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Original Research Article

Hypolipidemic And Testicular Cytoarchitecture Protective Effects of the Hydromethanol Leaf Extract of *Craterispermum schweinfurthi* in Male Wistar Rats

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Abstract: Hyperlipidemia is implicated in many disease states, including arteriosclerosis, diabetes mellitus, hypertension, obesity and stroke amongst other illnesses. The present study describes the hypolipidemic and testicular cytoarchitecture protective effects of hydromethanol leaf extract of C*raterispermum schweinfurthi* using male Wistar rats as models. 64 male Wistar rats were acclimatized and subsequently randomly divided into 8 groups of 8 rats each. Diabetes was induced in all rat groups except Groups 1 and 8 using alloxan at a dose of 200mg/kg bw administered intraperitonially. Diabetes was confirmed after 72 hours of alloxan administration if the blood glucose level is ≥ 11.1 mmol/L (200mg/dl) and were daily treated with different concentrations of extract and phytosterol only for 28 days. Expectedly, significantly higher values of total cholesterol, triglyceride, low density lipoprotein, low values of high-density lipoprotein and significant reduction in the population of epithelial germ cells and normal matured spermatozoa in the testes were observed amongst group 2 (Untreated Diabetes) rats administered 200mg/kg bw of alloxan, compared to group 1 (Control) rats ($p<0.05$). Suggesting a possible hyperlipidemic and harmful testicular effects of alloxan in male Wistar rats. By corollary, extract administration significantly lowered values of total cholesterol, triglyceride, low density lipoprotein, increased values of high-density lipoproteins and reversed the reduction in germ cells and matured spermatozoa population amongst Groups 4 and 5 rats administered 500mg/kg bw and 750mg/kg bw of the extract of C*raterispermum schweinfurthi* compared to Group 2 (Untreated Diabetes) rats ($p<0.05$). Suggesting a possible reversal and protective effects of the extract. C*raterispermum schweinfurthi* extract administration lowered total cholesterol, triglyceride, low density lipoprotein, increased serum high density lipoprotein concentration and promoted germinal epithelial cells growth, protected the cytoarchitecture of the testes from lesions due to the harmful effects of alloxan.

Keywords: Hydromethanol, Leaf extract, C*raterispermum schweinfurthi*, Lipid profile, Testicular histology.

1.0 INTRODUCTION

Globally, increase in plasma lipid has been of great concern to clinicians on account of its potential health implications. Hyperlipidemia is implicated in many disease states, including arteriosclerosis, diabetes mellitus, hypertension, obesity and stroke amongst other illnesses [1]. Lipid profile is a diagnostic tool which measures specific lipid levels like total cholesterol, triglycerides, low-density lipoprotein, and high-density lipoproteins. Abnormalities due to poor lipid metabolism are common in people with lipid disorders [2].

The use of medicinal plants in the treatment and management of illnesses has gained global recognition after several experimental studies proved the existence of inherent therapeutic bioactive compounds [3]. These

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plants with medicinal efficacies play a vital role in folklore medicine in various cultures of the world [3]. Most are considered apparently safe and good for consumption because of their availability, organic origin and minimal or no side effects [4]. The leaves of plants have been described as the most common source of active inherent phytochemicals [5-7]. A typical example of such plants with medicinal properties is C*raterispermum schweinfurthi*, readily and widely distributed in tropical Africa: It is accessible, and its leaves are acknowledged for its medicinal values [8]. All the morphological parts including the leaves, inner bark and seed have been anecdotally reported to show various therapeutic effects in diabetes, fever, stomach upset, anemia, and reproductive abnormalities in our environment [9-12]. Available scientific reports validating the described benefits of *Craterispermum schweinfurthii* are scanty. Therefore, the present study describes the hypolipidemic and testicular cytoarchitecture protective effects of hydromethanol leaf extract of C*raterispermum schweinfurthi* using male Wistar rats as models.

2.0 MATERIALS AND METHODS

2.1 Collection, Identification and Extraction of Plant Materials

Fresh leaves of *Craterispermum schweinfurthii* were obtained from the University of Port Harcourt Botanical Garden, Dr. Chimezie Ekeke of the Department of Plant Science and Biotechnology, University of Port-Harcourt, Nigeria identified and authenticated the specimen and assigned a code: UPH/V/296. Voucher specimen was subsequently deposited in the University Herbarium for future reference. The plant leaves were gathered, and all extraneous materials carefully removed. The leaves were air dried at room temperature for a minimum of 7 days after which it was pulverized into powder and the weighed quantity of 670.6g dissolved using Soxhlet device in 390ml of water-methanol mixture (25:75% v/v BDH) for three days in a jar. It was filtered and concentrated using a rotary evaporator at 40°C and the yield was 73%. Obtained extract was preserved in airtight containers and stocked at room temperature prior administration.

