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Yoyo Cleanser Bitters and Prevention of High Fructose Diet-Induced Hyperglycemia and Hyperinsulinemia in Wistar Rats

*Anionye J. C., Otasowie R. O. and Enemuwe V. C.

ABSTRACT

Background: The harmful effects of high fructose diets (HFD) on metabolic health, which includes hyperglycemia and hyperinsulinaemia, are well-documented. This study evaluates Yoyo Cleanser Bitters' efficacy in mitigating these effects induced in an animal model, by a high-fructose diet

Materials and Methods: 20 Male Wistar rats weighing between 180-220g were divided into four groups of five rats each. They were the control (normal diet), 60% High Fructose Diet (HFD) + 10% Fructose Water (FW), HFD+FW + Atorvastatin [3.52 mg/kg body weight (kg-b.w)], and HFD+FW + Yoyo cleanser bitters (3.52 ml/kg-b.w) groups. Fructose induces its deleterious effects by inducing dyslipidaemia, hence Atorvastatin was used as the standard preventive drug. After a 28-day experimental period, the rats were sacrificed and blood samples collected for fasting blood glucose (FBG) and insulin level analysis, using the glucose oxidase method, and the Enzyme linked immunosorbent assay (ELISA) technique, respectively. The Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) index was then calculated. The results were analyzed using the Statistical Package for Social Sciences (SPSS)-20 software for one-way ANOVA and Tukey's tests.

Results: The HFD+FW group showed significantly higher ($P<0.05$) levels of FBG (108.60±1.9 mg/dl), insulin (10.58±0.40 µU/ml), and HOMA-IR (2.83±0.06) compared with these same parameters in the control group. Yoyo cleanser bitters prevented significantly ($P<0.05$), this rise in FBG (51.40±4.34 mg/dl), insulin (5.61±0.20 µU/ml), and HOMA-IR (0.71±0.07). No significant differences ($P>0.05$) were observed between the Control, Atorvastatin, and Yoyo cleanser bitters groups.

Conclusion: Yoyo cleanser bitters demonstrated promise in preventing high-fructose diet-induced hyperglycemia and hyperinsulinaemia in Wistar rats, suggesting its potential role in preventing HFD-induced metabolic disorders.

Keywords: High fructose diet, Yoyo cleanser bitters, blood sugar, insulin levels, HOMA-IR.

INTRODUCTION

Previous research underscores the adverse impact of excessive fructose intake on metabolic health. Studies have demonstrated that high fructose consumption ultimately contributes to hyperglycemia by stimulating gluconeogenesis and impairing insulin sensitivity (1, 2). It does this after a prolonged high fructose consumption, by causing an increase in free fatty acid and a subsequent dyslipidaemia that stimulates gluconeogenesis along with hyperglycaemia, following the precipitation of an insulin resistance, characterized by reduced cellular response to insulin (3). These disturbances contribute to the onset of metabolic syndrome, a cluster of conditions predisposing individuals to cardiovascular ailments and type 2 diabetes (4).

Herbal remedies have been a subject of scientific exploration for their potential therapeutic benefits. Herbal formulations renowned for their diverse phytochemical composition, have shown promise in exerting anti-hyperglycaemic, anti-dyslipidaemic, anti-inflammatory and antioxidant effects (5, 6). Yoyo cleanser bitters stands out as one of the most widely used herbal bitters in Nigeria, gaining popularity since its introduction in 2003 by Abllat Nigeria Company Limited, an indigenous healthcare product supplier (6, 7). This herbal oral preparation has found extensive use across various regions of Nigeria, earning considerable acceptance among the general public. Yoyo Cleanser Bitters is composed of five herbal constituents, which includes *Aloe vera* (True aloe, Lily of the forest), *Acinos Arvensis* (Basil thyme), *Citrus aurantifolia* (Bitter orange), *Chenopodium murale* (Nettleleaf goosefoot), *and Cinamomum aromaticum* (Cassia) (6,7). Additionally, it also contains water-soluble vitamins (B1, B2, B3, B6, and B12) and minerals (copper, zinc, iron) which enhances the medicinal effects of the herbal mixture (6, 7). NAFDAC has declared Yoyo cleanser bitters safe for human consumption and preliminary toxicity studies also indicate that the recommended dose of 3.52 ml/kg body weight used in this study was effective and not toxic to living systems (6, 7).

