

Serum Lipid Profile of Alloxan-induced Diabetic Rats Fed *Triticum aestivum*-based diet

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Abstract: Diabetes mellitus (DM) is a metabolic disorder in which carbohydrate, protein and lipid metabolism is not properly regulated by insulin. Many indigenous medicinal plants have been successfully used to manage diabetes. However, the use of dietary management is most advocated. Thus, the aim of this study was to evaluate the antihyperlipidemic potential of wheat-based diet in alloxan-induced diabetic rats. Forty (40) albino rats (*Rattus norvegicus*) were grouped into four with ten (10) animals in each. Diabetes was induced by the intra-peritoneal injection of alloxan monohydrate (150mg/kg body weight). Group A consists of (non-diabetic) rats fed yam based-diet; group B, (diabetic) rats fed yam flour-based diet and treated with metformin; group C (diabetic) rats fed wheat-based diet while rats in group D (untreated) were fed yam based-diet for four (4) weeks. There was a significant reduction ($p < 0.05$) in the concentration of glucose, triglycerides, cholesterol, LDL cholesterol, VLDL cholesterol and a significant increase ($p < 0.05$) in the level of HDL cholesterol. It is considered that feeding diabetic patient with *Triticum aestivum* (wheat)-based diet would assist in the management of diabetes mellitus.

Key words: Albino rats, alloxan, wheat, hyperlipidemia, metformin

INTRODUCTION

Diabetes mellitus (DM) is the most common serious metabolic disorder in the endocrine system and is one of the three causes of death in the world (Hassan and Hassan, 2011; Islam and Choi, 2009). It is a growing health problem in most countries and its incidence is considered to be high all over the world (Hassan and Hassan, 2011; Tharkar *et al.*, 2010). Diabetes mellitus is a multifactorial disease which generally involves absolute or relative insulin deficiency (type I) and/or insulin resistance (type II) and ultimately leads to hyperglycemia (Hassan and Hassan, 2011; Nelson and Cox, 2003). DM either type I or type II is characterized by hyperglycemia, abnormal lipid and protein metabolism along with specific long-term complications affecting the retina, kidney and nervous system (Hassan and Hassan, 2011). It is a complex disease associated with myriad of debilitating complications among which cardiovascular diseases are on a resounding note. About 70 to 80% of deaths in diabetic patients are due to vascular diseases (Salau and Ajani, 2012; Chattopadhyay and Bandyopadhyay, 2005).

Cardiovascular diseases (CVD) contributed to one third of all global death with developing countries, low income and middle income countries accounting for 86% of disability-adjusted life years (WHO/FAO, 2003). Some of the risk factors implicated in cardiovascular disease are total plasma cholesterol (Richard *et al.*, 1989; Mazier and Jones, 1991), plasma triglycerides (Austin *et al.*, 2000; Van Lennep *et al.*, 2002), plasma low density lipoprotein (LDL) cholesterol, plasma very low density lipoprotein (VLDL) cholesterol (Yla-Herttuala *et al.*, 1989), while higher level of high density lipoprotein (HDL) cholesterol play an important role in removing cholesterol from the cells and transport it back to the liver for excretion (Nelson and Cox, 2005)

In addition, the pharmacological currently used for treatment of diabetes (both insulin and biguanides) produce serious side effects (Hassan and Hassan, 2011; Suba *et al.*, 2004; Reng *et al.*, 1991) and fail to significantly alter the course of diabetic complications are not safe for use during pregnancy (Hassan and Hassan, 2011) also the cost of administering these drugs is beyond the reach of people living in the rural area and low income rate people (Ozougwu, 2011).

Although, the uses of herbal drugs has been commonly practiced and considered to be less toxic with fewer side effects (Rao *et al.*, 2003). Furthermore, dietary management of diabetes has been believed locally to be helpful and example of such diet is *Triticum aestivum* (wheat),

Triticum aestivum belong to a family Poaceae with *Triticum species* which is a grass, originally from the Fertile Crescent region of the Near East, but now cultivated worldwide. It has high content of fiber, antioxidant (particularly antioxidant minerals and vitamins) and complex carbohydrate which are believed to exhibit antidiabetic effects (Belderok *et al.*, 2000; Mohan *et al.*, 2013). The methanolic extract of this plant has been reported by Mohan *et al* (2013) in the management of diabetic rats. Also, the uses of this plant as a source of diet in diabetes management have been acclaimed without scientific validation. Furthermore, the uses of diets will serve dual roles. Therefore, the aim of this work is to assess the hypolipidemic potential of wheat-based diet in alloxan induced diabetic rats

