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Lipid Profile and Cardiac Enzyme activities of high fat diet-streptozotocin (HFD-STZ) induced Type 2 Diabetic Wistar rats on Antioxidant Supplementation.

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<https://dx.doi.org/10.4314/sokjmls.v10i4.13>**Abstract**

Serum lipid profile and cardiac enzymes activities of high fat diet and low dose streptozotocin induced type 2 diabetic Wistar rats on antioxidant supplementation was monitored *in vitro*. Formulation of some recommended dietary approved (RDA) proportions of antioxidant rich vitamins, minerals and bio-flavonoids for management of diabetes. A total of five (5) groups of 10 rats each were adopted for this study. The serum levels of cholesterol (CHOL), Triglyceride (TG), High Density Lipoprotein (HDL), Low Density Lipoprotein (LDL), Very Low-Density Lipoprotein; and activities of Lactate dehydrogenase (LDH) and Creatine Kinase (CK) were measured using standard laboratory methods and kits. Data was analyzed using SPSS version 20.0 and the level of significance was set at $p < 0.05$. Lipid profile and cardiac enzyme activity indicated no statistical change ($p > 0.05$) in serum lipid profile parameters after 4 weeks of treatment. However, a significant ($p < 0.05$) but gradual and consistent decrease in serum cholesterol, triglyceride, LDL-C, and VLDL was observed after the 8th and importantly the 12th week of treatment. Results obtained after the 4th, 8th and 12th weeks of treatment revealed a relatively consistent levels of HDL-C across all study groups with no statistically significant change ($p > 0.05$). Furthermore, there was a significant decline ($p < 0.05$) in serum LDH and CK activities of the normal control and treated groups compared to the diabetic non-treated control group. From the results obtained, it is evident of the possible protective and restorative efficacy of antioxidants on obesity related complications and cardiac malfunction.

Keywords: Antioxidant, Cardiac enzyme, Lipid profile, Streptozotocin, Diabetes.**Introduction**

Diabetes mellitus type 2 as a heterogeneous disorder associated with continuous decline in insulin activity subsequently resulting in the inability of beta cells in the pancreas to compensate for insulin resistance. Such resistance in insulin action is usually augmented by the beta cells which secrete high amounts of insulin to maintain blood glucose homeostasis. In times when the insulin secretory function of beta cells become impaired due to increased oxidative stress and free radical generation, it further results in impaired glucose tolerance, loss of glucose homeostasis and eventual development of type 2 diabetes (Lebovitz and Banerji, 2004).

Oxidative stress characterized by free radical generation (reactive oxygen and nitrogen species) induces cell membrane damage, lipid peroxidation and DNA damage. It is mostly attributed to genetic mutation, increased aging, obesity and most diseases associated to metabolic defects.

Obesity and sedentary lifestyle are believed to be the major risk factors associated with type 2 diabetes mellitus development as most diagnosed diabetic patients are found to be obese (McIntosh and Pederson, 1999). High risk of morbidity and mortality associated with type 2 diabetes mellitus is mainly attributed to hypercholesterolemia, hypertriglyceridemia and hyperglycaemia resulting to atherosclerosis.

Abnormalities in glucose and lipid metabolism in the course of cellular respiration results in increased oxidative stress and free radical generation which in turn favours hyperglycaemia and dyslipidaemia. Cardiovascular disease known to be a major cause of mortality in type 2 diabetes mellitus patients is attributed to elevated cardiac fatty acid metabolism resulting in increased incidence of myocardial infarction (Dutka *et al.*, 2006; Boudina and Abel, 2007; Rijzewijk, *et al.*, 2009; McGill *et al.*, 2011; Labbe *et al.*, 2012).

It is therefore important to understand the metabolic relationship between type 2 diabetes mellitus, how it affects lipid and cardiac metabolisms abnormally, and to what extent antioxidants could be implicated in salvaging the resultant free radicals generated due to oxidative stress (Chinaka *et al.*, 2018). The potency of some exogenous antioxidants and antioxidant vitamins in lipid (fatty acid) metabolism and cardiovascular enzymes activity in type 2 diabetes mellitus patients is yet to be fully explored. Hence, this study is aimed at evaluating the effect of antioxidant supplement on lipid profile and cardiac enzyme activities in HFD-STZ-induced diabetic rats.

Materials and Methods

Materials

Chemical reagents like Streptozotocin (STZ), α -lipoic acid, resveratrol and quercetin purchased from Sigma Chemical Company (St. Louis, MO, USA); Standard supplement (name withheld due to patent right); glucose (GLUC), cholesterol (CHOL), triglyceride (TG), high density lipoprotein-cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C), very low density lipoprotein-cholesterol (VLDL-C), creatine kinase (CK) and lactate dehydrogenase (LDH) kits purchased from Randox, Agape and Abnova GmbH chemicals, USA and Germany, and all other chemicals used for this research were of analytical grade.

Methodology

Experimental animals and care

Wistar albino rats weighing between 50 – 70 grams were procured from the animal facility of the Department of Veterinary medicine,

University of Nigeria, Nsukka. The animals were relocated and housed (8 rats per cage) in standard polypropylene cages (34 x 47 x 18cm) with soft wood shavings as beddings with free access to clean water and commercially available rat pellet diet (Top feed, Nigeria) *ad libitum* prior to dietary manipulation of the study groups and maintained under normal laboratory conditions i.e. temperature ($22 \pm 24^{\circ}\text{C}$), relative humidity ($55 \pm 60\%$) and 12 hours light – dark cycle. The animals were handled in accordance with the National Institute of Health (NIH) Nigeria guideline for the care and use of laboratory animals and permission sought from the Faculty of Basic Medical Sciences, Ebonyi State University animal handling and ethics committee with code no EBSU/FBMS/02/042/21.

