International Research Journal of Gastroenterology and Hepatology

Volume 7, Issue 1, Page 44-60, 2024; Article no.IRJGH.117082

Biochemical Effects of High Concentration of Colocasia Esculenta Flour Fed on Streptozotocin-Induced Diabetic Rats

Uro-Chukwu, H.C [a,b,c*], Ezekwe, A.S [d], Roberts, F [d], Okari, K. A [d] and Uro-Chukwu, F.N.C [b]

[a] Department of Biochemistry, Coal City University, Enugu, Nigeria.
[b] Institute for Nutrition, Nutraceuticals & Public Health Research & Development, Nigeria.
[c] Department of Community Medicine, Ebonyi State University, Abakaliki, Nigeria.
[d] Department of Medical Biochemistry, Rivers State University, Nkporlu, Port Harcourt, Nigeria.

Authors' contributions

This work was carried out in collaboration among all authors. Author HCHC designed the study, searched for literatures and drafted the manuscript. Author EAS designed the topic, did statistical analyses and drafted the manuscript. Author RF analyzed the study and did literature searches. Author OKA wrote the manuscript. Author UCFNC executed the data and searched the resources. All authors read and approved the final manuscript.

Article Information

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/117082

Original Research Article

Received: 13/03/2024
Accepted: 17/05/2024
Published: 11/06/2024

ABSTRACT

Background: An endocrine and metabolic disease of the pancreas such as Diabetes Mellitus (DM), is of Public health dimension responsible for 536.6 million cases in the globe. The treatment of DM takes lots of resources, making alternative treatment options like the utilization of medicinal plants like Colocasia Esculenta (CYN) a point of research, hence this study involving biochemical

**Corresponding author: E-mail: hurochu@gmail.com;*

Cite as: H.C , Uro-Chukwu, Ezekwe, A.S, Roberts, F, Okari, K. A, and Uro-Chukwu, F.N.C. 2024. "Biochemical Effects of High Concentration of Colocasia Esculenta Flour Fed on Streptozotocin-Induced Diabetic Rats". International Research Journal of Gastroenterology and Hepatology 7 (1):44-60. https://journalirjgh.com/index.php/IRJGH/article/view/98.

evaluation of streptozotocin-induced diabetic rats (SIDR) fed on high concentration of the flour. **Methodology:** CYN was processed into pellets, dried in an oven at 60°C, and adequately stored for further use. Fourty-two male albino rats with weights ranging from 134 and 247 grammes, were purchased, acclimatized and induced with insulin resistance by the administration of 10% fructose diet, thereafter, the rats were made to develop type-2 diabetes mellitus (T2DM) by the intraperitoneal injection of streptozotocin. For 28 days, an intervention formulation consisting of 50:50% ratio of cocoyam flour and commercial rat feed, was administered at the end of which blood samples were collected from the slaughtered animals for various biochemical analyses.
Results & Discussion: The active biological substances in the cocoyam flour included phenolics, D-stilbene, phthalate, and artemisinin, along with more antioxidant minerals than those found in usual rat meals. The formulation exhibited CAT activity of 7.9 units/min and DPPH of 53.2%. Poor glycemic control was suggested by the persistently elevated random blood glucose readings observed along the time trend. Although the results of the liver function tests were similar for the intervention and standard control, the formulation was more effective than metformin at reducing lipid peroxidation and in the hypolipidemic effects.
Conclusion: Administration of high cocoyam flour concentration demonstrated comparable biochemical effects to the anti-diabetic drug metformin in SIDRs, despite its poor glycemic control. This suggests that cocoyam flour may be applied as a supplemental treatment for people with T2DM.

Keywords: Cocoyam flour; glycemic control; diabetic rats.

1. INTRODUCTION

Diabetes mellitus (DM) is responsible for 536.6 million cases in the world (10.5%) with a projected affected population of 783.2 million people by 2045 [1]. Various complications such as cardiovascular, renal and ocular diseases are among health effects of hyperglycemia brought on by pancreatic cell malfunction or inadequate insulin synthesis [2]. Cases of diabetes mellitus are rising faster in low-income countries—like Nigeria—than in high-income ones, with higher incidence, prevalence, and daily adjusted life years (DALYs) [3]. There are several challenges associated with managing diabetes, including those related to finances, labour, the infrastructure of healthcare, and managing complications [4]. For individuals impacted, this lowers quality of life, productivity, and life expectancy [5].

The high costs and complexity of managing diabetic complications pose a substantial challenge in countries with fragile healthcare systems and limited resources [6]. As a result, there is an urgent need to look into cost-effective techniques to reduce illness prevalence, severity, and complications while maximizing available resources, particularly in developing nations. Integrating lifestyle changes, such as following suggested dietary patterns and increasing physical activity, as supplementary management techniques have been demonstrated to dramatically reduce risk factors, lowering the frequency of new cases, disease severity, and related comorbidities [7]. Various management strategies such as use of Diabetic Medical Diet Therapy have been introduced with promising results [8]. Other dietary interventions have been proven to aid diabetes mellitus treatment [9]. Among such dietary interventions is the use of plants and plant-based diets which has been championed by the World Health Organization for the management of T2DM [10]. Bioactive substances with anti-inflammatory and antioxidant qualities are found in such therapeutic plants including cocoyam, whose *in vitro* and *in vivo*, activities are associated with immunomodulatory and antihyperglycemic effects [11,12].

The bioactive compounds in plant food extracts include peptides, amino acids, flavonoids, and polyphenols, which stimulate pancreatic β-cells and hepatic enzymes to regulate blood glucose levels [13]. Numerous investigations have demonstrated that the phytochemicals in cocoyam have hypoglycemic and antioxidant properties [14,15]. Eleazu and colleagues [16] found that the mechanism behind this antidiabetic activity was associated with the suppression of acute pancreatitis and the delay or regulation of the starch-to-glucose conversion process. Many other medicinal plants such as extracts from the bulb of Allium sativum L, the leaf extract of Aloe vera, and the seed kernel of Mangifera indica, have been demonstrated to provide anti-diabetic properties [17].

This study aimed to evaluate the antidiabetic and other biochemical benefits of cocoyam flour, a plant-based diet, administered to diabetic rats.

2. MATERIALS AND METHODS

2.1 Collection and Preparation of the Plant Food Material

The roots of a variety of cocoyam (*Colocasia Esculenta*) identified with the accession number NCe 005, was adequately processed and pelletized before storing them in an airtight container for future use.

2.2 Experimental Animals

Fouty-two (42) male albino rats weighing between 134 and 249 grammes were procured, and divided into set of four, tagged, A, B, C, and D. Each set had ten rats, identified by a permanent marker numbered 1–10. Weekly weights of the rats were kept, while food and drink were administered ad libitum for one week for acclimatization to occur. All laboratory animals were cared for following established procedures [18].

2.3 Induction of Insulin Resistance Using Low Fructose Diet

Low fructose diet (10%) was made by dissolution of 30 grammes of fructose in 300 millilitres of water and administered to the rats for one week, to achieve insulin resistance.

2.4 Induction of Type 2 Diabetes Mellitus using STZ

The rats were fasted overnight on the sixth day of the administration of 10% fructose diet, and their blood glucose levels were measured to establish normoglycemia. All normoglycemic rats except the normal control group of nine rats, were given intraperitoneal injections of Streptozotocin (STZ) by dissolving 1 g in 50 mL of freshly prepared sodium citrate buffer solution, using the formula for giving extracts to experimental animal subjects [19,20]. Before beginning the experimental feeding procedures, blood samples were taken from the treated rats' tail veins at 72 hours and day 12 after STZ exposure and tested for blood glucose levels using a blood glucose meter (Acu-check activeR). The hyperglycemic rats were randomly assigned to the standard control, negative control, and intervention groups. All the groups received treatment for 28 days. Groups A and B received commercial rat feed and water only, Group C received metformin at 200 mg/kg, as 0.002 ml per Kg body weight orally daily using an oral dispenser, and Group D received a blend of Colocasia esculenta flour and commercial rat feed at 50:50 ratio [21].

