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Combination Effect of Formulated High Glycemic Index Diet with Glibenclamide on Fasting Blood Sugar, Lipid Profile and CYP2C9 in Rats

Abdullahi Amoto Suberu[1], Aminu Ibrahim[1], Abdulrahman Itopa Suleiman[2,3*], Zainab Dauda Sule[1], Ahmad Abdulrazaq Itopa[1], Hamza Magaji[4], Abdulfatah Adaviruku Lawal[5] and Ayuba Suleiman Okatahi[6]

Department of Biochemistry, Bayero University, Kano, Nigeria [1], Department of Science Laboratory Technology, Kogi State Polytechnic, PMB 1101, Lokoja, Nigeria [2], Directorate of Research and Innovation, Kogi State Polytechnic, PMB1101, Lokoja, Nigeria [3], Department of Biological Sciences, Federal University of Technology, Babura, Jigawa State, Nigeria [4], Department of Public Health, National Open University of Nigeria [5], Department of Microbiology, Bayero University, Kano, Nigeria [6].

Author for Correspondence*: abdullahiamotosuberu@gmail.com/ itopa2020@gmail.com/
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Abstract

Interaction exists between natural products due to pharmacokinetic and pharmacodynamic principles of drug-drug interactions. This research was designed to investigate the combination effect of a diet formulated from rice and sweet potato with glibenclamide on alloxan-induced diabetic Wister rats. The diet was shade-dried, grounded and pelletized into serving sizes of 10g, 15g and 20g. A nutrient composition study was evaluated and glycaemic composition (index and load) of the formulated diet were determined to be 80.09% and 64.57g/100g respectively. Fifty-five (55) rats were randomized into eleven (11) groups of five (5) members and used for the study. Two of the groups were used as Normal and Negative control. The remaining nine (9) served as the experimental groups were divided into three (3), with each having three (3) sub-groups that were placed on three (3) varying doses of the formulated diet, glibenclamide, and both. The fasting blood glucose (FBG) of all the rats were evaluated for four weeks. The lipid profile parameters were determined and Cytochrome P4502C9 was done with CYP2C9 ELISA kit. From combination effect study, FBG result, it was observed that the diet is antagonizing with the drug all through, except additive effect observed in week two, when a lower dose of drug and diet were administered. All three doses of drug and diet showed synergistic effect on LDL-Cholesterol. This can be attributed to the diet having high glycaemic index with low fat which can be avoided in the dietary management of Diabetes. Lower dose of drug and diet showed synergistic effect while high and moderate doses showed antagonistic effect on triglycerides. The combination index values for lower, moderate and high doses of glibenclamide with the formulated diet on the CYP2C9 concentrations are 1, indicating that the formulated diet has an antagonistic effect on glibenclamide.

Keywords: Pharmacodynamics, Pharmacokinetics, Diabetes mellitus, Glibenclamide.

Introduction

One of the common major problems faced in patient contact-experience is the level of interaction of natural products and drugs. These interactions between these entities are in line with pharmacokinetic and pharmacodynamic fundamentals seen in drug-drug interactions. Fruits are generally implicated to constitute compounds that inhibit the activities of drug-metabolizing enzymes (Molden and Spigset, 2007). A food-drug interaction arises due to chemical, physical interplay involving drug and a product taken as nutrient available in a plant-based supplements (Santos and Boullata, 2005; Genser, 2008). This interconnection could occur medically as a result of vulnerable challenges in health affecting the mechanism and distribution of the drug (Santos and Boullata, 2005). Failure of interplay may arise due to lack of absorption of causal agents at the site of activity between transporter or enzyme molecule (Fleisher *et al*., 1999). An explanation of the various basic processes in applicable organ systems is crucial to address issues related to medical preparations, dosage regimen and optimum pharmacotherapeutic strategies (Li *et al.,* 2002; Lentz, 2008; Parrott *et al.,* 2009).

Current research has shown that the expression of Organic Anion Transporting Polypeptide B3, OATP1B3 in the pancreas of humans facilitate influx of glibenclamide into the cell (Meyer Zu Schwabedissen *et al*., 2014). Hence, OATP1B3 is liable to genetic variation reducing the efficiency of sulfonylureas. Sulfonylureas acts on blood sugar levels by inhibiting ATP potassium channels of the pancreatic β-cells. Glibenclamide, glimepiride and glipizide are the commonly utilized sulfonylureas utilized in the management of Diabetes (Rang and Dale, 2012). Sulfonylureas are characterized by increased bioequivalence with their metabolism involving CYP2C9 and to some extent CYP3A4 (Holstein and Beil, 2009). Molecules that are plasma protein bound within 95-99% are renally evacuated. Only a fraction of the drug is eliminated by feces (Holstein and Beil, 2009; Tornio *et al.,* 2012).

Diabetes mellitus is a known metabolic impediment involving hyperglycaemia resulting from a defect in the secretion of insulin and its response to cells. The long-term hyperglycaemia is linked to organ dysfunctions and tissues (ADA, 2012; Paneni *et al.,* 2013). Diabetes related problems are the major factors contributing to blindness, kidney failure and damage to nerve cells. Diabetes mellitus is often referred to as the main disease of the human race implicated with several medical symptoms. The World Health Organization (WHO) in its report projected that the total population of people with diabetes all over the world twice the actual amount by the year 2025 in relation to the amount ranging from 150 million to 300 million (Coskun *et al.,* 2005). The recent epidemic of diabetes mellitus (DM) in Africa, in addition to abject poverty, indicates clearly the sudden need to combine few of the over-the-counter antidiabetic drugs with some food substances that are cheaper and more available to fight this growing health challenge (ADA, 2014; Craig *et al.,* 2009; Galtier, 2010).

Diet therapy in most cases is not a remedy in itself but actually a way to make medical treatment more efficient. Therefore, physicians and dieticians should take into consideration the type of interactions that exists between certain food substances and commonly used drugs in managing diabetes (Hajime *et al*., 2008). Rice for example is a major staple food among Africans and Asians others include wheat, maize and white potatoes (Orthoefer, 2005). Despite the several research that have confirmed the negative role played by white rice and other high glycaemic index diets in management of diabetes. Medicines have been utilized to treat and cure many health challenges. These drugs used should be specific, effective for all patients, not influenced by concomitant food, possess linear effect, devoid of toxicity in any dosage and involve only single dose to effect a permanent cure. Nevertheless, this type of ideal drug has not been found (Frankel, 2003). A drug interaction is a phenomenon where a substance influences the effectiveness of a drug. These may arise due to misuse or little information about the active components involved in the relevant substance (Ayo *et al.*, 2005). Bioavailability is a salient parameter in pharmacology which is explained to be clinical efficacy of most drugs (Schmidt and Dalhoff, 2002; Nekvindova and Anzenbacher, 2007).

Gliblenclamide also referred to as Glyburide (GLB) is an orally administered sulfonylurea used for the control of Type 2 diabetes mellitus with an active and hypoglycemic potential (Feldman, 1985). Glyburide is also commonly taken for the cure of gestational diabetes mellitus (Langer *et al.*, 2000; Moore, 2007; Hebert *et al.*, 2009). Studies have shown the extensive break down of GLB in the liver, discovery of CYP enzymes in the liver necessary for GLB metabolism will have a crucial setback for rational design of optimal dosing regimen and better explanation behind the potentials of drug-drug interactions.