Composition of high fat diet (HFD) and STZ induction

After one week of acclimatization, the high fat diet composition and STZ induction procedure was according to the method of Srinivasan *et al.* (2004) with slight modifications. However, group 1 (Normal control) maintained consumption of standard pellet diet (SPD) throughout the study period while groups 2 - 5 received dietary manipulation (HFD). After eight (8) weeks of dietary manipulation, group 2 - 5 received a single dose (1 ml kg^{-1}) of intraperitoneal (i.p.) injection of STZ (35 mg kg^{-1}), while group 1 was administered same volume of citrate buffer (pH 4.5). Fasting blood glucose (FBG) level was measured 3 days after STZ injection and rats with FBG levels above 250 mg/dL were considered diabetic. The HFD was subsequently replaced with SPD, while treatment commenced throughout the study period.

Composition of antioxidant supplement

Exogenous antioxidant supplement (EAS) compounded for this study was a collection of recommended proportions of some antioxidant rich substances and ingredients which include; some vitamins (A, B₃, B₆, B₁₂, C and E), minerals (calcium, selenium, chromium, magnesium, potassium and zinc), α -lipoic acid, cinnamon powder, curcumin, cordyceps, resveratrol, quercetin and D-ribose-L-cysteine, mixed in corn oil and stored appropriately for use. Administration of the preparation was made twice daily for the period of the study.

Assay protocol

On the 4th, 8th and 12th weeks of treatment (4 weeks intervals), 3 rats per group were subjected on each occasion to overnight fast and blood sample collected after slight anaesthesia using a 5 ml syringe and needle by cardiac puncture. The blood sample is then transferred into a plain 5 ml sample container, spun at 5000rpm for 5 minutes, separated and the serum obtained were subsequently analyzed for fasting blood glucose estimation, lipid profile, creatine kinase activity and lactate dehydrogenase activity using their respective spectrophotometric kits.

Data analysis

The results obtained were analyzed statistically and expressed as mean ± standard deviation (SD). Differences between groups were ascertained by one-way analysis of variance

(ANOVA) version 20.1, followed by multiple comparison test (Turkey's), while intergroup comparison (Post-hoc test) was done using least significant difference (LSD) and p-value of <0.05 were considered significant.

Results

Fasting blood glucose level of HFD-STZ induced type 2 diabetic rats on antioxidant supplementation

The administration of antioxidant supplement preparation on HFD-STZ induced type 2 DM significantly (p<0.05) reduced hyperglycaemia when compared with the diabetic control group and this was consistent throughout the treatment test weeks (4, 8, 12). There was no significant difference (p>0.05) observed in the antioxidant treated groups compared with the normal control after 12 weeks of treatment (see Table 1).

Table 1: FBG estimation of HFD-STZ induced type 2 diabetic rats on antioxidant supplementation.

Parameters	Duration	Normal control	Diabetic control	Antioxidant Supplement	Standard supplement
FBG (mmol/l)	WK 4	4.62±0.83	16.4±1.22 ^a	11.16±1.20 ^c	10.28±1.88 ^c
	WK 8	5.12±0.48	16.9±0.44 ^a	9.89±0.41 ^c	9.50±1.02 ^c
	WK 12	4.98±0.31	17.3±0.11 ^a	7.72±0.22 ^b	8.00±0.98 ^b

Data are presented as the mean ± standard deviation (SD). ^aP<0.05 vs. Normal control (NC); ^bP<0.05 vs. Diabetic control (DC); ^cP<0.05 vs. Normal & diabetic control (N&DC). FBG, Fasting blood glucose; WK, week.

Lipid profile of HFD-STZ induced type 2 diabetic rats on antioxidant supplementation

The result of lipid profile indicates a significant decreasing effect of antioxidants on cholesterol, triglyceride, LDL-C and VLDL-C levels, with an increase in HDL-C compared to diabetic control. Administration of the antioxidant supplement significantly (p<0.05) decreased the HFD-STZ diabetes-induced increase in serum cholesterol, TG, LDL-C, VLDL levels of the treated group

progressively over the period (weeks) of testing (4, 8 and 12) compared to the diabetic control. A slight though significant (p<0.05) difference in serum HDL-C level was observed in the treated and diabetic control compared to the normal control group. Week 4 and 8 revealed a high statistically significant (p<0.05) increase in serum HDL-C levels of the antioxidant supplementation (see Table 2).

Table 2: Lipid profile result of HFD-STZ induced type 2 diabetic rats on antioxidant supplementation.

Parameters	Duration	Normal control	Diabetic control	Antioxidant Supplement	Standard supplement
CHOL (mU/ml)	WK 4	209.0±2.44	247.6±0.98	212.1±2.29	216.9±1.43
	WK 8	192.5±0.87	285.0±1.66 ^a	215.6±1.37 ^b	228.0±1.92 ^b
	WK 12	165.6±0.09	309.8±0.16 ^a	188.5±0.22 ^b	174.2±0.39 ^b
TG (mU/ml)	WK 4	158.5±1.21	254.3±6.53 ^a	152.3±3.63 ^b	169.4±2.18 ^b
	WK 8	158.5±1.21	254.3±6.53 ^a	152.3±3.63 ^b	169.4±2.18 ^b
	WK 12	242.1±1.57	245.9±6.94	176.3±6.22 ^c	220.3±4.27
HDL-C (mU/ml)	WK 4	119.1±0.20	145.6±0.78 ^a	161.0±5.57 ^a	134.3±0.37
	WK 8	117.5±1.06	132.1±4.09	146.6±2.28	153.3±0.35 ^c
	WK 12	137.9±0.13	148.4±0.05	120.3±0.08 ^b	99.7±0.15 ^c
LDL-C (mU/ml)	WK 4	43.61±0.42	64.03±0.04 ^a	43.33±1.30 ^b	48.80±1.36 ^b
	WK 8	26.60±1.61	79.73±0.43 ^a	57.77±1.24 ^b	30.62±0.72 ^b
	WK 12	17.32±0.05	75.08±0.01 ^a	27.43±0.20 ^b	35.66±0.45 ^c
VLDL-C (mU/ml)	WK 4	37.70±0.61	33.48±1.15	37.86±0.32	33.89±0.44
	WK 8	48.42±0.31	49.18±1.39	35.27±1.24 ^b	44.06±0.85
	WK 12	22.32±0.05	48.04±0.01 ^a	40.78±0.10 ^b	38.81±0.08 ^b

