



Research Article

High Fructose Diet Induced Hyperglycemia and Hyperinsulinemia: Preventive effects of Cellgevity®

John C. Anionye^{1,*}, Rawlings O. Otasowie¹¹ Department of Medical Biochemistry, College of Medical Sciences, University of Benin, Benin-City, Nigeria

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*CORRESPONDENCE

Anionye, J. C.
chukudi.anionye@uniben.edu

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ABSTRACT

High fructose diets are known to adversely affect human health because they can cause hyperglycemia and hyperinsulinaemia that can lead to a metabolic disease like diabetes mellitus. This study was aimed at investigating the ability of the supplement, Cellgevity® in preventing the onset of hyperglycemia and hyperinsulinaemia. Twenty experimental male Wistar rats, each weighing about 200 g, were divided into four groups of five rats each. For 28 days, the control (group 1) was fed normal rat chow, while groups 2 to 4 were fed with 60% High Fructose Diet + 10% Fructose Water (HFD+FW). Groups 3 and 4 were given alongside Atorvastatin (4.1 mg/kg rat b.w), and Cellgevity® (188.1 mg/kg rat b.w) respectively. After an overnight fast following the experimental period, blood samples were collected and analyzed using the glucose oxidase method for fasting blood glucose, and the ELISA technique for insulin levels. The Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) index was then calculated. The HFD+FW group displayed significantly higher ($P<0.05$) levels of fasting blood glucose (108.60 ± 1.9 mg/dl), insulin (10.58 ± 0.40 μ U/ml), and HOMA-IR (2.83 ± 0.06) compared to the control. The co-administration of Cellgevity® significantly prevented ($P<0.05$) the rise in these parameters, as it resulted in reduced fasting blood glucose (43.00 ± 4.10 mg/dl), insulin (5.95 ± 0.38 μ U/ml), and HOMA-IR (0.62 ± 0.05). There were no statistically significant differences ($P>0.05$) between the values of these parameters in the control, Atorvastatin, and Cellgevity groups. This study revealed that supplementation with Cellgevity® has the potential of preventing high-fructose diet-induced hyperglycaemia and hyperinsulinaemia in Wistar rats.

Keywords: High-fructose die; Hyperglycaemia; Hyperinsulinaemia; Mmetabolic syndrome; Cellgevity

INTRODUCTION

The surge in fructose consumption in modern diets has raised concerns due to its association with metabolic disturbances leading to conditions like hyperglycaemia and hyperinsulinaemia. These disruptions in glucose and insulin homeostasis are linked to an increased risk of metabolic syndrome, which ultimately leads to diabetes, and cardiovascular diseases (Bray, 2010, Stanhope *et al.*, 2011).

Metabolic syndrome, characterized by a cluster of metabolic abnormalities including dyslipidemia, insulin resistance, and hypertension, poses significant health risks worldwide (Shin *et al.*, 2013). The detrimental effects of excessive fructose intake on metabolic health have been extensively studied, highlighting the need for interventions that can mitigate these adverse outcomes (Johnson *et al.*, 2007).

High fructose diets, commonly consumed as fructose-enriched beverages by humans, have been shown to induce hyperglycaemia, hyperinsulinaemia and reduced insulin sensitivity in animal models, mirroring the effects observed in human studies (Johnson *et al.*, 2007). This dietary pattern has emerged as a significant contributor to a state of

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increased oxidative stress that precipitate further hyperglycaemia and a dyslipidaemia that cause persistent low-grade inflammation and more oxidative stress (Johnson et al., 2007), which leads to the development of insulin resistance, a precursor to type 2 diabetes (Ogunlabi et al., 2021). Therefore, combating the oxidative stress that can be precipitated by a high fructose diet, seem a desirable thing to do as this can help prevent the adverse metabolic changes it causes.

