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Influence of *Craterispermum schweinfurthi* leaf extract on glucose homeostasis in male Wistar rats

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Abstract

The present study aims to determine the potential influence of C*raterispermum schweinfurthi leaf* extract on glucose homeostasis using male Wistar rats as models. 48male Wistar rats were acclimatized and subsequently randomly divided into 6 groups of 8 rats each. Diabetes was induced in all rat groups except Group 1 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 was daily treated with different concentrations of extract.Compared to group 2 (Untreated Diabetic) rats, administration of graded doses ofthe extract of C*raterispermum schweinfurthi* amongst Groups 3, 4 and 5 rats demonstrated a dose dependent significant reduction ($p<0.05$)in blood glucose level and glycosylated hemoglobin concentration with the highest dose demonstrating the most impactful outcome. Suggesting possible hypoglycemic and anti-hyperglycemic effects of the extract. Similar results were observed amongst group 6rats following administration of Glibenclamide. Treatment of diabetic rats with hydromethanol leaf extract of *Craterispermum schweinfurthi* lowered blood glucose level and ameliorated glycosylated hemoglobin concentration in male Wistar rats.

Keywords:

Antihyperglycemic, Craterispermum schweinfurthi, diabetes, alloxan, anti-diabetic.

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INTRODUCTION

Diabetes mellitus, is a group of prevalent endocrine diseases characterized by sustained high blood glucose levels. Diabetes is due to either non production of enough insulin, by the pancreas or body cells becoming unresponsive to insulin actions [1-2]. Common symptoms are: polyphagia (excessive hunger), polydipsia (excessive thirst), weight loss, blurred vision and polyuria (excessive urination). If not properly managed, the disease can lead to serious health complications, including malfunctions of theeye, kidney, cardiovascular system, and nerves [3]. Diabetes accounts for about 4.2 million mortality rate yearly,with over 1.5 million caused by either untreated or poorly managed diabetes. Diabetes is either type 1 or type 2.The commonest available treatment for type 1 is insulin therapy through insulin injections, while anti diabetic interventions like metformin, semaglutide, glibenclamide couple with lifestyle modifications can be used to manage type 2 diabetes. Gestational diabetes, isanother form of diabetes whichis sometimes elicited by pregnancy, and is usually resolved shortly after parturition. Type 1 diabetes is an autoimmune disease whereby the body's immune system destroys pancreatic beta cells, preventing furtherinsulin production [2]. Type 2 diabetes on the other hand comes to play when the body becomes insulin resistant, implying that body cells do not respond maximally to insulin, and as a result, blood glucose remains high instead of being absorbed. Additionally, diabetes can also be caused by many other specific factors, like genetic conditions affecting the pancreas or exposure to some chemicals and medications like glucocorticoids [3].

Consumption of medicinal plants and supplements can serve as nutritional tools on account of their therapeutic efficacies: For instance, ingestion of C*raterispermum schweinfurthi* leaves has been reported to exhibit potent biologic and therapeutic benefits because of the inherent bioactive compounds and nutritional valuespossessed by the leaves [4-5].Globally, there is an increasing application of native medicinal plants in the treatment of various illnesses, because of the presence of phytochemicals which are extracted, characterized and used as raw materials in drugs production [6, 4].*Craterispermum schweinfurthi* species are shrubs with supra-axillary inflorescences, they are widely distributed in central West Africa and the Seychelles [7-8]. The traditional applications of C*raterispermum schweinfurthi* are many: the leaves, inner bark and seed have been reported to possess various beneficial biologic and pharmacologic effects in cases of stomach upset, anemia, diabetes, fever and reproductive disorders in our environment [9-12].Though available scientific reports validating the above-described benefits of *Craterispermum schweinfurthii*are considerably scanty. The present study therefore describes the potential influence of C*raterispermum schweinfurthi leaf* extract on glucose homeostasis using male Wistar rats as models. It is with the view of evaluating the anecdotal application of the leaves of C*raterispermum schweinfurthi* as an anti-diabeticagent in our environment.

MATERIALS AND METHODS

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 reference 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 and were subsequently 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. This was latter 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 before administration.

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.