Data are presented as the mean ± standard deviation (SD). ^aP<0.05 vs. Normal control (NC); ^bP<0.05 vs. Diabetic control (DC); ^cP<0.05 vs. Normal & diabetic control (N&DC). CHOL, Cholesterol; TG, Triglyceride; HDL-C, High density lipoprotein; LDL-C, Low density lipoprotein-cholesterol; VLDL-C, Very low-density lipoprotein-cholesterol; WK, week.

Cardiac enzyme activities of HFD-STZ induced type 2 diabetic rats on antioxidant supplementation

Administration of antioxidant supplements significantly (p<0.05) decreased the HFD-STZ diabetes induced increase in serum CK and LDH activity of the diabetic rats consistently

throughout the test period. A significant decrease in serum CK and LDH activity of the HFD-STZ diabetes-induced group treated with antioxidant supplement was observed, and this was consistent all through the study duration (see Table 3).

Table 3: Result of cardiac enzyme activity of HFD-STZ induced type 2 diabetic rats on antioxidant supplementation.

Parameters	Duration	Normal control	Diabetic control	Antioxidant Supplement	Standard supplement
CK-MB (U/I)	WK 4	0.55±0.04	1.13±0.76 ^a	0.64±0.08 ^b	0.60±0.02 ^b
	WK 8	0.52±0.00	1.07±0.72 ^a	0.57±0.06 ^b	0.55±0.01 ^b
	WK 12	0.50±0.01	1.49±0.01 ^a	0.49±0.03 ^b	0.46±0.03 ^b
LDH (U/I)	WK 4	19.97±0.20	22.29±0.27	19.01±0.31 ^b	20.40±0.00
	WK 8	21.25±0.06	24.70±0.59 ^a	21.21±0.21 ^b	20.94±0.06 ^b
	WK 12	20.34±0.00	26.11±0.00 ^a	20.89±0.07 ^b	21.82±0.14 ^b

Data are presented as the mean ± standard deviation (SD). ^aP<0.05 vs. Normal control (NC); ^bP<0.05 vs. Diabetic control (DC); ^cP<0.05 vs. Normal & diabetic control (N&DC). CK-MB, Creatine kinase-MB subunit; LDH, Lactate dehydrogenase; WK, week.

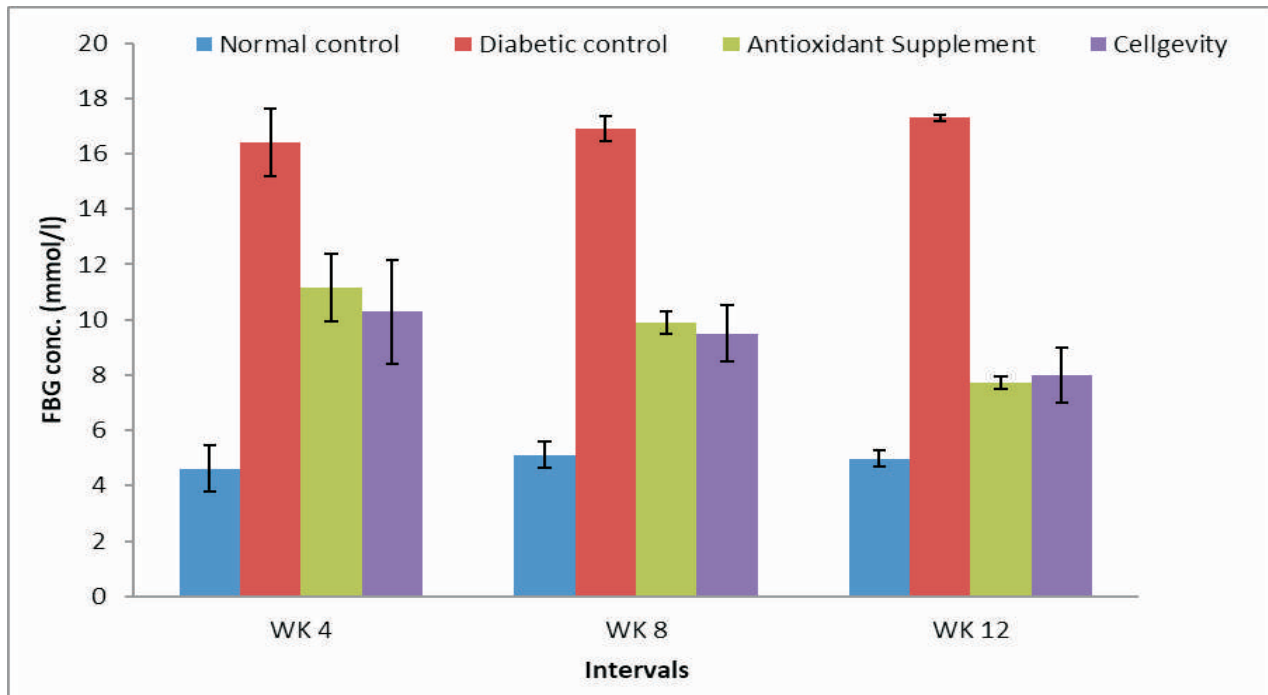


Figure 1: FBG estimation of HFD-STZ induced type 2 diabetic rats on antioxidant supplementation.