The groups were as follows:

Group A: Standard Control
Group B: Normal Control
Group C: Negative Control
Group D: STZ-induced diabetic rats administered with *Colocasia Esculenta* (Cocoyam) flour intervention feed

2.5 Biochemical Analysis

a. Estimation of blood glucose, lipid profile, liver function, kidney function and myocardial function tests

After 28 days, the rats were given an overnight fast, and their final body weights recorded. The blood glucose levels were determined using a glucometer (Acu-check activeR). The triglycerides (TG), total cholesterol (TC), and high-density lipoprotein cholesterol (HDL-C) were determined with Randox test diagnostic kits [22]. The levels of low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) cholesterol were also determined using Frieddewald *et al* formula [23]. The assessment of liver function parameters (serum bilirubin, total protein, serum glutamate oxaloacetate transaminase, ALT, and serum glutamate pyruvate transaminase, AST), as well as kidney and cardiac function (urea and creatinine), was carried out under the protocol described by Jin and colleagues [24].

b. Estimation of Antioxidant Mineral Analysis

The analysis of antioxidant minerals, including zinc, copper, magnesium, and manganese, was conducted using the Atomic Absorption Spectrophotometer (AAS) (Analyst 200, Perkin Elmer, Wallham, MA, USA).

c. Determination of antioxidant activities (DPPH)

The 2, 2-Diphenyl 1-picrylhydrazyl (DPPH) Free Radical Scavenging Activity was determined by spectrophotometric analysis. We followed the steps that Oulai and associates described [25]. The antioxidant was computed

using the sample extract's potential for free radicals.

d. Estimation of Antioxidant Enzyme System [Superioxide Dismutases (SOD), Catalase, (CAT), GLuthathione Peroxidase (GPx), Reduced and Oxidized Glutathione (GSH) and Glutathione-S-Transferase (GST)] Activities

A superoxide scavenging activity was carried out according to the modified NBT reduction approach proposed by Lalhminghlui and Jagetia [26], with a pure DMSO control employed to measure the mixture's absorbance at 560 nm and ascorbic acid (AA) serving as the reference standard for the percentage calculation to evaluate the free radical scavenging ability. The catalase activity was measured using a spectrophotometric method of Mukhtar and colleagues [27].

The quantification of glutathione peroxidase activity was done using erythrocyte hemolysate under Paglia and Valentine's criteria [28], and the findings were expressed in mg/gHb, while the reduction and oxidation of glutathione were quantified using the protocol described by Beutler and colleagues [29]. The calibration curve, which was made using GSH solutions at various concentrations, was used to translate the absorbance of the samples into concentrations. The GSH levels in erythrocytes were normalised to the haemoglobin value and expressed as mg/g GSH/Hb. mg/g was employed in the final results report.

e. Estimation of Lipid peroxidation

The lipid peroxidation test method created by Ohkawa and colleagues [30] was employed to determined lipid peroxidation which was recorded as MDA free radical scavenging activity.

2.6 Quantitative Analysis of Bioactive Compounds using Gas Chromatography-Mass Spectrometry (GC-MS)

After ten grammes (10 g) of cocoyam flour were added to 2.5 L of methanol and allowed to mix for 48 hours, a soxhlet apparatus was used to extract the filtrate for three hours at 500C. To search for phytochemical components in the extract, mass spectrometry (MS; 5975B MSD) and gas chromatography (GC; Agilent 6890N) were employed.

2.7 Statistical Analysis

The results were then gathered and expressed as the standard error of the mean (SEM) of triplicate for eight rats in each group using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL) version 20.0. The statistical significance of the mean difference was assessed using Tukey's post-hoc test, with a significance level of $P<0.05$. A one-way analysis of variance (ANOVA) was used to compare the means.

3. RESULTS AND DISCUSSION

3.1 Antioxidant Mineral Composition & Antioxidant Activities

Fig. 1 showed that the Cocoyam flour formulation was higher in magnesium, copper and manganese concentration when compared to the commercial rat feed.

The DPPH and CAT activities were higher in the cocoyam flour formulation when compared with the commercial rat feed.

3.2 Effect on Blood Glucose

Fig. 3 showed that the rat group fed on the cocoyam flour (Group D) had poor random blood glucose control when compared to the standard control (Group A) over time.

Fig. 4 showed that Group D rats fed on cocoyam flour had approximate fasting blood glucose values with the rats on standard treatment (Group A) on the 4th week of intervention.

3.3 Biochemical Changes

3.3.1 Oxidative stress markers

Fig. 5, showed that the oxidative stress marker, MDA, value was least in the normal control and cocoyam-administered groups just like the values of the antioxidant enzyme, SOD.

3.3.2 Inflammatory markers

Fig. 6 showed that the Group D rats fed on cocoyam flour had comparable mean values of the IL-10, CRP and NFkB with the normal control.

