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Evaluation of the sub-chronic toxicity profile of the corm of *Xanthosoma sagittifolium* on hematology and biochemistry of alloxan-induced diabetic Wistar rats

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Abstract:
Background: Hematological and biochemical changes associated with diabetes mellitus and probable reversal were assessed in alloxan-induced diabetic Wistar rats fed with varied percentages of *Xanthosoma sagittifolium* corm feed (Xs). The changes were compared to normoglycemic rats and diabetic rats treated with glibenclamide.
Methods: The study had eight groups in all with group 8 (control) consisting of five normoglycemic rats fed with normal rat pellets (Nrp). Diabetes was experimentally induced by intraperitoneal injection of alloxan to normoglycemic rats. Diabetic rats (serum glucose >200 mg/dL) at 48 h postinjection were randomly divided into the seven groups, each diabetic group consisting of five rats. One group was untreated and fed with Nrp, four groups were fed with 25 %, 50 %, 75 % or 100 % Xs, one group was fed with 100 % Xs and administered with glibenclamide, while a 7th group was fed with Nrp and administered with glibenclamide.
Results: This study shows that treatment of diabetes with corm of *X. sagittifolium* increases cellular response to inflammation which is required for body defense against assaulting agents. Decreased serum protein levels observed in untreated diabetic rats were restored in diabetic rats fed with *X. sagittifolium* corm with particular increase in serum albumin levels but depression of globulin fraction, except in rats fed with *X. sagittifolium* feed and administered with glibenclamide. *X. sagittifolium* showed a potent antihyperglycemic effect and corrected the dyslipidemia in a manner comparable to that observed for glibenclamide. Although HDL levels were still low, significant ($p<0.05$) decrease of LDL levels was a positive indicator of reduced risk for development of cardiovascular and/or coronary heart disease.
Conclusions: *X. sagittifolium* corm can be recommended for inclusion in diets of diabetics without causing further deterioration of health of the diabetic patients.

Keywords: biochemistry, cardiovascular complications, diabetes, hematology, *Xanthosoma sagittifolium*
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Introduction

Diabetes mellitus (DM) is usually characterized by persistent high blood glucose levels (BGLs) which may have resulted from failure of the pancreas to produce sufficient insulin (type 1) and or the body cells to respond to the insulin produced (type 2) [1]. Several complications have been associated with this metabolic disorder and these include renal failure, retinopathies, cardiovascular and/or coronary heart disease (CVD/CHD), stroke, ulceration of extremities, impaired wound healing, amongst others [2, 3]. Prevention and treatment of (DM) may involve adjustment to healthy diet, increased physical activity, maintenance of normal body weight using the body-mass index and control of hypertension. Prescription of medications such as insulin and or other oral hypoglycemic agent may also be necessary to control BGLs [4, 5].

Traditionally, food and medicinal plants have been employed for the management of this metabolic disorder. These plants are usually administered as an integral part of the diet or as extracts which are consumed orally [6–8]. One of such plants prescribed to diabetic patients in South West Nigeria is *Xanthosoma sagittifolium*, a root crop commonly known as cocoyam. Amongst root and tuber crops cultivated and consumed in Nigeria, *X. sagittifolium* ranks third in importance after cassava and yam [9, 10]. The two variants, white and pink,

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are nutritionally superior to cassava and yam, with a content of 20–25 % starch, 70–80 % water and significant amount of vitamins. It is particularly compatible with the diet requirement of diabetic patients, with very high protein content (2–3 %) in relation to other tropical tuber crops [11]. *X. sagittifolium* has broad leaves with long stem attached to a corm which grows into the soil with some cormels. All parts of the plant are utilized as food in a variety of forms [12]. It serves as both a source of food and income, especially in rural areas in eastern and western parts of Nigeria where it is most widely grown [13].

Previous researchers have reported that *X. sagittifolium* is a good base for infant food preparation due to its highly digestible starch and reasonable calcium and phosphorus (for bone building), B-complex vitamins and pro vitamin A [14, 15]. Akobundu and Hoskins [16] reported that infants in some countries were traditionally weaned solely on starch prepared from precooked, wet-milled and wet-sieved corn. A more recent study by Oti and Akobundu [17] also show that *X. sagittifolium* starch can be incorporated in the development of weaning food which is easily digestible and accessible to low-income earners in developing countries.

