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Nephrotoxic and *in vivo* Antioxidant Effects of *Citrullus Lanatus* Seed Extract

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Abbreviations: SOD: Superoxide Dismutase; ROS: Reactive Oxygen Species; BDH: British Drug House; GSH: Reduced Glutathione; MDA: Malondialdehyde

ABSTRACT

Background: *Citrullus lanatus* seeds are known to be highly nutritious, and rich sources of phenolic compounds. They are usually milled into flour and used for making sauces, snacks, and cooking oil.

Aim: To investigate the *in vivo* antioxidant capacity and effect of sub-chronic doses of methanol extract of *C. lanatus* seed on renal function.

Methods: Adult male Wistar rats (n = 35) weighing 130 to 170g (mean weight = 150 ± 20g) were randomly assigned to seven groups of five rats each: normal control, Tween 80 control, and five treatment groups. Rats in the treatment groups received graded doses of the extract (10 - 5000 mg/kg body weight, bwt) orally for 35 days. Indices of renal function and oxidative stress were assayed.

Results: The absolute and relative weights of kidneys of rats in each group were not significantly affected by extract treatment ($p > 0.05$). There were significant increases in the final body weight and percentage weight increase in the treatment groups, relative to normal control group ($p < 0.05$). Methanol extract of *C. lanatus* seed did not significantly alter the levels of electrolytes, creatinine, malondialdehyde (MDA) and reduced glutathione (GSH), as well as activity of Superoxide Dismutase (SOD) among the groups ($p > 0.05$). Moreover, Tween 80 significantly increased the levels of bicarbonate ion, urea and urea/creatinine ratio ($p < 0.05$).

Conclusion: These results show that methanol extract of *Citrullus lanatus* seed is not nephrotoxic and possesses high antioxidant activity *in vivo*.

Introduction

Citrullus lanatus (watermelon) seeds are often discarded after consumption of the pulp [1]. These seeds are sources of phytochemicals such as phenols, alkaloids and saponins. It was only recently attention was given to the possible utilization of *C. lanatus* seeds in the production of new ingredients for food enrichment [2,3]. *Citrullus lanatus* seeds are milled into flour and used to prepare snacks and sauces. The oil is used for cooking and production of cosmetics [4]. The seeds of this medicinal plant are rich in protein, vitamins, minerals and fat [5,6]. Secondary metabolites present in *C. lanatus* seeds are responsible for its many pharmacological activities, such as analgesic, anti-inflammatory, anti-ulcer, antioxidant, as well as hepatoprotective properties [7-9]. Antioxidants are substances/molecules that have the capacity to inhibit or counteract the damaging effects of oxidation in animal and plant tissues [10]. Reactive Oxygen Species (ROS) cause lipid peroxidation and oxidative stress which damage biological macromolecules such as proteins, lipids and DNA [11-13].

Oxidative stress has been linked with chronic diseases such as cancer, diabetes mellitus, aging and other degenerative diseases [4]. Phenolic compounds are the most active natural antioxidants in plants [14]. Their free radical scavenging ability is due to the presence of hydroxyl group which is directly bonded with the aromatic (phenyl) ring [15,16]. Equilibrium between the levels of ROS and antioxidants is vital for the elimination of the adverse effects of oxidative stress in biological systems [17-21]. Lipid peroxidation-induced renal injury is often initiated by free radical

attack on membrane polyunsaturated fatty acids leading to their transformation to alkanes and reactive aldehyde such as MDA [22]. Oxidative stress occurs when the production of harmful free radicals overwhelms the protective capability of antioxidant defense system [23]. Both enzymatic and non-enzymatic antioxidant systems exist to combat oxidative stress under physiological conditions [24-26].

Antioxidant enzymes such as catalase, SOD, glutathione peroxidase (GPx), glutathione reductase (GR), as well as molecule such as GSH are used as indices of oxidative stress [27-30]. Studies have shown that accumulated oxidative damage occurs from decreased levels of these enzymes rather than increased ROS production [31,32]. However, adequate levels of both are vital for normal cell function. Kidney, an organ that metabolizes harmful substances besides liver, is constantly perfused with huge volume of blood carrying different kinds of compounds, thereby making it at high risk of toxicity [33,34]. High levels of blood creatinine are found in renal dysfunction or muscle injury [35]. Levels of specific ions such as sodium (Na+), potassium (K+), chloride (Cl−) and bicarbonate (HCO3−) are used as biomarkers of electrolyte imbalance [36]. Electrolytes promote fluid balance via maintenance of blood volume, fluid absorption and generation of impulses.