2.2 Procurement and Handling of Experimental Wistar Rats

Male Wistar rats weighing between 100–250g were used for the study. Animals were kept at the Animal House, Department of Human Physiology, Faculty of Basic Medical Sciences, University of Port Harcourt, Nigeria. The rats were fed with normal rat pellet and tap water ad libitum and were subsequently acclimatized for two weeks and grouped for the study.

2.3 Ethical Approval and Acute Toxicity Test

Ethical approval was sought and obtained from the University of Port Harcourt Ethical Committee through a communication referenced: UPH/CEREMAD/REC/MM82/024 dated 23rd November, 2021. The acute toxicity of the hydromethanol extract of C*raterispermum schweinfurthi* leaves was determined using Karber's method as modified by Aliu and Nwude, 1982 [13]. Lethal dose (LD50) of the extract was found to be 3968mg/kg bw. The study was conducted in accordance with the guidelines for the care and use of laboratory animals [14].

2.4 Alloxan, Glibenclamide and Phytosterol Procurement

Alloxan monohydrate was obtained from Sigma-Aldrich Co., 3050 Spruce Street, St. Louis, USA. While Glibenclamide was obtained from Swiss Pharm Nigeria Ltd, 5, Dopemu Road, Agege, Lagos, Nigeria. Phytosterol was obtained from Wakunaga of America Co., LTD. Mission Viejo, CA92691 U.S.A.

2.5 Experimental Design

Experimental rats were acclimatized and subsequently randomly divided into 8 groups of 8 rats each. Experimental diabetes was induced in all rat groups except Groups 1 and 8 using alloxan monohydrate at a dose of 200mg/kg bw administered intraperitonially. Diabetes was confirmed after 72 hours of alloxan administration if the blood glucose is ≥ 11.1 mmol/L (200mg/dl) [15, 16]. Each rat group was subsequently treated as follows for 28 days:

Group 1: Untreated non-diabetic; Rats in this group had free access to extract vehicle.

Group 2: Untreated diabetic; Rats in this group received no further treatment after induction of diabetes.

Group 3: Diabetic + Low dose extract group; Rats in this group were treated with 250mg/kg/ of extract daily after the induction of diabetes.

Group 4: Diabetic + Medium dose extract group; Rats in this group were treated with 500mg/kg/ of extract daily after the induction of diabetes.

Group 5: Diabetic + High dose extract; Rats in this group were treated with 750mg/kg/ extract daily after the induction of diabetes.

Group 6: Diabetic + Standard drug; Rats in this group were treated with 0.6mg/kg/ bw of Glibenclamide daily after the induction of diabetes.

Group 7: Diabetes + Phytosterol; Rats in this group were treated with 2000mg/kg/ of phytosterol daily after the induction of diabetes.

Group 8: Phytosterol alone; Rats in this group were treated with 2000mg/kg/ of phytosterol daily 24 hours after the last administration, the rats were anaesthetized using 3.5% chloroform soaked in cotton wool, blood sample was collected by cardiac puncture into appropriate sample bottles for the estimation of serum lipid profile (Total cholesterol, Triglyceride, Low density lipoprotein-cholesterol and High-density lipoprotein-cholesterol). Rats' testes were harvested through dissection and

immediately transferred into sample tubes for the estimation of testicular histology.

2.6 Determination of Serum Lipid Profile

Serum total cholesterol, triglycerides, low density lipoprotein and high-density lipoprotein levels were determined using Randox kits from Randox Biosciences: Randox Korea Ltd, Heungan-daero, Dongan-gu, Anyang-si, Gyeonggi-do, Korea Republic. Determination of total cholesterol level was as previously described by Stein (1986) [17], serum triglycerides estimation was as described by Chawla (2003) [18]. Low-density lipoprotein and high-density lipoproteins were evaluated according to the method earlier described by Ijeoma *et al*., (2020) [19] and Saronee *et al.,* (2020) [20].