Cytochrome P4502C9 is a metabolic enzyme known for its high polymorphism. It is also called mixed function oxidase. Its variants CYP2C9*3/*3 homozygote or CYP2C9*1/*3 heterozygote, found to have lower catalytic performance in contrast to the wild-type CYP2C9*1/*1 (Cavallari and Limdi, 2009). Research conducted by Kirchheriner and Colleagues in 2002 revealed that the clearance of GLB for CYP2C9*3/*3 subjects (n = 3) was around 40% compared to CYP2C9*1/*1

subjects (n = 4). Niemi *et al*. (2002) in his research pointed in the same manner that area under the plasma concentration-time curve (plasma AUC) of GLB in individuals heterozygous for the CYP2C9*3 allele (n = 2) was 280% of the values compared to CYP2C9*1/*1 subjects (n = 5). Several research works that have been carried out to confirm the effect of white rice consumption in management of hyperglycemia, none of them exploited the possible combination effect rice diet may have on glibenclamide when taken simultaneously, hence results the need for conducting this research. This research investigates the combination effect of a formulated high glycemic index diet with Glibenclamide on fasting blood sugar, lipid profile, and CYP2C9 in alloxan- induced diabetic Wistar rats.

Materials and methods

Study area

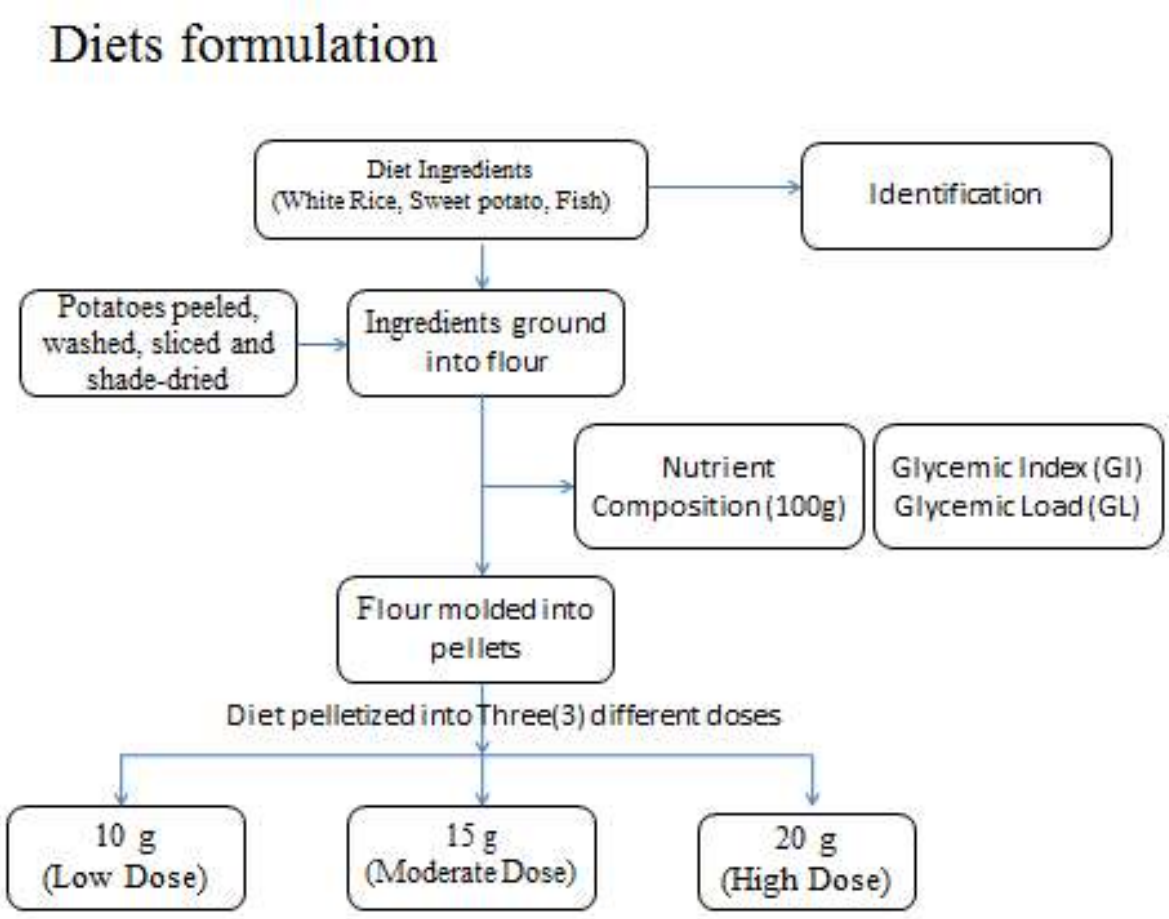
The study was carried out at the Department of Biochemistry, Faculty of Basic Medical Sciences, Bayero University, Kano, under the supervision of Dr Aminu Ibrahim.

Chemicals and Reagents

All the chemicals used for this research are of analytical grade.

Diet Formulation

Diet made from white rice, potato, and fish was formulated for the study. Rice, potatoes and fish used for the study were purchased from Kwanar Dawaki, Sharada and Yankura market in Kano State, Nigeria respectively. The ingredients for the diet were ground into smooth powder separately and then reconstituted into solid pastes with hot water under the supervision of a dietician to ensure consistency. The paste was modified into pellets for easy consumption of the animals and shade dried. The diet made was formulated using standard serving size with the supervision of a dietician. A four weeks diet plan was made according to the age and BMI of the rats. The animals were fed with three varying doses (lower, moderate, and high) of the diet according to their daily calorie requirement.



Determination of Protein

Kjeldahl's (1883) protocol was used to evaluate the protein content. Each of the samples 0.15g was weighed into the digestion tubes. Concentrated H_2SO_4 (2 mL) was added to each tube and swirled gently until the samples and the acid were evenly mixed. Kjeldahl catalyst (8 g) was added to each tube. The tubes were subjected to heating until clear solution was attained, boiled for 2 hours and allowed to cool. The content of each tube was transferred into 100 mL volumetric flasks and subjected to dilution to the mark. Then 2% boric acid (10 mL) and 5 drops of indicator were poured into a 250 mL Erlenmeyer flask. A portion of the digest (10 mL) was moved into the distillation flask and attached to the distillation apparatus. Sodium hydroxide (15 mL) was added to the distillation flask with the digest. Nitrogen was properly distilled into boric acid/mixed indicator receiver flask until the 150 mark was attained. The condenser tip was rinsed with distilled water and the distillate was subjected to titration using 0.025 N H_2SO4 until an endpoint of pink coloration was attained.

$$\% \text{ Nitrogen} = \frac{0.014\,(MeN/100\,g) \times T_V \times V_P \times N}{W_S V_A \times 100}$$

Where;
W_S = Weight of sample analyzed,
T_V = Titre value blank,
V_D = Total volume of digest,
N = Concentration of H_2SO_4,
V_A = Volume of digest distilled.

Total protein was estimated by taking the product of $\%N_2$ by a factor of 6.25.

