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Effect of Aqueous Leaf Extract of *Uvariaopsis tripetala* on Hyperglycaemia, Weight loss, Polydipsia and Polyphagia in Alloxan- induced Diabetic Wistar Rats

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Abstract

Diabetes, a disorder characterized by hyperglycaemia is the leading cause of death in developed, developing and underdeveloped nations around the world today. According to World Health Organization (WHO), its incidence is increasing and assuming epidemic proportions. In this chronic study the antidiabetic effect of orally administered aqueous crude leaf extract of the *Uvariopsis tripetala* was investigated in Alloxan (150mg/kg) induced diabetic albino rats. The results obtained indicated that after administration of the aqueous extract at different dosages (100, 200, 400 mg/kg body weight) for twenty eight (28) days, there was a time and dose-dependent significant ($P< 0.05$) reduction in FBS on days 7, 14, 21 and 28 compared to diabetic control. The body weight of rats in the treatment groups showed no statistically significant ($P>0.05$) difference on days 7 and 14 compared to diabetic control. However, a dose- dependent significant ($P<0.05$) increase was produced by the extract when compared to the diabetic control on days 21 and 28. The extract also showed time and dose- dependent significant ($P< 0.05$) reduction in food and water consumption in weeks 1, 2, 3 and 4 compared to diabetic control. It was concluded that the aqueous extract of *U. tripetala* exhibited anti-diabetic properties. Hence this plant may serve as a good candidate for alternative and/or complimentary medicine in the management of diabetes.

Keywords: *Uvariaopsis tripetala*, Hyperglycaemia, Polydipsia, Polyphagia

1. Introduction

Diabetes mellitus is chronic metabolic disorders that affect human body in terms of physical, psychological and social health. It is defined as a group of disorders characterized by hyperglycemia, altered metabolism of lipids, carbohydrates and proteins (Warjeet, 2011). It is becoming the third "killer" of the health of mankind along with cancer, cardiovascular and cerebrovascular diseases. Among all the cases of diabetes, type 2 diabetes was found to be more prevalent. Knowledge about diabetes mellitus existed in ancient Egypt and Greece. The word "diabetes" is derived from the Greek word "Diab" (meaning to pass through, referring to the cycle of heavy thirst and frequent urination); "mellitus" is the Latin word for "sweetened with honey" (refers to the presence of sugar in the urine) (Warjeet, 2011).

Hyperglycaemia which is the hallmark of diabetes mellitus is responsible for its cardinal symptoms namely: weight loss, polyphagia, polydypsia and polyuria (Robert, 2001). In hyperglycaemic state, the renal threshold for glucose is exceeded and it is thus excreted in the urine. The excreted glucose then acts as osmotic solute in urine, producing an excessive loss of water (polyuria). This excessive loss of water in urine also leads to another cardinal symptom of diabetes mellitus which is polydypsia. Polydipsia arises when there is a depletion of the Extra Cellular Fluid volume and dehydration following excessive loss of water in urine. This activates the thirst centre hence, the excessive thirst for water (polydypsia). Polyphagia in diabetes mellitus could be explained by the "Glucostat Theory of Feeding Regulation" which suggests that differences in the arteriovenous glucose content of the satiety and feeding centers in the hypothalamus regulates the feeding response (Guyton and Hall, 2006). It explains that if the difference is high due to high glucose utilization by the satiety center, then the satiety center is activated. However, if the difference is low, then feeding center is activated. In diabetes mellitus, the inability of glucose to permeate the cells of the satiety center leads to a low arteriovenous difference and the feeding center is chronically activated thus leading to polyphagia (Guyton and Hall, 2006; Gannong, 2006). In diabetes mellitus, the gluconeogenic pathway is activated as a result of the inability of the cells to utilize glucose for energy production. Thus the weight loss in diabetes mellitus is linked to the utilization of muscle protein and excessive mobilization of fats from the adipose tissues for energy production in the gluconeogenic (Champe *et al.,* 2005).