2.7 Determination of Testicular Histology

24 hours after the last administration, rats were anaesthetized and their testes harvested and sent to the laboratory for histopathological analysis. The rats' testicular tissues were deposited in Bouin's solution containing 10% formalin solution and picric acid, the tissues were processed using a tissue processor. The tissues were subsequently embedded in molten paraffin, and five micron-thick sections of the tissues were cut using a microtome. Lastly, for microscopic examination of testicular tissues, the tissues nuclei were stained blue and cytoplasm stained purple with the aid of hematoxylin and eosin stains. Pathological examination of the testes was conducted, and histopathological changes were noted.

2.8 Statistical Analysis

Results are as presented in Table 1 and Slides 1-8 as Means ± standard error of means (SEM). Significant differences were determined using one-way ANOVA and LSD Post Hoc test. A p value of less than 0.05 was considered statistically significant.

3.0 RESULTS

Table 1 shows values of lipid profile in alloxan induced diabetic rats treated with extract and phytosterol only. Expectedly, significantly higher values of total cholesterol, triglyceride, low density lipoprotein and low values of high-density lipoprotein were observed amongst group 2 (Untreated Diabetes) rats administered 200mg/kg bw of alloxan, compared to group 1 (Control) rats ($p<0.05$). Suggesting a possible hyperlipidemic effects of alloxan in male Wistar rats. By corollary, upon extract administration, significantly lower values of total cholesterol, triglyceride, low density lipoprotein and higher values of high-density lipoproteins were observed amongst Groups 3, 4 and 5 rats administered 250mg/kg bw, 500mg/kg bw and 750mg/kg bw of the extract of *Craterispermum schweinfurthi* compared to Group 2 (Untreated Diabetes) rats ($p<0.05$). Indicating a potential hypolipidemic and lipid scavenging effects of the extract. Similar results were observed amongst Groups 6, 7 and 8 rats administered Glibenclamide and phytosterol respectively.

Table 1: Values of lipid profile in alloxan induced diabetic rats treated with extract and phytosterol

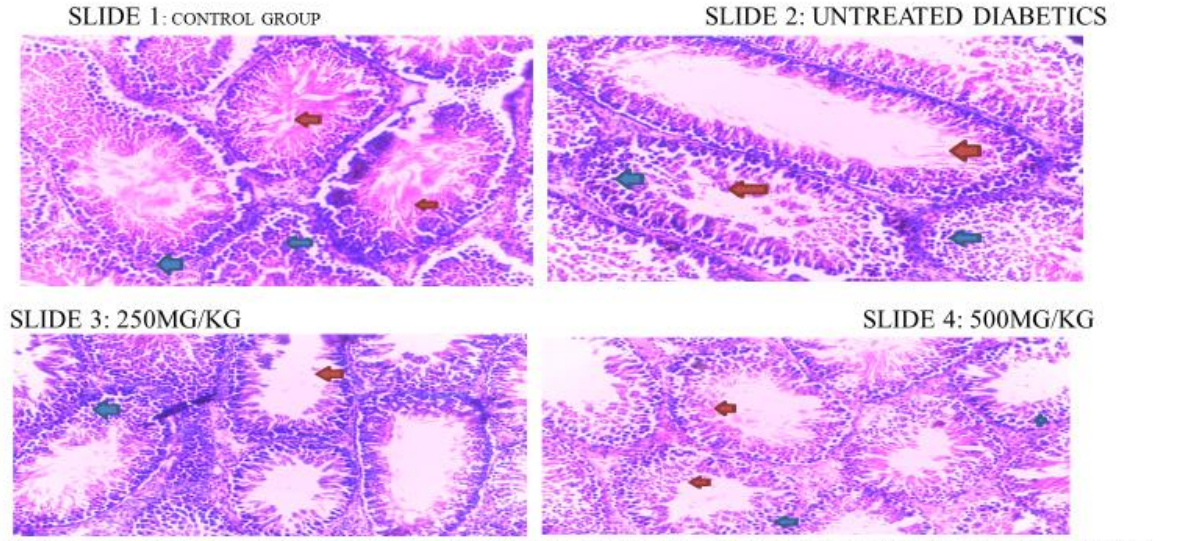
	Groups	Total Cholesterol (Mmol/l)	Triglyceride (Mmol/l)	High Density Lipoprotein (Mmol/l)	Low Density Lipoprotein (Mmol/l)
1	Control	2.63 ± 0.013^{b}	0.61 ± 0.005^{b}	0.75 ± 0.004^{b}	1.63 ± 0.003^{b}
2	Untreated Diabetes	3.34 ± 0.005^{a}	0.97 ± 0.005^{a}	0.41 ± 0.005^{a}	2.47 ± 0.004^{a}
3	Diabetes + 250mg/kg extract	3.30 ± 0.003^{a}	0.93 ± 0.003^{ab}	0.44 ± 0.002^{ab}	2.44 ± 0.005^{a}
4	Diabetes + 500mg/kg extract	3.26 ± 0.005^{a}	0.90 ± 0.002^{ab}	0.58 ± 0.005^{ab}	2.38 ± 0.006^{ab}
5	Diabetes + 750mg/kg extract	3.05 ± 0.012^{ab}	0.82 ± 0.009^{ab}	0.74 ± 0.006^{b}	2.23 ± 0.020^{ab}
6	Diabetes + Glibenclamide	2.94 ± 0.003^{ab}	0.80 ± 0.004^{ab}	0.58 ± 0.004^{a}	2.18 ± 0.047^{ab}
7	Diabetes + 2000mg/kg Phytosterol	3.24 ± 0.006^{ab}	0.92 ± 0.007^{ab}	0.43 ± 0.006^{a}	2.43 ± 0.009^{a}
8	2000mg/kg Phytosterol only	2.60 ± 0.013^{b}	0.60 ± 0.004^{b}	0.77 ± 0.005^{ab}	1.61 ± 0.003^{b}