However, some researchers have raised some questions with regards to the safety of the use of food and medicinal plants for treatment and or management of diseases including DM. Even, if the plants in themselves are relatively safe in normal bodies, it may be imperative to determine if the plant, *X. sagittifolium*, further progresses complications associated with diabetes [18–20]. This study aims to determine the effect of the therapeutic approach of *X. sagittifolium* inclusion in diabetic patient diet. Therefore, the toxicological profile of alloxan-induced diabetic rats fed with *X. sagittifolium* feed was assessed in this study using hematological and biochemical changes in these diabetic rats.

Materials and methods

Experimental animals

Wistar rats were obtained from and housed at the Department of Physiology Animal House, University of Ibadan, Ibadan, Nigeria. The rats were feed with commercially available pelletized rat ration and clean water *ad libitum*. The rats were handled humanely in accordance to the Experimental Animal Care and Use Ethics Committee of the Faculty of Veterinary Medicine, University of Ibadan, Ibadan, Nigeria. Only normoglycemic rats were included in the study.

Preparation of cocoyam feed

X. sagittifolium corm was washed, peeled and per boiled for 10 min. It was mashed, air dried, crushed and reconstituted with crushed commercial rat feed at 25 %, 50 %, 75 % and 100 % cocoyam feed.

Sub-chronic toxicity study

Induction of DM

Diabetes was induced by intraperitoneal injection of a single dose of alloxan monohydrate (100 mg/kg). BGL were monitored for 48 h by AccuChek® glucometer. Rats with BGL <200 mg/kg were excluded from the study from this stage. Hyperglycemic rats were randomly and equally divided into seven groups of five rats each.

Experimental procedure

Diabetic rats in group 1 were fed with 100 % commercial rat pellet serving as negative controls, while rats in groups 2, 3, 4 and 5 were fed with 25 %, 50 %, 75 % or 100 % cocoyam feed, respectively. Diabetic rats in group 6 were fed with 100 % cocoyam feed and administered with glibenclamide, a sulphonyl urea oral hypoglycemic agent at a dose of 5 mg/kg, while group 7 rats were fed with 100 % pelletized rat ration and administered with glibenclamide. Group 7 served as the positive controls for the study, while an 8th group of normoglycemic rats was included to the serve as the baseline controls for the study. The feed and or glibenclamide was administered to the diabetic rats in the test groups for 14 days.

Sample collection

After sub-chronic feeding of the diabetic rats with *X. sagittifolium* blood samples were obtained from the retro-orbital sinus of the rats on day 15 for hematological and serum biochemical analysis. Hematological parameters evaluated included packed cell volume (PCV), red blood cells, hemoglobin concentration, MCV, MCH, MCHC, erythrocyte sedimentation rate (ESR), white blood cell count, lymphocytes, neutrophil and platelet count. Serum biochemical parameters analyzed were total protein, albumin, globulin, alanine transaminase, aspartate transaminase, glucose, total cholesterol, triglycerides, low density lipoprotein (LDL), high density lipoproteins (HDLs) and some electrolytes, sodium (Na^+) and potassium (K^+).

Results

Hematology

PCV was unchanged in all groups of diabetic rats except diabetic untreated rats which had significantly ($p<0.05$) reduced PCV compared to normoglycemic control rats. Diabetic rats fed with *X. sagittifolium* and administered with glibenclamide had relatively higher values of red blood cell indices compared to other *X. sagittifolium*-fed or glibenclamide-treated rats (Table 1). Nonsignificant ($p>0.05$) increases were observed in the white blood cell count and its differentials of diabetic rats fed with *X. sagittifolium* and or administered with glibenclamide compared to normoglycemic control rats. Platelet count was not significantly ($p>0.05$) different for all the diabetic rats compared to the control rats (Table 2).

Table 1: Packed cell volume and red cell indices of alloxan-induced diabetic rats fed with *Xanthosoma sagittifolium* feed for 14 days.