* Correspondence: chukudi.anionye@uniben.edu
Department of Medical Biochemistry, University of Benin, Benin City, Edo State, Nigeria.
Full list of author information is available at the end of the article

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An antihyperlipidaemic drug (Atorvastatin) was chosen as the reference drug for this study, instead of an antidiabetic drug, because the study was a protective study in the context of inducing a metabolic syndrome involving an agent (fructose) whose aetiopathogenesis involves a lipid pathway (4). Atorvastatin was chosen, because it has been established that the pathogenesis of the anomalies of this study (hyperglycemia and hyperinsulinaemia) caused by a high fructose diet is majorly the direct consequence of the dyslipidaemia (increased in blood free fatty acids, hypercholesterolaemia and hypertriglyceridaemia), which the high fructose diet causes in the first place (4). A study done along with this study (result not shown) established dyslipidaemia from feeding the Wistar rats with the fructose diet.

However, while some studies have explored the potential of herbal interventions in addressing metabolic disorders, there remains a gap in understanding their specific impact on the hyperglycemia and insulin resistance induced by high fructose diets. Investigating the effects of Yoyo cleanser bitters in this context could offer valuable insights into its potential as an adjunctive therapy in mitigating the adverse effects associated with high fructose intake.

This study sought to contribute to the understanding of Yoyo cleanser bitters' potential in modulating glucose and insulin levels in rats consuming a high-fructose diet. By investigating the impact of Yoyo cleanser bitters on these metabolic parameters, this research aims to elucidate its protective or ameliorative effects against fructose-induced hyperglycemia and insulin deregulation, paving the way for potential therapeutic applications.

MATERIALS AND METHODS

Ethical Approval

Ethical approval for the study was obtained from the Research Ethics Committee (REC) of the College of Medical Sciences, University of Benin, with approval Number: CMS/REC/2023/485.

Materials and Reagents

Yoyo cleanser bitters by Abllat Nigeria Company Limited and Atorvastatin by Teva UK, were purchased from Thelver pharmacy store, opposite the University of Benin Teaching Hospital (UBTH), Ugbowo Lagos Road, Benin City, Edo State, Nigeria. The pure white crystalline powdered D (-) Fructose by Loba Chemie PVT Limited, India, was purchased from a reagent store, Emytex Biomedicals, opposite UBTH, Benin City, Edo State. The glucose kit utilized for the experiments was from Randox Lab UK, which contained various reagents including phosphate buffer (0.1mol/l, pH 7.0), Phenol (11mmol), and GOD-PAP reagent (4-aminophenazone (0.77mmol/l), Glucose oxidase (> 1.5kU/l), Peroxidase (> 1.5kU/l)). The CAL standard included in the glucose kit had a concentration of 5.49mmol/l, equivalent to 99mg/dl of glucose. These kits were purchased through the manufacturer's representative in Nigeria. Additionally, the Insulin ELISA kit, acquired from MyBioSource UK, encompassed materials like microwells 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 Diets

The experimental procedure involved the administration of a basal diet, comprising standard pelleted grower's mash (Table 1) and a high-fructose diet (HFD) engineered to induce hyperglycemia and hyperinsulinaemia (Table 2). The high-fructose diet which is also known to be a metabolic syndrome-inducing diet was formulated by supplementing a proportional quantity of the basal diet with white crystalline powdered D (-) Fructose, resulting in a diet with a 60% fructose content (9). This diet was supported by allowing the rats to drink *ad libitum*, 10% fructose water (FW) (10). The ingredients of the basal diet was based on of the standard pelleted growers mash of Jerrison Agro Allied Services, Benin City, Nigeria (11).