Values are shown as Mean ± SEM; n=5; [a] Significant at $P<0.05$ compared with Group 1 (control). [b] Significant at $p<0.05$ compared with Group 2 (untreated diabetic rats).

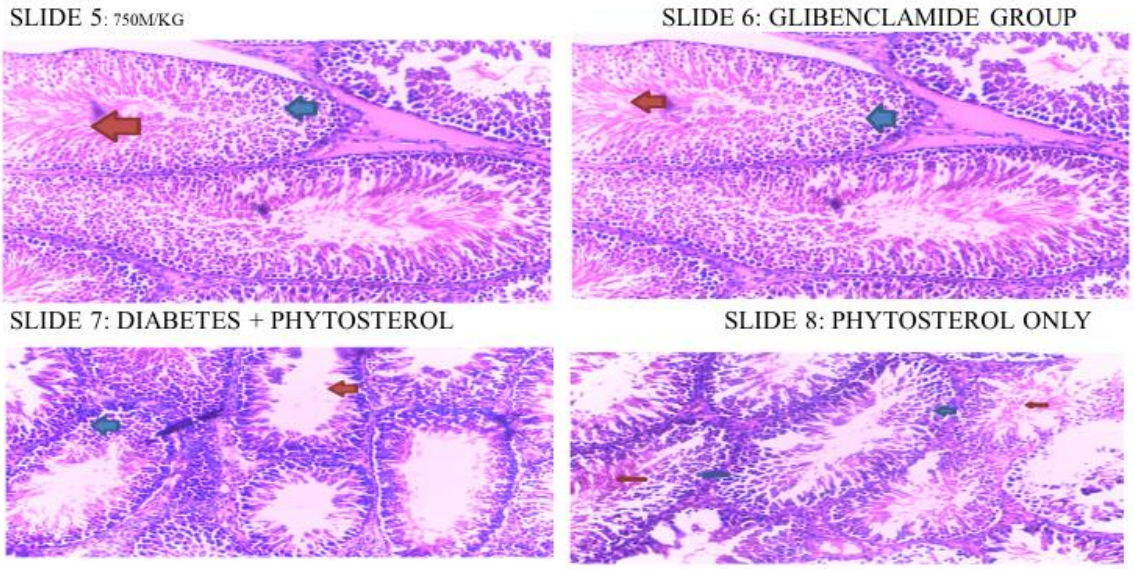
Effects of the hydromethanol leaf extract of C*raterispermum schweinfurthi* on testicular histology in male Wistar rats

Administration of 200mg/kg body weight of alloxan to Group 2 rats caused a significant reduction in the population of germ cells and normal matured spermatozoa in the testes of Group 2 (Slide 2) rats compared to Group 1 (Slide 1) rats. indicating a possible harmful effect of alloxan on the testes. However, germ cells and normal matured spermatozoa values and concentration were significantly reversed upon treatment with 500mg/kg and 750mg/kg body weight of the extract of C*raterispermum schweinfurthi* to Groups 4 and 5 rats (Slides 4 and 5) compared to Group 2 (Slide 2) rats: Suggesting a possible protective and reversal effects of the extract in male Wistar rats. Similar results were observed amongst Glibenclamide and Phytosterol treated rats in Groups 6, 7 and 8 (Slides 6, 7 and 8) rats respectively.