Determination of Fat

The composition of fat content in the feed was evaluated following the protocol of AOAC (1980). Petroleum ether (300 mL) was transferred into a clean, dried round bottom flask attached to the Soxhlet extraction unit. Three grams (3 g) of the ground sample (W1) was weighed with care into a fat-free filter paper and then weighed again (W2). It was folded properly and placed in the extraction thimble which in turn was then fixed into the Soxhlet extraction unit with a retort stand used as forceps and cold-water circulation made fixed. The heating mantle was turned on and the temperature was regulated to 70 °C until the solvent was flowing at a steady rate. The extrication was carried out for 2 hours and 30 minutes before the heating mantle was turned off. The thimble was pulled apart and the filter paper bearing the sample was dried and placed in an oven to get a constant weight. It was then weighed again (W3);

$$\% \text{ crude fat} = \frac{W2 - W3}{W1} \times 100$$

Hence; W1 = weight of sample
W2 = weight of sample + filter paper (before extraction)
W3 = weight of sample + filter paper (after extraction)

Determination of Ash Content

Ash content was resolved adopting the protocol of AOAC (1980), the method is based on the reduction in weight which involves igniting the sample in a muffle furnace with a temperature of 600^0C causing organic matter to burn completely without reduction of ash content. The crucibles were oven dried, and desiccator was used to control the temperature of the crucibles and weighed as W1. About 5g of the sample was weighed. The crucibles with samples were weighed as W2 and introduced into furnace, set at 600^0C and then ignited in the furnace for about 8 hours. The crucibles with ash were taken out and cooled in a desiccator and weighed as W3. Percent (%) ash composition was estimated as follows:

$$\% \text{ ash} = \frac{\text{Weight of ash}}{\text{Weight of sample}} \times 100 = \frac{W3 - W1}{W2 - W1} \times 100$$

Where; W1 = weight of crucible
W2 = weight of crucible + sample
W3 = weight of crucible + ash residue

Determination of Moisture Content

This method involves taking the difference between the net weight before and after drying process. Moisture and dry matter were evaluated following the protocol by AOAC (1990). Five (5) grams of diet (W0) were homogeneously spread in a porcelain crucible of a known weight (W1). The set porcelain crucible and samples were heated in an ovum at 105^0C for 24 hours.

After cooling to the desiccators, the weight of the set was determined. The dry material content (WD) was determined in g/100g of diet using the following the formulae:

$$WD(\%) = \frac{W2 - W1}{W0} \times 100$$

Where: W0 = Sample weight taken
W1 = Weight of empty porcelain crucible
W2 = (crucible + Sample) weight
WD = Dry matter composition (%)
moisture content was evaluated in g/100g of diet calculated as;
Moisture content (%) = 100 - WD

Determination of Carbohydrate
The calculation of total carbohydrate contents in feeds was done according to the relationship given by FAO (1998).
100% Carbohydrate = 100% - (%Protein + %Fiber + %Fat + %Moisture + %Ash)

Estimation of Energy Value
Estimation of the energy value of the diet was calculated according to the method proposed by FAO (2002). The mathematical representation is:
Energy Value (Kcal/100g) = [(2.44 X Protein) + (8.37 X Fat) + (3.57 X Carbohydrate)]

Determination of Vitamin C
Principle
Titration protocol was adopted to estimate the ascorbic acid content using iodine solution. The ascorbic acid was oxidized to dehydroascorbic acid, while the iodine is reduced to iodide ions (AOAC, 2005).

Ascorbic acid + $I_2 \rightarrow 2I^-$ + Dehydroascorbic acid

Determination of Mineral Elements by Atomic Absorption spectrophotometer (AAS)
AAS is an analytical tool utilized in the quantitative estimation of compounds using the absorption of optical radiation by free atoms in gaseous states. The sample must be subjected to digestion before atomic absorption spectrometry (Koirtyohann, 1991). Two grams (2g) of the sample was added to dry ash in a clean crucible at 550°C in a muffle furnace. The ashes were solubilized in 5 ml of HNO_3/ HCL/H_20 (1:2:3) and heated gently on digestion burner till brown fumes disappeared. To the remnant in the crucible, 5 ml of de-ionized water was added and heated until a colorless solution was formed. This solution was then subjected to atomic absorption spectrophotometry (AAS).

Glycemic index and glycemic load determination
The Glycaemic Index (GI) of the formulated diet was investigated *in vivo*, in six male Wistar rats following the methods of GI testing in humans (Wolever *et al*., 1991). The rats were meal trained up to nine (9) days and were provided. The formulated diet and one glucose control were determined.

Meal Training
The rats were acclimated for one week *ad libitum* on standard chow diet (Vita feed). Following acclimation, rats were fed at 7am and 4pm every day. Initially, they were exposed to the test diet for one day, 7am - 4pm, with chow provided at 4pm until the following day. To commence the training, rats were subjected to individual cages for both meals and allowed to eat chow for two hours.

GI Testing
GI testing was carried out on the rats trained to independently eat within 15 minutes at the beginning of the dark phase. On test days, rats were placed independently in a neat cage without bedding. To obtain a drop of blood, the end of the rat's tails was cut with a scalpel blade. The blood droplet was tested using an Accu-Chek Performa glucometer.

Determination of serving size
The GI test was based on 50g of test food of available carbohydrate, defined as:
Total carbohydrate - dietary fibre
Hence, the quantity of each test food varies in accordance to the amount of carbohydrate present in that food. 50 g of carbohydrate present was evaluated from results of proximate composition of the test sample. The dry weight was evaluated with formula below:
Dry weight (DW) = 100-moisture content
Weight of carbohydrate, in 100g dry weight

$$\frac{\%CHO\ of\ test\ sample \times DW}{100}$$

Glycemic Index Calculation

Blood glucose curves were obtained from blood glucose values of animals at time 0, after 15, 30, 45-, 60-, 90- and 120-minutes intervals after consumption of the glucose (control) and test food. The Incremental Area Under the Curve (IAUC) was calculated for reference food (glucose) by the trapezoidal rule (Gibaldi and Perrier, 1982).

Glycemic Index (GI) for the diet was estimated by taking the ratio of Incremental Area Under 2 hours of blood glucose response for test food following the protocol of Jenkins *et al*. (1981); Wolever and Jenkins (1986) and Wolever *et al*. (1991) in line with FAO/WHO (1996) following the equation:

$$GI = \frac{\text{Incremental Area Under the Curve for test food}}{\text{Incremental Area Under the Curve for glucose}} \times 100$$

Glycemic Load Calculation

Glycaemic Load (GL) done using the protocol of Salmeron *et al*. (1997). Glycaemic load was estimated by evaluating the percentage carbohydrate content in a normal serving food and multiplied by its glycaemic index value illustrated mathematically as:

$$GL = \frac{\text{Net carbohydrate (g)} \times \text{GI}}{100}$$

Animal condition and acclimatization

A total of 55 Adult Wistar albino rats of relatively same age, size and weight were purchased from Biological Sciences department, Bayero University, Kano for this study. They were maintained under normal processes of temperature (28±2^{0}C) and relative humidity (46±6%) with 12 hours light-dark cycle and proper aeration for a period of two weeks prior to the experiments to acclimatize. The animals were subjected to commercial diet (Vital Feed Nig. Ltd.) and water. The animals were subjected to 12 hours fasting before the experiment. Permission for the use of animals and animal protocols was gotten from the Animal Ethics Committee of Bayero University, Kano, prior to experimentation.