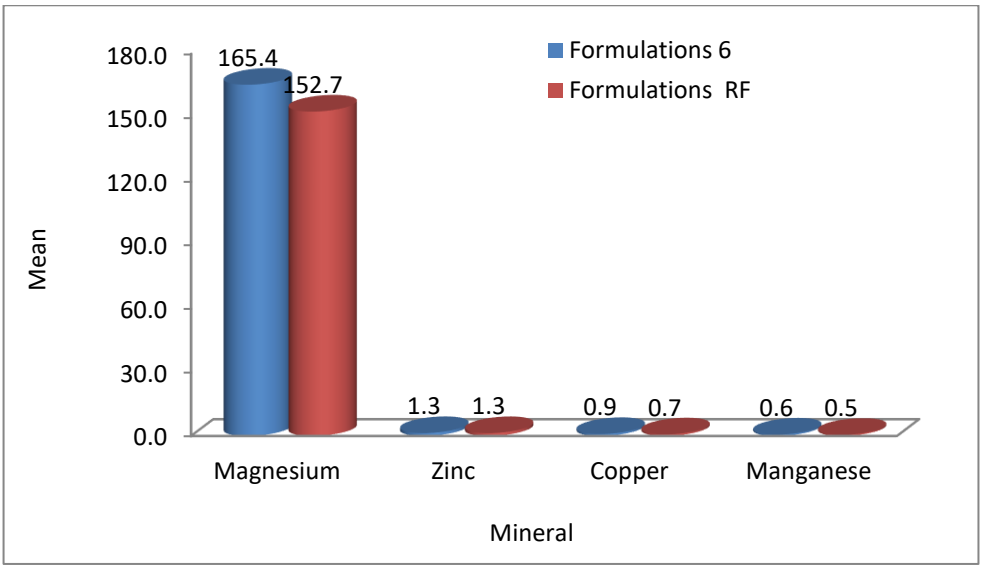

Fig. 1. Antioxidant mineral compositions of the cocoyam flour

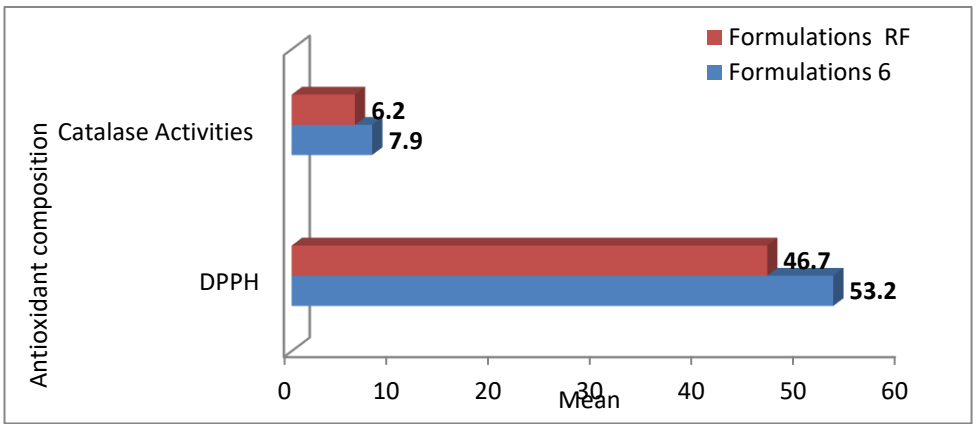

Fig. 2. Antioxidant activities of the cocoyam flour

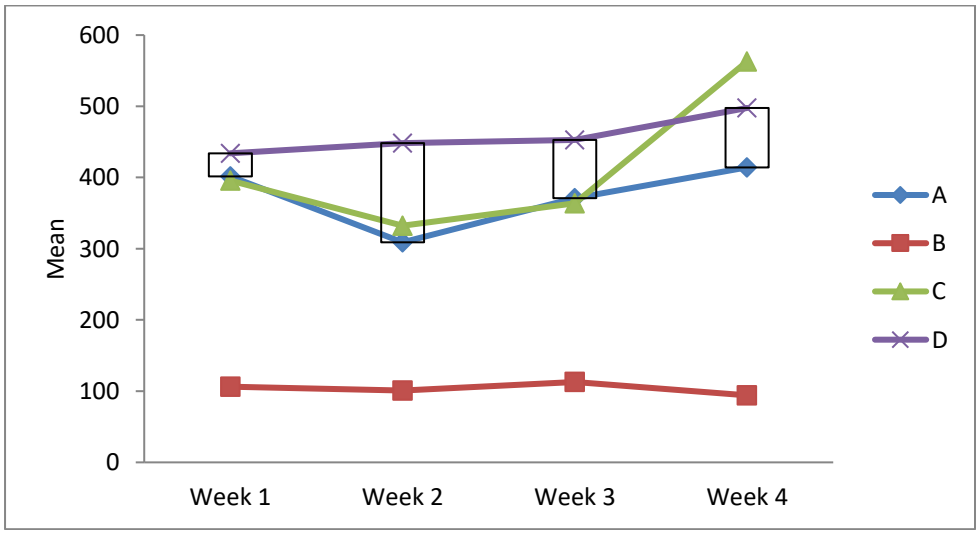

Fig. 3. Effect on blood glucose over time

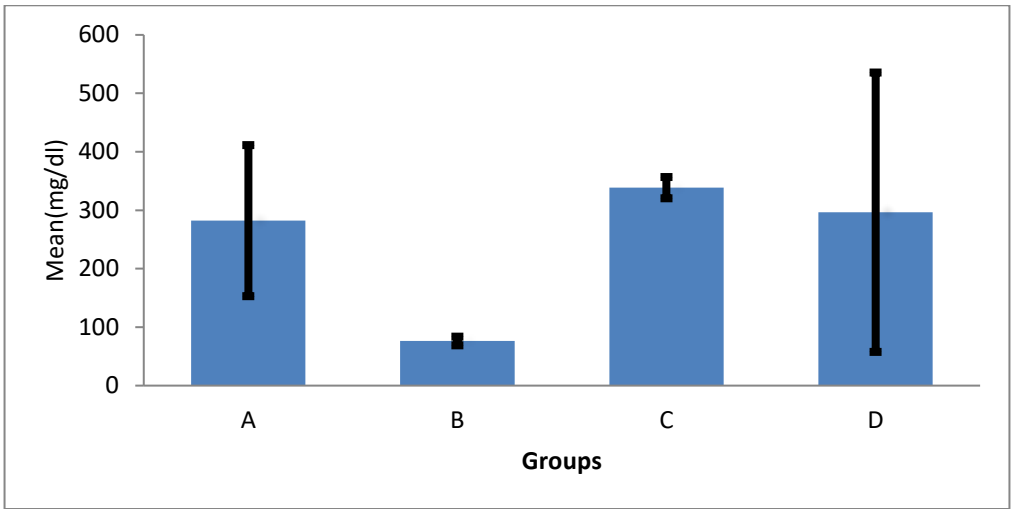

Fig. 4. Fasting blood glucose level on the day of sacrifice

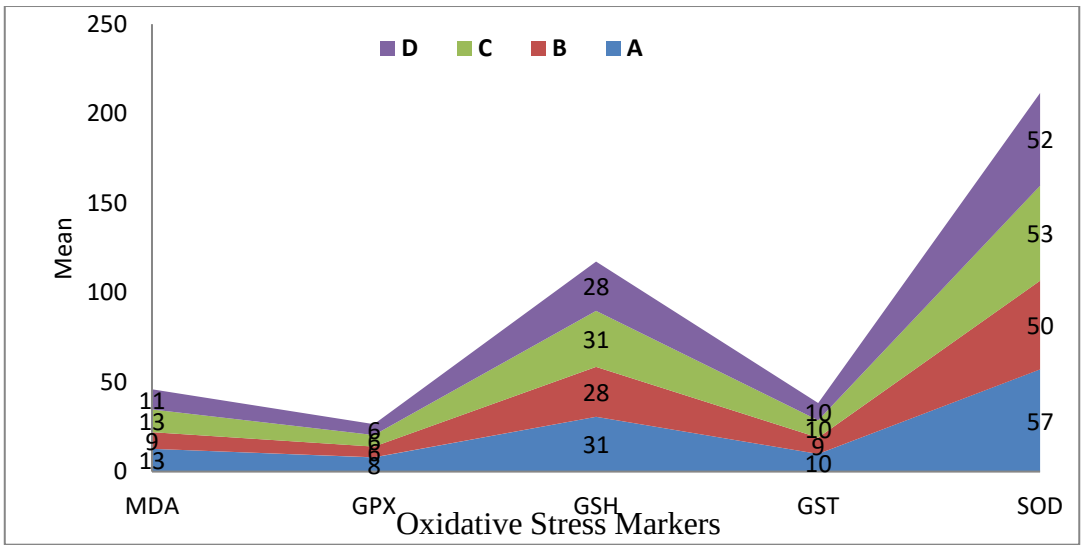

Fig. 5. The Oxidative stress markers in the various groups

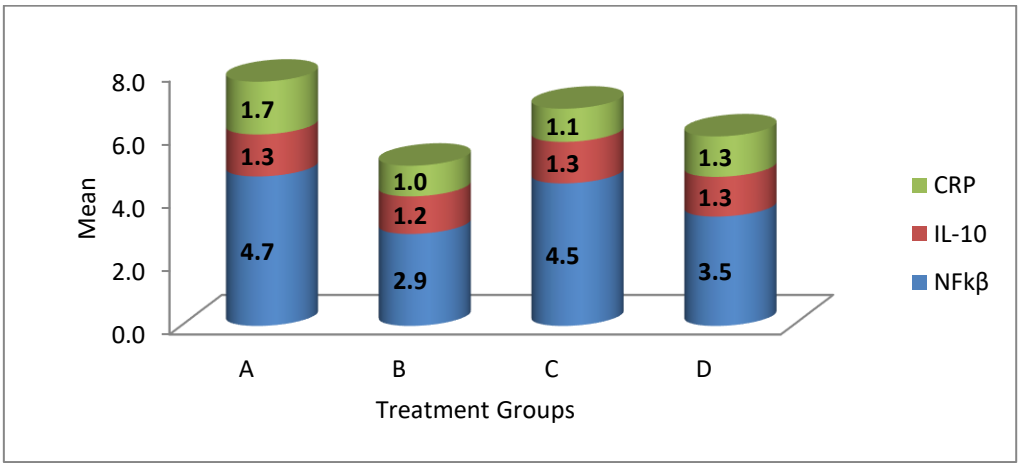

Fig. 6. Result of the inflammatory biomarkers of the various groups

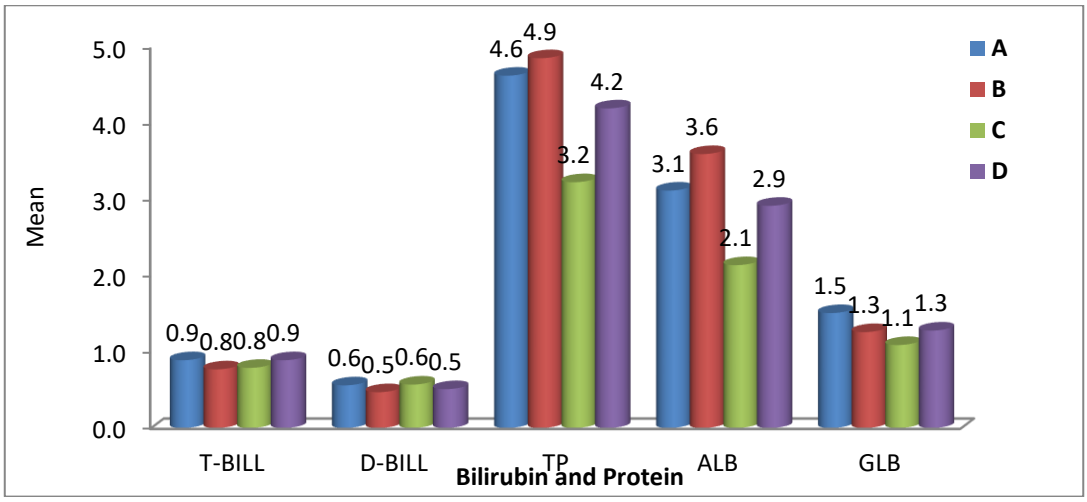

Fig. 7. Result of the serum bilirubin and protein levels

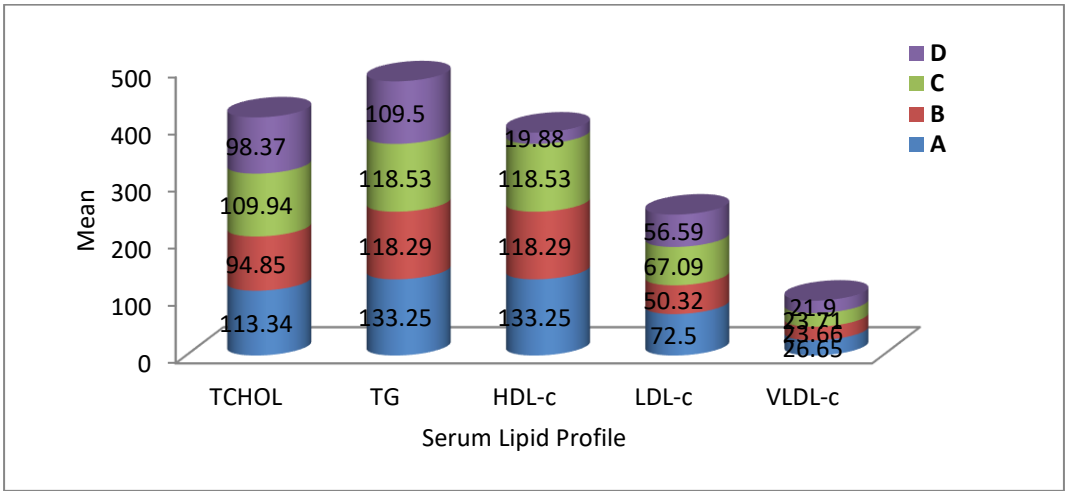

Fig. 8. Result of the groups` serum lipid profiles

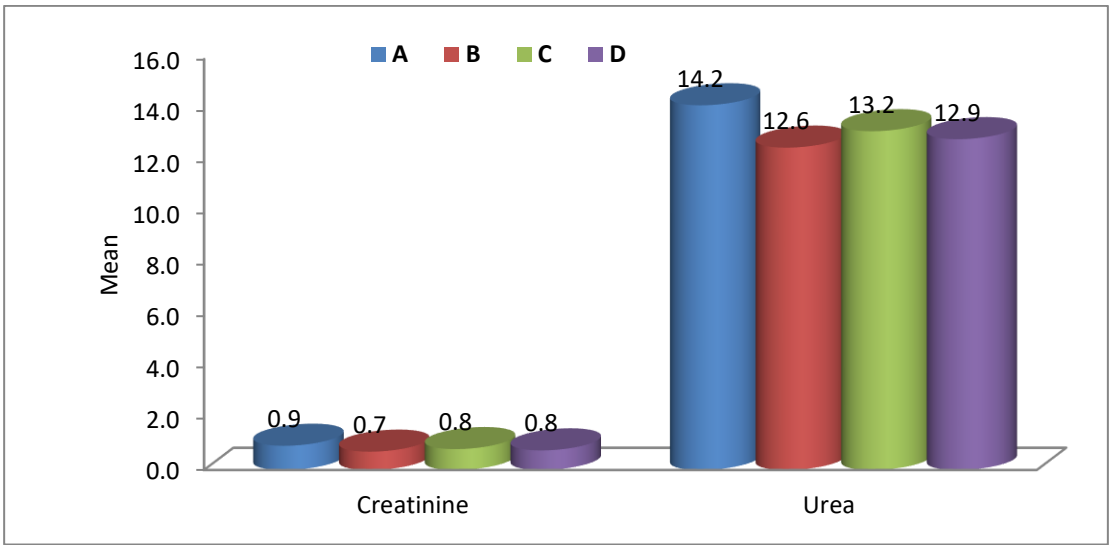

Fig. 9. Result of the urea and creatinine of the various groups

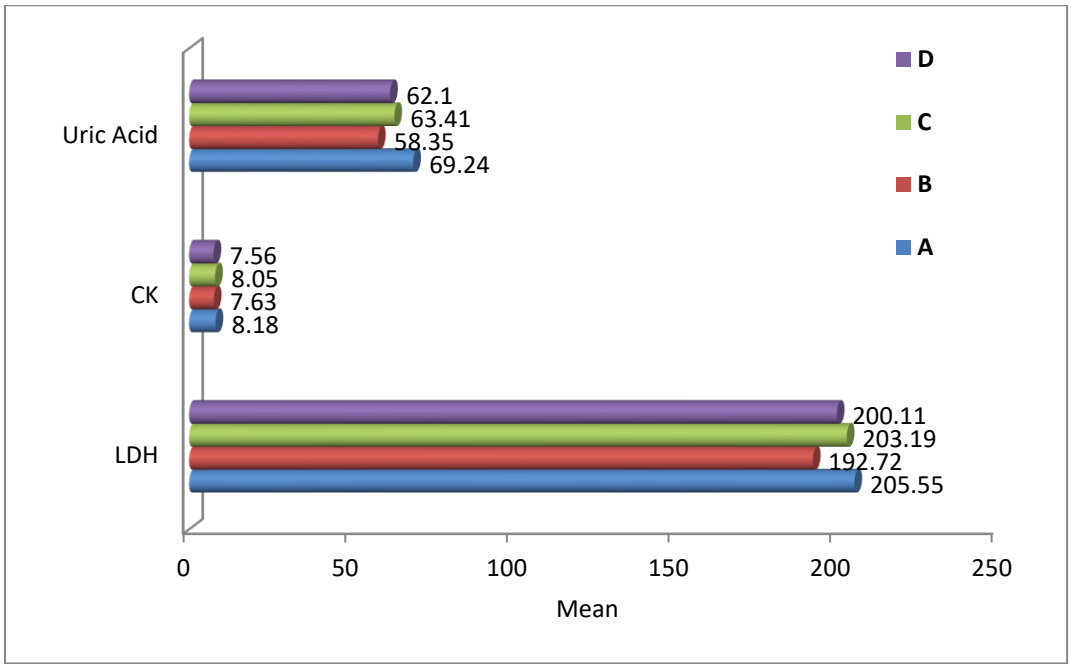

Fig. 10. Result of the LDH and CK for the groups

3.3.3 Serum bilirubin and protein levels

Fig. 7 showed that the direct bilirubin values were similar for Group D and normal control.

3.3.4 Serum lipid profile

Fig. 8 showed that the total cholesterol, triglyceride and LDL-C mean values were lowest in the normal control and group fed on cocoyam relative to the standard control.

3.3.5 Renal functions

Fig. 9 revealed that the mean urea values in group D and the normal control were the least comparable, much better than values obtained from the standard control.

3.3.6 Cardiac function texts

Fig. 10 revealed that the LDH mean values of the rats in Group D fed on cocoyam flour and that of the normal control had the least and comparable values for the CK and uric acid.

4. DISCUSSION

4.1 Antioxidant Compositions & Activities

The GC/MS analysis revealed that the cocoyam formulation contained different bioactive compounds such as benzofuran, 2,3-dihydro-, dihydroartemisinin, 10-O-(t-butyloxy)-, phenol, 2,6-dimethoxy, E)-Stilbene, 2-Methoxy-4-vinylphenol, and dibutyl phthalate. The results aligned with earlier research that documented the presence of polyphenolic compounds like 