Data are presented as the mean \pm standard deviation (SD). ^a $p < 0.05$ vs. Normal control (NC); ^b $p < 0.05$ vs. Diabetic control (DC); ^c $p < 0.05$ vs. Normal & diabetic control (N&DC). FBG, fasting blood glucose.

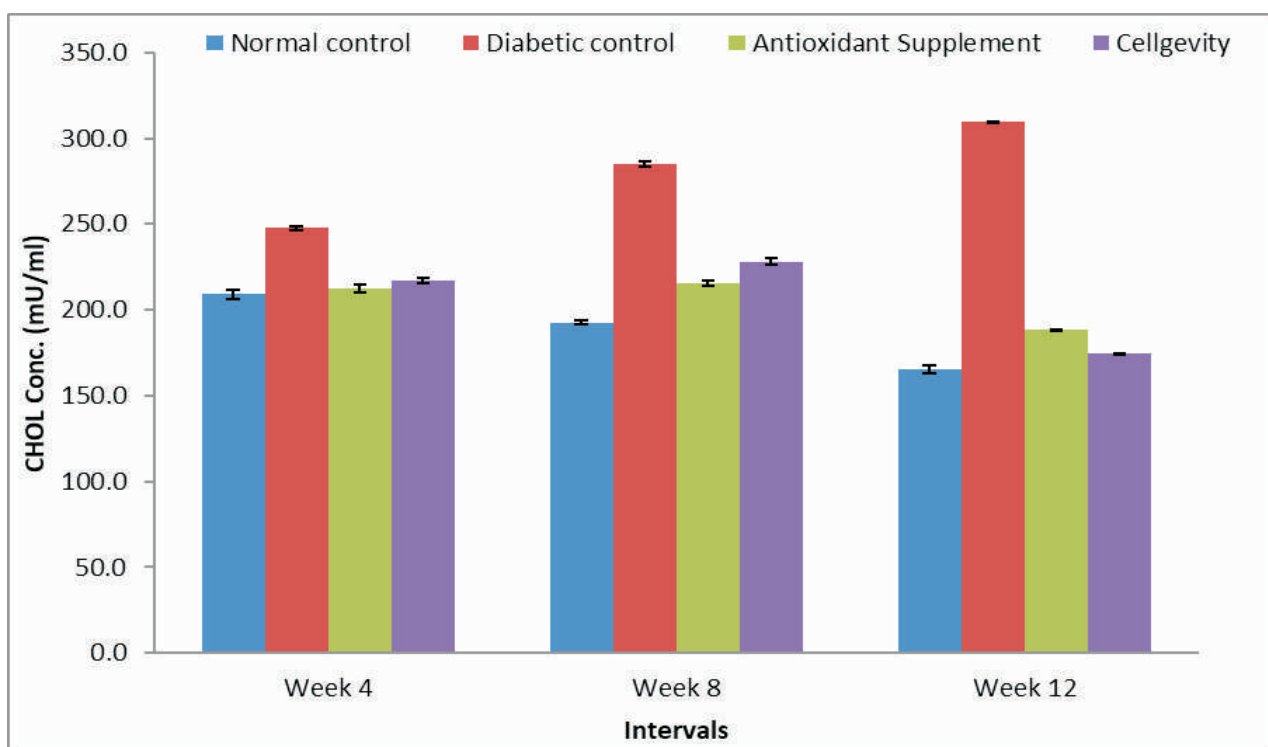


Figure 2: Cholesterol estimation of HFD-STZ induced type 2 diabetic rats on antioxidant supplementation.

Data are presented as the mean \pm standard deviation (SD). ^a $P < 0.05$ vs. Normal control (NC); ^b $p < 0.05$ vs. Diabetic control (DC); ^c $p < 0.05$ vs. Normal & diabetic control (N&DC). CHOL, cholesterol.

