

Full Length Research Paper

Antioxidant Status and Lipid Profile of Diabetic Rats Treated With Antioxidant Rich Locally Prepared Nutraceutical

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Diabetes mellitus is characterised by increased levels of oxidative stress markers and dyslipidemia, which are implicated in the development of diabetic complications. Antioxidants may be important in delaying the onset of the complications. The current work reports the effect of an antioxidant rich nutraceutical on serum lipid profile and antioxidant status of alloxan induced diabetic rats. The nutraceutical was prepared from onions, garlic, lemon, palm oil and Cray fish in ratio 6:6:2:1:5 respectively. The nutraceutical was administered orally to diabetic rats (wister strains) age ≥ 4 months for three weeks with and without treatment with metformin. Twenty four (24) hours after the last administration, blood samples were collected from the rats by cardiac puncture following anaesthesia in chloroform vapour. The effect of supplementation on serum levels of glucose, lipid profile, malondialdehyde, glutathione peroxidase, Cu, Mn, Zn, vitamins A, C and E were assessed. The results indicated that supplementation with the nutraceutical significantly ($P < 0.05$) reduced serum levels of glucose, malondialdehyde, cholesterol, triglyceride and atherogenic index. Supplementation also increased the serum levels of glutathione peroxidase activity, Zn, Cu, Mn, vitamins and HDL-cholesterol significantly ($P < 0.05$). The results suggest that supplementation may reduce the risk of oxidative stress and dyslipidemia associated with diabetes mellitus.

Key words: Antioxidant status, lipid profile, diabetes mellitus and nutraceutical.

INTRODUCTION

Diabetes mellitus (DM) is characterised by hyperglycaemia as a result of insulin inactivity or insufficiency (Maritim et al., 2003). The World Health Organization (WHO, 1999) defined DM as a fasting venous blood glucose level of greater than 7.0 mmol/l (126 mg/dl), or greater than 11.1 mmol/l (200 mg/dl) two hours after oral ingestion of 75g of glucose equivalent. As the disease progresses, patients are at increasing risk of developing specific complications, including retinopathy, nephropathy, neuropathy and atherosclerosis. The atherosclerosis may result in stroke, gangrene, or coronary disease (Carl and Burtis, 2001).

There is progressive increase in the global prevalence of diabetes (Shaw et al., 2010) probably due to life style changes (Wild et al., 2003). The current estimate shows that more than 285 million people worldwide are affected by the disease representing 6.4% of the world population (Shaw et al., 2010). It has been predicted that the worldwide estimate of diabetes will reach 7.7% by the year 2030 (Shaw et al., 2010). Nigerian diabetic population is put at 3.9% as at 2010 (Shaw et al., 2010). Experimental and clinical evidence suggest that oxidative stress plays a major role in the pathogenesis of diabetes mellitus and the associated dyslipidemia as well as other diabetic complications (Maritim et al., 2003; Quilliot et al., 2005). Diabetes is a metabolic disorder with micro and macro vascular complications that results in significant morbidity and mortality (WHO, 1994; Edemeka

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Table 1. Amount of antioxidants administered per kg body weight.

Vit A(μ g)	Vit C(mg)	Vit. E(μ g)	Cu(μ g)	Cr(μ g)	Mn(μ g)	Zn(μ g)
310.28	15.00	813.75	250.90	4.65	598.60	730.50

et al., 1999). They are characterised by low plasma level of both enzymatic and non enzymatic antioxidant defences, which make the cells of the diabetic subjects prone to oxidative attack (Maritim et al., 2003). Nigerian diabetic subjects have been reported to possess low serum levels of antioxidant vitamins and minerals (Aliyu et al., 2005; Adewumi et al., 2007; Wali et al., 2011). Multiple factors have been associated with increased oxidative stress in diabetes mellitus. These factors include glucose autooxidation that results in the production of free radicals, an increase in protein glycation and a decrease in antioxidant defences (Bilbis, 2008). Enhanced oxidative stress is considered an underlying condition that is responsible for some of the complications of diabetes (Packer, 2002).

