics. Cyanide impairs some of these functions by inhibiting the activities of Na^+ - K^+ - ATPase (Okolie *et al*., 1994). Thus, it could be correct to assert that the high levels of potassium, urea and bicarbonate recorded in the acute and sub-acute phases of this study could be partly due to the effect of these anti nutrients that could have accumulated due to high doses or prolonged administration of the extract. This assertion obtains its validity from the observation that significantly high levels of serum urea and creatinine resulted from an experimental animal group treated with added cyanide than control (Okolie and Osagie, 1999; Elsaid and Eikomy, 2006). It could also be correct to assert that, higher level of K^+ and urea recorded in this study could be due to high levels of K^+ found in the extract, and urea, as a by-product of amino acid metabolism as the extract may provide enough substrate to the urea cycle through its high amino acid content. At high doses of the extract, serum K^+ and urea level may be elevated as noted in this study. Extract of *T. occidentalis* may therefore be renal protective or toxic depending on the dose and duration of administration. This finding could inform practitioners and users for dosage adjustment in patients with impaired renal functions, taking K^+ sparing drugs, on a high protein diet, and patients with metabolic alkalosis. Paradoxically, higher potassium level could be useful in patients with metabolic alkalosis, diabetic keto acidosis, gastrointestinal fluid loss (diarrhea, vomiting), and those on potassium losing diuretics (e.g. Furosemide). Thus, precautional use of the extract could provide benefits while misuse could lead to serious adverse health effect.

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