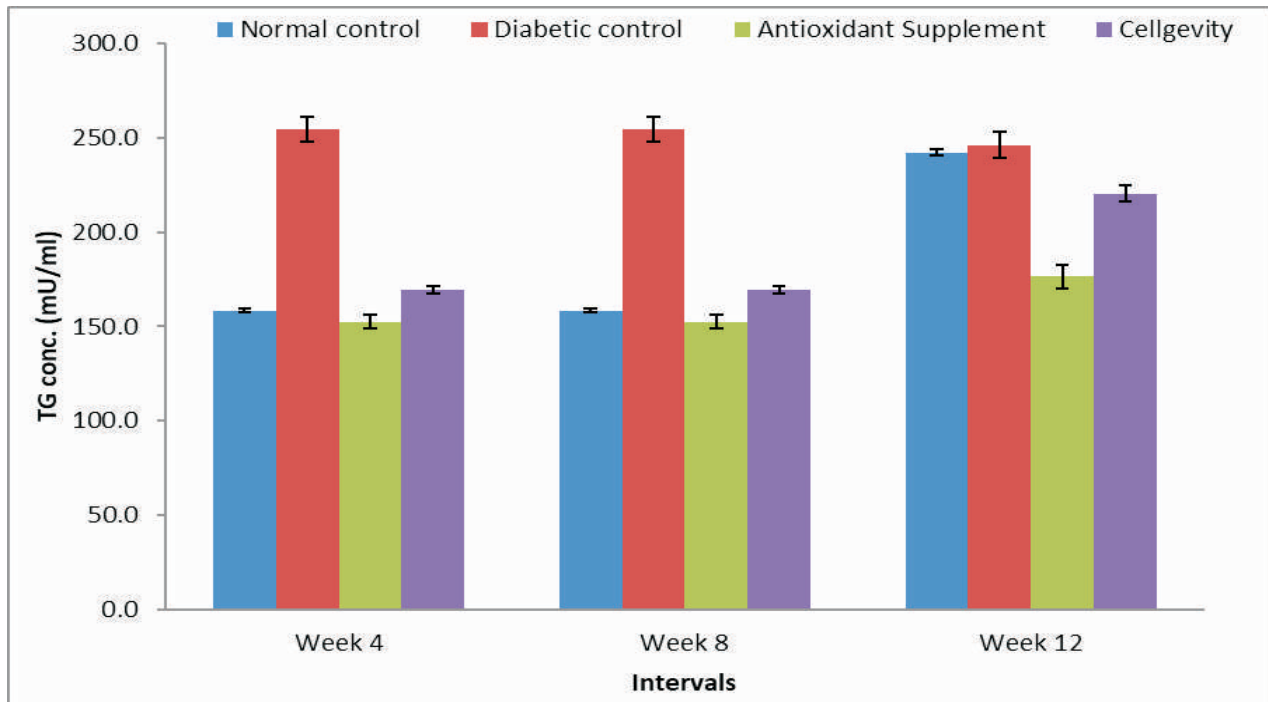


Figure 3: Triglyceride estimation of HFD-STZ induced type 2 diabetic rats on antioxidant supplementation.

Data are presented as the mean \pm standard deviation (SD). ^a $p < 0.05$ vs. Normal control (NC); ^b $p < 0.05$ vs. Diabetic control (DC); ^c $p < 0.05$ vs. Normal & diabetic control (N&DC). TG, triglyceride.

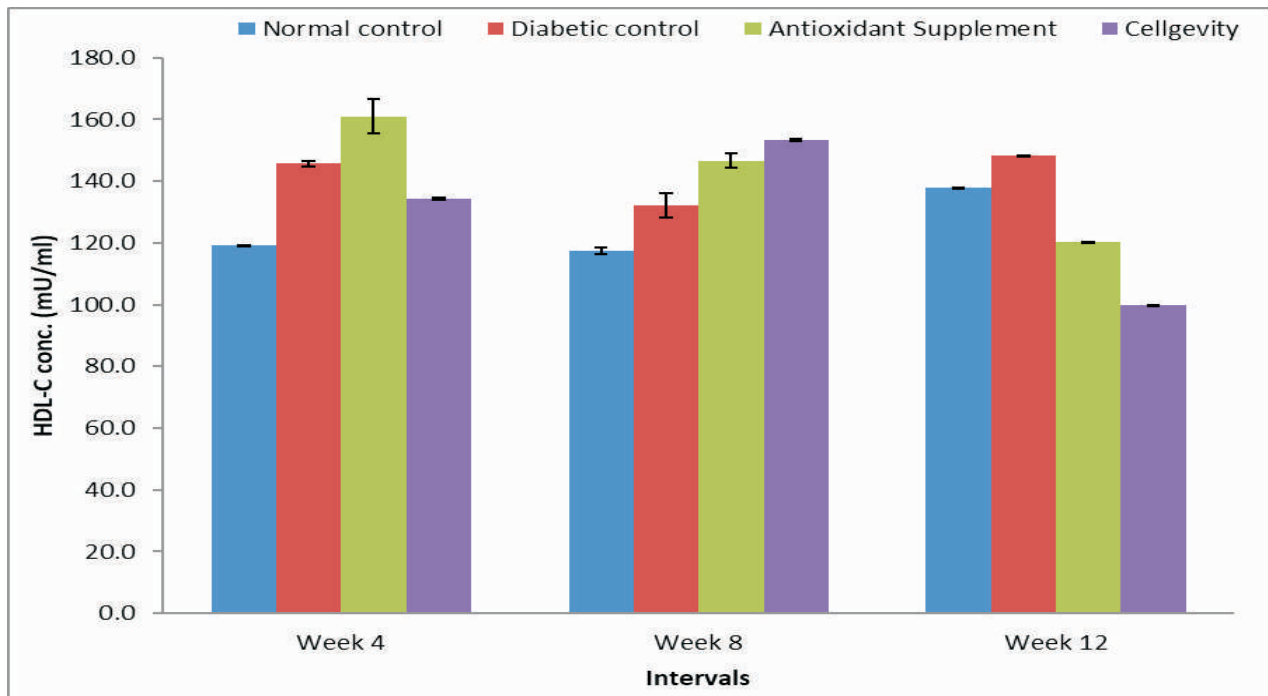


Figure 4: HDL-C estimation of HFD-STZ induced type 2 diabetic rats on antioxidant supplementation.

Data are presented as the mean \pm standard deviation (SD). ^a $P < 0.05$ vs. Normal control (NC); ^b $p < 0.05$ vs. Diabetic control (DC); ^c $p < 0.05$ vs. Normal & diabetic control (N&DC). HDL-C, high density lipoprotein-cholesterol.