Antioxidant micronutrients have been indicated to boost the antioxidant defences and curtail the deleterious effects of reactive oxygen species (Armstrong, 1996). Deficiencies of micronutrients may increase susceptibility of diabetic mellitus and the associated complications (Aliyu et al., 2005). Complex antioxidant mechanism including antioxidant vitamins and trace elements exists to limit the effects of these reactions (Packer, 2002).

In this study an antioxidant rich nutraceutical (Containing Vitamins A, C and E, Cu, Cr, Mn and Zn) was formulated and administered orally to alloxan-induced diabetic rats (wister strains). The effect of the supplementation on antioxidant status, lipid peroxidation and lipid profile of alloxan-induced diabetic rats (wister strains) were assessed.

MATERIALS AND METHODS

Experimental Animals: Thirty nine (39) apparently healthy mature albino rats (wister strains) age \geq 4 months of both sexes purchased from the Faculty of Pharmaceutical Sciences Ahmadu Bello University, Zaria, Nigeria. Weighing between 130 and 220g were used for the study. They were allowed to acclimate at the animal house of the Department of Biochemistry, Usmanu Danfodiyo University, Sokoto, for a week before commencement of the experiment. During this period, they were fed on grower mash a product of GCOM Bukura Jos, Nigeria and allowed access to clean water *ad libitum*.

Chemicals: All the reagents used for the study were of analytical grade. Alloxan monohydrate and metformin

were purchased from Lab Tech Chemicals, Idia, kits for the assay of malondialdehyde (MDA) and glutathione peroxidase (GPX), were purchased from Northerwest Life Science Specialist, Vancouver, Canada. Kits for the glucose, total cholesterol, triglyceride and HDL-Cholesterol were obtained from Randox Laboratories, Switzerland. Antioxidant rich nutraceutical sources were purchased from Sokoto Central Market, Nigeria.

Induction of diabetes:- Experimental rats (wister strains) were made diabetic by intraperitoneal injection of 80mg/kg body weight alloxan monohydrate for three consecutive days (Kato and Miura, Pari and Maheswari, 1999; Stanley et al., 2000). A week after the last dose, the animals were observed for polydipsia, polyuria and polyphagia as well as general reduction of body weight by physical examination using diabetic cage. The animals were then allowed to fast overnight and the fasting blood glucose was estimated using a commercial glucose kit. Only rats that had fasting blood glucose level of \geq 7.0mmol/l (126 mg/dl) and partial destruction of pancreas tested with positive response to metformin as described by Dulin and Soret, (1978) were included in the study.

Experimental design: The rats (wister strains) were divided into 4 groups as follows:

- i. **NDNS:** normal, non-diabetic rats. They received neither the diabetic drug nor supplemented with the nutraceutical.
- ii. **DNTNS:** alloxan-induced diabetic rats which were neither treated with antidiabetic drug nor supplemented with the nutraceutical.
- iii. **DTNS:** alloxan – induced diabetic rats treated with 250mg/kg body weight metformin but not supplemented with nutraceutical.
- iv. **DTS:** alloxan – induced diabetic rats treated with 250mg/kg body weight metformin and 200mg/kg body weight nutraceutical.

The nutraceutical was prepared from onions, garlic, lemon, palm oil and cray fish in ratio 6:6:2:1:5 respectively and administered orally to alloxan induced diabetic rats for three weeks with and without treatment with metformin (250mg/kg/day). The rat feed *ad libitum* with rat chaw throughout the experimental period.