Group	PCV, %	RBC, $\times10^6/\mu L$	Hb, g/dL	MCV, fL	MCHC, g/dL	MCH, ρg	ESR
Diab	37.40±2.16[a]	10.46±2.21	12.44±0.69	39.40±5.06[a]	33.00±0.00	12.80±1.71[a]	3.20±0.58
25% Xs	43.60±1.97	15.74±0.71[b]	14.48±0.67	36.00±2.88	33.00±0.00	9.60±1.03[a]	5.60±0.25
50% Xs	43.20±0.66	11.87±0.44	14.34±0.21	36.80±1.66	33.00±0.00	11.80±0.66	7.60±0.40[b]
75% Xs	46.00±0.55[b]	12.56±0.99	15.22±0.18[b]	36.60±2.46	33.00±0.00	11.80±0.86	10.00±0.63[a,b]
100% Xs	44.40±0.51	11.01±1.03	14.74±0.16	41.40±3.86	33.00±0.00	13.20±1.39	13.60±0.40[a,b]
100% Xs+Glib	48.00±0.16[b]	9.91±0.71[b]	15.72±0.14[b]	49.20±3.84[b]	33.00±0.00	15.80±0.97	5.40±1.66
Glib	45.40±0.25	10.36±1.33	15.02±0.07[b]	46.00±4.83[b]	33.00±0.00	13.80±1.90	5.40±0.25
Nondiab	44.67±1.28	10.44±0.55	14.83±0.43	43.00±2.99	33.00±0.00	14.00±1.00	3.67±0.62

Values with [a] on a column are significantly ($p<0.05$) different compared to the non-diabetic rats; values with [b] on a column are significantly ($p<0.05$) different compared to diabetic rats. Diab, diabetic untreated; Xs, *Xanthosoma sagittifolium*; Glib,glibenclamide; Nondiab, nondiabetic rats.

Table 2: White cell indices and platelet count of alloxan-induced diabetic rats feed with *Xanthosoma sagittifolium* feed for 14 days.

Treatment	WBC, $\times10^3/\mu L$	LYMPH, %	NEUT, %	Platelet, $10^5/\mu L$
Diab	12.80±1.41	70.40±0.25[a]	28.40±0.25[a]	1.08±0.80
25% Xs	14.68±2.85	63.60±0.25	35.40±0.25	1.28±0.80
50% Xs	12.76±0.66	57.20±0.37[b]	41.40±0.25[b]	1.24±0.40
75% Xs	11.36±2.48	66.80±0.37	31.80±0.20	1.40±0.00
100% Xs	14.32±2.14[b]	75.60±0.25[a]	23.40±0.25[a]	1.28±0.49
100% Xs+Glib	12.12±0.85	53.40±0.40[b]	45.60±0.25[b]	1.40±0.00
Glib	11.44±1.76	74.20±0.37[a]	25.40±0.25[a]	1.40±0.00
Nondiab	11.37±1.27	61.83±0.31	37.50±0.22	1.33±0.42

Values with [a] on a column are significantly ($p<0.05$) different compared to the nondiabetic rats; values with [b] on a column are significantly ($p<0.05$) different compared to diabetic rats. Diab, diabetic untreated; Xs, *Xanthosoma sagittifolium*; Glib, glibenclamide; Nondiab, nondiabetic rats.

Serum biochemistry

Serum biochemistry showed that total protein and its constituent fractions significantly ($p<0.05$) reduced in diabetic but untreated rats. However, diabetic rats fed with *X. sagittifolium* had significantly unchanged protein levels compared to the normoglycemic control rats (5.3±0.13 g/dL). An increase in total protein was observed in rats fed with *X. sagittifolium* and administered with glibenclamide (6.56±0.04 g/dL), but a significant reduction was observed in rats fed standard rat feed and administered with glibenclamide (4.12±0.08 g/dL) compared to the normoglycemic rats (Table 3).

Table 3: Protein, serum enzymes and glucose levels of alloxan-induced diabetic rats feed with *Xanthosoma sagittifolium* feed for 14 days.

Treatment	Total protein, g/dL	Albumin, g/dL	Globulin, g/dL	ALT, U/L	AST, U/L	Glucose, mg/dL
Diab	3.92±0.32[a]	2.60±0.14[a]	1.32±0.02	38.8±1.86	44.6±0.97[a]	349±23.2[a]
25% Xs	5.32±0.04[b]	3.22±0.02	2.10±0.03	51.2±1.85[b]	64.4±0.70[b]	185.2±36.1[a,b]
50% Xs	4.32±0.04	3.18±0.02	1.14±0.02	42.4±0.75	55.2±0.40	166±46.2
75% Xs	4.60±0.05	3.48±0.04[b]	1.12±0.02	53.8±0.50[b]	62.4±0.70[b]	125±11.3[b]
100% Xs	5.58±0.06[b]	3.46±0.04	2.12±0.02	46.0±0.54[b]	65.8±0.60[b]	124±15.3[b]
100% Xs+GLB	6.56±0.04[b]	4.38±0.06[b]	2.18±0.04	56.0±0.50[b]	56.4±0.68	131±19.0[b]
Glib	4.12±0.08	3.08±0.06	1.04±0.02	49.7±1.50[b]	45.6±0.68	127±28.2[b]
Nondiab	5.30±0.13	3.25±0.10	2.08±0.03	42.8±0.82	53.3±0.72	112±7.3