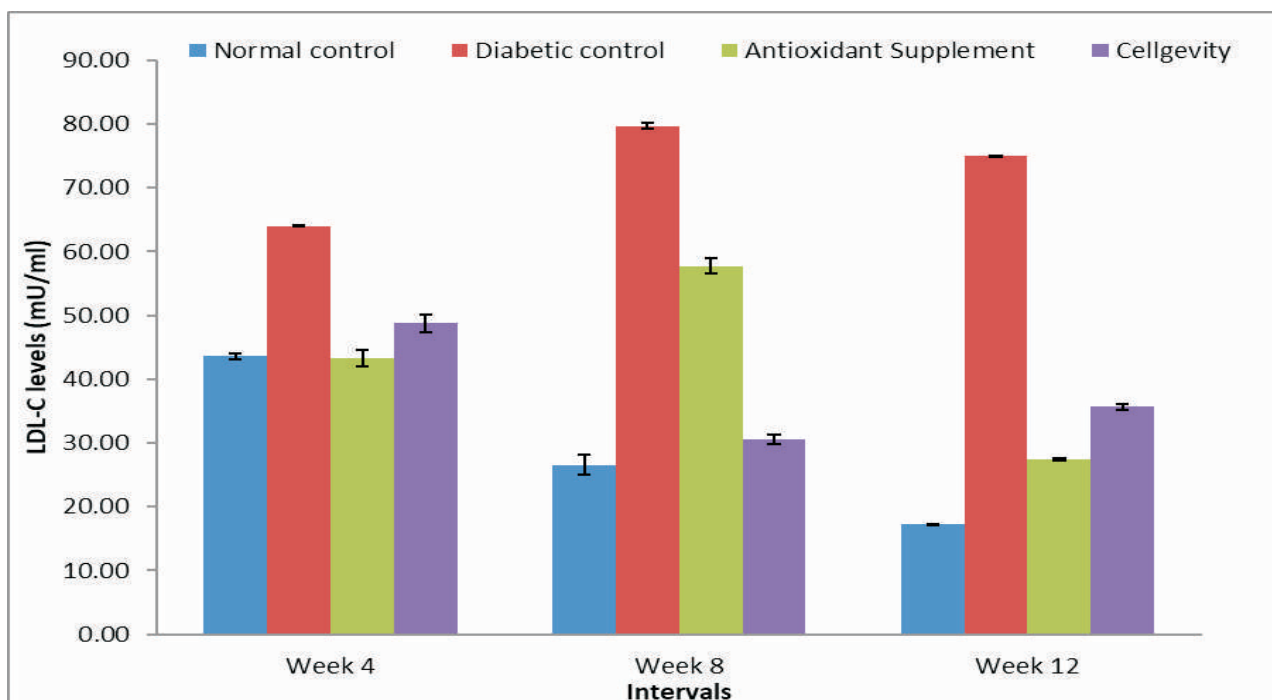


Figure 5: LDL-C estimation of HFD-STZ induced type 2 diabetic rats on antioxidant supplementation.

Data are presented as the mean \pm standard deviation (SD). ^aP<0.05 vs. Normal control (NC); ^bp<0.05 vs. Diabetic control (DC); ^cp<0.05 vs. Normal & diabetic control (N&DC). LDL-C, low density lipoprotein-cholesterol.

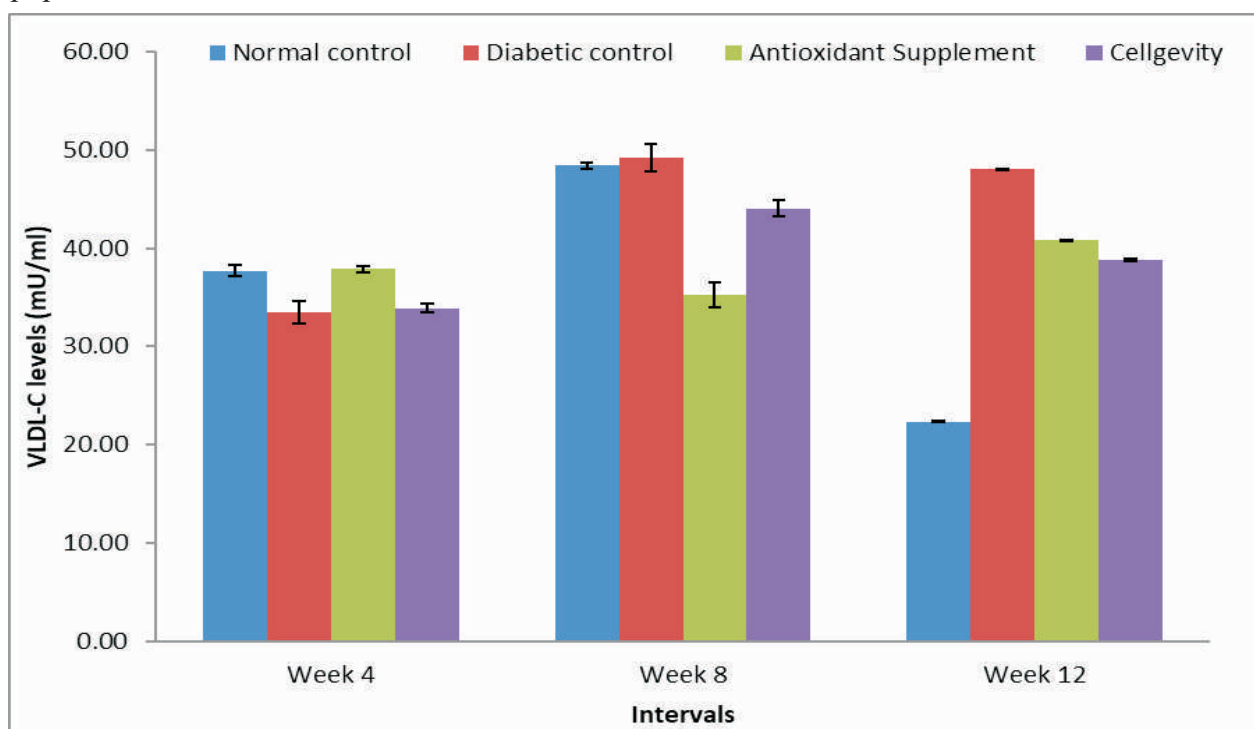


Figure 6: VLDL-C estimation of HFD-STZ induced type 2 diabetic rats on antioxidant supplementation.