In pathological conditions, electrolyte imbalance occurs with increased sodium and chloride, and decreased potassium levels [37,38]. Nephrotoxicity is characterized by morphological destruction of intracellular organelles, necrosis, and functional alterations such as depletion of antioxidant defense system and mitochondrial damage [39]. Oxidative damage is thought to be one of the major mechanisms involved in nearly all chronic renal pathologies [40-42]. Reports on the beneficial effects of *C. lanatus* seed abound, but little or nothing is known about its nephrotoxic effect. This study investigated the nephrotoxic and *in vivo* antioxidant effects of *C. lanatus* seed extract.

Materials and Methods

Chemicals and Reagents

All reagents used were of analytical grade. Electrolytes assay kits were products of Randox Laboratories Limited (UK). All other chemicals were obtained from British Drug House (BDH) (England), Merck (Germany) and Sigma-Aldrich Chemical Company (USA).

Plant Sample Collection

Citrullus lanatus seeds were obtained from a major market in Benin City, Edo State, Nigeria, and authenticated at the herbarium of the Department of Plant Biology and Biotechnology, University of Benin, Benin City, Nigeria.

Plant Preparation and Extraction

Plant seeds were washed and shade-dried at room temperature for a period of two weeks and pulverized using a mechanical blender. Methanol extract of the seeds was obtained using cold maceration method. Exactly 2kg of powdered seeds was extracted with 5L of absolute methanol for 96h with intermittent stirring. The extract was concentrated using rotary evaporator and freeze-dried via lyophilization.

Experimental Rats

Adult male Wistar rats (n = 35) weighing 130-170g (mean weight = 150 ± 20g) were obtained from the Department of Anatomy, University of Benin, Benin City. The rats were housed in metal cages under standard laboratory conditions: average temperature of 25 °C, 55-65 % humidity and 12-h light/12-h dark cycles. They were allowed access to rat feed (pelletized growers mash) and clean drinking water. Prior to commencement of the study, the rats were acclimatized to the laboratory environment for one week. The study protocol was approved by the Faculty of Life Sciences, University of Benin, Ethical Committee on Animal Use.

Experimental Design

The rats were randomly assigned to 7 groups (5 rats/group): normal control, Tween 80 control, and five treatment groups. Tween 80 was used to solubilize the extract before administration. Rats in the treatment groups received graded doses of the extract (10 - 5000 mg/kg bwt) orally for 35 days.

Collection of Blood and Tissue Samples: At the end of the treatment period, the rats were anaesthetized with chloroform vapor. Blood samples were drawn from each rat heart via cardiac puncture into heparin containers and centrifuged at 3000 rpm for 10 min to obtain plasma which was used for biochemical analysis. The kidneys were excised, weighed and used to prepare 20 % tissue homogenate.

Biochemical Analysis: Kidney function parameters (creatinine, urea and electrolytes) and levels of GSH and MDA, and activity of SOD were determined using their respective assay kits.

Statistical Analysis

Data are expressed as mean ± SEM. Statistical analysis was performed using SPSS (21.0). Groups were compared using Student t-test. Statistical significance was assumed at $p < 0.05$.

Results

Effect of Methanol Extract of *C. lanatus* Seed on Body and Organ Weights of Rats

The absolute and relative weights of kidneys of rats in each group were not significantly affected by extract treatment ($p > 0.05$). There were significant increases in the final body weight and percentage weight increase in the treatment groups, relative to normal control group ($p < 0.05$). These results are shown in (Tables 1&2).

Table 1: Changes in Body Weight of Rats Administered Methanol Extract of *C. lanatus* Seed.