3-5-di-t-butyl phenol, and fatty acid derivatives like octadecanoic acid, in cocoyam [16], with such compounds possessing hypoglycemic and antioxidant activities [14,15]. Various concentrations of antioxidant minerals such as Zinc (1.30 mg/100 g), copper (0.86 mg/100 mg), manganese (0.61 / 100 mg), and magnesium (165.36 mg/100 mg) were also found in the cocoyam flour formulation, with the mean values being statistically significant variations between the values obtained from the conventional rat meal and the cocoyam formulation. Notably, the cocoyam formulation has higher concentrations of all four (100%) antioxidant minerals. Variations in the mineral contents of several cocoyam types, such as Zn, Cu, Mn, and Mg, have been noted in earlier studies [31]. For instance, Coronell-Tovar and colleagues [32] reported that the Mg, Cu, and Mn values in cocoyam corm flour were 0.72 mg/g, 6.90µg/g, and 4.42 µg/g, respectively, while Wada and colleagues [31] reported that the Zn, Cu, Mn, and Mg contents in green cocoyam were 3.06 mg/100g, 1.04 mg/100g, 2.48 mg/100g, and 78.77 mg/100g, Mn, and Mg, respectively. The presence of bioactive compounds and antioxidant minerals in cocoyam helps them scavenge free radicals. The

cocoyam formulation's DPPH activity in this investigation was 53.21%, a significantly higher value than the conventional rat meal's 46.02% (Figure 2). Different scholars have reported the antioxidant capacity of cocoyam plant extract [33-35], with polyphenols adduced to be responsible for such activity [16,34].

The CAT activity of the flour formulations and commercial rat feed was 7.07 and 6.15 units/min, respectively, indicating a 15% increase of CAT activity in cocoyam compared to the (Figure 2). The antioxidant enzyme catalase plays a critical role in preventing oxidative damage brought on by elevated levels of reactive oxygen species. Superoxide dismutase (SOD) facilitates the conversion of the highly reactive superoxide anion into O_2 and, subsequently, the less reactive species H_2O_2, which is further converted to water by the enzymatic processes of catalase or glutathione peroxidase.