Alloxan Preparation and *Induction of Diabetes*

Alloxan monohydrate is standard drug used for chemical induction of diabetes using a dose of 84 mg/kg for rat via intraperitoneally as reported in literatures (Workman *et al*., 2010; Maxwell *et al*., 2014). The dose of alloxan monohydrate used for experimental induction of diabetes intraperitoneal route in a rat weighing 100 g at a standard dose of 150 mg/kg can be resolved as follows;

$$\text{Worked dose for 100g rat} = \frac{\text{weight of animal (g)}}{1000\text{g}} \times$$

$$\text{Standard Dose (mg)} = \frac{100\text{g}}{1000\text{g}} \times 84\text{mg} = 8.4\text{mg}$$

For intraperitoneal route, volumes range between 2 ml/kg to 5 ml/kg in rats is encouraged. Using 2ml/kg volume selection, 8.4mg (0.0084g) of alloxan monohydrate was constituted in: $\frac{100\text{g}}{1000\text{g}} \times 2\text{ml} = 0.4\text{ml}$ of a vehicle (normal saline) tally with the volume required for 100g rat.

All rats, except the Negative Control Group were intraperitoneally injected with 84mg/kg body weight of the alloxan monohydrate prepared with normal saline. After 6 hours of alloxan injection, rats in their cages were then given 10% glucose solution for 24 hours in order to avoid alloxan-induced hypoglycaemia. The animals were subjected to overnight fasting and diabetes was validated through estimation of their fasting blood glucose level with the help of a single touch glucometer. Rats that have fasting blood glucose level higher than 7.0mmol/l (126mg/dl) using glucometer with blood sample from the tail vein were termed diabetic and included in the study (Kandur and Goyal, 2005).

Glibenclamide Preparation

Glibenclamide (5mg/kg) was a reference drug purchased from Pharmacy shop, Lamco Pharmacy, Kano, Nigeria. The required dose of glibenclamide (5mg per tablet) for a rat weighing 100 g at a standard dose 5mg/kg was calculated as follows:

Step 1: Calculation of dosage

$$\text{Worked dose for 100g rat} = \frac{\text{weight of animal (g)}}{1000\text{g}} \times$$

$$\text{Standard Dose (Mg)} = \frac{100\text{g}}{1000\text{g}} \times 5\text{mg} = 0.5\text{mg}$$

Step 2: Solubilization of glibenclamide in a suitable volume of vehicle for oral administration

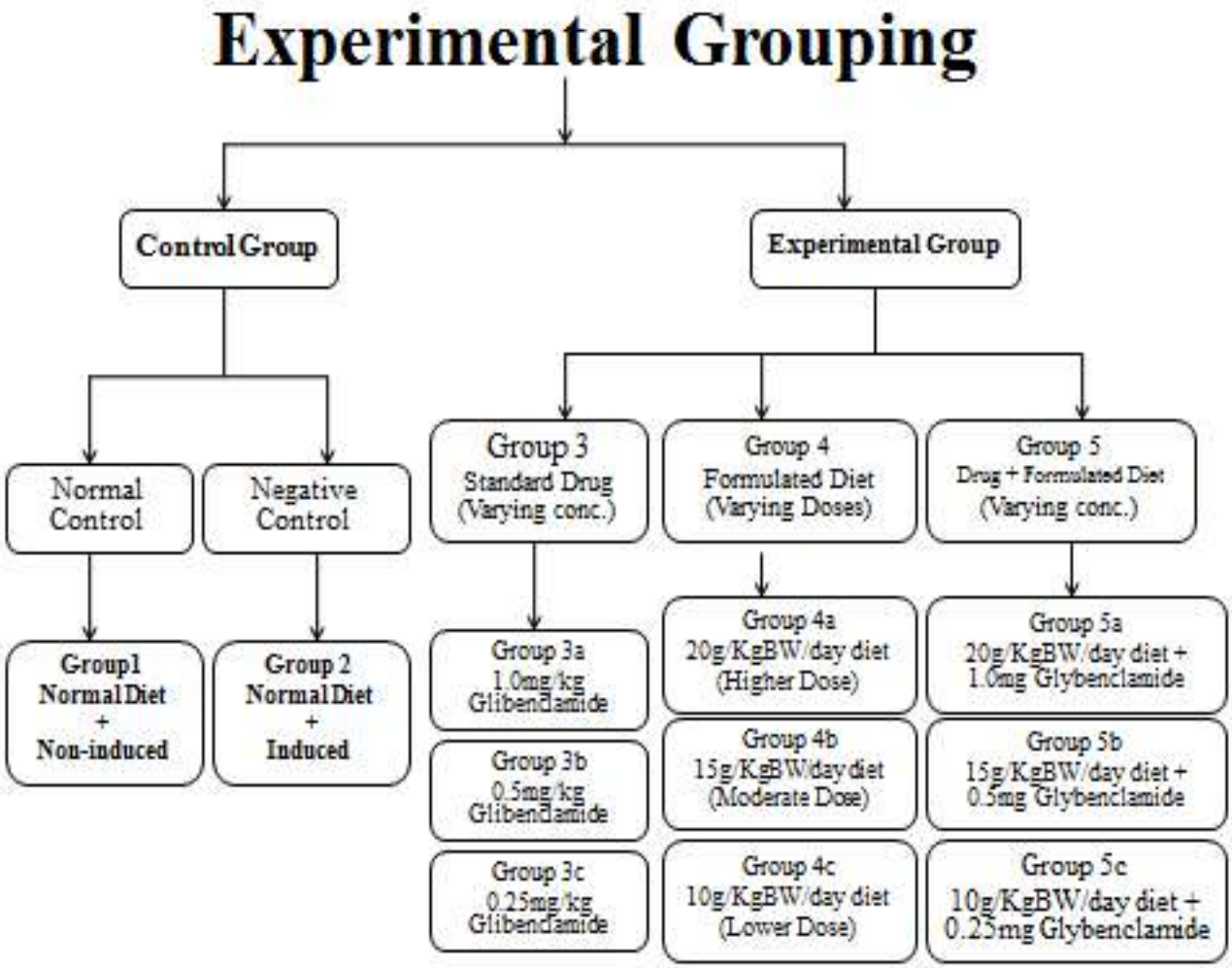
From the above calculation, 100 g rat requires 0.5mg of glibenclamide and this dosage (0.5 mg) should be constituted in not more than 10 ml of normal saline according to the OECD's guideline (OECD, 2000).

In summary, 10 g ≡ 0.5 mg ≡ 1.0 ml of normal saline. If 0.5 mg would be constituted in 1.0 ml of normal saline,
Then, one tablet of glibenclamide (5mg) would be constituted in:

$\frac{1.0ml}{0.5mg} \times 5mg = 10ml$ of normal saline.