Slides 1-8: Testicular Histology of Male Wistar Rats



Slides 1 and 4: Show sections of the testis with normal seminiferous tubules containing numerous germ cells (blue) with normal spermatozoa (red) at the center of the tubules. Slide 2: Shows sections of the testis with normal seminiferous tubules containing only average number of germ cells (blue) with fewer spermatozoa (red) at the center of the tubules. Slide 3: Shows sections of the testis with seminiferous tubules containing numerous germ cells (blue) with reduced number of mature spermatozoa (red) at the center of some of the tubules



Slides 5, 6 and 8: Show sections of the testis with normal seminiferous tubules containing numerous germ cells (blue) with normal matured spermatozoa (red) at the center of the tubules. Slide 7: Shows sections of the testis with seminiferous tubules containing numerous germ cells (blue) with reduced number of matured spermatozoa (red) at the center of most of the tubules.

4.0 DISCUSSION

The present study investigated the effects of C*raterispermum schweinfurthi* on lipid profile and testicular histology in male Wistar rats. Lipid profile serves as an initial broad medical screening tool for lipid abnormalities; results obtained may be useful in identifying hidden genetic and cardiovascular related diseases. Lipid profile is commonly considered in the prognosis of dyslipidemia, but emphasis has always been on low density lipoprotein cholesterol (LDL-c) which is said to be a "bad lipoprotein" [21]. There are readily available reports suggesting that an elevated LDL-c concentration is atherogenic while, high HDL-c is cardioprotective [22-24]. Results from the present study demonstrates a dose dependent effect of the extract of C*raterispermum schweinfurthi.* Significant decrease in total cholesterol, triglycerides, low-density lipoprotein and significant increase in high density lipoprotein were observed for the duration of our study. Suggesting that the extract may have ameliorative and lipid scavenging

effects, as a result, reduces the risk of lipid associated cardiovascular events. Phytochemical examination of C*raterispermum schweinfurthi* has shown an array of phytochemicals including: flavonoids, tannins, phytosterol, neophytadiene glycosides and sterols compounds [25]. These compounds may have demonstrated therapeutic potentials in ameliorating possible complications associated with hyperlipidemia and diabetes [25].

Effects of the hydromethanol leaf extract of C*raterispermum schweinfurthi* on testicular histology in male Wistar rats

Alloxan monohydrate is a well-documented environmental and industrial toxicant [12]. Literature reports that exposure of experimental animals to either the inorganic or organic forms of alloxan is associated with oxidative stress induction [26]. Oxidative damage may be due to decreased clearance of reactive oxygen species (ROS) by scavenging mechanisms. ROS generation in the cytoplasm of cells may cause the formation of hydrogen peroxide and lipid peroxidation in the mitochondrial membrane, leading to loss of cell membrane structural integrity through necrosis or apoptosis [27].

In the present study, reduction in germ cells and normal matured spermatozoa population in the testes were caused following exposure to 200mg/kg bw alloxan which suggest that alloxan may interfere with spermatogenesis by gaining access to germinal cells. The harmful effects of alloxan on rat testicular tissues have been widely reported with marked testicular spermatogenic degeneration [28]. The spermatozoa membranes houses polyunsaturated fatty acids, which makes them susceptible to ROS attack and lipid peroxidation due to alloxan exposure [29].

Several active inherent compounds identified in the leaf extract of C*raterispermum schweinfurthi* may scavenge alloxan generated ROS, reduce lipid peroxidation and enhance the antioxidant activity of enzymes leading to protection against alloxan induced testicular toxicity manifested by increase in the population of germ cells and normal matured spermatozoa in the treatment groups [25, 30]. These findings suggest that C*raterispermum schweinfurthi* extract has testicular cytoarchitecture protective effects on alloxan induced testicular toxicity.

We conclude therefore, that alloxan caused an increase in plasma total cholesterol, triglyceride, low density lipoprotein and decrease high density lipoprotein in experimental rats. It further interferes with the structural cytoarchitecture of the testes thereby reducing the population of germ cells and normal matured spermatozoa. However, C*raterispermum schweinfurthi* extract administration lowered total cholesterol, triglyceride, low density lipoprotein and increased serum high density lipoprotein concentration, it further promoted germinal epithelial cells growth, protected the cytoarchitecture of the testes from lesions due to the deleterious effects of alloxan. We may infer based on the above findings from our study that *Craterispermum schweinfurthi leaf extract* has hypolipidemic and pro-fertility properties.

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