Original Research Article

EFFECTS OF THE ADMINISTRATION OF VARIOUS FORMULATIONS OF COCOYAM-BAMBARA GROUNDNUT-SOYA BEAN FLOUR BLENDS ON THE SERUMLIPIDS & INFLAMMATORY BIOMARKERS OF STREPTOZOTOCIN-INDUCED DIABETIC RATS.

.ABSTRACT

Background: Diabetes mellitus has assumed a Public Health prominence as a result of the global prevalence, mortality and disability. With effective and affordable management not universally in focus, as a result of the huge financial burden associated with its management, attention has been shifted to medicinal food plants, most of which have been administered singly. The aim of this study is to determine the effect of flour blend of the commonly consumed cocoyam, Bambara groundnut and soya beans, on the serum lipid, bilirubin and inflammatory biomarkers` levels, in streptozotocin-induced diabetic rats (SIDRs), in order to build scientific evidence on the use of such food mix by diabetics. Methodology: Locally sourced cocoyam (CY) roots, Bambara groundnut (BGN) and Soya bean (SB) seeds were peeled in the case of cocoyam, washed, boiled and dried separately with oven-dryer, until constant weights were obtained, before grounding them and the formulations blended and pelletized. The three controls and seven intervention groups were appropriately placed on commercial rat feed, metformin and the pelletized flour blends for 28 days, after which, the blood specimen were collected for serum lipids, bilirubin and inflammatory biomarkers determination. Results & Discussion: The generated data were statistically analysed using SPSS, and one-way ANOVA, while the mean difference were determined by Turkey`s post-hoc test. Formulation 1(16.6%CY: 16.6%SB: 16.6%BGN: 50%RF)-treated rats had the least mean values of NFkB and IL-10, total and direct bilirubin levels, total cholesterol and LDLc, which were comparable to those of the normal control, but higher than those from the standard and diabetic controls. Conclusion: Various formulations of the Cocoyam-bambara groundnut-soya bean flour blend, exerted varying effects on the inflammatory biomarkers, serum bilirubin and lipid profile in SIDRs, with formulation one showing more potent hypocholesterolamic and anti-inflammatory activities than the antidiabetic drug. The blend can be said to have a place in the nutritional management of diabetes mellitus.

Key words: *Medicinal plant foods, Serum lipids, diabetic rats*

1. INTRODUCTION

Diabetes mellitus affects various age-groups globally and at a rate considered of Public Health importance due to the prevalence, disability and mortality [1]. As a pancreatic organ disorder, it makes insulin production inadequate and ineffective [2]. Its prevalence in the Asian and African continents far surpasses that in the Western nations and Europe [3]. Arising from dilapidated health infrastructure, shortage of human resource for health, and limited funding, the disease outcome is poor, thereby affecting productivity and worsening disability [4, 5, 6]. In finding solutions to these menace a critical alternative to the expensive and ineffective orthodox management strategies has led to the choice of dietary and other lifestyle modifications as treatment and prophylactic adjuncts [7], with the diabetic diets used in the Western Nations proving effective in T2DM management [8, 9] and its use and the utilization of nutraceuticals and functional foods recommended by World Health Organization [10]. The presence of bioactive compounds in these functional foods and their biochemical effects *invivo,* have been the basis for their usage in managing non-communicable diseases [11, 12]. Several bioactive compounds have been identified in these plant foods, including the isoflavones, stilbene, and flavonoids, with reported actions on the pancreatic cells [13]. For instance, the hypoglycemic bioactivity of the chemical constituents in cocoyam [14-16], antioxidant and antidiabetic actions of Bambara groundnut (*vigna subterranean*), attributed to the chemical constituents [17-31], and the use of Soya Bean (*Glycine max. (L) Merrill*), in non-communicable diseases management, linked to the same bioactive compounds and their biochemical actions [32-46]. Rarely are these medicinal food plants consumed singly without mixing two or more of them as food mixtures. Consequently, understudying the effects of such flour blends on biochemical parameters such as the serum lipids and inflammatory biomarkers is the focus of this study.