MATERIALS AND METHODS

Wheat was obtained from local farmer in Kastina, Kastina State and oven dried at 60 °C. *Dioscorea rotundata* (white yam) was used as yam flour (because it is one of the most staple food consumed mainly in the Western Part of Nigeria), obtained from Oja Oba Market in Ilorin, Kwara State, which was peeled, sliced and oven dried (60 °C). Soybean and cellulose were also obtained from Oja Oba market in Ilorin, Kwara State. Then each sample was milled separately with local grinding machine. Soybean oil was obtained from Sunola Refined Soybeans, Kewalram Nigeria Limited, and vitamin/mineral mix was obtained from Rofat Feed Nigeria Limited, Ilorin, Kwara State

Also, alloxan monohydrate (for inducing diabetes) was obtained from Sigma Chemical Company, St Louis Mo U.S.A, while Accu – check active glucometer (for determining the glucose level) was obtained from Roche Diagnostic, Mannheim, Germany.

Animals and Treatments

A total of 40 male and female albino rats (*Rattus norvegicus*) were used for the experiment with an average weight of 150 ± 20g. They were obtained from the Animal House of the Department of Biochemistry, University of Ilorin, Nigeria.

The animals were kept under standard environmental conditions, with 10 albino rats housed in a cage. All the animals were acclimatized for seven days to the laboratory condition and they received human care accordingly.

Induction of Diabetes

Alloxan monohydrate of 150mg/kg bodyweight (dissolved in 0.9% sterile NaCl solution of pH 7) (Osinubi *et al.* 2004; Habib *et al.* 2005) was administered intraperitoneally to rats in group II to IV to induced diabetes, of which their blood glucose level have been previously determined.

Thereafter, blood was collected from the tail artery of the animals (Burcelin *et al.*, 1995) to determine their glucose levels using the Accu-check active glucometer. Rats with serum glucose levels between (250–400mg/dl), showing clear signs of polyuria, polyphagia and polydipsia after one day were considered diabetic and used for the experiment (Eyo *et al.*, 2010).

Experimental design

The animal's groups are as follows:

Group A: Non-diabetic rats fed with yam flour-based diet.

Group B: Diabetic rats fed with yam flour- based diet plus metformin

Group C: Diabetic rats fed with wheat-based diet

Group D: Untreated diabetic rats fed with yam flour-based diet

The various diets were compounded as shown in Table 1. The diet and water (*ad libitum*) were given to the appropriate animals in their respective groups.

Table 1: Diets composition of various groups (g/100)

Ingredient	Group A	Group B	Group C	Group D
Wheat	-	-	57.6	-
Yam flour	57.6	-	-	57.6
Yam flour + metformin	-	57.6	-	-
Soyabeans	25	25	25	25
Soyabeans oil	6	6	6	6
Cellulose	6	6	6	6
D-methionine	0.4	0.4	0.4	0.4
Vitamin/mineral	5	5	5	5

The animals were fed for 4 weeks and blood glucose level was monitored on every two day. At the end of the feeding period the animals were sacrificed using diethyl ether as anesthesia and blood samples were collected from each animal for serum (in clean sample tubes) parameters analyses. The method of Akanji (1986) was employed for serum preparation.

Parameters studied: Proximate, minerals and amino acid profile were done using Association of Analytical Chemist (AOAC) (2005). *In vitro* antioxidants such as DPPH, nitric oxide, ferric reducing power (FRAP), Fe²⁺ chelation, total phenol and total flavonoid were determined using Cao *et al*, (1997), Mondal *et al*, (2006), Pulido *et al*, (2000), Puntel *et al*, (2005), Singleton *et al*, (1999) and Harborne (1984) method respectively. Cholesterol, High density lipoprotein cholesterol (HDL-c) and triglycerides were determined by enzymatic method using Randox kits. Low density lipoprotein cholesterol (LDL- c) and very low density lipoprotein cholesterol (VLDL- c) were obtained by deduction using Friedwald equation (Friedewald *et al*., 1972)

Statistical analysis: The data were analyzed using one-way ANOVA. Level of significance was assessed using Duncan Multiple Range Test (DMRT) at p<0.05 (SPSS 14.0 software was used for data analyses).