4.2 Effect on Blood Glucose

The study concluded that there were notable differences in the average random blood glucose (RBG) levels between the groups ($F= 13.963$, $p<0.001$) and that these differences changed steadily from the first to the fourth week with a positive trend. The group administered with cocoyam formulation exhibited a consistent upward trend in RBG values over time, higher than the normal, standard, and diabetic controls Figure 3), suggesting that cocoyam given at high concentration did not control random blood glucose (Figures 3 and 4). These results are not in conformity with other studies on the hypoglycemic effects of cocoyam flour. Prior research by Eleazu and colleagues showed that feeding lower doses of cocoyam flour to STZ-induced diabetic mice for three to four weeks reduced blood glucose levels by 38% to 58.75% [15,16]. Even though phenolics and artemisinin are bioactive chemicals with known antidiabetic properties, the formulations' observed hyperglycemic effects could be the result of antioxidants' pro-oxidative properties at higher dosages [36,37].

4.3 Biochemical Activities

a. Effect on Oxidative Stress Markers

Oxidative stress resulting from Diabetes mellitus affects the body's antioxidant reserves thereby causing imbalance in the antioxidants and reactive oxygen species (ROS) ratio [38], reduced redox ratio [39] and reduction in the concentration of the scavenging enzymes catalase (CAT), glutathione peroxidase (GPx), and superoxide dismutase (SOD) [40]. Protein glycation that leads to higher products of lipid peroxidation including carbonyls, malondialdehyde (MDA), and advanced glycation end products (AGEs), in T2DM plasma. [41]. When antioxidants are given, these products of lipid peroxidation are reduced [42]. In this study, the normal control group's MDA mean value of 9.29 mg/g, compared to that of the negative control group of 12.65 mg/g, meant an increase of peroxidation in the negative control group, by 36.06% (Figure 5). This finding was in tandem with recent reported works that documented an increased MDA level in hyperglycemia and diabetes mellitus [42]. The group treated with cocoyam flour displayed a decreased MDA value (11.28 mg/g) in comparison to the normal control group (12.77 mg/g), with the difference being statistically significant. Since this value in group D was far better than in the standard control, the implication was that cocoyam had higher potency in amelioration of lipid peroxidation than metformin, the antidiabetic drug. This contradicts the results of other studies [42]. The findings of our investigation in streptozotocin (STZ)-induced diabetic rats may have been influenced by the fact that metformin toxicity at certain doses can result in oxidative stress, which in turn increases lipid peroxidation and, in this case, MDA levels [43]. The levels of the antioxidant enzymes GSH, GST, and SOD rose relative to the normal control, but none of the groups' increases were statistically significant (Figure 5). This outcome is consistent with some earlier studies that found diabetic patients on antidiabetic drugs having higher levels of GSH, catalase, and antioxidants than those not receiving medication [42].

b. Effect on Inflammatory Biomarkers

Important mediators of leucocyte recruitment in both acute and chronic inflammation are soluble cytokines [44]. Serum, plasma, and tissues contain proinflammatory cytokines such as the c-reactive proteins, interleukins (IL)-1α, IL-1β, IL-2, IL-6, IL-8, IL-12, tumour necrosis factor-alpha (TNF-α), and interferon-gamma (IFNγ) [45]. Anti-inflammatory (IL-4, IL-5, IL-10, and Transforming growth factor β1 (TGF-β) are also present in these tissues but the results from one tissue cannot be used interchangeably [46]. The activation of the nuclear factor kappa B (NF-kB) results in overexpression of the proinflammatory cytokines [47]. In this study, the mean average

values of CRP and NFkB. showed significant differences among the groups (Figure 6). The CRP levels in the cocoyam flour intervention group (1.28 ng/ml) were greater than those in the normal control group (0.97 ng/ml) but lower than those in the standard control group (1.67 ng/ml) (Figure 6). The high potency of the bioactive compounds in the cocoyam flour resulted in the reduced inflammatory response as shown by the lower CRP and NFkB values. Comparing the NFkB levels of the diabetic rats fed cocoyam (4.46 x 10-6 mg/g), normal control (2.91 x 10-6 mg/g), negative control (4.51 x 10-6 mg/g), standard control (4.73 x 10-6 mg/g), and other groups revealed an identical trend with statistically significant differences. Similarly, compared to the negative and normal controls, the IL-10 levels in the cocoyam flour intervention group were statistically significantly lower (Fig. 6).

Insulin resistance and hyperinsulinemia were found to be strongly correlated with CRP levels by Nakano and colleagues [48]. This research validates prior investigations that discovered higher CRP levels in individuals with diabetes mellitus compared to those without the condition [50]. Additionally, the study discovered that diabetic rats had higher CRP levels. The presence of bioactive compounds such as artemisinins, stilbenes and phenolics might have been responsible for the anti-inflammatory properties of the cocoyam flour as earlier reported by previous studies [49, 51, 52].

c. Effect on Liver Enzymes and Liver Proteins

Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyltransferase (GGT) are raised in liver cell damage and hepatic insulin resistance [53, 54], with ALT specific for liver disease [54]. AST can be raised in other disease condition such as liver, mitochondria, among others and hence is less specific [55]. In diseases of the pancreas, kidney, and liver GGT is elevated [56, 57]. In chronic inflammatory cases such as oxidative stress, GGT, glutathione absorption, and the possible development of Type 2 Diabetes Mellitus are linked [58]. In this study, the AST value of 0.788 mg/g in the normal control outperformed the standard control (0.86 mg/g), negative control (0.83 mg/g), and intervention group (0.81 mg/g), though the values were not significantly different. However, none of the groups' ALT measurements demonstrated any appreciable differences. It is possible that the raised levels of ALT, AST, and GGT may be arising from the accumulation of fat in the liver fat due to insulin resistance, dyslipidemia, metabolic syndrome, and Type 2 Diabetes Mellitus since fatty liver raises liver enzymes [59]. Yazdi and colleagues found a positive correlation between elevated liver enzymes and body weight, along with other elements of the metabolic syndrome [60, 61].

The group given cocoyam flour in this study, had lower liver enzyme levels than the negative control group, demonstrating that even at greater dosages, the cocoyam formulation has hepatoprotective effects on diabetic rats. Such preventative benefits of cocoyam flour pellets on diabetic rats have previously been shown [16]. There were no significant differences in total liver protein (TP) levels between the groups in this study, possibly because the liver enzyme ALT and the oxidative stress markers GST, GSH, and SOD were unaltered, preventing a major shift in TP levels. Nonetheless, there was a substantial difference in total blood protein levels between diabetes and normal control groups.

d. Effect on Bilirubin

When haem are catabolized, bilirubin, an antioxidant agent, is produced [62] and the presence of such compounds, results in risk reduction for metabolic syndrome and chronic illnesses [63]. When the level of bilirubin is moderately raised, its physiological benefits for disease prevention and management manifests [64] and are linked to the antioxidative and anti-inflammatory qualities [65]. In this study, the mean bilirubin levels were not significantly different among the groups but the total and direct bilirubin levels were significantly lower in the standard control group (Figure 7). Comparative to the normal control group, the group given cocoyam flour had comparable total and direct bilirubin levels, indicating that both antidiabetic medications and cocoyam flour were beneficial (Figure 7). Wang and colleagues [66] observed a higher concentration of direct bilirubin in persons with Type 2 Diabetes Mellitus (T2DM), although serum levels of bilirubin subtypes are enhanced in cases of impaired fasting glucose and the initiation of new T2DM. If T2DM is sustained, the level of bilirubin drops, because hyperglycemia produces oxidative stress, which boosts the activity of heme oxygenase-1, an enzyme that increases bilirubin production and raised serum levels. With the prolongation of the hyperglycemia, more reactive oxygen species

are released leading to increased bilirubin consumption and, eventually, lower bilirubin levels [67]. Studies have found lower serum bilirubin levels in diabetic patients [65], indicating prolonged hyperglycemia.

e. Effect on Serum Lipid Profile

In the present investigation, there were no statistically significant differences in triglyceride or very low-density lipoprotein levels but the Total cholesterol levels varied significantly between groups, with the normal control group having the lowest amount (94.85 mg/dl). The group administered with cocoyam flour, had a lower value (98.37 mg/dl) than the normal control (113.34 mg/dl) and negative control (109.94 mg/dl) (Figure 8). The levels of high and low-density lipoproteins followed comparable trajectories; those who received the cocoyam formulation had mean values of 19.88 and 56.59 mg/dl and mg/dl, respectively (Figure 8).

