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Research Article

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Effects of Consumption of Various Formulations of Cocoyam-Bambara Groundnut-Soya Bean Flour Blends on the Pancreatic Beta-Cell Functions of Streptozotocin-Induced Diabetic Rats

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Introduction

Diabetes mellitus is an endocrine system disease affecting people of diverse race, ages and regions globally, increasing in number annually due to its long course and recalcitrant to conventional treatment [1]. Its clinical presentations are multi-system based, affecting virtually all key organs and which as a result of the chronicity of its course ends in organ failures [2]. The disease affects more people in economically disadvantaged countries compared to economically buoyant countries [3]. This high prevalence in low-income nations has been attributed to the weak health systems, dearth of health personnel, modern equipment, infrastructure and disappointing management outcomes [4-6]. In finding solutions to such negative outcomes, management protocols have been expanded to target lifestyle modifications including focus on dietary plan and increased physical activity levels [7]. Consequently food-based plans have been incorporated as immediate and long term critical component in T2DM management, the positive results of which have made global experts and bodies, including the World Health Organization to encourage adoption of medicinal plant foods in T2DM treatment and prophylaxis [8-10]. The major scientific basis for utilization of medicinal plant foods is its composite bioactive compounds with reported biological invivo activities [11,12]. These bio-actions ranges from potent effects against free radicals, its actions against inflammation, the pro-hypoglycemic effects and their activities that boost the immune system [11,12]. Bioactive compounds associated with these bio-actions include low-molecular weight compounds like peptides, amino acids, and other biological agents such as flavonoids, and polyphenols, all of which acting on the pancreatic β-cells and involved in the hepatic glycol-regulatory enzymes [13]. In the developing countries, commonly consumed plant foods such as the roots of Cocoyam, have been demonstrated to contain biologically active substances with established anti-hyperglycemic effects [14-16]. Legumes like Bambara groundnut (vigna subterranean), also contain several biologically active compounds in addition to its nutrients [17-26]. These compounds found in bambara groundnut use various mechanisms of actions to effect hypoglycemic actions [27-31]. Another ubiquitous legume, Soya Bean (Glycine max. (L) Merrill), also has abundant biologically active compounds responsible for beneficial effects when incorporated in the management of diabetic mellitus [32-36]. Most of these mechanisms of actions have been adequately reported from studies [37-46]. Since these plant foods are usually consumed in combinations, this study intended to evaluate the effect of these flour blends in the pancreatic tissues of diabetic rats.

Collection and Preparation of the Plant Food Material

Locally sourced soy bean seeds, roots of cocoyam and seeds of Bambara groundnut were processed into pellets by first washing them, peeling the cocoyam, and soaking each in water for 10

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min, then rinsing and boiling them. They were later oven-dried at a temperature of 60ºC. Once the weights of the products became constant, they were ground into fine flour, pelletized, oven-dried again and stored for subsequent use in a well-sealed container.

Experimental Animals

A total of Eighty-five (85) male albino rats whose total body weights ranged from 134 - 249 grams were purchased from a reputable breeder. The rats were separated into groups of eight with each rat marked on the tail, using an indelible, and the marks depicting its number (1 - 8). In all, ten sets of the rats, A-J, were used in the experiment, with the weight of each rat in the set, documented, every week. All the rats were fed with commercial rat feeds and water for one week ad libitum to allow for acclimatization. The standard recommended protocol for administration of laboratory animals in experiment were strictly followed [47].

Induction of Insulin Resistance Using Low Fructose Diet

After acclimatizing the experimental animals for one week, a low-dose fructose diet was instituted to replace the drinking water, by administering the rats with 300 mls of 10% fructose ad libitum, in order to induce Insulin resistance. The commercial rat feeds were equally administered ad libitum within this period.

Induction of Type 2 Diabetes Mellitus Using STZ

The 10% fructose diet is administered for 6 days at the end of which the rats are fasted overnight and the fasting blood glucose level measured. Rata that was normoglycemic were then administered with Streptozotocin (STZ) which was prepared fresh by dissolving 1g of STZ in 50 mL of freshly prepared sodium citrate buffer, 0.1M, pH 4.5), at the recommended dose for extracts in experimental animals [48,49]. Following the administration of the STZ, the rat blood samples were collected for blood glucose level evaluation, at the tail veins at specified periods of 72 hours and on day 12. All the rats whose blood glucose levels were hyperglycemic were then randomly assigned to different groups: the standard control, negative control, and seven intervention groups. The rats who were not treated to the STZ and which remained normoglycemic, were assigned as the normal control group. Common to all the ten rat groups was the administration of commercial rat feeds for 28 days, but the specific rat groups were additionally given metformin at 200 mg/kg, as 0.002 ml per Kg body weight orally daily using oral dispenser (standard control), formulations 1, 2, 4, 7, 5, 6 and 3 for rat groups A, E, F, G, H, I and J respectively, according to the work of Nnadi and colleagues (Table 1) [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

Estimation of Blood Glucose and Insulin Concentrations

The interventions in each of the rats in groups A - J, were conducted for a total of 28 days, with the random and fasting blood glucose levels checked weekly. At the end of 28 days, the rats were fasted overnight and the fasting blood glucose and insulin concentrations, measured.