2.0 Materials and Methods

2.1 Collection and Preparation of the Plant Food Material

The Bambara groundnut, soya bean and cocoyam were purchased from the local market and prepared by washing, peeling and soaking (cocoyam), washing and rinsing (Bambara groundnut and soya bean). All the three plant foods were then boiled, oven-dried at a temperature of 60^0C until a constant weight was achieved, before being ground and formulated as pellets. The pelletized blends were oven-dried and stored for future use.

2.2 Experimental Animals

A total of eighty-five (85) male albino rats (134 – 249 grams), were purchased locally and segregated in groups of eight per cage, with each rat marked on the tail, in circles of 1-8 as identification marks. Ten groups, A- J were mapped out, and fed with commercial rat feed and water administered *ad libitum* for seven days to allow for acclimatization. The body weights of the rats were recorded and the protocols for handling experimental animals followed [47].

2.3 Induction of Insulin Resistance Using Low Fructose Diet

Once the acclimatization period was completed, 30 g of fructose was dissolved in 300 mL of water and administered *ad libitum* as low dose fructose diet for six days. The commercial rat feeds were maintained throughout this period.

2.4 Induction of Type 2 Diabetes Mellitus using STZ

The rats in the ten groups were fasted overnight at the 6^{th} day of the fructose diet and the fasting blood glucose recorded. All the normo-glycemic rats were administered with streptozotocin (STZ) prepared as 1 g in 50 mL of freshly prepared sodium citrate buffer and given by intra-peritoneal route using the formula for extracts to experimental animal subjects to estimate the dose [48, 49]. Post STZ treatment, blood samples were collected from the rats and estimated for blood glucose levels at days 6 and 12. The rats that were hyperglycemic were randomly assigned to standard control, negative control and intervention groups. The rats that were not administered with STZ and normoglycemic, acted as the normal control. The various groups were assigned to interventions as shown in Table 1, according to Nnadi and colleagues [50].

Table 1: The Formulations and Their Compositions given to Each Rat Group

Rat Groups	Formulations	Formulation Compositions
A	1	16.6%CY: 16.6%SB: 16.6%BGN: 50%RF
B	Standard Control	Metformin + 100% Rat Feed (RF)
C	Normal Control	100% RF
D	Negative Control	100% RF
E	2	12.5%CY: 12.5%SB: 25%BGN: 50%RF
F	4	12.5%CY: 25%SB: 12.5%BGN: 50%RF
G	7	0%CY: 50%SB: 0%BGN: 50%RF
H	5	0%CY: 0%SB: 50%BGN: 50%RF
I	6	50%CY: 0%SB: 0%BGN: 50%RF
J	3	25%CY: 12.5%SB: 12.5%BGN: 50%RF

RF =Rat Feed

CY = Cocoyam

SB = Soya Bean

BGN = Bambara Groundnut

2.5 Estimation of Serum Lipids and Inflammatory Biomarkers

The interventions were conducted for 28 days, following which, blood samples were collected for lipid using the Randox assay diagnostic kits [51], with the LDLc and VLDLc concentration obtained using the formula according to Frieddewald and colleagues [52]: LDL-C = Total cholesterol – (HDL-C + [TG/5]).

For the serum inflammatory biomarkers determination, the blood specimen, was collected and allowed to clot, then centrifuged at 2000 RPM for 10 min at 4^0C and the serum obtained, used to determine the interleukin-6 and IL-8 with the aid of human Enzyme-linked Immunosorbent Assay (ELISA) kits (Elabscience, Quangzhou, China) [53]. The C-reactive proteins, NFkβ, and IL-10 were measured using a highly sensitive commercial method in Hitachi 917 autoanalyzer [54].

2.6 Statistical Analysis

The Statistical Package for Social Sciences (SPSS Inc., Chicago, IL) version 20.0, one-way analysis of variance (ANOVA) and the Turkey's post-hoc test were

employed for data analysis, standard error of mean and the mean differences respectively. The statistically significant was pegged at $p<0.05$.