Cellgevity®, a dietary supplement containing key precursors and cofactors for glutathione synthesis, and other extracts from plants with antioxidant and anti-inflammatory properties, has gained attention for its potential in addressing oxidative stress and the metabolic deregulations they foster (Ogunlabi et al., 2021). Glutathione, a pivotal antioxidant, plays a crucial role in cellular redox balance and oxidative stress mitigation (Jones, 2006). “The active compound in Cellgevity®, known as RiboCeine, primarily contains D-Ribose and L-Cysteine, which are important in the synthesis of glutathione. Additionally, Cellgevity® includes other components that attract scientific interest, such as vitamin C, selenium, alpha-lipoic acid, broccoli seed extract, curcumin, resveratrol, grape seed extract, quercetin, milk thistle seed extract, cordyceps, black pepper, and aloe leaf, which contain phytochemicals and substances that have anti-inflammatory, antioxidant, anticancer properties, just to mention but a few (Ogunlabi et al., 2021). The potential of Cellgevity® in preventing high fructose-induced metabolic abnormalities is therefore an important research area of interest.

This study aimed to explore the preventive effects of Cellgevity® against the deleterious effects induced by a high fructose diet which results in hyperglycaemia, hyperinsulinaemia and reduced insulin sensitivity. By elucidating the potential of Cellgevity® in counteracting these metabolic disruptions, this research hoped to contribute to the body of knowledge about preventive strategies against diet-induced metabolic imbalances.

MATERIALS AND METHODS

Chemical, drugs and kits

Cellgevity® produced by Max International Supplement Company and Atorvastatin produced by Roche Pharmaceutical Company, were obtained from a reputable pharmacy store. The glucose kit used in this research, was produced by Randox Lab. UK. It contains several components including a phosphate buffer (0.1 mol/l, pH 7.0), Phenol (11 mmol), and GOD-PAP reagent (comprising 4-aminophenazone (0.77 mmol/l), glucose oxidase (> 1.5 kU/l), Peroxidase (> 1.5 kU/l)). The standard included in this kit had a concentration of 5.49 mmol/l, equivalent to 99 mg/dl glucose. Similarly, the Insulin ELISA kit, was sourced from MyBioSource UK. It contained specific materials such as microwell's coated with Insulin Monoclonal Antibody, Insulin Standard solutions, Insulin Enzyme Conjugate, Assay Diluent, TMB (Tetramethylbenzidine) Substrate, Stop

Solution, and Wash Concentrate. This kit was also purchased through the manufacturer's representative in Nigeria.

Experimental animals

Ethical clearance was granted by the Research Ethics Committee (REC) of the College of Medical Sciences, University of Benin, with REC Approval No: CMS/REC/2023/485. Male Wistar rats (n=20) were obtained from the Anatomy Department, School of Basic Medical Sciences, University of Benin, Benin City, Nigeria. These rats underwent a two-week acclimatization period and were treated in accordance with international protocols on care of animals (Canadian Council on Animal Care, 1984) throughout the 28-day period of the research.

Experimental diets

Regarding the experimental diets, the study involved the administration of two distinct diets: a locally produced standard rat chow diet (pelleted grower's mash), as reproduced in table 1 (Anionye et al., 2018) and a 60% high-fructose diet designed to induce hyperglycaemia and hyperinsulinaemia (Abdelrahman et al., 2018). The 60% high fructose diet was formulated by adding white crystalline powdered D (-) Fructose, to appropriate quantity of the locally produced standard growers mash and both of them mixed together and pelleted, in such a way that the resulting diet was composed of 60% fructose and 40% growers mash as shown in table 2. Additionally, this dietary regimen was supported by providing 10% fructose in the drinking water (Lírio et al., 2016).

Sampling techniques

The subjects (breastfeeding mothers plus infants and non-breastfeeding mothers plus infants) were carefully chosen using systematic sampling techniques with a sampling interval of 5. The first subject was carefully chosen by a simple random sampling method. Successive subjects were carefully chosen at a regular interval of the 5th subjects until the required sample size was achieved. Seventy-five subjects were selected from each of the four health centres. All subjects were given a unique code to be recognized during study period.