Table 1: Composition of the basal diet (g/1000g)

Ingredients	Basal diet (g)
Maize	280
Wheat Offal	280
Palm Kernel Cake	208
Soyabean Meal	48
Groundnut Cake	100
Fish Meal (65%)	12
Lysine	1.6
Bone Meal	12
Limestone	52
Methionine	0.8
Grower Premix	2.4
Salt	3.2
Total	1000

Table 2: Composition of the 60% high fructose diet (g/1000g)

Ingredients	**High-Fructose Diet (g)**
Basal diet in Table 1	400
Pure white crystalline powdered Fructose	600
Total	**1000**

Experimental Animals

Male Wistar rats (n=20) weighing between 180g to 220g were sourced from the Anatomy Department, School of Basic Medical Sciences, University of Benin, Benin City, Nigeria.

These rats were acclimatized for two weeks, adhering to international guidelines (8).

Experimental Design

The animals were randomly divided into four groups, each serving a specific purpose:

- Group 1: Received a basal diet with clean tap water (negative control group)
- Group 2: Given a 60% fructose diet (HFD) along with 10% fructose-water (FW) *ad libitum* (positive control group)
- Group 3: Given a 60% fructose diet, 10% fructose-water *ad libitum* and Atorvastatin [3.52 mg/kg-body weight (kg-b.w)]
- Group 4: Given a 60% fructose diet, 10% fructose-water *ad libitum* and Yoyo cleanser bitters (3.52 ml/kg-b.w)

Dosage Regimen

Dosage determinations for Yoyo cleanser bitters and Atorvastatin were established based on established human doses and then adjusted according to the weight of the rats (6, 7, 12, 13, 14, 15). The dosage calculations aimed to ensure equivalence to the effective human dose.

For Yoyo Cleanser bitters: The manufacturer's recommended human oral dose is 0.57ml/kg (6, 7). To convert this to an appropriate rat equivalent dose (RED), body surface area normalization was employed using the FDA-recommended Km values for dose translation (13):

RED (ml/kg) = Human dose × (Km human / Km rat)

RED = 0.57 ml/kg × (37 / 6) ≈ 3.52 ml/kg

This rat-equivalent dose of 3.52 ml/kg was therefore used for this study.

For Atorvastatin: The manufacturer's recommended human oral dose is 0.57 mg/kg (6, 7, 12, 15). To convert this to an appropriate rat equivalent dose (RED), body surface area normalization was employed using the FDA-recommended Km values for dose translation (13):

RED (mg/kg) = Human dose × (Km human / Km rat)

RED = 0.57 mg/kg × (37 / 6) ≈ 3.52 mg/kg

This rat-equivalent dose 3.52 mg/kg was therefore used for this study.

The Feeding Protocol

The feeding protocol involved providing the rats (according to their groupings) with the normal diet, high fructose diet and fructose water *ad-libitum.* The daily intake of their prescribed feed and water was closely monitored throughout the four-week study period (16, 17). Cages were managed within a 12-hour light-dark cycle, and regular cleaning and disinfection procedures were implemented to maintain a hygienic environment. The Yoyo Cleanser bitters and the Atorvastatin drug were administered using an oro-gastric gavage.

Blood Sample Collection

Blood samples were obtained on the 29th day, after the 28 days experimental period. This was after an overnight fast and under chloroform anesthesia, through cardiac puncture. The samples were put into fluoride oxalate bottles for the evaluation of fasting blood glucose and lithium heparin bottles for the evaluation of plasma insulin levels (18).

Determination of Fasting Blood Glucose (FBG)

The Randox glucose kit was utilized, employing the glucose oxidase method as reported by Barham and Trinder, 1972 (19). Standard and sample solutions underwent preparation, treatment with Randox Glucose Reagent, incubation, and subsequent measurement of absorbance at 500nm. Glucose concentration was computed using absorbance ratios alongside known standard concentrations.

Determination of Insulin Level

The insulin level was determined by the ELISA method described by Engvall and Perlman, 1971 (20). The process involved a solid-phase two-site enzyme immunoassay, encompassing incubation, washing, substrate reaction, and culminating in a colorimetric endpoint measurement. Insulin activity was determined from a standard calibration curve.