That is $\frac{5mg}{10ml} = 2.5mg/ml$

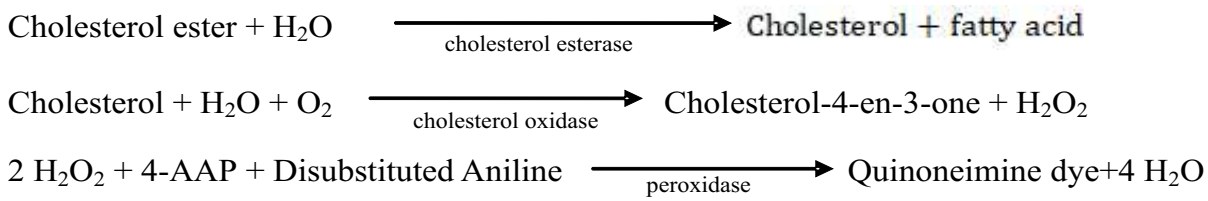
Animal Grouping and Treatment
The 55 rats were randomly grouped into eleven (9) groups, with each group comprising of five (5) members:
Group 1 Served as negative control, were not induced and were placed on only normal feeds (vital feeds).
Group2 Served as positive control, were induced but were placed on only normal feeds (vital feeds).
Group 3 Comprised of three sub-groups i.e 3a, 3b and 3c were placed on Glibenclamide (standard antidiabetic drug) in three (3) varying dosages of 1.0mg, 0.5mg and 0.25mg respectively.
Group 4 Comprised of three sub-groups i.e 4a, 4b and 4c were placed on only Diet in three (3) varying dosages 20g/KgBW/day, 15g/KgBW/day and 10g/KgBW/day respectively.
Group 5 Comprised of three sub-groups i.e 5a, 5b and 5c were placed on both Glibenclamide (standard antidiabetic drug) and the Diet in three (3) varying dosages of 20g/KgBW/day diet + 1.0mg drug, 15g/KgBW/day diet + 0.5mg drug, and 10g/KgBW/day diet + 0.25mg drug for sub-groups 5a, 5b, and 5c respectively.



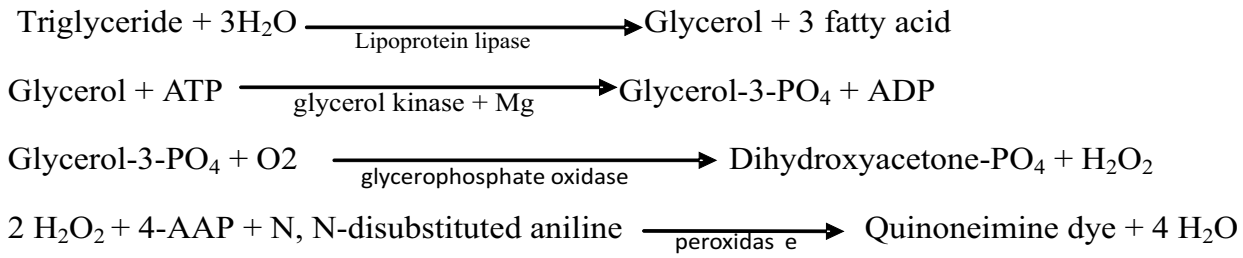
Determination of Fasting Blood Sugar (FBS)
Collection of blood was done by nipping the tail with a sharp razor blade. Blood sugar was estimated from a drop of blood so collected with a glucometer (ACCU-CHEK ACTIVE GUROCHE MANNHEIM GERMANY). Glucose level was estimated weekly throughout the time frame of the research.

Determination of lipid profile
Total Cholesterol, HDL Cholesterol, Triglycerides and LDL Cholesterol were measured with Cardio Check Professional Analyzer using PTS lipid panels test strips.

Principles of the test
Application of blood to a test strip triggers reaction which produce red color that is recorded through analyzer utilizing reflectance photometry. The amount of color produced varies directly to the concentration. The enzymatic reactions that occur are given below;



For Triglycerides



For LDL- Cholesterol
LDL-Cholesterol level was estimated using the mathematical equations proposed by Friedewald *et al*. (1972).

LDL-C = TC – (HDL-C + (TG/5))
Where: LDL-C = LDL-Cholesterol, TC = Total Cholesterol, HDL-C = HDL- Cholesterol, and TG = Triglyceride

Cytochrome P450 2C9 (CYP2C9) Assay
CYP2C9 Assay was carried out with microplate reader using CYP2C9 ELISA kit purchased from Melson Medical Corporation Limited, Shanghai China. The stop solutions alter the color from blue to yellow and color intensity was estimated spectrophotometrically at 450nm.

Sample Collection and Storage
All animals were sacrificed and whole blood samples were collected using EDTA samples containers. The samples were centrifuged at 1000xg for 15 minutes within 30 minutes of collection. Plasma was removed and stored in aliquot at -20^{0}C throughout prior to the assay to avoid repeated free/thaw cycles. Standard and test wells were set. Standard solution (50µl) was included in the standard well. Blank well was set aside (Sample and HRP-Conjugate reagent were not added to the Blank well, other each step operations were same). To the test sample wells, 40µl sample dilution was added, then 10µl of the testing sample was added (final dilution was 5-fold). Samples were added to Sample wells. The set up was gently mixed while close to the well wall was avoided as much as possible. The HRP-Conjugate (100µl) was added to all wells except Blank well. The set up was closed with closure plate membrane and incubated for 60 minutes at 37^{0}C.

Statistical Analysis
Statistical Analysis was done on the generated data using SPSS (Version 23) one-way repeated ANOVA. Data were expressed as mean ± standard deviation.

Results and Discussions

Results

Table 1 illustrates nutrient composition of formulated diet. The diet is rich in carbohydrates (above 80%), protein (above 10%), and some vital minerals like iron and magnesium of 44.7mg and 15.9mg respectively. There is a significant amount of fiber content (approximately 3%) in the diet. However, the formulated diet has a relatively low-fat content of approximately 1%.

Table 1: Nutrient composition of the Formulated Diet

Parameters	Values
Energy Value (Kcal/100g)	322.28 ± 10.50
Moisture (g/100g)	1.79 ± 0.20
Carbohydrates (g/100g)	80.52 ± 3.68
Protein (g/100g)	10.70 ± 1.13
Fat (g/100g)	1.08 ± 0.09
Fiber (g/100g)	2.80 ± 0.27
Ash (g/100g)	1.24 ± 0.25
Vitamin C (mg/100g)	3.77 ± 0.26
Magnesium (mg/100g)	15.90 ± 0.28
Sodium (mg/100g)	25.90 ± 1.60
Potassium (mg/100g)	183.50 ± 12.07
Zinc (mg/100g)	0.40 ± 0.03
Iron (mg/100g)	1.34 ± 0.15

Mean ± Standard deviation of the determined nutrients present in 100g of the formulated diet.

Figure 1 shows the plot of level of blood sugar for two sets of rats fed with standard glucose and the formulated diet at intervals of time for two (2) hours. The Area under the Curve (IAUC) for standard glucose and that for formulated diet were computed and employed in the estimation of the glycemic index (GI) and glycemic load (GL) of the formulated diet as 80.09% and 64.57g/100g respectively. The formulated diet is a high glycemic index diet (>70) according to diet categories by AICR 2008.

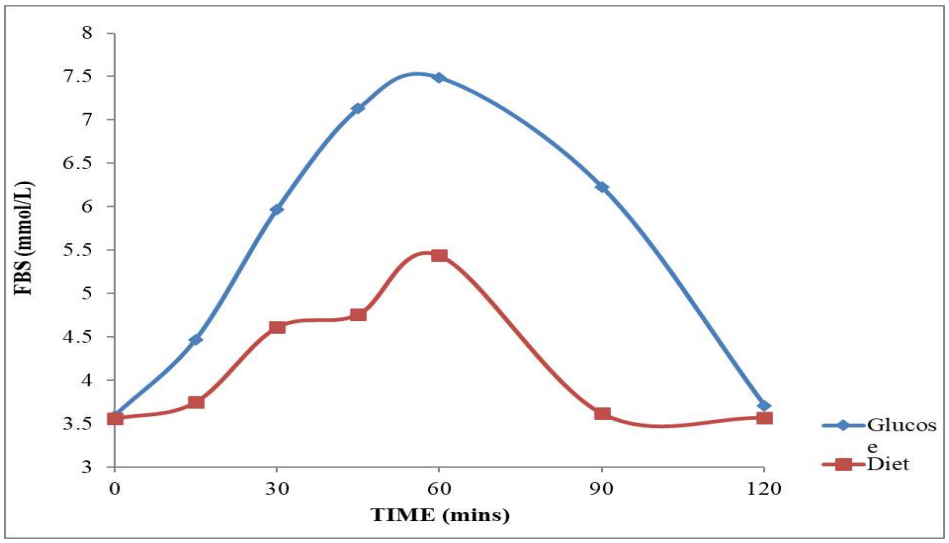


Figure 1: Graph of Blood Sugar level against time for rats fed with standard glucose and those fed with the formulated diet.