Statistical Analysis

The Statistical Package for Social Sciences (SPSS Inc., Chicago, IL) version 20.0 was used to analyze the data so obtained. The data were expressed as the standard error of the mean (SEM) of the triplicate values for each of the rats per group and the mean recorded. The mean difference was determined using Turkey's post-hoc test with the level of statistical significance put at $P<0.05$. The means were compared using a one-way analysis of variance (ANOVA).

Results

Random Blood Glucose Concentration, mg/dl, (Weeks 1-4) of the Various Groups of STZ-Induced Diabetic and Non-Diabetic Rats.

Table 2: Showing Result of the Random Blood Glucose Concentration, mg/dl, (Weeks 1-4) of the Various Groups of STZ-Induced Diabetic and Non-Diabetic Rats

Groups	Week 1 Mean (SEM)	Week 2 Mean (SEM)	Week 3 Mean (SEM)	Week 4 Mean (SEM)
A (n=7)	315.83(22.23)^{b}	396.33(11.61)^{bc}	457.67(24.91)^{b}	512.67(8.67)^{b}
B(n=7)	401.50(13.98)^{bc}	309.00(48.32)^{b}	371.00(67.06)^{b}	414.25(75.15)^{b}
C(n=9)	106.25(3.05)^{a}	101.00(6.22)^{a}	112.88(4.25)^{a}	94.13(1.49)^{a}
D(n=5)	395.67(30.98)^{bc}	332.33(34.61)^{bc}	364.00(15.36)^{b}	563.00(11.32)^{b}
E(n=7)	400.20(23.02)^{bc}	320.60(21.43)^{b}	392.20(25.30)^{b}	526.80(14.65)^{b}
F(n=7)	365.33(17.12)^{bc}	356.67(9.49)^{bc}	410.67(10.46)^{b}	542.67(20.15)^{b}

G(n=7)	367.86(49.08)^{bc}	326.43(42.40)^{bc}	379.43(45.85)^{b}	457.43(59.59)^{b}
H(n=7)	362.00(17.66)^{bc}	291.20(48.44)^{b}	313.60(59.36)^{b}	481.60(45.55)^{b}
I(n=7)	434.00(14.55)^{c}	448.33(32.06)^{c}	453.00(23.95)^{b}	497.67(3.78)^{b}
J(n=7)	367.17(13.60)^{bc}	366.50(11.91)^{bc}	403.00(6.82)^{b}	481.83(12.17)^{b}
F	14.10	7.10	6.41	10.89
p-value	<0.001	<0.001	<0.001	<0.001
Repeated Measures Test				
Equal Level (Mean difference among Groups)		Parallelism (Pattern of all groups across time points) i.e. within/between group interactions		Flatness (Trend)
F-value	p-value	F-value	p-value	F-value	p-value
13.963	<0.001	79.106	<0.001	76.755	<0.001

The Table 2, The ANOVA result depicting blood glucose concentration mean differences among groups A-J and as well as determining the trend over time are captured in Table 2, revealing the significant difference in the mean over time among the groups (F= 13.963, p<0.001), the parallel pattern of changes over time which was also significant (F=79.106, p<0.01) as well as the significant positive trend (F=76.755, p<0.001).

Table 3: Showing the Result of the Fasting Blood Glucose (mg/dl) (Day of Sacrifice) of the various Groups of STZ-Induced Diabetic and Non-Diabetic Rats

Group	Mean	Standard Error of Mean	Minimum	Maximum
A (n=7)	294.57^{b}	44.94	75	416
B(n=7)	282.25^{ab}	64.62	89	360
C(n=9)	76.38^{a}	2.63	65	85
D(n=5)	338.67^{b}	10.51	324	359
E(n=7)	286.20^{ab}	36.71	170	395
F(n=7)	361.14^{b}	20.96	291	422
G(n=7)	318.00^{b}	43.35	81	416
H(n=7)	312.40^{b}	56.54	89	405
I(n=7)	296.67^{b}	138.12	96	561
J(n=7)	241.00^{ab}	38.37	110	318
F	4.38			
p-value	<0.001			

Table 3 captured the mean fasting blood glucose concentrations for the various Groups with Groups C and F showing the least and highest values respectively, Groups E, and J were not significantly different from the standard control.

Figure 1 is the Pareto bar for the insulin concentrations depicting the highest mean value from the standard control and the least value from group A. With the exception of Group B, all the group means were not statistically different from one another.