RESULTS

Table 2, 3, 4 and 5 shows the result of proximate analysis, in-vitro antioxidant, mineral analysis and amino acids analysis of the formulated diets. There were significant increase in crude fibre, soluble fibre, insoluble fibre, protein, zinc, selenium, copper, seventeen amino acids, DDPH, NO

amongst others ($p < 0.05$) in wheat-based diet (Feed B) when compared with control diet (Feed A), with no significant difference in their moisture content. The results of the lipid profile indicated that alloxan administration significantly increased ($p < 0.05$) total cholesterol, triglyceride, VLDL and LDL levels above the normal control value with significant reduction in HDL levels (Figure 1). Treatment with wheat-based diet reduced the abnormal increase in total cholesterol, very low density lipoprotein (VLDL) and low density lipoprotein (LDL) with significant increase in the high density lipoprotein (HDL) levels when compared with the normal group and metformin treated group. Also, Figure 2 shows the result of glucose, with highest level in alloxan induced diabetes but was reduced to minimal level when treated with wheat based-diet and metformin.

Table 2: Percentage proximate analysis of the formulated diets

Parameters (%)	Feed A	Feed B
Ash	2.39 ± 0.15^a	5.59 ± 0.55^b
Lipid content	6.50 ± 0.12^a	8.44 ± 1.12^b
Protein	16.89 ± 0.07^a	20.63 ± 0.03^b
Moisture Content	1.56 ± 0.39^a	1.75 ± 0.02^a
Fibre	8.39 ± 0.04^a	16.62 ± 0.01^b
*Insoluble dietary fiber	6.39 ± 0.05^a	12.34 ± 0.01^b
*Soluble dietary fiber	2.00 ± 0.02^a	4.28 ± 0.02^b
Carbohydrate (by different)	64.27 ± 0.35^a	46.97 ± 0.45^b

Each value is a mean of three determinations $\pm$ SEM,

Values with different superscripts across the row are significantly different ($p < 0.05$)

145 Legend
 146 Feed A = yam flours based-diet, B = wheat based-diet,

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148 **Table 3: In-vitro antioxidant parameters of the formulated diets**

Parameters	Feed A	Feed B
DPPH	23.01±0.02 ^a	40.00±0.02 ^b
Nitric Oxide	2.34±0.03 ^a	6.12±0.06 ^b
FRAP	0.68±0.09 ^a	6.89±0.04 ^b
Fe ⁺² chelation	34.23±0.03 ^a	58.77±0.02 ^b
Total phenol	1.99±0.2 ^a	2.38±0.2 ^b
Total flavonoid	2.84±0.02 ^a	3.34±0.02 ^b

149 Each value is a mean of three determinations ± SEM,
 150 Values with different superscripts across the row are significantly different (p<0.05)

151 **Legend**

152 Feed A = yam flours based-diet, B = wheat based-diet,

153 **Table 4: Minerals composition of the formulated diets**

Minerals	Feed A	Feed B
Na	248.21±0.02 ^a	979.10±0.22 ^b
Ca	1.32±0.02 ^a	4.83±1.02 ^b
Mg	38.96±0.32 ^a	87.56±1.22 ^b
Zn	10.21±0.02 ^a	26.05±0.08 ^b
Se	0.21±0.32 ^a	1.46±1.02 ^b
P	134.05±0.02 ^a	176.01±0.02 ^b
Fe	1.02±0.42 ^a	14.36±0.02 ^b

154 Each value is a mean of three determinations ± SEM,
 155 Values with different superscripts across the row are significantly different (p<0.05)

156 Legend
 157 Feed A = yam flours based-diet, B = wheat based-diet,

158

159 **Table 5: Amino acids composition of formulated diets**

Amino acids	Feed A	Feed B
*Glycine	1.89 ±0.01 ^a	4.20±0.32 ^b
*Alanine	3.24±1.02 ^b	6.98±1.08 ^b
*Serine	3.21±0.12 ^a	5.20±0.12 ^b
*Proline	3.82±1.00 ^a	5.54±0.15 ^b
*#Valine	2.96±1.02 ^a	5.32±0.05 ^b
*#Threonine	1.48±0.22 ^a	3.69±0.05 ^b
#Isoleucine	2.40±0.12 ^a	3.96±0.05 ^b
#Leucine	4.90±1.02 ^a	11.52±0.05 ^b
*Aspartate	5.20±0.02 ^a	9.92±0.05 ^b
#Lysine	2.20±0.02 ^a	7.35±1.02 ^b
*#Methione	1.20±2.02 ^a	1.49±0.02 ^b
*Glutamate	12.20±2.02 ^a	19.48±1.02 ^b
#Phenylalanine	4.20±0.02 ^a	8.39±1.03 ^b
*#Histidine	2.22±0.02 ^a	3.40 ±0.02 ^b
*#Arginine	3.27±1.12 ^a	6.92±1.02 ^b
*Tyrosine	1.01±1.02 ^a	2.24 ±1.02 ^b
*cysteine	1.16±1.02 ^a	1.24±1.14 ^b