Group	Final Weight (g)	Initial Weight (g)	Increase in Weight (g)
Normal control	167.20 ± 6.73	139.80 ± 4.58	27.40 ± 4.37a
Tween 80 control	228.60 ± 5.51	159.60 ± 2.01	69.00 ± 3.65b
10 mg extract/kg bwt	221.40 ± 8.76	145.60 ± 7.55	75.80 ± 2.03b
100 mg extract/kg bwt	221.00 ± 10.04	130.80 ± 9.81	79.20 ± 2.71b
1000 mg extract/ kg bwt	231.40 ± 9.34	153.20 ± 7.93	78.20 ± 2.75b
2000 mg extract/kg bwt	235.20 ± 10.37	157.20 ± 11.60	78.00 ± 0.45b
5000 mg extract/kg bwt	235.40 ± 11.41	148.40 ± 11.41	77.00 ± 3.92b

Note: Data are reported as mean ± SEM (n = 5). The values with different superscript within the same row or column showed significant differences ($p < 0.05$).

Table 2: Relative organ to body weight of rats administered methanol extract of *C. lanatus* seed.

Group	Kidney Weight (g)	Final Body Weight (g)	Kidney Weight/Body Weight
Normal control	0.53 ± 0.03	167.20 ± 6.37	3.20 ± 0.23
Tween 80 control	0.64 ± 0.03	228.60 ± 5.51a	2.80 ± 0.19
10 mg extract/kg bwt	0.65 ± 0.04	221.40 ± 8.76a	3.50 ± 0.73
100 mg extract/kg bwt	0.68 ± 0.07	210.00 ± 10.04a	3.30 ± 0.45
1000 mg extract/ kg bwt	0.61 ± 0.06	231.40 ± 9.34a	2.60 ± 0.12
2000 mg extract/kg bwt	0.63 ± 0.02	235.20 ± 10.73a	2.70 ± 0.16
5000 mg extract/kg bwt	0.65 ± 0.47	225.40 ± 11.41a	2.90 ± 0.34

Note: Data are expressed as mean ± SEM (n = 5). Values with superscript (a) differ significantly from the normal control value ($p < 0.05$).

Effect of Methanol Extract of *C. lanatus* Seed on Levels of Electrolytes

Methanol extract of *C. lanatus* seed did not significantly alter the levels of electrolytes and creatinine ($p > 0.05$). Moreover, Tween 80 significantly increased the levels of bicarbonate ion, urea and urea/creatinine ratio ($p < 0.05$; Tables 3 and 4).

Table 3: Effect of Methanol Extract of *C. lanatus* Seed on Levels of Electrolytes.

Group	Parameter			
	Na+ (µM)	K+ (µM)	HCO3- (µM)	Cl- (µM)
Normal control	140.00 ± 3.51	7.90 ± 0.35	14.67 ± 1.36	102.67 ± 2.60
Tween 80 control	140.00 ± 0.58	7.89 ± 0.96	22.33 ± 1.76a	103.67 ± 1.20
10 mg extract/kg bwt	135.00 ± 4.04	5.37 ± 0.32	20.00 ± 1.15a	99.00 ± 4.04
100 mg extract/kg bwt	135.00 ± 3.79	6.73 ± 0.90	21.00 ± 1.53a	101.00 ± 4.16
1000 mg extract/ kg bwt	139.33 ± 1.20	8.70 ± 0.60	22.33 ± 1.45a	106.00 ± 1.15
2000 mg extract/kg bwt	145.33 ± 4.41	6.70 ± 0.96	21.00 ± 1.15a	106.67 ± 3.53
5000 mg extract/kg bwt	142.33 ± 1.33	8.20 ± 0.93	21.00 ± 1.00a	106.67 ± 1.86

Note: Data are levels of electrolytes and are expressed as mean ± SEM (n = 5). Values with superscript (a) differ significantly from the normal control value ($p < 0.05$).

Table 4: Effect of Methanol Extract of *C. lanatus* Seed on Levels of Urea and Creatinine.

Group	Urea (mg/dL)	Parameter Creatinine (mg/dL)	Urea/ Creatinine
Normal control	37.67 ± 3.38	0.83 ± 0.03	45.39 ± 3.11
Tween 80 control	50.00 ± 2.65a	0.83 ± 0.20	60.24 ± 3.09a
10 mg extract/kg bwt	44.00 ± 1.53a	0.77 ± 0.15	57.14 ± 2.01a
100 mg extract/kg bwt	50.00 ± 6.11a	1.00 ± 0.10	50.00 ± 0.80a
1000 mg extract/ kg bwt	48.00 ± 3.46a	0.77 ± 0.09	62.34 ± 2.16a
2000 mg extract/kg bwt	51.67 ± 3.71a	0.83 ± 0.15	62.25 ± 2.81a
5000 mg extract/kg bwt	47.67 ± 2.73a	1.00 ± 0.00	47.67 ± 1.01

Note: Data are renal function indices and are expressed as mean ± SEM (n = 5). Values with superscript (a) differ significantly from the normal control value ($p < 0.05$).