Table 2 shows the effect of the high glycemic index diet and glibenclamide on the fasting blood glucose with their combination index (CI) value. After induction prior to treatment, the fasting blood sugar level of all induced groups show significant increase in contrast to the normal control group (non-induced). In the first two weeks of treatment (i.e week one and week two), the significant difference between Group 1 (normal control) and the induced groups were maintained, but no statistically significant difference was recorded between the groups on treatments.

In the third week, the significance difference between Group 1; Normal control group (non-induced) and other groups that were observed in the previous weeks was maintained except for Group 5B (group placed on Diet 15g/Kg/day + Glibenclamide 0.5mg/Kg) and Group 5C (group placed on Diet 10g/Kg/day + Glibenclamide 0.25mg/Kg) which shows no significant difference.

In the last week of treatment (i.e week four), the significance difference between Group 1; Normal control group (non-induced) and other groups that were observed in the previous weeks was maintained except Group 5C (group placed on diet 10g/Kg/day + Glibenclamide 0.25mg/Kg) which shows no significant difference. There is also significant difference between the negative control group (i.e Group 2; Induced but neither on glibenclamide nor formulated diet) and Group 3A (Group placed on Glibenclamide 1.0 mg/Kg only), Group 3B (Group placed on Glibenclamide 0.5 mg/Kg only), Group 4B (group placed on diet 15g/Kg/day only), Group 4C (Group placed on diet 10g/Kg/day only), Group 5B (group placed on diet 15g/Kg/day + Glibenclamide 0.5mg/Kg), and Group 5C (group placed on diet 10g/Kg/day + Glibenclamide 0.25mg/Kg). There is a significant difference between Group 3A (Group placed on Glibenclamide 1.0 mg/Kg only) and Group 4A (group placed on diet 20g/Kg/day only). There is a significant difference between Group 3B (Group placed on Glibenclamide 1.0 mg/Kg only) and Group 4A (group placed on diet 20g/Kg/day only). There is a significant difference between Group 3C (Group placed on Glibenclamide 0.25 mg/Kg only) and Group 5C (group placed on diet 10g/Kg/day + Glibenclamide 0.25mg/Kg). There is a significant difference between Group 4A (group placed on diet 20g/Kg/day only) and Group 5B (group placed on diet 15g/Kg/day + Glibenclamide 0.5mg/Kg) and Group 5C (group placed on Diet 10g/Kg/day + Glibenclamide 0.25mg/Kg). There is a significant difference between Group 4B (group placed on diet 15g/Kg/day only) and Group 5C (group placed on diet 10g/Kg/day + Glibenclamide 0.25mg/Kg). There is a significant difference between Group 5A (group placed on Diet 20g/Kg/day + Glibenclamide 1.0mg/Kg) and Group 5C (group placed on diet 10g/Kg/day + Glibenclamide 0.25mg/Kg).

Table 2: Effect of High Glycemic Index Diet and Glibenclamide on the Fasting Blood Glucose (FBG) of Alloxan Induced Diabetic Rats with their Combination Index (CI) Values.

Group	Post-Induction	WEEK1	WEEK2	WEEK3	WEEK4
1	$3.73 \pm 0.49^{abcdefghij}$	$3.93 \pm 0.53^{abcdefghij}$	$4.03 \pm 0.47^{abcdefghij}$	4.18 ± 0.61^{abcdefgh}	4.39 ± 0.38 abcdefghi
2	15.49 ± 1.58^{a}	13.24 ± 2.22^{a}	13.18 ± 2.45^{a}	$12.58 \pm 2.30^{a,i}$	$9.01 \pm 0.83^{a,j,k,l,m,n,o}$
3A	$20.11 \pm 2.04^{b,k,l,m}$	17.37 ± 3.92^{b}	13.35 ± 2.15^{b}	10.46 ± 0.65^{b}	$6.39 \pm 0.50^{b,j,p}$
3B	16.48 ± 2.23^{c}	14.50 ± 1.74^{c}	11.93 ± 1.14^{c}	10.09 ± 1.11^{c}	$6.66 \pm 0.46^{c,k,q}$
3C	$13.14 \pm 4.39^{d,k}$	12.10 ± 3.79^{d}	10.86 ± 3.10^{d}	11.45 ± 4.52^{d}	$7.78 \pm 0.60^{d,r}$
4A	15.99 ± 1.00^{e}	15.71 ± 0.49^{e}	13.14 ± 1.78^{e}	10.89 ± 1.38^{e}	$8.49 \pm 0.63^{e,p,q,s,t}$

4B	12.89 ± 2.56^{fl}	12.50 ± 1.98^{f}	11.04 ± 1.63^{f}	9.52 ± 1.45^{f}	7.31 ± 0.62^{f,l,u}
4C	11.99 ± 1.26^{g,m}	11.31 ± 0.92^{g}	9.95 ± 0.70^{g}	8.93 ± 0.54^{g}	6.95 ± 0.84^{g,m}
5A	18.28 ± 2.66^{h}	14.07 ± 2.63^{h} **5.39**	11.72 ± 2.09^{h} **2.30**	9.43 ± 1.94^{h} **14.64**	7.57 ± 0.76^{h,v} **3.95**
5B	14.65 ± 2.61^{i}	12.53 ± 2.52^{i} **2.77**	9.99 ± 1.51^{i} **1.57**	8.00 ± 0.41 **6.57**	6.48 ± 0.44^{i,n,s} **2.23**
5C	17.64 ± 3.77^{j}	14.31 ± 3.67^{j} **2.28**	10.39 ± 1.63^{j} **0.87**	7.51 ± 0.83^{i} **32.11**	5.54 ± 0.66^{o,r,t,u,v} **5.04**

Key: 1=Normal Control, 2=Negative Control, 3A= Glibenclamide 1.0mg/Kg, 3B= Glibenclamide 0.5mg/Kg, 3C= Glibenclamide 0.25mg/Kg, 4A= Diet 20g/Kg/day, 4B= Diet 15g/Kg/day, 4C= Diet 10g/Kg/day, 5A= Diet 20g/Kg/day + Glibenclamide 1.0mg/Kg, 5B= Diet 15g/Kg/day + Glibenclamide 0.5mg/Kg, 5C= Diet 10g/Kg/day + Glibenclamide 0.25mg/Kg.

Values are means ± standard deviations; values bearing the same superscripts in the same column are significantly different ($p<0.05$). CI Value less than 1 presents synergistic potential, CI value equals 1 indicates additive effect, CI value greater 1 implies antagonistic activity.