Values with [a] on a column are significantly ($p<0.05$) different compared to the nondiabetic rats; values with [b] on a column are significantly ($p<0.05$) different compared to diabetic rats. Diab, diabetic untreated; Xs, *Xanthosoma sagittifolium*; Glib, glibenclamide; nondiab, nondiabetic rats.

Liver enzymes alanine transferase (ALT) and aspartate transferase (AST) were significantly increased in diabetic rats fed with *X. sagittifolium* and those also administered with glibenclamide compared to the normoglycemic rats (42.8±0.82 U/L and 53.3±0.72 U/L). However, diabetic rats fed with standard rat feed and administered with glibenclamide had significantly reduced AST levels (45.6±0.68 U/L) compared to the normoglycemic rats (Table 3). BGLs were significantly ($p<0.05$) reduced in all rats fed with *X. sagittifolium* and or administered with glibenclamide (124±15.3–185.2±36.1 mg/dL) compared with the diabetic untreated rats (349±23.2 mg/dL). The decrease was dose dependent with the higher feed percentages (75 %–125±11.3 mg/dL and 100 %–124±15.3 mg/dL) showing BGL which are comparable to normoglycemic rats (112±7.3 mg/dL) (Table 3).

Lipid profile showed a significant ($p<0.05$) increase in cholesterol, triglyceride and LDL of diabetic untreated rats, while HDL was significantly ($p<0.05$) reduced. Diabetic rats fed with *X. sagittifolium* showed a dose-dependent reduction in the lipid profile, with significant ($p<0.05$) reduction in HDLs as well. Serum electrolytes sodium and potassium were significantly increased in all diabetic rats (Table 4).

Table 4: Lipid profile and serum electrolyte levels of alloxan-induced diabetic rats feed with *Xanthosoma sagittifolium* feed for 14 days.

Treatment	Cholesterol, mg/dL	Triglyceride, mg/dL	HDL, mg/dL	LDL, mg/dL	AIP	Na^+, mg/dL	K^+, mg/dL
Diab	51.2±1.01[a]	54.4±0.75[a]	27.0±2.10	36.3±0.85	2.01	52.4±0.75	61.6±0.75
25% Xs	51.2±0.48[a]	53.2±0.48[a]	22.2±0.09	16.7±0.07	2.40	63.0±0.89	53.6±0.75
50% Xs	42.4±0.75	43.6±0.40	34.2±0.09	21.1±1.61	1.27	53.8±0.49	42.6±0.87
75% Xs	45.2±0.20	54.8±0.37[a]	23.2±0.10	17.7±0.33	2.36	54.2±0.66	64.4±0.75
100% Xs	57.0±0.89[a]	61.2±0.90[a]	23.4±0.08	17.7±0.07	2.62	75.2±0.37	65.0±0.32
100% Xs+GLB	52.8±0.49[a]	55.2±0.37[a]	22.4±0.54	16.2±0.54	2.46	65.4±0.75	76.4±0.75
Glib	42.8±0.48	45.8±0.58	25.3±0.14	18.5±0.46	1.81	55.8±0.58	43.4±0.60
Nondiab	38.0±2.51	41.6±0.75	54.4±0.08	18.3±0.11	0.76	44.6±0.97	34.2±0.66

Values with on a [a] column are significantly ($p<0.05$) different compared to the nondiabetic rats; values with [b] on a column are significantly ($p<0.05$) different compared to diabetic rats. Diab, Diabetic untreated; Xs, *Xanthosoma sagittifolium*; Glib, Glibenclamide; Nondiab, nondiabetic rats.

Discussion

This study showed that DM, a metabolic derangement of glucose metabolism, also presents with anomalies in hematology and serum biochemistry [21, 22]. Treatment of the experimentally induced diabetes in Wistar rats with feedstuff prepared using *X. sagittifolium* corm reversed some of these anomalies. The underlying pathology leading to development of alloxan-induced diabetes is the rapid depletion of β-cells of Islets of Langerhans by DNA alkylation and accumulation of cytotoxic free radicals, initiating the inflammatory response. A subsequent infiltration of activated macrophages and lymphocytes occurs, accompanied by a reduction in insulin release and a stable hyperglycemic state [23, 24].