3.1RESULTS

3.1.1 Inflammatory Markers Results

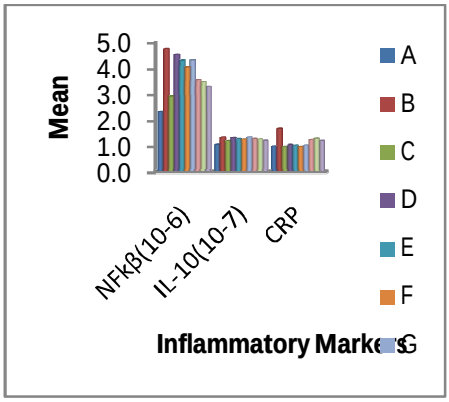

Figure 1: Bar Charts for the NFkB, Interleukin (IL)-10 and C - reactive protein (CRP) for the various diabetic and non-diabetic rat groups showing the lowest values for Group A in the pro-inflammatory and anti-inflammatory biomarkers**.**

Figure 1 showed that Group A were least while Group B and D were the highest for both markers NFkβ and IL-10. For CRP, Groups A, C and F had least mean CRP while Group B had highest mean CRP.

3.1.2 Serum bilirubin and Protein Results

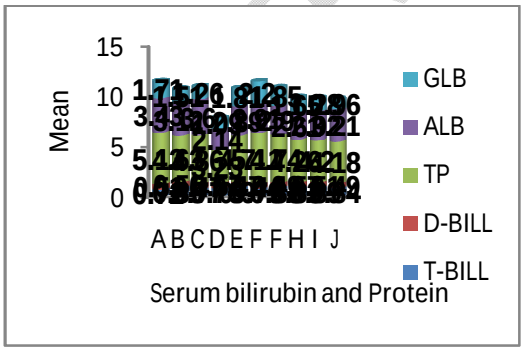

Figure 2: Bar Charts for the Serum bilirubin and Serum Protein for the various diabetic and non-diabetic rat groups showing that the diabetic control, had the least values of the bilirubin and serum total protein.

Figure 2 revealed that T-BILL and D-BILL has no significant ($p>0.05$) mean difference among the groups, however mean values for TP, ALB and GLB were significantly ($p<0.05$) different. Mean TP and ALB were minimum in group D while mean GLB were least in group J.

3.1.3 Results of Serum Lipid Profile

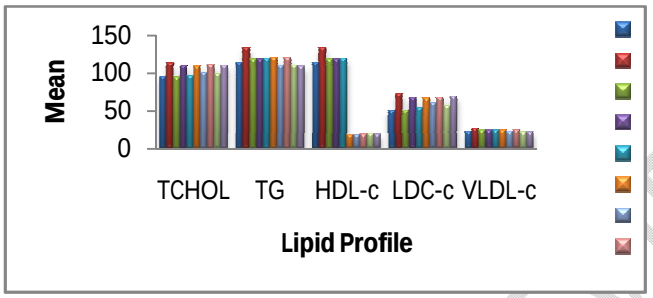

Figure 3: Bar Charts for the Serum Lipid Profile for the various diabetic and non-diabetic rat groups showing the comparable values of Groups A and C.

Figure 3 is the result of mean analysis of serum lipid profile among various groups. Significant ($p<0.05$) difference among the groups were observed for the TCHOL, HDL-c and LDL-c only.

3.2 DISCUSSION

3.2.1 Effects on Inflammatory Biomarkers

In acute and chronic inflammation, cytokines which are soluble factors are engaged in recruiting leucocytes [55] and exhibit synergistic and antagonist effects [56]. NF-kB is activated in prolonged hyperglycemia, with resultant expression of genes for TNF-α, IL-6, IL-8, MCP-1, MIP-1α, MIP-2, resistin, ICAM-1 and VCAM-1 [57]. These expressed cytokines, regulate growth factor, apoptotic genes, cell-cycle programme and inflammation [58]. Circulating cytokines can provide the general state of inflammation in the individual. Inflammatory markers –CRP, IL-6 and TNF-α are raised in patients with metabolic syndrome and sub-clinically overt T2DM [59]. Transforming growth factor β1 [60], MCP-1 [61] or Lipoprotein Associated Phospholipase A2 (LP-PLA2) [62] also increase in T2DM.

When the Acute phase proteins are chronically raised, it promotes IR in skeletal muscles and endothelial dysfunction and release of CRP from the liver [63]. There is significant correlation between CRP level and features of metabolic syndrome such as hyper-insulinaemia and IR [64].