Data are presented as the mean \pm standard deviation (SD). ^aP<0.05 vs. Normal control (NC); ^bp<0.05 vs. Diabetic control (DC); ^cp<0.05 vs. Normal & diabetic control (N&DC). VLDL-C, very low-density lipoprotein-cholesterol.

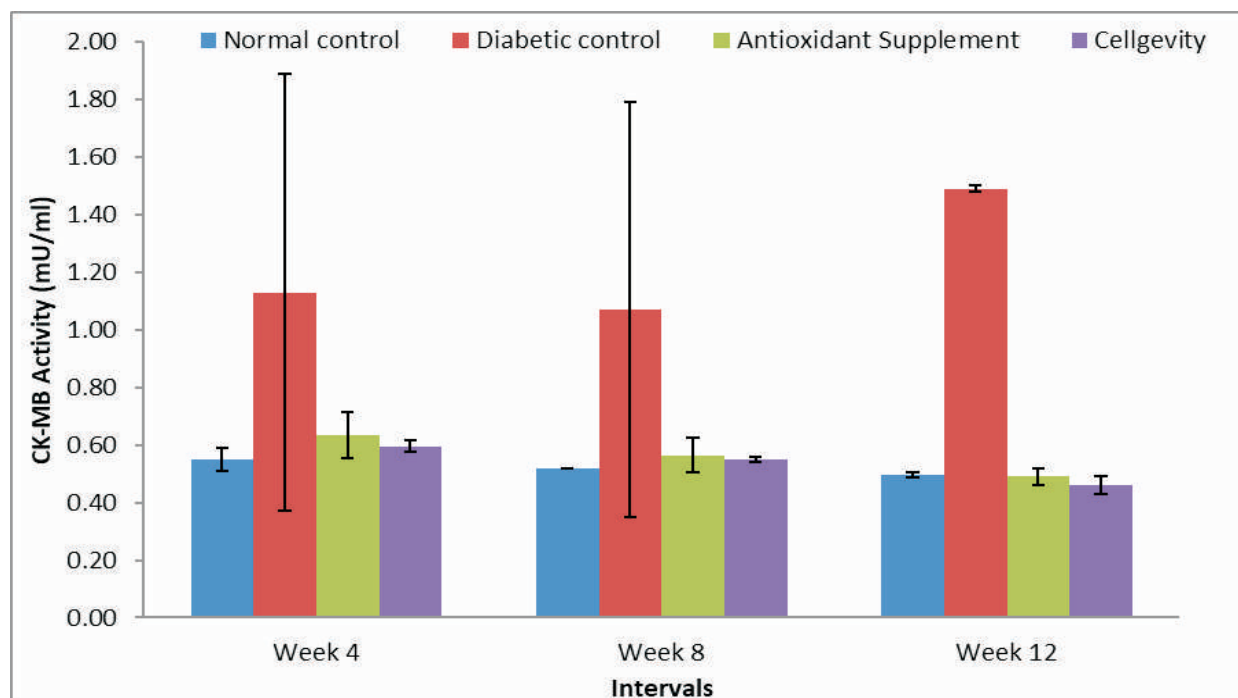


Figure 7: Estimation of serum CK-MB activity in HFD-STZ induced type 2 diabetic rats on antioxidant supplementation.

Data are presented as the mean \pm standard deviation (SD). ^aP<0.05 vs. Normal control (NC); ^bp<0.05 vs. Diabetic control (DC); ^cp<0.05 vs. Normal & diabetic control (N&DC). CK-MB, creatine kinase MB subunit.