The low-density lipoprotein levels in this group were 75.20 mg/dl, while the high-density lipoprotein levels were 133.25 mg/dl (Figure 8). These results were less than what was seen in the normal control group. These findings revealed that the cocoyam formulation outperformed metformin, the antidiabetic medication used in group B, in terms of hypolipidemic effects in diabetic rats. Dyslipidemia, characterized by elevated levels of low-density lipoproteins (LDL), decreased levels of high-density lipoproteins (HDL), and elevated triglyceride levels, is frequently linked to Type 2 Diabetes Mellitus (T2DM). Increased plasma triglyceride levels induce HDL to break down, lowering HDL levels and increasing LDL levels. Low HDL and hypertriglyceridemia increase fatty acid levels, leading to insulin resistance and β-cell dysfunction. Lipid profiles have been shown to improve with the administration of extracts with strong antioxidant capabilities like polyphenols. Taurine-treated diabetic rats showed improved lipid profiles, as evidenced by lower levels of triglycerides, cholesterol, and LDL and increased levels of HDL [67]. Cocoyam flour extract contains phenolic compounds which could be responsible for its hypolipidemic effect in this study.

f. Effect on Renal Function

The correlation between kidney damage and uncontrolled type 2 diabetes, as well as elevated serum creatinine and urea levels, highlights the significance of prompt intervention in halting the advancement of end-stage renal failure [68,69]. The study's findings on creatinine mean values between groups showed no significant difference ($P<0.05$) (Figure 9). However, the normal control group's mean urea levels were much lower (12.55 mg/dl) than those of the other groups (Figure 9). The mean urea readings (13.03 mg/dl) of the cocoyam formulation group were considerably lower than those of the standard and negative control groups (14.20 mg/dl and 13.19 mg/dl, respectively) (Figure 9). In diabetic rats, the cocoyam formulation outperformed the anti-diabetic medicine in terms of kidney protection. The study's findings revealed that diabetic controls had greater levels of urea and creatinine than normal controls, which is consistent with previous research that found diabetic rats with STZ-induced renal failure had higher levels of urea, creatinine, and uric acid than controls [70]. Compared to the standard and negative control groups (69.24 mg/dL and 63.41 mg/dL, respectively), the mean uric acid levels in the diabetic rats fed with cocoyam were considerably lower (Figure 10). This demonstrates that metformin is not as effective as cocoyam flour at protecting the kidneys of diabetic rats. The increased plasma uric acid levels in chemically induced diabetic rats are similar to those found in diabetic controls [71].

The polyphenol content of cocoyam has been connected to the formulation's beneficial benefits on diabetic nephropathy [72,73]. Polyphenols can reduce TGF-β expression and matrix-degrading enzymes, including MMP-2/MMP-9, in hyperglycemia-induced renal injury (characterized by extracellular matrix buildup, glomerular fibrosis, and renal failure) [74]. Inhibiting TGF-β and matrix-degrading enzymes can help control diabetic renal failure by reducing inflammation, fibroblast development, and fibrosis [75,76]. In STZ-induced diabetic rats treated with a polyphenol mixture, leukocyte infiltration and necrotic cell count were reduced and the kidney structure was maintained [70].

g. Effect on Cardiac Function

Creatine kinase (CK) is an essential enzyme involved in the production of adenosine triphosphate during muscle contractions [77]. Certain muscle activities and metabolic syndrome lead to an increase in CK concentration [78]. According to Frank and Finsterer [79], higher levels of CK and lactate dehydrogenase (LDH) in type 2 diabetes are

useful predictors of the disease's cardiac complications since they are markers of heart damage. Advanced glycated end products (AGEs), which have cardiotoxic implications such as cardiac fibrosis, are generated as a result of chronic hyperglycemia, which might trigger the fibrotic response [80].

In this study, the mean values of CK and LDH showed no significant differences between the groups, indicating that the different types of interventions among the rat groups, in this study, did not affect these enzyme levels (Figure 10). According to Kotb and colleagues' findings [81], there were no discernible differences in the levels of CK and LDH between T2DM patients on metformin and healthy controls, contradicting another study [78] which reported a little increase in CK levels or sub-clinically raised CK in the T2DM patients [78, 79]. The reasons for these varying findings may be due to the duration of the hyperglycemia. Asmat and colleagues have shown that prolonged exposure to high glucose makes cells, particularly cardiac cells, vulnerable to glucose toxicity [82]. This could account for the lack of significant variations in mean LDH and CK levels across groups. Comparative analysis of the duration of hyperglycemic stress on the Kotb and colleagues study and this research showed, a duration of four and eight weeks, respectively, periods considered not long enough for cardiac toxicity by the high blood glucose and hence the reported normal CK and LDH levels.

5. CONCLUSION

Cocoyam flour delivered in significant doses to STZ-induced diabetic rats did not appear to effectively manage blood glucose levels. Nonetheless, it has similar biochemical effects as conventional antidiabetic drugs like metformin do. Furthermore, even at high concentrations, cocoyam flour appears to prevent lipid peroxidation in people with diabetes. The research results indicate that diabetes patients should be encouraged to take cocoyam, especially given its potential benefits in lowering the risk of diabetic hepato-renal injury. In addition, more research is needed to discover how cocoyam impacts diabetes complications and how it interacts with other anti-diabetic medicines.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

ACKNOWLEDGEMENTS

Authors wish to acknowledge the technical support of Dr. Eleazu chinedu and Dr. Okorie, uchechukwu for their technical support during the experiment.

CONSENT

Not applicable

ETHICAL APPROVAL

Ethical approval number RSU /FBMS /REC /23/032, was obtained from the faculty of basic medical sciences, college of medical sciences, rivers state university, Port Harcourt, Nigeria.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, Stein C, Basit A, Chan JCN, Mbanya JC, Pavkov ME, Ramachandaran A, Wild SH, James S, Herman WH, Zhang P, Bommer C, Kuo S, Boyko EJ, Maqliano DJ. IDF Diabetes Atlas: Global, Regional and Country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes Research and Clinical Practice. 2022; 183:109119. Available:https://doi.org/10.1016/j.diabres.2021.109119
2. Van Belle TL, Coppieters KT, Von Herrath MG. Type 1 diabetes: Aetiology, immunology and therapeutic strategies. Physiological Reviews. 2011;91:1.
3. Lin X, Xu Y, Pan X, et al. Global, regional, and national burden and trend of diabetes in 195 countries and territories: An analysis from 1990 to 2025. Sci Rep. 2020;10:14790.
4. Kirigia JM, Sambo HB, Sambo LG, Barry SP. Economic burden of diabetes mellitus in the WHO African region. BMC International Health and Human Rights. 2009;9:6.