In this study, the mean values of NFkB and IL-10 among the groups, showed significant differences, with Group A having the least and the standard and negative controls having the highest values, and these higher values were significantly different that of the normal control and the groups on intervention formulation. The normal control and intervention groups had no significant difference. Similar results have been gotten when whole grains, and foods containing high amounts of antioxidants and phytochemicals, are consumed with resultant improved glycemic index [65, 66].

In terms of the c-reactive proteins, Groups A,C and F had the least values, meaning that the formulations 1 and 4 respectively given to these groups, had as good anti-inflammatory protection as the normoglycemic group which was better than the effect of the standard control. Other intervention formulations used in groups E, G, H, I and J were not as protective as those used in Groups A and F as they had higher CRP values.

Group A rats were given formulation 1 (Table 1) which contained mainly phenolic compounds and stilbene [67]. Among the several mechanisms of action of phenolic are inhibition of transcription factors [68], pro-inflammatory cytokines release [68, 69] and enzymes associated with inflammation such as cyclo-oxygenase [70’ 71], lipoxygenases, inducible nitric oxide synthase (iNOS) [72]. To exert anti-inflammatory activities, polyphenols, block MAPK-mediated pathway, an action that has been linked to their structure [70, 73].

Stilbene in the same vein, inhibits nucleotide-binding and oligomerization domain (NOD)-Like receptors (NLRP)-3 [74], which is activated by myeloid cells in obesity [75] and by Danger Associated Molecular Patterns (DAMPs) in chronic inflammation and insulin resistance [76], with subsequent release of IL-1β and IL-18 [77]. Studies have shown that absence of NLRP3 gene, protects against obesity-

induced inflammation is prevented [78]. The actions of Stilbenes have been linked to silent information regulator 1 (SIRT1) activation [79] or by thioredoxin-interacting protein (TXNIP) inhibition [80, 81]. Activation of SIRT1, promotes the deacetylation of peroxisome proliferator activator gamma co-activator 1 alpha (PGC-1α), critical in regulating mitochondrial biogenesis [82]. Thirdly, stilbene modulates pro-inflammatory cytokines, which occurs in the presence of infectious agents, with resultant IL-1β release [83]. Hence by arresting its activation stilbene inhibits the development of T2DM [84]. Fourthly, stilbene inhibits the overexpression of IL-6 through downregulation of NF-κB and activator protein-1 (AP-1) in different cells [85] and by so acting, there is non-induction of the intercellular adhesion molecule (ICAM-1) expression, non-phosphorylation of signal transducer and activator of transcription 3 (STAT3) [86] and downregulation of suppressor of cytokine signaling (SOCS3) expression in Hep G2 cells in rat liver cells resulting in improved insulin signaling [87]. Additionally, Stilbene, downregulates the p38 MAPK pathway thereby modulating NFκB that causes TNF-α and IL-1β release and upregulates heme-oxygenase-1 (HO-1),, with the later resulting in the upregulation of enzymatic antioxidants such as catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPX) [88].

Also stilbene reduces the endoplasmic reticulum (ER) stress, through the activation of transcription factor 4 (ATF-4) and Tribbles Pseudokinase 3 (TRIB3) [89, 90], downregulation of protein kinase-like ER kinase (PERK) and eukaryotic initiation factor 2 alpha (eIF2 alpha) [91] and hence improve insulin sensitivity [91]. Stilbene also acts on innate and adaptive immunity. Stilbene inhibits the proliferation of CD4+ and CD8+ T cells. When this happens, cytokines are not released [92] thereby affecting the type 1 (IL2, IFN-g, and lymphotoxin) cell mediated inflammatory response and type 2 (IL4, IL5, IL10, and IL13) antibody-mediated immune response T cells.

3.2.2 Effect on Bilirubin

The bilirubin can be indirect bilirubin or direct bilirubin, and each of these subtypes having clinical relevance. When moderate hyperbilirubinemia involve all subtypes, physiological benefit and disease prevention and management occurs [93] because their antioxidant and anti-inflammation properties manifest [94].