Hematology revealed that *X. sagittifolium* feed significantly reversed the depression in PCV observed in the diabetic rats but increased ESR. This suggests increased inflammatory response which was corroborated by the increased neutrophil count of these rats. Typically, clinical or experimentally induced diabetes is characterized by consistently defective neutrophil chemotactic, phagocytic and microbicidal activities [25, 26]. This is evidently seen as neutrophils act as first-line cellular defense and the reduction of their function contributes to the high susceptibility to and severity of infections in diabetics [27]. This study shows that treatment of diabetes with corm of *X. sagittifolium* increases cellular response to inflammation which is required for body defense against assaulting agents, although caution should be exercised as the response observed may be uncontrolled or exaggerated up to pathological levels. Platelet count was also reversed to normal in all test rats.

The result of biochemical assays showed significantly ($p<0.05$) depressed serum protein levels in diabetic untreated rats which were restored in diabetic rats fed with *X. sagittifolium* corm or administered with glibenclamide, with particular increase in serum albumin levels. Serum proteins are synthesized by the liver; thus, deficiencies or increased serum levels can be directly related to liver function [28]. Serum proteins are essential in the blood for maintenance of osmotic pressure and as carrier vehicles for classes of substances ranging from lipid to drugs across biological membranes [29]. In pathologic states, liver-specific enzymes ALT and AST increase in proportion to the level of hepatic damage. All diabetic, but treated rats showed marginal increases in these enzyme activities, but the diabetic untreated rats showed significantly ($p<0.05$) reduced levels of these liver enzymes.

It can be inferred that diabetes-induced hepatic injury may have resulted in cellular necrosis and fibrosis [30, 31] in these diabetic untreated rats, thus the significant reduction in protein synthesis and enzyme activities. The hepatic damage may also be due to direct hepatic injury by alloxan [32, 33]. Thus, *X. sagittifolium* may have some hepatoprotective effects which prevented a significant progression of hepatic injury. A dose-dependent reversal of hyperglycemia was also observed in the diabetic rats fed with *X. sagittifolium* at the end of the 14-day treatment period, especially by the higher percentages of *X. sagittifolium* feed. The observed antihyperglycemic effect of *X. sagittifolium* was comparable to that observed in glibenclamide.

The lipid profile of all diabetic rats showed hypercholesterolemia, hypertriglyceridemia with increased LDLs, but significantly ($p<0.05$) reduced HDLs as expected in diabetes [34]. Cholesterol content of HDL is least of all lipoproteins, but it increases with decreasing density of the lipoprotein. This makes HDL the least atherogenic lipoprotein. LDL and lesser density lipoproteins can easily penetrate the endothelial lining of blood vessels and ultimately cause CVH/CHD, major complications of diabetes [35, 36]. It is widely reported that increased plasma levels of LDL with decreased HDL levels are indicators of increased risk of development of CVH/CHD [37–39].

Findings from this study showed that dyslipidemia observed in the treated rats was gradually reversed as shown by significantly ($p<0.05$) reduced LDL levels. Although HDL levels were still low, decreased LDL levels are a positive indicator of reduced risk for development of CHD [36]. Previous researchers have also linked lipoprotein sizes and hypertriglyceride levels to insulin resistance [40], which may further complicate the underlying pathology. Insulin synthesis is impaired due to destruction of the Islet cells of the pancreas by alloxan and insulin resistance in cells occurs due to increased atherogenic lipoprotein levels and hypertriglyceride, thus enhancing the progression of diabetes [41]. The atherogenic index of plasma was increased in the diabetic rats, but rats fed with 50 % *X. sagittifolium* feed showed significantly ($p<0.05$) reduced risk of development of cardiovascular complications comparable to that observed for glibenclamide.

In conclusion, *X. sagittifolium* corm reversed some of the hematological and biochemical anomalies accompanying diabetes and reduced risk for development of CHD/CVD, major complications of diabetes. *X. sagittifolium* corm showed potent antihyperglycemic effect, corrected some of the dyslipidemia and reduced the risk of development of CHD/CVD. It can therefore be inferred from this study that *X. sagittifolium* corm can be recommended for inclusion in diets of diabetic patients without further progression of the disease.

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