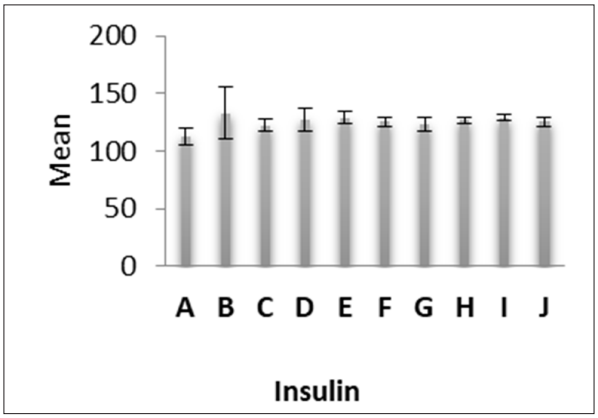

Figure 1: Pareto Bar Chart of Insulin

Table 4: Calculated HOMA-IR and HOMA-β Values for diabetic and non-diabetic Rat Groups

Groups	Fasting Blood Glucose (mg/dl) (Day of Sacrifice)	Fasting Plasma Insulin (mIU/mL) Mean(SEM)	HOMA-IR	HOMA-β
A	294.571^{b}	112.49(2.79)^{a}	0.82	1.75
B	282.250^{ab}	133.17(8.31)^{b}	0.94	2.18
C	76.375^{a}	122.45(1.95)^{ab}	0.23	32.83
D	338.667^{b}	127.43(3.74)^{ab}	1.06	1.66
E	286.200^{ab}	128.83(2.01)^{b}	0.9	2.08
F	361.143^{b}	125.33(1.49)^{ab}	1.11	1.51
G	318.000^{b}	122.84(2.29)^{ab}	0.97	1.74
H	312.400^{b}	126.68(1.49)^{ab}	0.98	1.83
I	296.667^{b}	128.80(1.00)^{b}	0.94	1.99
J	241.000^{ab}	125.66(1.51)^{ab}	0.75	2.55

Table 4 shows the calculated values of HOMA-IR and HOMA-β from the study results of the fasting blood glucose and fasting blood insulin on the day of sacrifice of the non-diabetic and STZ-induced diabetic rats. While the HOMA-IR reports in all the groups were within the normal range with those of groups D and F recording the highest values and tending towards the upper limits of normal, the HOMA-β values were higher than the controls signifying a decrease in the pancreatic β-cell function possibly due to the hyperglycemic effects and toxicity of the STZ.

Discussion

Effects on Blood Glucose Concentrations

Over the four weeks period, the random blood glucose (RBG) values showed significant differences for each group ($F= 13.963$, $p<0.001$). These differences had similar pattern for the whole group and such differences were significantly parallel ($F=79.106$, $p<0.01$), even in terms of the time trend ($F=76.755$, $p<0.001$). There were two distinctive groups, Group C, Group B and Group D, representing the control, standard and negative groups respectively in ascending order of values on one hand, and the intervention groups E,F,G and H which had low RBG values and which when compared with the standard and diabetic control groups showed lower RBG values, implying that the formulations 2, 4, 7 and 5 respectively used in these groups (Table 1) regulated the blood glucose better than the RF used in the diabetic control and the metformin used in the standard control.

The Fasting Blood Glucose (FBG) measured after an overnight fast showed that the standard control, Group E and J had values which were not significantly different from one another but higher and significantly different from the normal control (Table 3). FBG is a better indicator of diabetic control than RBG.

It is possible that constituents like the bioactive compounds seen in the formulations 2 and 3 used for groups E and J respectively, had better efficacy when compared with metformin used in the standard control. The variations in FBG values observed over the time trend are similar to therapeutic responses observed human diabetics, hence the use of multiple anti-diabetic drug regimen [51,52]. Among the BACs found in formulations 2 and 3 are phenolic compounds which causes hypoglycemia by acting on 5' adenosine monophosphate-activated protein kinase (AMPK) pathway, improving glucose metabolism enhancing the α-amylase and α-glucosidase inhibitory activities [53-55]. Many studies have associated presence of phenolic compounds with hypoglycaemia [56-58].

Monoterpenoids have also been reported to be present in formulation 7 given to group G (53) and their derivatives exert inhibitory actions on some enzymes to effect hypoglycaemic effects [59,60].

Rats in Group I who received formulation 6, might have had artemisinin compounds whose derivatives have been associated with hypoglycaemic effects as a result of their inhibitory actions on α-glucosidase activity [61]. Other invivo action of the derivatives of artemisinin are improvement of insulin release and its actions on the pancreas [62-64]. Studies have linked artemisinin with amelioration of diabetic complications [65]. Various other studies detailing several mechanisms of action have given boost to the antidiabetic effects of artemisinin [63,65-69].