Eligibility criteria and data collection

Consented participants in this study were verbally asked about their breastfeeding status which was used to determine the breastfeeding mothers. Participants were verbally asked if there had taken any anthelmintic drugs and those that responded that they had any form of anthelmintic therapy within the past twenty-one days were excluded from the research.

Table 1: Composition of the Locally Produced Standard Rat Chow (g/1000g)

Ingredients	Rat chow Normal diet (g)
Maize	280.0
Wheat Offal	280.0
Palm Kernel Cake	208.0
Soyabean Meal	48.0
Groundnut Cake	100.0
Fish Meal (65%)	12.0
Lysine	1.6
Bone Meal	12.0
Limestone	52.0
Methionine	0.8
Grower Premix	2.4
Salt	3.2
Total	1000.0

Table 2: Composition of the 60% High Fructose Diet (g/1000g)

Ingredients	High-Fructose Diet (g)
Rat Chow (Growers Mash, as in Table 1)	400.0
Pure white crystalline powdered Fructose	600.0
Total	1000.0

Experimental design

Twenty male *Wistar* rats, ranging in weight from 180 g to 220 g were divided randomly into 4 groups of 5 rats each:

Group 1: Received the standard pelleted growers mash diet along with clean tap water (normal control).

Group 2: Administered the HFD + FW

Group 3: Fed with the HFD + FW and Atorvastatin (4.1 mg/kg-b.w).

Group 4: Given the HFD + FW and Cellgevity® (26.15 mg/kg b.w)

For a duration of 4 weeks.

Dosage regimen

Dosage calculations for Cellgevity® and Atorvastatin were determined based on established human doses and then adjusted according to the weight of the rats. The aim of these dosage calculations was to ensure equivalence to the effective human dose.

For cellgevity®: 4 cellgevity capsules containing a powdered substance weighing 1.83 g are usually consumed by a 60 kg man, this corresponds to a human equivalent dose of 30.5 mg/kg. This translates to a rat equivalent dose of 188.1 mg/kg body weight (b.w) of rats (Reagan-Shaw *et al.*, 2008)

For atorvastatin: A 60 kg man usually takes the equivalent of 40 mg of atorvastatin in tablet form (EM DEX, 2007). This translates to a rat equivalent dose of 188.1 mg/kg b.w of rats. (Reagan-Shaw *et al.*, 2008).

The feeding protocol

The feeding procedure included allowing the rats unrestricted access to food and water, with careful monitoring of their daily consumption over the four-week research duration. The Cellgevity® and Atorvastatin were first dissolved in distilled water and an oro-gastric gavage used in orally administering them to the rats. The rats were maintained on a 12-hour light-

dark cycle, and the cages housing them were routinely cleaned and disinfected to ensure a clean environment.

Observation and toxicity evaluation

Regular observations were carried out to assess any signs of toxicity, physiological changes, or mortality among the animals. The animals were observed for toxic symptoms such as weakness or aggressiveness, food refusal, loss of weight, diarrhoea, discharge from the eyes and ears, noisy breathing and other physiological changes including mortality, (Fielding and Metherson, 1991; Vijoyalakshmi *et al.*, 2000).

Clinical signs that were assessed before dosing, immediately and 4hrs after dosing, include level of sedation, restlessness, changes in nature of stool, urine and eye colour, excretion of worms, diarrhoea, haematuria, uncoordinated muscle movements, etc. (Fielding and Metherson, 1991; Vijoyalakshmi *et al.*, 2000).

Blood sample collection and assessment

At the end of the experimental period of 28 days, the animals were fasted overnight and blood samples were collected on the morning of the 29th day. The animals were first anaesthetized before the blood was collected via the inferior vena cava and cardiac puncture. Fluoride oxalate bottle was used in collecting the blood for fasting blood glucose evaluation, while a plain bottle was used to collect the blood for the estimation of the insulin level (Aniagu, *et al.*, 2005).

Assessment of Fasting Blood Glucose (FBG): The Randox glucose kit was employed, utilizing the glucose oxidase method developed by Barham and Trinder (1972). This involved preparing standard and sample solutions, treating them with Randox Glucose Reagent, incubating, and measuring absorbance at 500 nm. Glucose concentration was determined using absorbance ratios and known standard concentrations.