Table 3 shows the effect of the high glycemic index diet and glibenclamide on the lipid profile parameters with their combination index (CI) value. There is a significant decrease in the total cholesterol level of Group 3A (Group placed on Glibenclamide 1.0 mg/Kg only), Group 3B (Group placed on Glibenclamide 0.5 mg/Kg only), Group 3C (Group placed on Glibenclamide 0.25 mg/Kg only), Group 4B (group placed on Diet 15g/Kg/day only), and Group 5C (group placed on Diet 10g/Kg/day + Glibenclamide 0.25mg/Kg) when compared with the negative control group (i.e Group 2; Induced but neither on glibenclamide nor formulated diet). No significant difference was recorded in the HDL-Cholesterol level of all groups. There is a significant decrease in the triglycerides level of Group 3B (Group placed on Glibenclamide 0.5 mg/Kg only), and Group 4B (group placed on Diet 15g/Kg/day only) in contrast with the negative control group (i.e Group 2; Induced but neither on glybenclamide nor formulated diet). There is a significant decrease in the level of LDL-Cholesterol of all groups compared to the negative control group (i.e Group 2; Induced but neither on glybenclamide nor formulated diet).

From the combination effect study, all three doses of drug and diet showed antagonistic effect on the total cholesterol (CI Value <1). For Triglycerides, Group 5A (group placed on Diet 20g/Kg/day + Glibenclamide 1.0mg/Kg) and Group 5B (group placed on Diet 15g/Kg/day + Glibenclamide 0.5mg/Kg) showed antagonistic effect on the total cholesterol (CI Value < 1) while Group 5C (group placed on Diet 10g/Kg/day + Glibenclamide 0.25mg/Kg) showed synergistic effect on the total cholesterol (CI Value < 1). For LDL- cholesterol, all three doses of drug and diet showed synergistic effect on the total cholesterol (CI Value < 1).

Table 3: Effect of High Glycemic Index Diet and Glibenclamide on the Lipid Profile Parameters of Alloxan Induced Diabetic Rats with their Combination Index (CI) Values.

Group	Treatments	Total Chol (mmol/L)	HDL-Chol (mmol/L)	Triglycerides (mmol/L)	LDL-Chol (mmol/L)
1	Normal Control	3.22 ± 0.28	1.93 ± 0.22	2.37 ± 0.67	0.81 ± 0.14 [h]
2	Negative Control	3.81 ± 0.26 [a,b,c,d,e]	1.34 ± 0.13	3.85 ± 0.72 [f,g]	1.74 ± 0.18 [h,I,j,k,l,m,n,o,p,q]
3A	Glibenclamide 1.0mg/Kg	2.96 ± 0.13 [a]	1.79 ± 0.21	2.13 ± 0.95	0.68 ± 0.11 [i]
3B	Glibenclamide 0.5mg/Kg	2.84 ± 0.22 [b]	1.33 ± 0.25	2.12 ± 0.54 [f]	1.09 ± 0.38 [j]
3C	Glibenclamide 0.25mg/Kg	3.00 ± 0.17 [c]	1.43 ± 0.38	2.61 ± 0.99	1.05 ± 0.20 [k]
4A	Diet 20g/Kg/day	3.34 ± 0.19	1.78 ± 0.36	2.88 ± 0.87	0.98 ± 0.12 [l]
4B	Diet 15g/Kg/day	3.03 ± 0.28 [d]	1.82 ± 0.35	1.55 ± 0.33 [g]	0.90 ± 0.18 [m]
4C	Diet 10g/Kg/day	3.23 ± 0.16	1.79 ± 0.28	2.82 ± 0.11	0.87 ± 0.18 [n]
5A	Diet 20g/Kg/day + Glibenclamide 1.0mg/Kg	3.02 ± 0.54 **5.74**	1.40 ± 0.26 **1.01**	2.94 ± 0.16 **13.39**	1.03 ± 0.33 [o] **0.74**
5B	Diet 15g/Kg/day + Glibenclamide 0.5mg/Kg	3.30 ± 0.44 **20.44**	1.84 ± 0.32 **1.20**	2.71 ± 0.34 **29.00**	0.98 ± 0.24 [p] **0.76**
5C	Diet 10g/Kg/day + Glibenclamide 0.25mg/Kg	2.83 ± 0.28 [e] **6.81**	1.38 ± 0.20 **0.98**	2.34 ± 0.51 **0.14**	0.98 ± 0.12 [q] **0.50**

Values are means ± standard deviations; values bearing the same superscripts in the same column are significantly different ($p<0.05$). CI Value less than 1 presents synergistic effect, CI value equals 1 indicates additive potential, CI value greater 1 presents antagonistic activity.

Table 4 shows the effect of the high glycemic index diet and glibenclamide on the concentration of CYP2C9 with their combination index (CI) value. There is a significant difference in the CYP2C9 level of Group 3C (Group placed on Glibenclamide 0.25 mg/Kg only), and Group 5C (group placed on Diet 10g/Kg/day + Glibenclamide 0.25mg/Kg) when compared with Group 1 (Normal control; non-induced group). There is also significant difference between the negative control group (i.e Group 2; Induced but neither on glibenclamide nor formulated diet) and Group 5C (group placed on Diet 10g/Kg/day + Glibenclamide 0.25mg/Kg). Group 3B (Group placed on Glibenclamide 0.5 mg/Kg only) shows significant difference with Group 3C (Group placed on Glibenclamide 0.25 mg/Kg only) and Group 5C (group placed on Diet 10g/Kg/day + Glibenclamide 0.25mg/Kg). From the combination effect study, all three doses of drug and diet showed antagonistic effect on CYP2C9 (CI Value <1).

Table 4: Effect of High Glycemic Index Diet and Glibenclamide on the Cytochrome P450 (CYP2C9) of Alloxan Induced Diabetic Rats with their Combination Index (CI) Values.

Group	Treatments	CYP2C9 (pg/dL)
1	Normal Control	$11.25 \pm 1.46^{a,b}$
2	Negative Control	11.53 ± 0.77^{c}
3A	Glibenclamide 1.0mg/Kg	7.65 ± 4.54
3B	Glibenclamide 0.5mg/Kg	$12.02 \pm 1.51^{d,e}$
3C	Glibenclamide 0.25mg/Kg	$6.45 \pm 0.97^{a,d}$
4A	Diet 20g/Kg/day	10.99 ± 1.65
4B	Diet 15g/Kg/day	9.14 ± 0.99
4C	Diet 10g/Kg/day	9.65 ± 1.47
5A	Diet 20g/Kg/day + Glibenclamide 1.0mg/Kg	10.99 ± 1.14
		50.58
5B	Diet 15g/Kg/day + Glibenclamide 0.5mg/Kg	11.12 ± 1.11
		29.837
5C	Diet 10g/Kg/day + Glibenclamide 0.25mg/Kg	$6.08 \pm 1.09^{b,c,e}$
		38.58

Values are means ± standard deviations; values bearing the same superscripts in the same column are significantly different ($p<0.05$). CI Value less than 1 indicates synergistic potential, CI value equal 1 indicates additive effect, CI value greater 1 present antagonistic activity.