Another bioactive compound found in formulation 2 and the commercial rat feed (RF) is the Thiadiazole [53]. The chemical structure of thiadiazole lend credence to their anti-diabetic effects and that of their derivatives through their inhibitory actions on carbonic anhydrase [70-73]. Formulation 2 was the intervention formulation given to rats in group E and the FBG values measured in those groups of diabetic rats, depicted similarity with values obtained from the standard control in this work (Tables 2 & 3).

Thiourea and Naphthalene were found in formulations 4 and 7, respectively, with the former already in use for its various therapeutic effects especially too in the synthesis of sulfonylureas for diabetic management and with their derivatives acting through different mechanisms to achieve hypoglycemic effects [74-76]. Similarly, naphthalene inhibits Fatty acid binding protein 4 (FABP4), besides exerting peroxisome proliferator-activated receptor gamma (PPARγ) agonistic activity, all of which have been implicated in fasting blood glucose reduction [64,77]. The rats in Group G were fed with formulation 7, and exhibited lower FBG than in Group D rats.

Effect on Pancreatic Cell Function and Heart Disease Risk

Insulin resistance (IR) and pancreatic β-cell function have been linked with the development of T2DM. Homeostatic Model Assessment (HOMA) has been used to assess both the IR and pancreatic β-cell function because it reveals the quantity of functional insulin, the pancreas should produce to control the blood sugar level [78,79]. Decreased pancreatic β-cell function in an existing IR is an important determinant of T2DM incidence and advancement [80]. In this study, the HOMA IR and HOMA-β were calculated using the formula of Katsuki and colleagues, with glucose in mass unit mg/dl as follows [81]:

HOMA-IR = Glucose x Insulin% / 405
HOMA- β = 360 x Insulin% / Glucose -63

The values obtained (Table 4) were interpreted using the standard blood code (thebloodcode.com), while for HOMA- β, higher levels is assumed to be protective of the pancreatic cell function but lower values signify non-protection. The more significant the IR, the higher indication of the heart disease risk.

All the groups in this study, when compared to normal control, had higher HOMA-IR values (Table 4). This documented report was in tandem with some other works which reported that subjects with IR and T2DM, had higher HOMA-IR than controls [82,83]. The HOMA-IR values in this study were between 0.23 - 1.11, which were all within the normal limit of 0.5 - 1.9, meaning that the formulations and the antidiabetic drug used in the study, exerted a balance in the dynamics between the FBG and the responsive insulin, thereby limiting the development of IR. Groups D and F had the highest values of 1.06 and 1.11 respectively, which tended towards the upper limit of normal, depicting a reduced potency of formulation 4 (12.5%CY: 25%SB: 12.5%BGN: 50%RF) used for group F and the non-protective nature of non-intervention in the diabetic control (Table 4).

On the HOMA- β, the study showed that all the groups had high values with group C exhibiting the highest value, while group F and the diabetic control, had the least. High HOMA- β

is an indication of protection of pancreatic- β cells and hence against T2DM [84]. The documented reports from this study were not in tandem with the report by Sung and colleagues, since the HOMA-β in all the groups were far lower than the value of 32.83 obtained in the normal control (Table 4). Previous studies have reported that low HOMA-β levels were predictive of T2DM [85,86]. HOMA calculations is based on a computer-solved model that assumes certain relationship between basal plasma glucose and insulin concentration [86,87]. Using reports from the values of the HOMA-β in this study, it can be inferred that there was a reduction in the pancreatic β-cells with the administration of the STZ and the resultant hyperglycemia but the administration of the intervention formulations might have aided the regeneration of the beta cells which histological studies showed and which other reports had documented [88-90].

Conclusions

Flour blend formulations from cocoyam-soya bean-Bambara groundnut, when administered to SIDRs in various ratios exerted improvement in the pancreatic β-cell functions and limited the advancement of insulin resistance and development of T2DM in SIDRs, and these actions were comparable to the effect of metformin, anti-diabetic drug. Among the various blend formulations, formulation 4 (12.5%CY: 25%SB: 12.5%BGN: 50%RF) had the least potency, while formulation 3 (25%CY: 12.5%SB: 12.5%BGN: 50%RF) had the highest potency in HOMA-β. The implication of this study is that the consumption of cocoyam-soya bean- bamabara groundnut food mix can be considered beneficial to people at risk of developing T2DM and hence recommended as a nutritional management support.

Authors` Contributions:

HU =Topic design, Proposal writing, Literature search, draft manuscript
AE = Topic design, Statistical analysis, draft manuscript
FR = Study Analysis, Literature search
KO = Manuscript writing
FU = Data Entering and literature search
All authors read and approved the final manuscript

Competing Interest

There is no competing interest.

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