Evaluation of Insulin Levels: The ELISA technique as described by Engvall and Perlman, (1971) was utilized. A solid-phase two-site enzyme immunoassay was conducted, including incubation, washing, substrate reaction, and a colorimetric endpoint measurement. Insulin level was derived from a standard calibration curve.

Assessment of Insulin Resistance and Sensitivity: Measurement of Insulin Sensitivity: The Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) was calculated using fasting blood glucose and insulin levels (Matthews *et al.*, 1985). $HOMA-IR = (Fasting\ Glucose\ (mg/dL) \times Fasting\ Insulin\ (\mu U/mL)) / 405$. Usually in humans a HOMA-IR < 2.5: Indicates normal insulin sensitivity. HOMA-IR between 2.5 and 3.8: Suggests borderline insulin resistance. HOMA-IR > 3.8: Indicates a probability of insulin resistance.

Statistical analysis

Statistical analysis of the results was done using the one-way ANOVA followed by Tukey's test at a 95% confidence level using the SPSS-20 software. Results with $p < 0.05$ were considered significant.

RESULTS

As shown in tables 3, 4, and 5, the HFD + FW induced a significant increase ($p < 0.05$) in fasting blood glucose level, Insulin level and the HOMA-IR index in the “high fructose fed untreated” group, compared to the normal feed fed group of rats (Group 1). Atorvastatin and Cellgevity, significantly prevented ($p < 0.05$) the increase in fasting blood glucose level, insulin level and the HOMA-IR index in the rats.

Table 3: Fasting Blood Glucose Levels of the Rats Fed a High Fructose Diet

Groups	Fasting Blood Glucose (mg/dl)
Group 1 (Control)	53.40±1.54 ^a
Group 2 (HFD + FW)	108.60±1.9 ^b
Group 3(HFD+FW+ Atorvastatin)	54.00±1.90 ^a
Group 4 (HFD + FW + Cellgevity)	43.00±4.10 ^a

The research results are expressed as mean ± SEM (= standard error of the mean), Means in the same column with different superscript alphabets, differ significantly from each other at 95% level of significance ($p < 0.05$).

HFD + FW: 60% High fructose diet + 10% fructose water, HOMA-IR: Homeostatic Model Assessment of Insulin Resistance

Table 4: Insulin Levels of the Rats Fed a High Fructose Diet

Groups	INSULIN(μU/ml)
Group 1 (Control)	5.70±0.36 ^a
Group 2 (HFD + FW)	10.58±0.40 ^b
Group 3 (HFD + FW + Atorvastatin)	5.40±0.11 ^a
Group 4 (HFD + FW + Cellgevity)	5.95±0.38 ^a

The results are expressed as mean ± SEM. Means in the same column with different superscript alphabets, differ significantly from each other at 95% level of significance ($p < 0.05$).

Table 5: HOMA-IR Index in the Rats Fed a High Fructose Diet.

Groups	HOMA-IR
Group 1 (Control)	0.75±0.05 ^a
Group 2 (HFD + FW)	2.83±0.06 ^b
Group 3 (HFD + FW + Atorvastatin)	0.72±0.02 ^a
Group 4 (HFD + FW + Cellgevity)	0.62±0.05 ^a

The results are expressed as mean ± SEM. Means in the same column with different superscript alphabets, differ significantly from each other at 95% level of significance ($p < 0.05$).

DISCUSSION

The observed outcomes of this study, demonstrated a significant increase in fasting blood glucose (FBG), insulin levels, and Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) in rats fed with a 60% high-fructose diet and 10% fructose water (Group 2). These elevated levels

in the high-fructose diet fed group, confirmed the efficacy of the diet of this study, in inducing metabolic perturbations similar to human hyperglycaemia and hyperinsulinaemia, consistent with previous studies (Basciano, 2005; Le and Tappy 2006; Johnson, 2009; Rippe, 2013).