Discussions

From Table 1, the formulated diet is rich in carbohydrate (80.52%), protein is over 10%, but low in fat content (1%). It has a high energy value of 322.28Kcal/100g. The high carbohydrate and energy value is as a result of the rice and potato, which are the major ingredients of the diet that constitute about 65% and 30% respectively by size of the formulated diet. The improved protein content of the diet however could be from the fish that was added as additive to spice the diet for easy feeding of the experimental animals which constitute about 5% of the diet by size. This can also be as a result of the high amount of the white potatoes present in the formulated diet according to the research conducted by Camire and his colleagues in 2009 where they observed that in several consumed potato foods, over half of the energy is provided by fat. In the absence of fat during preparation, the lipid composition of potatoes is reduced. Roughly one third of the total fat in white potatoes is made of SFAs, while on the contrary the other is essentially made of PUFAs. Also, the lipid composition of potatoes is less compared to the quantity in rice (0.2%) and pasta (0.9%). The protein content of potatoes is minute, around 1-1.5% of fresh weight in relation to the cultivar (Camire *et al*., 2009).

The formulated diet also shows a significant amount of some of mineral elements, for example; Magnesium (~16mg), Sodium (~26mg) and Potassium (~184mg). These minerals play important biochemical role which includes cofactors for enzymes involved in the breakdown of glucose and including important pathways or neurotransmitters for hormonal actions) in the management of diabetes mellitus (Tosiello, 1996; Candilish, 2000; Raju *et al.,* 2006; Pham *et al.,* 2007; Piero, *et al.,* 2015; Naga). The glycaemic index (GI) and glycemic load (GL) of the formulated diet is 80.09 % and 64.57g/100g respectively as computed using the incremental area under curve (IAUC) from the plot of blood sugar level against time (Figure 1). Therefore, the formulated diet having GI of 80.09% (>70%) is a high glycemic index diet in line with diet categories by AICR (2008). Based on GI, rice diet is grouped into three forms, namely low GI (55 or

less), medium GI (56 - 69), and high GI (70 or more). Furthermore, based on GL, the diets are classified into low GL (10 or less), medium GL (11 - 19), and high GL (20 or more). (Jenkins *et al*., 2002). The glycemic load value incorporates the quantity of rice in a serving order to better gauge the role of diet on postprandial glucose response (Wolever *et al*., 1991).

From Table 2; after induction, the fasting blood sugar level of all induced groups show significant increase compared to the normal control group (non-induced). This statistical difference between the normal control and the induced groups were maintained after the first and second week of treatment, but no statistically significant difference between the groups on treatment. In the third week, significant decrease was recorded between the negative control group (Group 2: Induced, but neither on glybenclamide nor formulated diet) and the groups on either glybenclamide, formulated diet, or both. This statistical difference was maintained in the last week of the experiment (week 4). The poor blood sugar level control observed in the early weeks of the treatment could be due to the high carbohydrate content of the diet. This is in line with the findings of a randomized controlled trial carried out by Foster *et al*. (2003), in research conducted in women where they revealed that carbohydrates like rice and barley exhibited deleterious effects on HbA1c.

Similarly works of Dolson in 2009, stated that rice eaters who are Type II diabetics will do better eating slowly digestible rice varieties compared to white rice. Brown rice, for instance, has a slow starch digestibility too and some starch never transforms into sugar at all till it gets to the large intestine intact (Dolson, 2009).

Research by Qi (2010) justified the substitution of white rice by brown rice or other whole grains was implicated with reduced risk of diabetes while findings by Qureshi, (2002) showed that stabilized rice bran immensely lowers the glucose and fat level in both Type I and Type II diabetics (Frei and Becker, 2004). The positive effect observed in the blood glucose level in the later weeks of this study can be as a result of the high protein content (above 10% by mass) of the formulated diet. This corresponds to a previous study carried out by Wallin and Colleagues in 2012, who revealed that consumption of fish rich in omega 3 fatty acids have significant metabolic effects in diabetics. Wallin *et al.* (2012) revealed from the research conducted on type 2 Diabetes mellitus patients that fish intake had encouraging effects on their glycaemia control, glucose tolerance and microalbuminuria. In Asian population involving Chinese and Japanese, excessive intake of white rice is linked with a significant rise in type II diabetes (Hu *et al*., 2012). Another study conducted in Japan revealed that increase consumption of white rice promotes the risk of type II diabetes in women (Nanri *et al*., 2010).

From table 3; there was significant decrease recorded in the total cholesterol level of the groups treated with glibenclamide in contrast with the untreated induced group (Negative control), but no significant difference with groups placed on formulated diet only, or those on glibenclamide combined with formulated diet. There is a significant decrease in the LDL-Cholesterol level of the groups placed on glybenclamide only, formulated diet only, or combined as compared with the untreated induced group (Negative control). From combination effect study, in the FBG result, it was seen that the diet has an inhibitory effect with the drug at weeks 1, 2, 3 and 4, but an additive effect was observed in week two, when a lower dose of the drug and diet were administered. The antagonistic effect can be as a result of the diet being high glycaemic index as such can lead to higher blood glucose levels, which is not recommended for diabetics. All three doses of drug and diet showed synergistic effect on LDL-Cholesterol. This can be attributed to the fact that though the diet is a high glycemic index diet, is also a low-fat diet, as such this food should be avoided or given in low quantity in the dietary management of type 2 DM. Lower dose of drug and diet showed synergistic effect (CI Value < 1) while high and moderate doses showed antagonistic effect on triglycerides (CI Value < 1).

From Table 4, the highest concentration of CYP2C9 (~12 pg/dL) was observed in Group 3B where 0.5mg/Kg (which is the normal dosage) of glibenclamide was administered, compared to Group 3A administered with higher dose of glibenclamide (1.0mg/Kg) and Group 3C

administered with lower dose of glibenclamide (0.25mg/Kg) with CYP2C9 concentrations of ~7.65 pg/dL and ~6.45pg/dL respectively. This conforms to previous findings that CYP2C9 plays prominent role in the metabolism of glibenclamide and that the normal dose of the drug exacts the highest activity in the induction of the CYP2C9 (Cavallari and Limdi, 2009; Niemi *et al*., 2002; Yin *et al.,* 2005). However, the concentration of CYP2C9 decreased from ~12pg/dL in Group 3B, which was administered with 0.5mg/Kg glibenclamide to ~11pg/dL in Group 5B where same 0.5mg/Kg glibenclamide was administered but combined with 15g/KgBW/Day of the formulated diet. This is an indication of a decreased inducing ability of the glibenclamide on CYP2C9. The combination index values for lower, moderate and high doses of glibenclamide with the formulated diet on the CYP2C9 concentrations are all greater than one (Table 4) which indicates that the formulated diet has an antagonistic effect on glibenclamide.

Conclusions

This research showed that the nutrient value of rice diet can be improved with vegetables like sweet potato. The formulated diet may have no ameliorating effect on blood sugar level of diabetic individual, however, when consumed at low quantity, show the potency to reduce the risk of cardiovascular complication associated with diabetes. This is as shown by the significant decrease observed in total cholesterol level and LDL- cholesterol. Secondly, combination effect study shows antagonistic effect on blood sugar level and CYP2C9.

Recommendations

The formulated diet being a low-fat diet can be recommended for individuals suffering from cardiovascular diseases, owing to the decreased in total cholesterol and LDL-cholesterol with observable increase in HDL-cholesterol. For further studies, the following issues are recommended: firstly, the work should be repeated with complete nutrient and anti-nutrient component determination of the formulated diet. Secondly, more research work should be carried out on possible interactions between glibenclamide and various food nutrients.

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