160 Each value is a mean of three determinations ± SEM,
 161 Values with different superscripts across the row are significantly different (p<0.05)
 162 Legend
 163 Feed A = yam flours based-diet, B = wheat based-diet,
 164 * = glucogenic amino acids
 165 # = essential amino acids

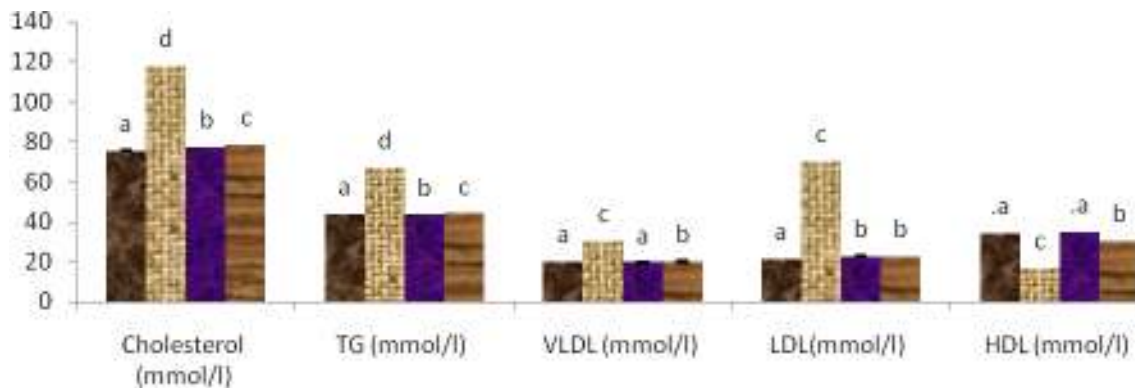


Figure 1: Effect of formulated diets on lipid profile of alloxan-induced diabetic rats
Each value was mean $\pm$ SEM of 10 rats in each group. Values with different superscripts letter (such a, b, c and d) differ significantly ($p < 0.05$). **Legend:** WD = wheat-based diet

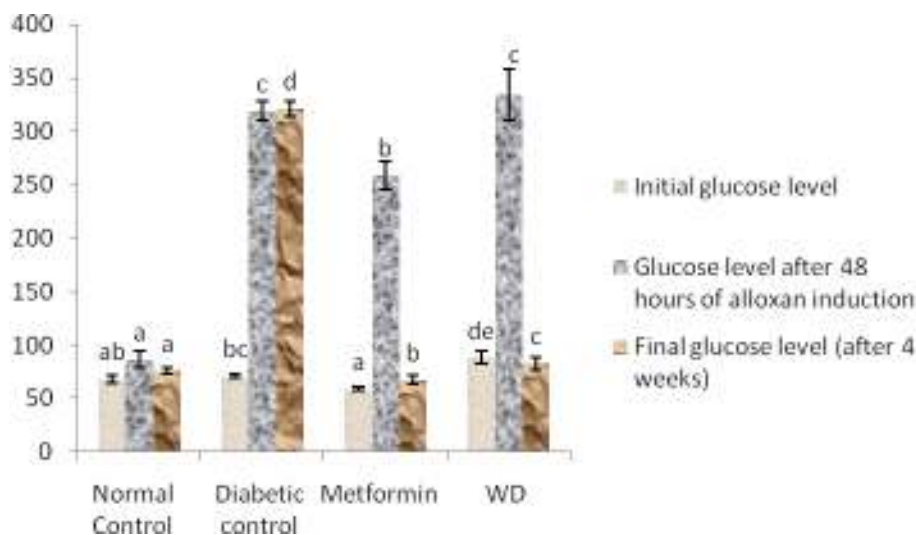


Figure 2: Effect of formulated diets on serum glucose of alloxan-induced diabetic rats
Each value was mean $\pm$ SEM of 10 rats in each group. Values with different superscripts letter differ significantly ($p < 0.05$), **Legend:** WD = wheat based-diet