Plants have always been a good source of drugs. The ethno-botanical information reports about 800 plants that may possess anti-diabetic potential (Grover *et al*., 2002; Jung *et al*., 2006). The beneficial uses of medicinal plants in traditional system of medicine of many cultures are extensively documented. Several plants have been used as dietary adjuvant and in treating the number of diseases even without any knowledge on their proper functions and constituents. This practice may be attributed to the uncompromised cost and side effects of synthetic hypoglycemic agents (Balaraman *et al*., 2010). Although numerous synthetic drugs were developed for the treatment of diabetes mellitus but the safe and effective treatment paradigm is yet to be achieved. Medicinal foods are prescribed widely even when their biologically active compounds are unknown, because of their safety, effectiveness, and availability (Dewanjee *et al*., 2009). The World Health Organization (WHO) has recommended the evaluation of traditional plant treatments for diabetes as they are effective, non-toxic, with less or no side effects and are considered to be excellent candidates for oral therapy (Shokeen *et al*., 2008). This study evaluates the effect of *Uvariopsis tripetala* on hyperglycemia, body weight loss, polyphagia and polydipsia in diabetic Wistar rats.

2. Materials and Methods

2.1 Collection and Identification of Plant Materials

The medicinal plant was identified by a Taxonomist at the at the Herbarium unit of the Department of Biological Sciences, Federal University Lokoja, Kogi State. A voucher specimen was kept in the herbarium for future reference.

2.2 Preparation of Aqueous Extract

The leaves were rinsed properly with sterile water and spread on a clean floor and allowed to air dry for about 10 days. It was ground into fine powder using electric blender and stored in air-tight bags until the extract was required. Five hundred grams (800g) of the fine powder of the sample was weighed into a clean 5L bucket and 4000 ml of distilled water was added. The mixture was thoroughly shaken and stirred at intervals in order to have proper mixing and extraction by the solvent. This was carried out for 3days (72hrs), after which the resultant mixture was filtered using a sieve and a funnel stuffed with cotton wool to obtain a crude filtrate. The filtrate was concentrated using a freeze dryer to obtain the aqueous leaf extract of *Uvariaopsis tripetala* (UTAE).

2.3 Chemicals and Materials

Chlorpropamide (Diabenese) was purchased locally, Alloxan was purchased from the country representative of Sigma Chemical, St. Loius USA while a digital glucometer and corresponding test strips (ACCU- CHECK) was purchased from a pharmacy store. All other chemicals used were of analar grade and obtained commercially.

2.4 Animals

Male Wistar rats weighing between 100-180g were used for this study. They were fed twice daily with growers mash diet and were given free access to water, during the experimental period. The food and water was replaced each day except on days prior to testing for their fasting glucose level.

2.5 Experimental Design

2.5.1 Acute toxicity study

The oral median lethal dose (LD_{50}) of the extract was determined in rats according to the method described by Lorke, 1983. The study was carried out in two phases. In the first phase, nine rats were randomized into three groups of three rats which were given 10, 100, and 1000mg extract/kg body weight. The rats were kept under the same conditions and observed for signs of toxicity which included but were not limited to paw- licking, stretching, respiratory distress and mortality for the first 4h and thereafter daily for two weeks. Based on the results of the initial phase, the following doses- 1600, 1900 and 5000mg extract/kg body weight were administered to another set of three groups of three rats in the second phase. These rats were also monitored closely for the first 4 h after treatment and subsequently daily for14 days for signs of toxicity and/or mortality. The results obtained in the second phase were used to calculate the $LD_{50.}$

2.5.2 Induction of diabetes

The animals were injected intraperitoneally with a single dose of 150mg/kg of the body weight Alloxan. Diabetes was confirmed by the presence of fasting plasma glucose level above 200mg/dl on the third day post administration of streptozotocin.