After the last day, the animals were fasted overnight and anaesthetized by dropping each in a transparent plastic jar saturated with chloroform vapour. Blood specimen was collected through cardiac puncture and placed in labeled centrifuge tube allowed to clot. The blood speci-

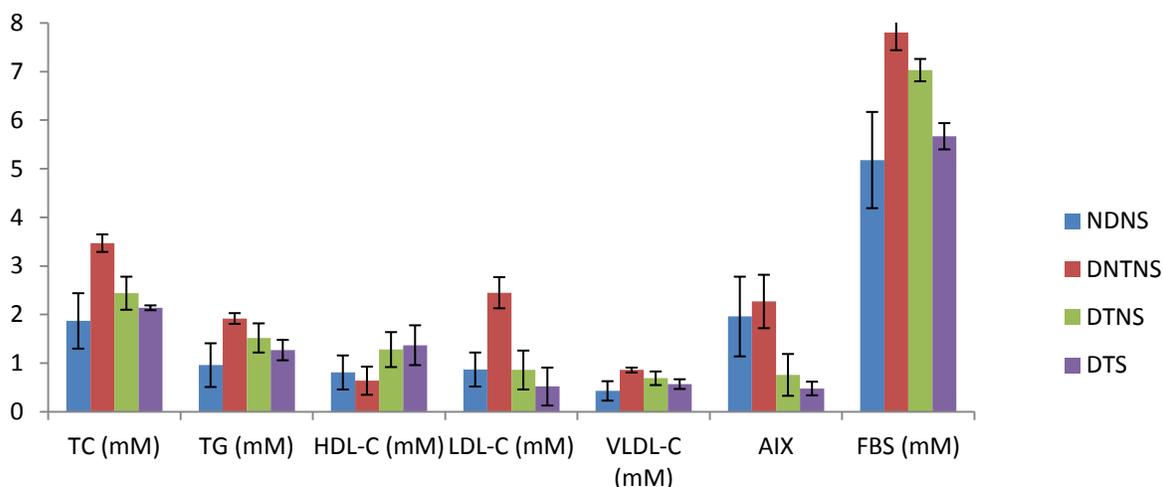


Figure 1. serum glucose level and lipid profile of diabetic rats supplemented with the nutraceutical.

Supplementation reduced FBS,TC,TG,LDL-C,VLDL-C and AIX significantly ($p < 0.05$).HDL-C raised significantly ($p < 0.05$).

mens were centrifuged in a Bench Top Centrifuge at 4000 rpm for 5 minutes. The serum was collected from the centrifuged blood using a Pasteur pipette transferred into labeled specimen bottle and stored at -20°C until required. Serum glucose was determined immediately within 6 hours from blood collection.

Measurement of Biochemical Parameters: Serum glucose concentration was estimated using glucose oxidase method (Trinder,1969),malondialdehyde (MDA) level was assayed based on MDA reaction with Thiobarbituric acid (TBA) (Chandra *et al.*,1994).Glutathione peroxidase (GPX) activities was assessed by NADPH oxidation (Paglia and Valentine,1969). Total Cholesterol (TC) was determined by cholesterol oxidase/peroxidase method (Trinder,1969). Triglyceride (TG) was determined using enzymatic method (Trinder,1969). High density lipoprotein cholesterol (HDL- C) was assessed by method of Burstein (1979). Low density Lipoprotein cholesterol (LDL-C) and Very Low Density Lipoprotein Cholesterol (VLDL-C) were estimated by Friedewald formulae (Friedewald *et al.*,1999).Atherogenic index (AIX) was calculated as the ratio of LDL-cholesterol to HDL-cholesterol (Abbott *et al.*,1988). Concentrations of all lipid profile and glucose were expressed in mmol/l. MDA and GPX expressed as $\mu\text{g}/\text{mg prot.}$ Vitamin A was determined by method of Bassey *et al.*(1946).Vitamin C was determined by method of Roe and Kuether (1943).Vitamin E was determined by method of Neild and Pearson (41).Trace elements were determined using UNICAM 969 Atomic Absorption Spectrophotometer(AAS)(Neild and Pearson,1967).

Statistical Analysis: All data were expressed as mean \pm standard deviation (S.D). Data was analysed using analysis of variance (ANOVA) by instat 3 software. Differences in mean (\pm SD) were considered to be significant when $P < 0.05$.

RESULTS

The results indicated that supplementation with the nutraceutical significantly ($P < 0.05$) reduced serum levels of glucose, cholesterol, triglyceride and atherogenic index (Figure. 1). HDL-cholesterol was increased as a result of supplementation. This might reduce the risk of cardiovascular diseases and metabolic syndrome that are usually associated with diabetes mellitus.