Atorvastatin, a known drug used to mitigate dyslipidemia associated with high fructose intake, showed efficacy in preventing the rise in FBG, insulin, and HOMA-IR levels. This aligns with previous research highlighting the protective effects of Atorvastatin against metabolic abnormalities induced by high fructose diets (Stanhope, 2009; Sathyapalan, 2013). Both Cellgevity and Atorvastatin exhibited similar efficacy in their ability to prevent the deleterious effect of a high fructose diet, as there was no significant difference ($P > 0.05$) in the values of the parameters obtained for their respective groups. Atorvastatin was used as the reference drug of this study because apart from its known anti-dyslipidaemic effect, previous studies have shown that it has the ancillary effect of reducing oxidative stress associated with hyperglycaemia and dyslipidaemia, which are characteristic effects of a high fructose diet (Tziomalos, 2011; Costa, 2016).

The introduction of Cellgevity® alongside the high fructose diet resulted in a significant prevention of an increase in FBG, insulin, and HOMA-IR levels (Group 4), effectively countering the adverse effects induced by the high-fructose diet. This outcome suggests the potential of Cellgevity in ameliorating hyperglycaemia and hyperinsulinaemia associated with excessive fructose consumption and it aligns with earlier studies which suggested that Cellgevity® may be protective against damages that can lead to hyperglycaemia (Adegbesan, *et al.*, 2021).

Several mechanisms could underlie the observed effects of Cellgevity®. Given its composition rich in antioxidants like glutathione precursors and other redox-active ingredients (Buettner, 1993; Ballatori *et al.*, 2009; Ogunlabi *et al.*, 2021; Adegbesan, *et al.*, 2021), Cellgevity® might have modulated oxidative stress, thereby enhancing insulin sensitivity and glucose metabolism. Glutathione, a pivotal cellular antioxidant, has been associated with improved insulin sensitivity and reduced oxidative stress (Richie, *et al.*, 1994; El-Demerdash, 2004; Gao *et al.*, 2008; Kleinbongard *et al.*, 2010; Adegbesan, *et al.*, 2021), so the administration of Cellgevity® rich in precursors of glutathione and phytochemicals, vitamins and other products known to have antioxidant and anti-inflammatory properties and other protective effects, might have contributed to maintaining redox balance and protecting against other deleterious effects of a high fructose diet on the rats organs and tissues, consequently mitigating or preventing the occurrence of the observed metabolic disruptions, seen in rats not given Cellgevity®, but fed only the high fructose diet.

The current findings, indicating the efficacy of Cellgevity® in preventing the onset of hyperglycemia and hyperinsulinaemia induced by a high fructose diet, open new avenues for potential adjunct therapies or preventive measures against metabolic disturbances. However, further

investigations are needed to elucidate the precise molecular mechanisms and long-term effects of Cellgevity supplementation in managing metabolic disorders associated with high fructose consumption.

CONCLUSION

This study underscores the potential of Cellgevity® as a promising therapeutic agent in preventing hyperglycemia and hyperinsulinaemia induced by a high fructose diet. These findings contribute to the growing body of evidence suggesting the utility of antioxidants in mitigating metabolic abnormalities and highlight avenues for further exploration in the realm management of metabolic disorders.

Institutional review board

The study was conducted according to the guidelines of the international protocols on care of animals promoted by the Canadian Council on Animal Care, (1984), and was approved and given ethical clearance by the Research Ethics Committee (REC) of the College of Medical Sciences, University of Benin. The REC Approval Number being: CMS/REC/2023/485.

Data availability

The data supporting reported results of this research will be freely made available to any interested person by a request to the corresponding author via email.

AUTHORS' CONTRIBUTIONS

Conceptualization, JCA; methodology, JCA.; validation, JCA.; formal analysis, JCA and ROO.; investigation, JCA and ROO.; resources, JCA and ROO.; data curation, JCA and ROO.; writing — original draft preparation, JCA and ROO.; writing—review and editing, JCA.; supervision, JCA.; project administration, JCA and ROO.; funding acquisition, JCA and ROO. All authors have read and agreed to the published version of the manuscript.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest

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