2.5.3 Grouping and treatment

Twenty five (25) diabetic rats were weighed and randomly divided into five (5) groups of five rats each and treated daily for 28 days as follows:

Group I (control): Normal saline only.
Group II: 250mg/kg body weight of chlorpropamide (an anti-diabetic drug).
Group III: 100mg/kg body weight of the extract.
Group IV: 200mg/kg body weight of the extract.
Group V: 400mg/kg body weight of the extract.

2.5.4 Assay of Fasting Blood Glucose Level

The ACCU-CHEK Glucometer with its corresponding test strips was used to determine the fasting blood glucose levels of the rats.

2.5.5 Estimation of Body Weight

The body weight of the rats was monitored weekly throughout the duration of the study.

2.5.6 Daily Food/ Water Consumption

The quantity of food and water consumed by rats in each group were measured daily as the difference between the quantity of feed and water supplied and the quantity remaining after 24 hours respectively and a weekly average determined.

2.6 Statistical Analysis

Statistical analysis was carried out using SPSS version 20.0. All the data were expressed as mean ± SEM and the statistical differences between the means were determined by one way analysis of variance (ANOVA) which was followed by Duncan test and difference between means at $P > 0.05$ were considered significant.

3. Results

3.1 Acute Toxicity Study

The results of acute toxicity studies showed no mortality or physical changes in skin and fur, eyes and mucus membrane, respiratory rate, circulatory signs, autonomic and central nervous system effects up to a dose of 5000 mg/kg of UTAE. The oral LD_{50} of the extract was then taken to be > 5000 mg/kg.

3.2 Fasting Blood Sugar (FBS)

The effect of the extract and chlorpropamide on the FBS of diabetic Wistar rats is presented in Table 1. Administration of alloxan significantly ($P<0.05$) elevated the FBS as seen on day 0 in the diabetic control and treatment groups. Treatment with the extract showed time and dose- dependent significant ($P< 0.05$) reduction in FBS on days 7, 14, 21 and 28 compared to diabetic control.

Table 1: Effect of Aqueous Leaf Extract of *Uvariaopsis tripetala* on Fasting Blood Sugar (FBS) (mg/dl) of Alloxan Induced Diabetic Wistar Rats

Treatment (mg/kg)	FASTING BLOOD GLUCOSE LEVEL (mg/dl)				
	DAY 0	DAY 7	DAY 14	DAY 21	DAY 28
N/S (1ml)	383.4± 56.15^{a}	376.1 ± 89.18^{b}	393.6 ± 76.33^{b}	381.5 ± 75.32^{b}	370.3 ± 64.51^{b}
CHLOR (250)	368.5±77.24^{a}	375.4±92.71^{b}	368.6±90.76^{b}	348.4±81.22^{b}	333.4±51.32^{ab}
UTAE (100)	378.4±17.25^{a}	322.3±67.22^{ab}	310.4±73.85^{ab}	289.3±54.27^{a}	279.3±44.12^{a}
UTAE (200)	362.2±71.22^{a}	325.2±73.24^{ab}	298.3±44.17^{a}	273.4±37.12^{a}	263.5±42.11^{a}
UTAE (400)	367.5±45.51^{a}	295.4±34.45^{a}	287.5±34.65^{a}	257.4±65.53^{a}	200.6±28.24^{a}

Data are presented as mean ± SD of FBS (mg/dl). Data was analysed by one- way ANOVA followed by Duncan post-hoc test for multiple comparisons, (n=6). Mean values having different lower case alphabets as superscripts are considered significant (p< 0.05) across the columns.

3.3 Body weight BW) (g)

Table 2 shows the effect of UTAE and Chlorpropamide on the body weight of the alloxan- induced diabetic rats. Following alloxan administration, the body weight of rats in the control and treatment groups was significantly (p< 0.05) reduced. The body weight of rats in the treatment groups showed no statistically significant (P>0.05) difference on days 7 and 14compared to diabetic control. However, a dose-dependent significant (P<0.05) increase was produced by the extract when compared to the diabetic control on days 21 and 28.