NDNS: non diabetic non supplemented; DNTNS: Diabetic non treated non supplemented; DTNS: Diabetic treated non supplemented; TC: total cholesterol; TG: triacylglycerol; HDL-C: HDL cholesterol; LDL-C: LDL cholesterol; VLDL-C: VLDL cholesterol; FBS: Fasting blood glucose; Aix is the ratio of LDL-Chol. to HDL-Chol. Supplementation of the diabetic rat significantly ($P < 0.05$) increased the serum glutathione peroxidase (GPX) activity, a major antioxidant enzyme responsible for the detoxification of reactive oxygen species. serum level of malondialdehyde (MDA), which is a marker of oxidative stress was increased as a result of supplementation (Figure 2).

Values are mean+SD.Values bearing different bars differ significantly ($p < 0.05$).NDNS:non diabetic non-supplemented;DNTNS: diabetic non-treated non-

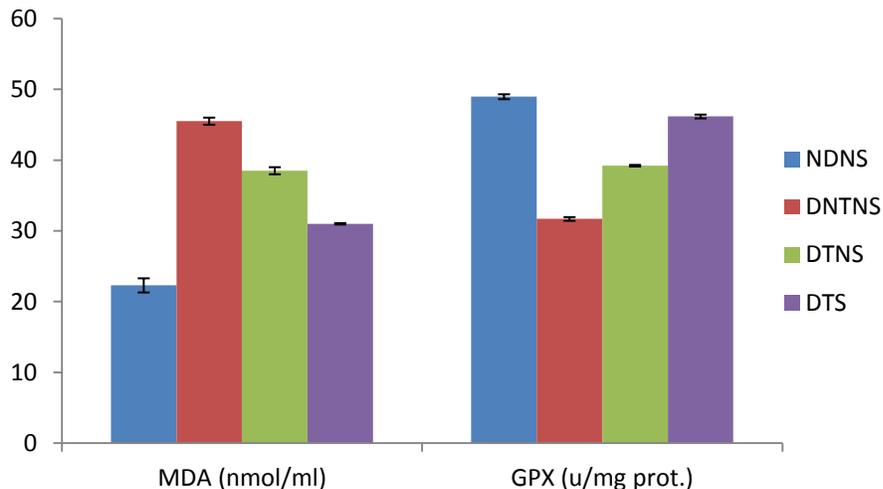


Figure 2. Serum Glutathione peroxidase (GPX) and malondialdehyde (MDA) of diabetic rats supplemented with the nutraceutical

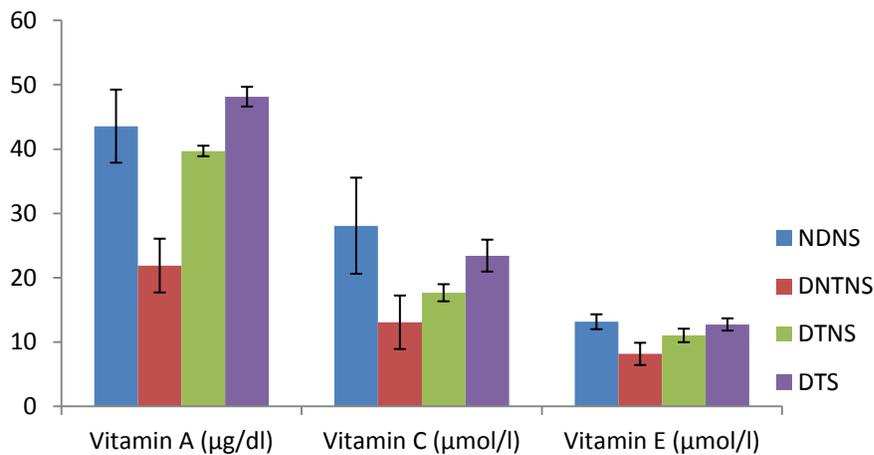


Figure 3. Serum levels of Vitamins A,C and E in diabetic rats supplemented with the Nutraceutical

supplemented; DTNS:diabetic treated non-supplemented;DTS:diabetic treated supplemented;MDA:malondialdehyde;GPX:Glutathione peroxidase.