In this study, the bilirubin mean values were not significantly different among the groups though the total bilirubin and direct bilirubin were least in the normal control, and in Groups A, E and F rats. The diabetic and standard control groups were among the groups with highest values of total and direct bilirubin, in line with previous study that reported raised level of direct bilirubin in T2DM [95]. Presence of elevated levels of direct bilirubin is more related to metabolic syndrome and stroke [96] than total bilirubin and indirect bilirubin. However in chronic hyperglycemia,,more free radicals are and more bilirubin consumed, resulting in decreased bilirubin [95, 97]. In view of the short duration of this study and the non-chronicity of the raised glucose levels, low concentration of the bilirubin as reported in the intervention groups could be attributed to the presence of bioactive compounds in the formulations which might have not only regulated the blood glucose but also reduced the free radicals.

3.2.3 Effect on Serum Lipid Profile

Groups A, E and I had the least mean values of the Total Cholesterol (TC) in this study and this was comparable with values in the normal control. For the triglyceride, there was no significant difference among the groups, while in the case of HDLc, Groups A, B, C and D showed significant difference when compared to those in Groups F, G, H, I and J. The LDLc, values in Groups A, C and E were the least and were significantly different from the diabetic control and other groups. For the VLDLc, there was no significant difference among the group means. Overall, in this study, there were elevated plasma values of the TC and LDLc in the diabetic control when compared to the normal control and this was in agreement with earlier reports by other researchers [98]. The remarkably low values of TC and LDL in

Group A relative to the diabetic control, was equally in tandem with the work of Wang and colleagues [99].

T2DM is often associated with dyslipidemia, in which there is elevated levels of triglycerides and low levels of high-density lipoproteins (HDL) and elevated low-density lipoproteins (LDL) [100]. The more plasma triglycerides increases, the more, HDL is broken down, resulting in reduced level of HDL which in turn leads to raised LDL [101]. A hypertriglyceridemia state with low levels of HDL aids elevated fatty acids, which stimulate insulin resistance and cause β-cell dysfunction [102]. Such alterations in lipid profile, impairs the ability of insulin to inhibit hormone-sensitive lipase and hence cause an increase in serum concentrations of free fatty acids [103], which further induce insulin resistance in adipose tissue and skeletal muscle [104]. The resultant DNA damage activates DNA repair enzyme which inhibits metabolic enzymes such as glyceraldehyde-3-phosphate dehydrogenase which ultimately leads to *de novo* synthesis of diacylglycerides, up-regulation of PKC pathway, stimulation of free radical generating-enzymes like lipooxygenses and the development of deteriorating toxic environment [105].

Studies have reported significant correlation between serum triglyceride and blood sugar levels [106] and the association in diabetics between high levels of LDL cholesterol and higher risk of diabetic complications such as cardiovascular diseases [98]. When compounds with potent antioxidant properties are given, there is improved lipid profile. Wang and colleagues reported that taurine-treated diabetic rats showed a significant improvement in lipid profile through reduction in triglyceride, cholesterol and LDL and elevated HDL [99].

4. CONCLUSION

Various formulations of the cocoyam-bambara groundnut-soya bean flour blend, exerted varying effects on the inflammatory biomarkers, serum bilirubin and lipid profile in stz-induced diabetic rats. Formulation 1 composed of 16.6%cy: 16.6%sb: 16.6%bgn: 50%rf, and administered to rats in group a, had the least mean values of nfkb and il-10, total and direct bilirubin levels, total cholesterol and ldlc. These values were comparable to values obtained in the normal control, but higher than values obtained in the standard and diabetic controls, thereby implying that formulation 1 had better hypocholesterolamic and anti-inflammatory activities than

metformin antidiabetic drug. However, this blend formulation had no effect on the triglyceride and vldlc levels. It can therefore be inferred that utilization of a blend of cocoyam-bambara ground nut- soya bean, at the ratio of 16.6% could be administered as a therapeutic and prophylactic adjunct in t2dm management.

CONSENT (WHEREEVER APPLICABLE)
NOT APPLICABLE

ETHICAL APPROVAL (WHEREEVER APPLICABLE)

Ethical approval was sought and obtained from the Research Ethical Committee of the Faculty of Basic Medical Sciences, Rivers State University, Port Harcourt, Nigeria.

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