Effect of Methanol Extract of *C. lanatus* Seed on Oxidative Status of Normal Rats

There were no significant differences in MDA and GSH levels and activity of SOD among the groups ($p > 0.05$; Table 5).

Table 5: Effect of Methanol Extract of C. lanatus Seed on Oxidative Status of Normal Rats.

Group	MDA (mole/mg protein) $x10^{-5}$	Parameter GSH (mg/dL)	SOD (unit/mg protein) $x10^{-4}$
Normal control	8.90 ± 1.30	17.17 ± 0.05	1.20 ± 0.09
Tween 80 control	6.50 ± 1.10	15.02 ± 0.41	2.10 ± 0.06
10 mg extract/kg bwt	5.70 ± 4.80	16.30 ± 0.37	1.40 ± 0.09
100 mg extract/kg bwt	7.10 ± 0.57	16.45 ± 0.34	1.80 ± 0.06
1000 mg extract/ kg bwt	8.60 ± 2.10	17.27 ± 0.82	1.60 ± 0.03
2000 mg extract/kg bwt	6.00 ± 1.00	17.08 ± 0.61	0.90 ± 0.02
5000 mg extract/kg bwt	5.30 ± 3.50	15.58 ± 0.23	0.94 ± 0.04

Note: Data are oxidative stress markers and are expressed as mean ± SEM (n = 5).

Discussion

Electrolyte balance is crucial for normal cellular function. Electrolytes promote fluid balance via maintenance of blood volume, facilitation of fluid absorption and generation of impulses. Decreased electrolyte levels affects nerve conduction, as well as cell function [37]. Blood urea and creatinine are considered traditional indices of kidney function. Urea is a by-product of protein catabolism. About 90 % of urea produced is excreted through the kidneys [41]. Creatinine, a waste product of muscle catabolism, is excreted exclusively via the kidneys [42]. Therefore, renal damage reduces the kidney's capacity to excrete both urea and creatinine, thereby making them to accumulate in the blood. The results of this study showed that methanol extract of *C. lanatus* seed did not significantly alter the levels of electrolytes and creatinine. The observed increases in the levels of bicarbonate ion, urea and urea/creatinine ratio may have been due to Tween 80 that was used to solubilize the extract. Free radical generation leads to lipid peroxidation that causes renal injury [12]. Anti-oxidation is a significant event used as a preventive strategy against diseases [13].

Antioxidant enzymes such as catalase, SOD, GPx, GR, as well as molecule such as GSH are used as indices of oxidative stress [27-30]. Studies have shown that accumulated oxidative damage occurs from decreased levels of these enzymes rather than increased ROS production [31,32]. Superoxide Dismutase (SOD) catalyzes the dismutation of superoxide anion [24]. Therefore, marked reduction in its activity produces several deleterious effects due to accumulation of superoxide anion. Reduced Glutathione (GSH) is vital for recycling of cellular antioxidants, suppression of free radical-induced damage, detoxification of harmful compounds, as well as maintenance of redox status of the cell [43]. Increased GSH level protects tissues against organ-associated injury via reduction in susceptibility to toxic radicals [44]. Extracts of plants have been reported to potentiate the activity and level of SOD and GSH, respectively [45,46]. Malondialdehyde (MDA) is a commonly used index of lipid peroxidation [22]. In this study, there were no significant differences in the levels of GSH and MDA, and activity of SOD among the groups, an indication that methanol extract of *C. lanatus* seed may not alter the redox status of the cell in normal Wistar rats. The absolute and relative weights of kidneys of rats in each group were not significantly affected by extract treatment. Moreover, there were significant increases in the final body weight and percentage weight increase in the test groups when compared with the normal control group. The increase was not dose-depended on and may be attributed to Tween 80.

Conclusion

The results obtained in this study show that methanol extract of *Citrullus lanatus* seed is not nephrotoxic and possesses high antioxidant activity *in vivo*.

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