Supplementation increased the serum levels of vitamins A, C and E significantly (P<0.05) (Figure 3). Deficiencies of these vitamins have been reported in diabetic subjects. The vitamins have antioxidant roles and may thus reduce the risk of oxidative stress in diabetics.

Supplementation increased vitamins A,C and E significantly (p<0.05). NDNS:non diabetic non-supplemented;DNTNS:diabetic non-treated non-supplemented;DTNS:diabetic treated non-supplemented;DTS:diabetic treated supplemented.

Supplementation with the nutraceutical also increased the serum levels of Cu, Cr, Mn and Zn (Figure 4). Deficiencies of these micronutrients have been reported in diabetic subjects and implicated to cause significant

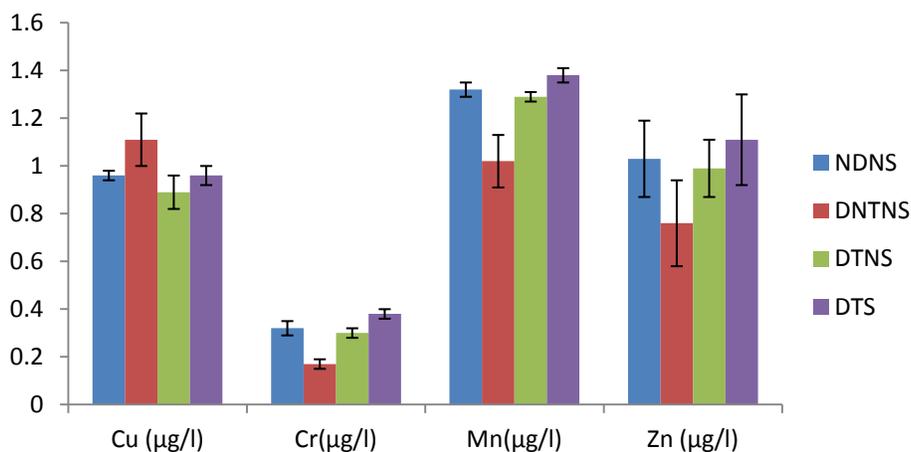


Figure 4. Serum levels (µg/l) of some micronutrients of diabetic rats supplemented with the nutraceutical.

glucose intolerance and hyperglycaemia. The micronutrients are important cofactors in energy metabolism and insulin secretion and signaling.

Supplementation increased copper(Cu),chromium(Cr),manganese(Mn) and zinc(Zn) significantly ($p < 0.05$). NDNS:non diabetic non-supplemented;DNTNS:diabetic non-treated non-supplemented;DTNS:diabetic treated non-supplemented;DTS:diabetic treated supplemented.

DISCUSSION

Diabetes mellitus is characterised by elevated level of oxidative stress indices, decreased level of antioxidants defences and lipid abnormalities due to lipid peroxidation (Asayama et al.,1993). The results of the current study support this fact. Supplementation with antioxidants are thought to be effective in increasing the activities of antioxidant defence enzymes, scavenging free radicals, preventing oxidative damage and thereby sparing lipid components of the cells against lipid peroxidation(Zingg et al.,2000).

In the current study, it was observed that there was decrease in concentration of fasting blood sugar (FBS) in diabetic treated and supplemented group compared with diabetic treated non-supplemented group ($P < 0.05$). This might be connected with increased availability of antioxidants that are important components and co-factors of the antioxidant enzymes (Fridovich,1995). Serum concentration of total cholesterol (TC), triglyceride (TG), low density lipoprotein cholesterol (LDL-C) and very low density lipoprotein cholesterol (VLDL-C) were all higher in diabetic non-treated non-supplemented