Ethical Approval and Acute Toxicity Test

Ethical approval was communicated with a referenced code: UPH/CEREMAD/REC/MM82/024 dated 23rd November, 2021. The acute toxicity of 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].

Alloxan and Glibenclamide 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.

Experimental Design

Experimental rats were acclimatized and subsequently randomly divided into 6 groups of 8 rats each. Experimental diabetes was induced in all rat groups except Group 1 using all oxan 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 followsfor 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/ bwof Glibenclamide daily after the induction of diabetes.

Determination of Blood Glucose Level and Glycosylated Haemoglobin Concentration
Blood glucose concentration was determined using the method described by Saronee *et al* (2019) [16].During the period of the study, blood glucose concentration was determined six times: firstly, prior to administration of alloxan to induce diabetes (Day 0); secondly, 72 hours (three days) after the administration of alloxan (Day 1; to confirm diabetic rats subsequently used for the study); and third to the sixth time, at the end of 7 days (7 days interval), that is on the 7th day, 14th day, 21st day and 28th day of the study respectively: to determine weekly blood glucose concentration. Glycosylated haemoglobin concentration was determined at the end of the study (Day 28) using the method earlier described by Saronee *et al.*, (2019) [16].

Statistical Analysis
Results are as presented in Tables 1 and 2 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.

RESULTS AND DISCUSSION

Table 1: Values of blood glucose in alloxan induced diabetic rats treated with leaf extract of *Craterispermum schweinfurthii*

	Groups	Day 1	Day 7	Day 14	Day 21	Day 28
1	Control	94.00±5.621^{b}	100.60±4.749^{b} (7.02)	99.20±3.541^{b} (1.39)	99.20±4.872^{b} (0)	112.00±0.242^{b} (1.02)
2	Untreated Diabetes	421.00±2.943^{a}	420.60±2.231^{a} (-0.09)	395.00±5.308^{a} (-6.08)	347.20±1.958^{a} (-12.10)	433.60±0.136^{a} (24.88)
3	Diabetes + 250mg/kg extract	296.20±2.517^{a} b	287.80±3.527^{ab} (-2.83)	268.60±6.046^{ab} (-6.67)	265.20±0.755^{ab} (-1.26)	220.60±0.896^{ab} (-16.81)
4	Diabetes + 500mg/kg	328.00±9.849^{a}	314.20±7.516^{ab} (-4.20)	267.00±6.401^{ab}	237.00±1.135^{ab}	211.20±1.263^{ab} (-

	extract	[b]		(-15.02)	(-11.23)	10.88)
5	Diabetes + 750mg/kg extract	403.60±4.144[a]	346.20±3.365[ab] (-14.27)	290.80±2.374[ab] (-16.0)	237.20±1.717[ab] (-18.43)	213.40±0.864[ab] (-10.03)
6	Diabetes + Glibenclamide	354.60±3.463[a b]	305.00±5.968[ab] (-13.98)	294.40±2.720[ab] (-3.47)	267.20±0.562[ab] (-9.23)	228.20±0.077[ab] (-14.59)

Values are shown as Mean ± SEM; n=8; [a] Significant at P<0.05 compared with Group 1 (control). [b] Significant at p<0.05 compared with Group 2 (untreated diabetic rats).

Table 1 shows the values of blood glucose in alloxan induced diabetic rats treated with leaf extract of *Craterispermum schweinfurthii*. Predictably, administration of alloxan monohydrate amongst Group 2 rats caused a significant increase in blood glucose level (p<0.05), compared to Group 1 **(**Control) rats, indicating a possible diabetogenic effect of alloxan in experimental animals. Compared to Group 2 (Untreated Diabetes) rats, administration of extract of C*raterispermum schweinfurthi* to rats in Groups 3, 4 and 5 demonstrated a weekly dose dependent significant reduction in blood glucose level (p<0.05). Suggesting a possible anti-hyperglycemic and glucostatic effects of the extract. Similar results were observed amongst group 6 (Diabetes + Glibenclamide) rats following the administration of Glibenclamide.

Table 2: Values of glycosylated hemoglobin concentration in alloxan induced diabetic rats treated with leaf extract of *Craterispermum schweinfurthii*.