Table 2: Effect of Aqueous Leaf Extract of *Uvariaopsis tripetala* on Body weight (g) of Alloxan Induced Diabetic Wistar Rats

Treatment (mg/kg)	BODY WEIGHT (g)				
	DAY 0	DAY 7	DAY 14	DAY 21	DAY 28
N/S (1ml)	132.4±11.33^{a}	134.2±22.46^{a}	133.5±32.21^{a}	128.6±18.17^{a}	129.8±16.42^{b}
CHLOR (250)	133.8±21.44^{a}	135.3±28.21^{a}	140.1±24.24^{a}	143.9±21.11^{ab}	148.4±26.77^{ab}
UTAE (100)	139.5±26.42^{a}	141.2±17.26^{a}	143.1±26.26^{a}	145.3±22.16^{ab}	153.4±39.21^{a}
UTAE (200)	130.7±12.78^{a}	134.6±23.44^{a}	140.4±27.24^{a}	151.4±17.34^{a}	159.8±24.16^{a}
UTAE (400)	137.9±34.33^{a}	140.1±29.97^{a}	143.6±22.17^{a}	153.7±24.14^{a}	161.6±28.39^{a}

Data are presented as mean ± SD of body weight (g). Data was analysed by one- way ANOVA followed by Duncan post- hoc test for multiple comparisons, (n=6). Mean values having different lower case alphabets as superscripts are considered significant (p< 0.05) across the columns.

3.4 Food Consumption

Table 3 shows the effect of UTAE and Chlorpropamide on the weekly food consumption of the alloxan-induced diabetic rats. Following alloxan administration, the food consumption of rats was significantly (p< 0.05) increased. Treatment with the extract showed time and dose- dependent significant (P< 0.05) reduction in food consumption in weeks 1, 2, 3 and 4 compared to diabetic control.

Table 3: Effect of Aqueous Leaf Extract of *Uvariaopsis tripetala* on Food consumption (g) of Alloxan Induced Diabetic Wistar Rats

Treatment	FOOD CONSUMPTION (g) Week 1	Week 2	Week 3	Week 4
N/S (1ml)	178.4±43.19^{b}	187.4±21.19^{b}	190.0±64.36^{b}	187.3±17.36^{b}
CHLOR (250)	165.5±10.23^{b}	160.1±14.23^{b}	150.7±15.41^{a}	139.2±11.43^{a}
UTAE (100)	156.9±11.21^{ab}	143.4±22.17^{a}	142.8±16.29^{a}	1365.±15.31^{a}
UTAE (200)	153.4±16.21^{ab}	139.4±15.16^{a}	137.5±14.13^{a}	132.4±12.40^{a}
UTAE (400)	140.3±17.51^{a}	140.1±17.48^{a}	141.3±20.11^{a}	138.2±14.21^{a}

Data are presented as mean ± SD of weight of food (g) consumed. Data was analysed by one- way ANOVA followed by Duncan post- hoc test for multiple comparisons, (n=6). Mean values having different lower case alphabets as superscripts are considered significant (p< 0.05) across the columns.

3.5 Water Intake

Table 4 shows the effect of UTAE and Chlorpropamide on the weekly water consumption of the alloxan-induced diabetic rats. Following alloxan administration, the water consumption of rats was significantly ($p< 0.05$) increased. Treatment with the extract showed time and dose- dependent significant ($P< 0.05$) reduction in food consumption in weeks 1, 2, 3 and 4 compared to diabetic control.