5. Ashcroft FM, Ashcroft SJH. Insulin, molecular biology to pathology. Oxford University Press. 1992;266-284.
6. Sobngwi E, Mauvais-Jarvis F, Vexiau P, Mbanya JC, Gautier JF. Diabetes in Africans. Epidemiology and clinical specificities. Diabetes Metab. 2001;27(6):628-634.
7. Piero MN. Hypoglycemic effects of some Kenyan plants traditionally used in the management of diabetes mellitus in the eastern province, MSc thesis, Kenyatta University; 2006.
8. Wylie-Rosett J, Delahanty LM. Nutrition in the Prevention and Treatment of Disease (Fourth Edition). 2017;691-707. Available:https://doi.org/10.1016/B978-0-12-802928-2.00031-X
9. Forouhi GN, Misra A, Mohan V, Taylor R, Yancy W. Dietary and nutritional approaches for prevention and management of type 2 Diabetes, Science and Politics of Nutrition, BMJ 361; 2018. Available:https://doi.org/10.1136/bmj.k2234
10. Piero MN, Njagi JM, Kibiti CM, Ngeranwa JJN, Njagi ENM, Miriti PM. The Role of Vitamins and Mineral Elements in Management of Type 2 Diabetes Mellitus: A Review South As. J. Biol.Sci. 2012;2(Supp. 1):107 –115.
11. Merida LA, Mattos EB, Correa AC, Pereira PR, Paschoalin VM, Pinho MF, Vericimo MA. Tarin stimulates granulocyte growth in bone marrow cell cultures and minimizes immunosuppression by cyclo-phosphamide in mice. Plos One. 2018;13:e0206240. DOI: 10.1371/journal.pone.0206240
12. Chukwuma CI, Islam MS, Amonsou EO. A comparative study on the physicochemical, anti-oxidative, anti-hyperglycemic and anti-lipidemic properties of amadumbe (*Colocasia esculenta*) and okra (*Abelmoschus esculentus*) mucilage. J. Food Biochem. 2018;42:e12601. DOI: 10.1111/jfbc.12601
13. Prabhakar PK, Doble M. A target based therapeutic approach towards diabetes mellitus using medicinal plants. Current Diabetes Reviews. Bentham Science Publishers Ltd. 2008;291-308.
14. Kumawat NS, Chaudhari SP, Wani NS, Deshmukh TA, Patil VR. Antidiabetic activity of ethanol extract of *Colocasia esculenta* leaves in alloxan-induced diabetic rats. International Journal of Pharmaceutical Technique Research. 2010;2:1246–1249.
15. Eleazu CO, Iroaganachi M, Eleazu KC. Ameliorative potentials of cocoyam (*Colocasia esculenta* L.) and unripe plantain (*Musa paradisiaca* L.) on the relative tissue weights of streptozotocin-induced diabetic rats. J Diabetes Res. 2013;1–8 Available:https://doi.org/10.1155/2013/160964
16. Eleazu CO, Eleazu KC, Iroaganachi MA. Effect of cocoyam (*Colocasia esculenta*), unripe plantain (*Musa paradisiaca*) or their combination on glycated haemoglobin, lipogenic enzymes, and lipid metabolism of streptozotocin-induced diabetic rats, Pharmaceutical Biology. 2016;54(1):91-97. DOI: 10.3109/13880209.2015.1016181
17. Shakya AK. Medicinal plants: Future source of new drugs International Journal of Herbal Medicine. 2016;4(4):59-64
18. NRC (National Research Council). Guide for the care and use of laboratory Animals. Bethesda (MD): National Institute of Health. 1985;8523.
19. Nair AB, Jacob S. A simple practice guide for dose conversion between animals and humans. J Basic Clinical Pharmacology. 2016;7(2):27-31. DOI: 10.4103/0976-0105.177703
20. Pneu-Dart. Dosage Calculation; 2023. Available:https://www.pneudart.com. Accessed 14th April 2024
21. Nnadi NN, Ezekwesili CN, Ezeigwe OC. Effects of formulated unripe plantain and millet dietary feeds in alloxan-induced diabetic albino rats. International Journal of Innovative Research and Advanced Studies (IJIRAS). 2022;9(6).
22. Tietz NW. Clinical Guide to Laboratory Tests. 3rd Edn. Philidelphia, PA: WB Saunders Company; 1995.
23. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma without the use of preparative ultracentrifuge. Clin Chem. 1972;18:499-505
24. Jin XH, Ohgami K, Shiratori K, Suzuki Y, Koyama Y, Yoshida K, Ilieva I, Tanaka T, Onoe K, Ohno S. Effects of blue honeysuckle (*Lonicera caerulea L.)* extract on lipopolysaccharide-induced inflammation *in vitro* and *in vivo*.

Experimental Eye Research. 2006;82:860–867.
DOI: 10.1016/j.exer.2005.10.024

25. Oulai AC, Dje KM, Eba KP, Adima AA, Kouadio EJP. Chemical composition, antioxidant and antimicrobial activities of capsicum annuum var. annuum concentrated extract obtained by reverse osmosis. GSC Biological and Pharmaceutical Sciences. 2018;05(02):116-125
26. Lalhminghlui K, Jagetia GC. Evaluation of the free-radical scavenging and antioxidant activities of Chilauni, Schima wallichii Korth *In vitro*. Future Science. 2018;4(2):283.
27. Mukhtar A, Latif S, Rojas AAS, Muller J. Catalase activity in hot-air dried mango as an indicator of heat exposure for rapid detection of heat stress. Applied Sciences. 2022;12(3):1305.
DOI: 10.3390/app12031305
28. Paglia DE, Valentine WN. Studies on the quantitative and qualitative characterization of erythrocyte glutathione peroxidase. Journal of Laboratory and Clinical Medicine. 1967;70:158–169.
29. Beutler E, Duron O, Kelly BM. Improwed method for the determination of blood glutathione. Journal of Laboratory and Clinical Medicine. 1963;61:882–888.
30. Ohkawa H, Ohishi N, Yagi K. Assay for lipid peroxides in animal tissues by thiobarbituric acid reaction. Anal Biochemistry. 1979;95(2):351-358.
31. Wada, E., Feyissa, T., Tesfaye, K (2019) Proximate, Mineral and Antinutrient Contents of Cocoyam (*Xanthosoma sagittifolium* (L.) Schott) from Ethiopia. International Journal of Food Science, Vol. 2019. Article ID 8965476
32. Coronell-Tovar DC, Chavez-Jauregui RN, Bosques-Vega A, Lopez-Moreno ML. Characterization of cocoyam (*Xanthosoma spp*.) corn flour from the Nazareno cultivar. Food Science and Technology, Campinas. 2019;39(2):349-357.
33. Aini F, Maritsa H, Riany H. Antioxidant activity of nipahendophytic fungi (Nypha fruiticans Wurmb) from Tanjung Jabung Timur Jambi.Jurnal Biota. 2019;5:104-109.
34. Kurniawan YS, Priyangga KTA, Krisbiantoro PA, Imawan AC. Green chemistry influences in organic synthesis: A review. Journal of Multidisciplinary Applied Natural Science. 2021;1:1-12.
35. Amrulloh H, Fatiqin A, Simanjuntak W, Afriyani H, Annissa A. Bioactivities of nanoscale magnesium oxide prepared using aqueous extract of Moringaoleifera leaves as a green agent. Advances in Natural Sciences: Nanoscience and Nanotechnology. 2021;12:015006
36. Jiang Y, Shui J, Zhang B, Chin J, Yue R. The potential roles of artemisinin and its derivatives in the treatment of type 2 diabetes mellitus. Frontiers in Pharmacology. 2020;11:585487
37. Farrag EAE, Hammad MO, Safwat SM, Hamed S, Hellal D. Artemisinin attenuates type 2 diabetic cardiomyopathy of AGE-RAGE/HMGB-1 Signaling pathway. Scientific Reports, 13. Article 11043; 2023.
38. Maschirow L, Khalaf K, Al-Aubaidy HA, Jelinek HF. Inflammation, coagulation, endothelial dysfunction and oxidative stress in prediabetes – Biomarkers as a possible tool for early disease detection for rural screening. Clinical Biochemistry; 2015
Available:http://dx.doi.org/10.1016/j.clinbiochem.2015.02.015
39. Morel Y, Barouki. Repression of gene expression by oxidative stress. Biochemical Journal. 1999;342:481–496.
40. He X, Gao F, Hou J, Li T, Tan J, Wang C, Liu X, Wang M, Liu H, Chen Y. Metformin inhibits MAPK signalling and rescues pancreatic aquaporin 7 expression to induce insulin secretion in type 2 diabetes mellitus. Journal of Biological Chemistry. 2021;297.
41. Byrne NJ, Rajasekaran NS, Abel ED, Bugger H. Therapeutic potential of targeting oxidative stress in diabetic cardiomyopathy. Free Radical Biology and Medicine. 2021;169:317-342.
42. Rabhi H, Guermouche B, Merzouk H, Merzouk SA. The Mediterranean diet biodiversity impact on metabolic and oxidative stress parameters in type 2 diabetes. Genetics and Biodiversity. 2022;6(2):87-102.
43. El-Naggar SA, Elwan M, Abo M, Basyouny E, Elshennawy EO, El-Said K0S. Metformin Causes Hepato-renal Dysfunctions in Obese Male Rats. Brazilian Archives of Biology and Technology. 2021;64:e21210188.
Available:www.scielo.br/babt
https://doi.org/10.1590/1678-4324-2021210188