	Groups	**HBAIC (%)**
1	Control	3.48±0.024[b]
2	Untreated Diabetes	9.17±0.008[a]
3	Diabetes + 250mg/kg extract	8.46±0.007[b]
4	Diabetes + 500mg/kg extract	6.01±0.004[b]
5	Diabetes + 750mg/kg extract	4.00±0.009[b]

6	Diabetes + Glibenclamide	3.95±0.034 [b]

Values are shown as Mean ± SEM; n=8; [a] Significant at P<0.05 compared with Group 1 (control). [b] Significant at p<0.05 compared with Group 2 (untreated diabetic rats).

Table 2 shows values of glycosylated hemoglobin concentration in alloxan induced diabetic rats treated with leaf extract of *Craterispermum schweinfurthii*. Significant increase in glycosylated hemoglobin concentration was observed amongst Group 2 (Untreated Diabetes) rats following administration of 200mg/kg bw of alloxan monohydrate when compared to group 1 (Control) rats (p<0.05). Perhaps suggesting a possible hyperglycemic effect of alloxan in male Wistar rats. Significant and dose dependreduction in glycosylated hemoglobin concentration was observed amongst Groups 3, 4 and 5 rats, following administration of graded doses of extract compared to Group 2 rats (p<0.05). Indicating a possible beneficial effect of the extract. This effect of C*raterispermum schweinfurthi* is comparable to the effect of the administration of Glibenclamide observed amongst Group 6 rats.

DISCUSSION

The present study describes the potential influence of C*raterispermum schweinfurthi leaf* extract on glucose homeostasis using male Wistar rats as models. The significant reduction in blood glucose concentration because ofadministration of hydromethanol leaf extract of C*raterispermum schweinfurthi* suggests therefore, that the extract possess possible hypoglycemic properties, which is indicative of apotential beneficial effect of the extract in alloxan induced diabetes. Profoundly, the effects of the extract are similar to that of Glibenclamide: a known anti-diabetic drug. Our findings are consistent with Saronee *et al.*, 2019 [16] in which extracts of S*pondias mombin* and C*urcuma longa* rhizomes were observed to demonstrate anti-diabetic properties in male Wistar rats.Hypoglycemic activity displayed by the extract could be due to the presence of important phytochemicals like tannin, glycosides, flavonoids, phytosterol, neophytadiene and sterol compounds amongst other bio-active compounds identified in the extract [4].These compounds have been previously reported to exhibit synergistic propertiesand ameliorate associated diabetic complications [4, 17-18]. The possible mechanisms of action of identified compounds in the leaf extract include stimulation of insulin from residual beta cells [17]; glucose uptake [19];and inhibition of gastrointestinal glucose absorption [20].

Glycosylated haemoglobin (HbA1c) values of diabetic untreated rats were significantly higher than that of control rats. This is attributed to the hyperglycemic effect of alloxan [21].Prolong elevation of plasma glucose level causes addition of glucose to free amino N-terminal haemoglobin beta chain formingglycated haemoglobin [22]. Remarkably, all treatment groups recorded significantly lower glycosylated hemoglobin values in the present study. Decrease in glycosylated hemoglobin score observed amongst treatment groups indicate a possible hypoglycemic and antihyperglycemic effects of the extract of C*raterispermum schweinfurthi*. The effects of the extract were interestingly found to be dose-dependent with the highest dose demonstrating the most impactful outcome. The mechanism

by which *Craterispermum schweinfurthi* exhibited its effects on blood glucose and glycosylated haemoglobin values was not specifically determined or investigated in the present study, but possible mechanisms include increasing insulin production, decrease in liver glucose production and elevated free radical scavenging enzymes levelsin blood [23].Our findings are in agreement with Anand *et al.*(2007) [24]and Yu *et al.* (2006) [25]who reported ameliorating effects of *Brassica nigra and Astragalus membranaceus* respectively on glycosylated haemoglobin in diabetic rats.

CONCLUSION

In conclusion, treatment of diabetic rats with hydromethanol leaf extract of *Craterispermum schweinfurthi* lowered blood glucose level and ameliorated glycosylated haemoglobin in a dose dependent manner.

Conflict of Interest: No conflict of interest

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