Table 4: Effect of Aqueous Leaf Extract of *Uvariaopsis tripetala* on Water intake (ml) of Alloxan Induced Diabetic Wistar Rats

	WATER INTAKE(ml)			
Treatment	Week 1	Week 2	Week 3	Week 4
N/S (1ml)	300.3±51.04[b]	383.3±35.59[b]	421.7±65.23[b]	366.7±65.23[b]
CHLOR (250)	234.5±50.11[a]	246.0±34.61[a]	245.0±20.74[a]	213.3±31.61[a]
UTAE (100)	254.5±28.13[a]	246.7±33.50[a]	228.3±29.14[a]	206.3±21.37[a]
UTAE (200)	217.3±45.11[a]	238.7±13.35[a]	221.5±29.17[a]	205.4±10.54[a]
UTAE (400)	218.2±31.44[a]	235.0±41.11[a]	216.4±25.45[a]	191.5±25.15[a]

Data are presented as mean ± SD of volume of water (ml) consumed. Data was analysed by one- way ANOVA followed by Duncan post- hoc test for multiple comparisons, (n=6). Mean values having different lower case alphabets as superscripts are considered significant ($p< 0.05$) across the columns.

4. Discussion

Diabetes mellitus is possibly the world's highest metabolic disorder, and as knowledge of its heterogeneity is advancing, the need for more appropriate therapy increases. This disease causes many chronic complications such as vascular disease, retinopathy, neuropathy, kidney disease and heart disease. There is an increase demand to use natural products (herbs) with anti-diabetic activity due to the side effects associated with the use of insulin and oral hypoglycaemic agent (kameswara *et al.,* 1997). This present study therefore evaluated the effect of the aqueous leaf extract of *Uvariopsis tripetala* on some classical symptoms of diabetes.

In this study alloxan was used to induce experimental diabetes. Alloxan induces diabetes by damaging the insulin secreting pancreatic beta-cells of the islets of Langerhans resulting in reduced synthesis and release of endogenous insulin (Ghosh, 2005).

The cytotoxic action of alloxan is mediated by reactive oxygen species with a simultaneous massive increase in cytosolic calcium concentration leading to a rapid total destruction of beta-cells producing a type 1-like diabetes mellitus (Szkudelski, 2001). Polyphagia, polydypsia, polyuria and weight loss are established classical symptoms and signs of diabetes mellitus. These were clearly demonstrated in this study, with increased food and water intake in the diabetic groups and also marked weight loss in these groups when compared to the non-diabetic control. Hyperglycemia gives rise to glycosuria which is accompanied by osmotic diuresis (Polyuria). Polyuria which causes water depletion, signals the thirst centre in the hypothalamus for increased water intake. This cycle of polyuria and polydypsia continues depending on the level of hyperglycemia (Okon *et al.,* 2012).

Treatment with the extract of *Uvariopsis tripetala* reduced hyperglycemia dose and time– dependently. The anti-hyperglycaemic activity of the plant could be attributed to the ability of the antioxidants present in it to scavenge the free radicals generated by alloxan hence, regenerating the destroyed beta-cells and subsequently, release of insulin. The aqueous extract of *Uvariopsis tripetala* leaves also reduced the magnitude of food and water intake though out the duration of this study when compared to the diabetic group. Given that food and water intake are controlled by satiety and thirst centers respectively in the hypothalamus, it could also be that apart from controlling glycaemia, the extract stimulated the satiety centre and inhibited the thirst centre as well as hunger (Okon *et al.,* 2012). The body weights of diabetic rats decreased following alloxan treatment. This is in agreement with the symptoms of diabetes as stated by American Diabetic Association (ADA) (2000) to include unexplained weight loss. This observation could be attributed to the increased conversion of storage fat and proteins to glucose (gluconeogenesis) (Champe *et al.,* 2005). However, after the first week of treatment, probably with improvement in glucose uptake by cells and subsequent reversal of gluconeogenesis, the body weights of the treated diabetic groups showed a significant increase throughout the course of the experiment.

5. Conclusion

In conclusion, the aqueous extract of *U. tripetala* exhibited anti-diabetic properties. Hence this plant may serve as a good candidate for alternative and/or complimentary medicine in the management of diabetes.

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