DISCUSSION

Diabetes mellitus remains the most common chronic disorder of carbohydrate, fat and protein metabolism. It is characterized by chronic and persistent hyperglycemia, degenerative vascular changes and neuropathy due to complete or partial insulin secretion or insulin resistance (Murray and Pizzorno, 1998). Moreover, diabetes mellitus is accompanied by hypercholesterolemia, hyperlipidemia and hepatic steatosis (Harris and Crabb, 1982). The hypercholesterolemia is a consequence of accelerated fatty acid oxidation to acetyl CoA which is the primary substrate for cholesterol synthesis (West *et al.*, 1966). Similarly, the hyperlipidemia associated with diabetes mellitus results from accelerated *de novo* hepatic biosynthesis and release of VLDLc without a corresponding increase in the rate of clearance from the blood by the lipoprotein lipase whose activity is dependent on high insulin: glucagon ratio (Harris and Crabbs, 1982).

Metformin, a prototype of the second generation sulfonyurea class of the oral hypoglycemic agents, is known to mediate its hypoglycemic effect by stimulating insulin release from the pancreatic β cells, reducing hepatic insulin clearance, stimulating the release of somatostatin and suppressing the secretion of glucagon (Davis and Granner, 2001). Sulfonyureas have also been shown to suppress hepatic gluconeogenesis (Blumenthal, 1977).

In the present study, there were abnormal increases in all the lipid profiles studied as shown alloxan induced untreated group except in HDL (lower concentration) when compared to treated groups (Figure 1). But comparing the results of yam flour based-diet plus metformin with those obtained in wheat based-diet. It appears that the latter may be eliciting its normoglycemic effect through enhancement of peripheral glucose utilization (Alamgeer *et al.*, 2012). The observed significant reduction in the serum concentrations of triglycerides, total cholesterol and cholesterol fractions could also be due to depressed hepatic gluconeogenesis by wheat based-diet. It may also due to the fact that wheat based-diet significantly elevated the activity of hepatic cholesterol 7-alpha-hydroxylase which is a rate-limiting enzyme in the biosynthesis of the bile acids and stimulates the conversion of cholesterol to bile acids leading to the excretion of cholesterol from the body (Naik, 2011). Furthermore, it may also due to the inhibition of fatty acid synthesis (Chi and Koh, 1982), enhanced excretion or lowered absorption of cholesterol (Vinson and Dabbagh, 1998) although this claim remains a speculation until it is subjected to further scientific validation by the key enzymes regulating this pathway. A positive relationship between gluconeogenesis and lipogenesis has been well documented in literature (Harris and

Crabbs, 1982). The bioactive compounds (total phenol, total flavonoid, DPPH, Fe²⁺ chelation etc) and antioxidant substances (selenium, zinc, vitamin A, vitamin E etc) present in the wheat based-diet may be responsible for the hypolipidemia potential of the diet by reversing the effects of alloxan (Baublis, 1999; Belderok *et al.*, 2000; Aurand, 1987). Also the present of glycine, methionine, cysteine in the diets may be responsible for detoxification of reactive oxygen species, produced by induction of alloxan (Naik, 2011). In addition, the present of both soluble and insoluble dietary fibre in the diet may also responsible for lowering rate of bad cholesterol, by retarding the absorption of cholesterol (Naik, 2011)

Also, the lowering of glucose concentration in wheat based-diet (Figure 2) when compared with alloxan untreated group shows significant difference but there was no significance difference in yam based-diet plus metformin group when compared with wheat based-diet group. This hypoglycemic effect of wheat based-diet may due to insulin release from pancreatic cells of diabetic rats, improving insulin action and binding (Khan *et al.*, 1990), increasing glucose metabolism (Broadhurst, 1997), and high level of soluble and insoluble fiber which interfere with carbohydrate absorption, makes the stomach full and retard the absorption of glucose from gastrointestinal tract (Nelson *et al.*, 1991). The present of immune system booster antioxidant vitamins and minerals which has been described with the potential to scavenge reactive oxygen species produced by alloxan coupled with glucogenic amino acids in the wheat based –diet (Alvarado-Vásquez *et al.*, 2003).

CONCLUSION

The study clearly demonstrated that wheat based-diet have antihyperlipidemia potential which may make it highly useful in the management of type II diabetes.

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