(DNTNS) group compared with non-diabetics non-supplemented (NDNS) group. The high density lipoprotein cholesterol (HDL-C) was lower in DNTNS group compared with NDNS group. The result also revealed decreased concentrations of TC, TG, LDL-C, VLDL-C and AIX in diabetic treated and supplemented group (DTS) compared with diabetic treated and not supplemented (DTNS) ones ($P < 0.05$). Similar results have earlier been reported (Hunker et al.,2002), in which streptozotocin-induced diabetic rats, supplemented with cod liver oil showed reduced concentrations of TG, TC and MDA. Dallatu et al.(2009) also observed a decreased concentration of TC, TG, LDL-C, VLDL-C, MDA and GPX in alloxan-induced diabetic rats supplemented with synthetic antioxidant vitamin and trace elements. Treatment with antioxidant nutraceutical might produce better control of hyperglycaemia and dyslipidemia and prevent oxidation and lipid peroxidation (Hunker et al.,2002). The improvement in the HDL-C of the DTS compared with the DNTNS may be due to improvement in the antioxidant status as a result of the nutraceutical supplementation. Dallatu et al., (2009) reported earlier that there was an increase serum concentration of HDL-C in alloxan-induced diabetic rats treated and supplemented with synthetic vitamins and minerals. Praveen et al., (2005) reported that oxidative stress is positively linked with LDL-C and negatively linked with HDL-C.

Serum concentration of malondialdehyde (MDA), a marker of lipid peroxidation was significantly higher in diabetic non treated non-supplemented rats compared with the non-diabetic non-supplemented ones ($P < 0.05$). Glutathione peroxidase (GPX) activity, an antioxidant enzyme, significantly decreased in diabetic non-treated, non-supplemented rats compared with

non – diabetic non – supplemented ones ($P < 0.05$). There was also decreased concentration of malondialdehyde in diabetic treated and not supplemented ones ($P < 0.05$). Significantly increased activity of GPX was observed in diabetic treated and supplemented group compared with diabetic treated non – supplemented ones. Increased MDA, a maker of lipid peroxidation, in diabetes mellitus is due to an altered intracellular ratio between free radicals and antioxidant capacity which leads to oxidative stress, which in turn is associated with the development of cardiovascular disease. The decreased concentration of MDA and increased activity of GPX observed in diabetic treated and supplemented group compared with diabetic treated and non – supplemented ones might be connected with the increased availability of these micronutrients that are important components and co – factors of the antioxidant enzyme molecules (Fridovich,1995).

Supplementation also increased concentration of vitamins A, C and E significantly ($P < 0.05$). The vitamins have antioxidant roles and may thus reduce the risk of oxidative stress in diabetics. This might be so because supplementation with vitamin C and E reduce protein glycosylated protein (Polidori,2005). Vitamin E lowers LDL-oxidation, thus lowering the risk of diabetic cardiovascular complications (Ceriello et al.,1992;Fuller et al.,1996,).

The result also revealed that diabetic treated and supplemented rats had higher values of Cr, Mn and Zn and decreased Cu compared with diabetic treated non-supplemented, A study conducted by Chung et al., (1998) showed that nutrients including vitamins C and E, Mg, Cr, Zn and Mn all have beneficial effects on the symptoms or complications associated with diabetes. Many of these nutrients appear to be closely associated with insulin metabolism and help maintain proper blood glucose level (Chung et al.,1998). Chromium has been reported to increase insulin binding to cells, number of insulin receptors and activates insulin receptor kinase leading to increased insulin sensitivity (Anderson,2000). Accordingly, severe Cr deficiency was implicated as cause of impaired glucose tolerance and subsequent hyperglycemia and glucosuria (Anderson,2000). Mn has been shown to be important insulin in synthesis and secretion (Korc,1983). It has been shown that type II diabetic subjects responded well to oral doses of Mn (Rubeenstein et al.,1962). High dose of oral Zn might enhance wound healing (Tuvemo and Gebre-Medhin,1985).

CONCLUSION

The results suggest that supplementation with the nutraceutical rich in antioxidants may reduce glucose, the risk of oxidative stress and dyslipidemia in diabetic

mellitus. The results further support the idea that “food” rather than purified antioxidants may be required in the management of diabetes.

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