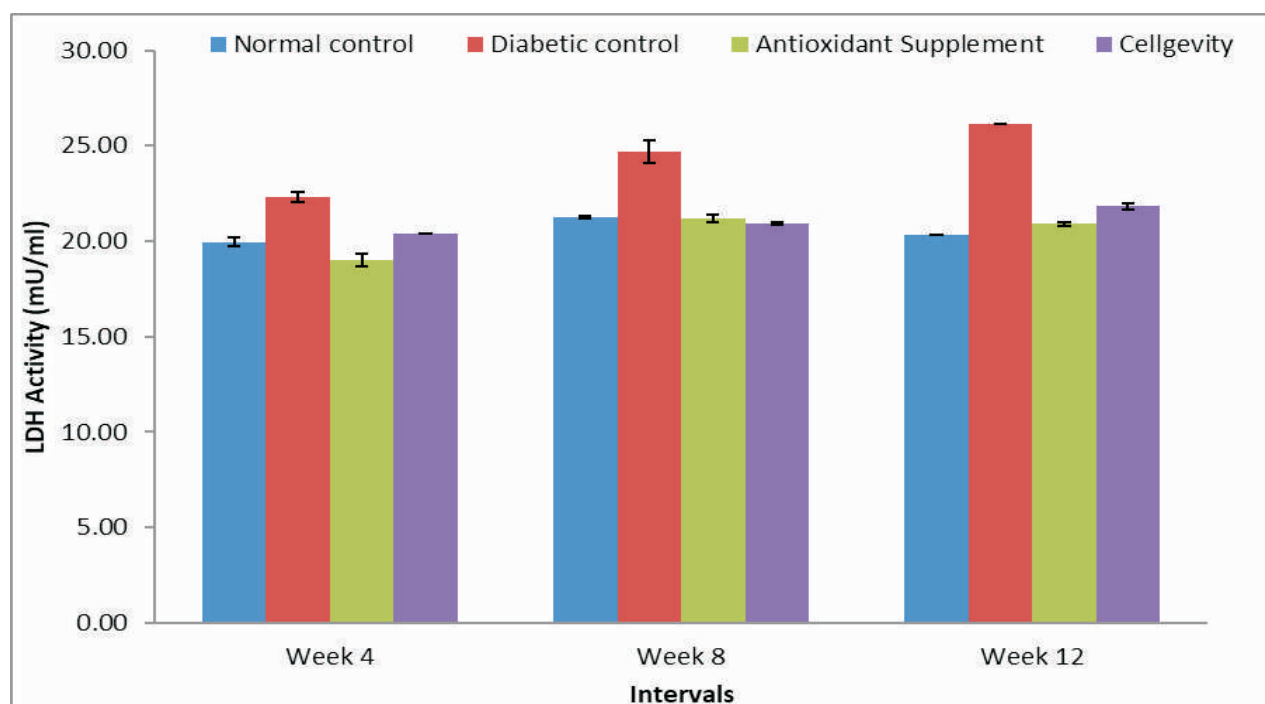


Figure 8: Estimation of serum LDH activity in HFD-STZ induced type 2 diabetic rats on antioxidant supplementation.

Data are presented as the mean \pm standard deviation (SD). ^aP<0.05 vs. Normal control (NC); ^bp<0.05 vs. Diabetic control (DC); ^cp<0.05 vs. Normal & diabetic control (N&DC). LDH, lactate dehydrogenase.

Discussion

Diabetes mellitus (DM) as one of the major global health challenges of the 21st century in association with cardiovascular disease and cancer have been attributed to a daily sporadic increase in persons' with the disease (Wild *et al.*, 2004; WHO, 2014). Potential complications and mortalities associated with DM can be attributed to lack of permanent cure, which is greatly attributed to the devastating adverse impact of oxidative stress related free radical generation. The need to profile therapeutic dormancy of some exogenous and endogenous antioxidants in alleviating this condition and its related complications like dyslipidemia, atherosclerosis and cardiovascular diseases is hence imperative. The insignificant difference observed in FBG estimation of the antioxidant supplement formulated and the standard supplement (name withheld due to patent right) treated groups as against the normal control after 12 weeks of treatment is indicative of the effect of antioxidants on DM type 2. This clearly validates the hypoglycaemic effect of antioxidants on oxidative stress and ROS induced diabetic complications.

HFD in combination with low dose STZ administration has been shown to affect lipid metabolism. The result of the present investigation indicated an increase in CHOL, TG, LDL-C and VLDL-C concentrations, with a decrease in HDL-C level in diabetic control, as against the diabetic treated and normal control groups. This report correlates with several other investigations (Palumbo, 1998; Arvind *et al.*, 2002; Achi *et al.*, 2016; Hu *et al.*, 2016; Zhang *et al.*, 2016). These alterations in lipid profile components especially cholesterol and triglyceride is reported to be responsible for the increased risk factors (hypercholesterolemia and hypertriglyceridemia) associated with coronary heart disease (Palumbo, 1998; Arvind *et al.*, 2002; Maghrain *et al.*, 2004). Administration of antioxidant supplements significantly lowered cholesterol, triglyceride, LDL-C, and VLDL-C levels across the test week (4, 8, 12). The significant reduction in cholesterol, triglyceride, LDL-C and VLDL-C is associated with an increase in HDL-C level, indicating a desirable lipid metabolism and biochemical state in the prevention of diabetes related atherosclerotic

condition. This clearly indicates the efficacy of antioxidants in alleviating oxidative stress related lipid dysfunction.

An increase in serum CK-MB and LDH activities were observed in the diabetic control group which is most likely to be associated with myocardial infraction as stated in previous reports (Hall, 1991; Hagar, 2002). Their reports held that increased CK-MB and LDH activities influenced cardiac muscle degeneration, a risk factor and marker for cardiovascular disease. From the result of the present study, the attenuating effect of the antioxidant supplement was observed in the HFD-STZ induced diabetes treated group, indicating the potency of antioxidants and antioxidant supplement in alleviating myocardial infraction due to cardiac muscle damage. Similar observations have been noted in folic acid and vitamin B₁₂; gallic acid; and vitamin E supplementation (Hagar, 2002; Patel and Goyal, 2011; Almeida *et al.*, 2012).

Conclusion

Conclusively, there exist increasing evidence of the potency and efficacy of antioxidant supplements, natural food and plant components in the management and treatment of diabetes mellitus and its attendant complications. This study evaluates the hypoglycaemic, hypolipidemic and anti-cardiovascular degeneration activities of antioxidant supplement preparation on high fat diet and low dose streptozotocin (HFD-STZ) induced type 2 diabetic Wistar rats. Based on the experimental results, treatment of HFD-STZ induced type 2 diabetes with antioxidant supplement preparation ameliorated hyperglycaemia, hyperlipidaemia, and cardiac dysfunction.

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Institutional Review Board

The researchers were closely and regularly monitored on animal handling compliance in accordance with the National Institute of Health

(NIH) Nigeria and Helsinki Declaration guidelines for the care and use of laboratory animals as being permissible by the Faculty of Basic Medical Sciences, Ebonyi State University animal handling and ethics committee with code no EBSU/FBMS/02/042/21.

Conflicts of interest

There was no conflict of interest regarding the publication of this paper as it was a sole authored research study.

Data Availability

Data for and supporting this research can be obtained from the Department of Biochemistry and School of Post Graduate Studies, University of Port Harcourt digital repository with deposition code as G2012/PhD/FT/393 where soft and hard copies of studies can be accessed since this is an original scientific research study and not a review.

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