44. Mak TW, Saunders ME. The immune response. Basic and clinical principles. In: Press EA, editor, San Diego, CA Elsevier Academic Press. 2006;464–516.
45. Dinarello CA. Proinflammatory cytokines. Chest. 2000;118:503–508.
46. Wong HL, Pfeiffer RM, Fears TR, Vermeulen R, Ji S, Rabkin CS. Reproducibility and correlations of multiplex cytokine levels in asymptomatic persons. Cancer Epidemiology, Biomarkers and Prevention. 2008;17: 3450–3456.
47. Shoelson SE, Lee J, Goldfine AB. Inflammation and insulin resistance. J. Clin. Invest. 2006;116(7):1793–1801. DOI: 10.1172/jci2906
48. Nakano S, Kuboki K, Matsumoto T, Nishimura C, Yoshino GSmall, dense LDL and high-sensitivity C-reactive protein (hs-CRP) in metabolic syndrome with type 2 diabetes mellitus. Journal of Atherosclerosis and Thrombosis. 2010;17(4):410–415
49. Fu W, Ma Y, Li L, Liu J, Fu L, Guo Y, Zhang Z, Li J, Jiang H. Artemether regulates metaflammation to improve glycolipid metabolism in db/db mice. Diabetes Metab. Syndr. Obes. 2020;13:1703–1713. DOI: 10.2147/dmso.S240786
50. Pickup JC, Chusney GD, Thomas SM, Burt D. Plasma interleukin-6, tumour necrosis factor alpha and blood cytokine production in type 2 diabetes. Life Sci. 2000;67(3):291–300. DOI: 10.1016/S0024-3205(00) 00622-6
51. Olcum M, Toston B, Ercan I, Eitutan IB, Genc S. Inhibitory effects of phytochemicals on NLRP3 inflammasome activation: A review. Phytomedicine. 2020;75:153238. Available:https://doi.org/10.1016/j.phymed. 2020.153238
52. Karlsen A, Retterstol L, Laake P, Paur I, Kjolsrud-Bohn S, Sandvik L, Blomhoff R. Anthocyanins inhibit nuclear factor-kappaB activation in monocytes and reduce plasma concentrations of pro-inflammatory mediators in healthy adults. Journal of Nutrition. 2007;137:1951–1954.
53. Hanley AJ, Williams K, Festa A. Elevations in markers of liver injury and risk of type 2 diabetes: The insulin resistance atherosclerosis study. Diabetes. 2004; 53(10):2623-2632.
54. Giannini EG, Testa R, Savarino V. Liver enzyme alteration: A guide for clinicians. CMAJ. 2005;172(3):367-379.
55. Lee SH, Parka HJ, Chuna HK, Choa SY, Junga HJ, Choa SM, Kimb DY, Kangb MS, Lillehojc HS. Dietary phytic acid improves serum and hepatic lipid levels in aged ICR mice fed a high-cholesterol diet. Nutrition Research. 2007;27(8):505-510.
56. Hanigan MH, Frierson HF. Immunohistochemical detection of gamma-glutamyl transpeptidase in normal human tissue. The Journal of Histochemistry and Cytochemistry. 1996; 44(10):1101-1108
57. Berk P, Korenblat K. Approach to the Patient with Jaundice or abnormal liver tests.In Goldman`s Cecil Medicine: 24th Edn, Vol.1: 956-966. Elsevier Inc; 2011. DOI: 10.1016/B978-1-4377-1604-7.00149-4
58. Wang Y, Koh WP, Yuan J, Pan A. Association between liver enzymes and incident type 2 diabetes in Singapore Chinese men and women. BMJ Open Diabetes Res Care. 2016;4(1):e000296.
59. Finelli C, Tarantino G. What is the role of adiponectin in obesity-related non-alcoholic fatty liver disease? World J Gastroenterol WJG. 2013;19(6):802.
60. Yazdi HB, Hojati V, Shiravi A, Hosseinian S, Vaezi G, Hadjzadeh MA. Liver dysfunction and oxidative stress in streptozotocin-induced diabetic rats: Protective role of *Artemisia* Turanica. Journal of Pharmacopuncture. 2019;22(2): 109-114. DOI: 10.3831/KPI.2019.22.014
61. Islam S, Rahman S, Haque T, Sumon AH, Ahmed AM, Ali N. Prevalence of elevated liver enzymes and its association with type 2 diabetes: A cross-sectional study in Bangladeshi adults. American Journal of Physiology-Endocrinology and Metabolism. 2020;3(2).
62. Wu TW, Fung KP, Wu J, Yang CC, Weisel RD. Antioxidation of human low-density lipoprotein by unconjugated and conjugated bilirubin. Biochemical Pharmacology. 1996;51:859–862.
63. Troughton JA, Woodside JV, Young IS, Dominique A, Philippe A, Ferrie` res, et al. Bilirubin and coronary heart disease risk in the Prospective Epidemiological Study of Myocardial Infarction (PRIME). European

Journal of Cardiovascular Prevention and Rehabilitation. 2007;14:79–84,
DOI: 10.1097/01.hjr.0000230097.81202.9f (2007).

64. Gazzin S, Vitek L, Watchko J, Shapiro SM, Tiribelli C. A novel perspective on the biology of bilirubin in health and disease. Trends in Molecular Medicine. 2016;22(9):758–768.
65. Dong H, Huang H, Yun X, Kim D, Yue Y, Wu H, Sutter A, Chavin KD, Otterbein LE, Adams DB, Kim Y, Wang H. Bilirubin increases insulin sensitivity in leptin-receptor deficient and diet-induced obese mice through suppression of ER stress and chronic inflammation. Endocrinolog. 2014;155:818–828.
DOI: 10.1210/en.2013-1667
66. Wang J, Li Y, Han X, Hu H, Wang F, et al. Serum bilirubin levels and risk of type 2 diabetes: Results from two independent cohorts in middle-aged and elderly Chinese, Scientific Reports. 2017;7:41338.
67. Wang G, Li W, Lu X, Zhao X, Xu L. Taurine attenuates oxidative stress and alleviates cardiac failure in type I diabetic rats. Croatian Medical Journal. 2013;54:171-9.
DOI: 10.3325/cmj.2013.54.171
68. Shlomo M, Polonsky KS, Larsen PR, Kronenberg HM. Diabetes Mellitus. Willams textbook of endocrinology, 12th Ed. Philadelphia: Elsevier/Saunders. 2011;1371-1435
69. Ali AA, Faris HA. Prevalence and determinants of microalbuminuria among type 2 diabetes mellitus patients, Baghdad, Iraq, 2013. SJKDT. 2016;27(2):348-355.
70. Yassine C, Maram M, Rahma M, Rania M, Mohamed J, Ines E, Hamadi F, Najet S, Naziha M, Jed J. Investigation of the renal protective effect of combined dietary polyphenols in streptozotocin-induced diabetic aged rats. Nutrients. 2022;14(14):2867.
Available:https://doi.org/10.3390/nu14142867 0
71. Andonova M, Petko D, Krastina T, Penka Y, Nikola K, Krasimira N, Veselin I, Krasimira G, Nikola N, Ilia T, Chernev C. Metabolic Markers Associated with Progression of Type 2 Diabetes Induced by High-Fat Diet and Single Low Dose Streptozotocin in Rats Veterinary Sciences. 2023;10(7):431.
Available:https,//doi.org/10.3390/vetsci10070431
72. Rana S, Dixit S, Mittal A. In silico target identification and validation for antioxidant and anti-inflammatory activity of selective phytochemicals. Braz. Arch. Boil. Technol. 2019;62(4).
73. Rudrapal M, Khairnar SJ, Khan J, Dukhyil AB, Ansari MA, Alomary MN, Alshabrmi FM, Palai S, Deb PK, Devi R. Dietary Polyphenols and Their Role in Oxidative Stress-Induced Human Diseases: Insights Into Protective Effects, Antioxidant Potentials and Mechanism(s) of Action. Front. Pharmacol. 2022;13: 806470.
74. Forbes JM, Fukami K, Cooper ME. Diabetic nephropathy: Where hemodynamics meets metabolism. Exp Clin Endocrinol Diabetes. 2007;115(2):69–84.
75. Cabral-Pacheco GA, Garza-Veloz I, Castruita-De la Rosa C, Ramirez-Acuña JM, Perez-Romero BA, Guerrero-Rodriguez JF, Martinez-Avila N, Martinez-Fierro ML. The Roles of Matrix Metalloproteinases and Their Inhibitors in Human Diseases. International. Journal of. Molecular. Science. 2020;21:9739.
76. Catania JM, Chen G, Parrish AR. Role of matrix metalloproteinases in renal pathophysiologies. American Journal of Physiology.-Renal Physiology. 2007;292:F905–F911.
77. Field ML, Khan O, Abbaraju J, Clark JF. Functional compartmentation of glycogen phosphorylase with creatine kinase and Ca2+ ATPase in skeletal muscle. J Theor Biol. 2006;238(2):257–68.
Epub 2005/07/12.
78. Al-Hail N, Butler AE, Dargham SR, Abou SA, Atkin SL. Creatine kinase is a marker of metabolic syndrome in qatari women with and without polycystic ovarian syndrome. Front Endocrinology (Lausanne). 2019;10,659. Epub 2019/10/15.
79. Frank M, Finsterer J. Creatine kinase elevation, lactacidemia, and metabolic myopathy in adult patients with diabetes mellitus. Endocr Pract. 2012;18(3):387–393.
80. Leask A, Abraham DJ. All in the CCN family: Essential matricellular signalling modulators emerge from the bunker. Journal of Cell Science. 2006;119:4803-4810.
Available:https://doi.org/10.1242/jcs.03270

81. Kotb AS, Abdel-Hakim S, Ragy M, Elbassuoni E, Abdel-Hakeem E. Metformin ameliorates diabetic cardiomyopathy in adult male albino rats with type 2 diabetes. Minia Journal of Medical Research. 2022;33(4):128-138.

82. Asmat U, Abad K, Ismail K. Diabetes mellitus and oxidative stress-A concise review. Saudi Pharm J. 2016;24(5):547 553.
DOI: 10.1016/j.jsps.2015.03.013

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/117082