Determination of Insulin Resistance and Insulin Sensitivity

Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) was computed based on fasting glucose and insulin levels (21). HOMA-IR was calculated using the equation

HOMA-IR = (Fasting Glucose (mg/dL) × Fasting Insulin (µU/mL)) / 405.

Statistical Analysis

The assessment of statistical significance was conducted using ANOVA and Tukey's post hoc test, at a 95% confidence level, employing the Statistical Package for Social Sciences (SPSS)-20 (SPSS-20) software statistical package. Results with $P < 0.05$ were considered significant.

RESULTS

The high fructose diet + 10% fructose water induced a significant increase ($P < 0.05$) in FBG (108.60±1.9 mg/dl), Insulin level (10.58±0.40 µU/ml), and HOMA-IR index (2.83±0.06), in the rats compared to their levels in the control rats (53.40±1.54 mg/dl; 5.70±0.36 µU/ml; 0.75±0.05, respectively) (Tables 3, 4 and 5). Atorvastatin significantly prevented this escalation ($P < 0.05$) by keeping the FBG level

at 54.00±1.90 mg/dl (Table 3); the insulin level at 5.40±0.11 µU/ml (Table 4); and the HOMA-IR index at 0.72±0.02 (Table 5), when compared with the values of these same parameters in the HFD group. The Yoyo Cleanser bitters effectively prevented ($P < 0.05$) the elevation in fasting blood glucose by keeping it at 51.40±4.34 mg/dl (Table 3), the insulin levels, by keeping it at 5.61±0.20 µU/ml (Table 4), and the HOMA-IR index, by keeping it at 0.71±0.07 (Table 5), when compared to the values of these same parameters in the HFD group (group 2), triggered by the high-fructose diet. Both Yoyo Cleanser bitters and Atorvastatin exhibited similar efficacy in their actions, as the values of the respective parameters measured had no significant differences ($P < 0.05$) between them.

Table 3: Fasting blood glucose levels of the rats fed 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 + YOYO)	51.40±4.34[a]

The results are expressed as mean ± SEM (= standard error of the mean). Means with different superscripts differ significantly from one another at 95% level of significance ($P < 0.05$). **HFD+FW:** 60% High fructose diet + 10% fructose water, **YOYO:** Yoyo cleanser bitters, **HOMA-IR:** Homeostatic Model Assessment of Insulin Resistance

Table 4: Insulin levels of the rats fed 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 + YOYO)	5.61±0.20[a]

The results are expressed as mean ± SEM (= standard error of the mean). Means with different superscripts differ significantly from one another at 95% level of significance ($P < 0.05$).

Table 5: HOMA-IR index of the rats fed 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 + YOYO)	0.71±0.07[a]

The results are expressed as mean ± SEM (= standard error of the mean). Means with different superscripts differ significantly from one another at 95% level of significance ($P < 0.05$).

DISCUSSION

High fructose consumption, particularly in the form of a high fructose diet and fructose-rich beverages, has been linked to metabolic abnormalities such as hyperglycemia and hyperinsulinaemia. Metabolic syndrome, characterized by increased blood sugar levels, insulin resistance, and altered lipid profiles, amongst other physiological and biochemical derangements, is a known consequence of excessive fructose intake (22). The present study delved into the impact of Yoyo cleanser bitters on glucose and insulin levels in male *Wistar* rats fed a high fructose diet, aiming to explore its potential as a possible therapeutic intervention against fructose-induced metabolic disturbances. Atorvastatin, acknowledged for mitigating metabolic disruptions like the dyslipidaemia common with a high fructose diet, and its ancillary effect of preventing hyperglycaemia and hyperinsulinaemia, served as the standard positive control drug.

The results as reflected in group 2 (Table 3) shows that consumption of a high fructose diet (HFD) in conjunction with 10% fructose water (FW) by the rats, resulted in a substantial elevation ($P<0.05$) in FBG, insulin, and HOMA-IR compared to the results of the normal control rats (Group 1). This aligns with previous studies that have consistently shown the adverse metabolic effects of high fructose intake, promoting insulin resistance and elevated blood glucose levels (3, 14, 23)

However, the co-administration of Yoyo cleanser bitters as well as the drug Atorvastatin, alongside the HFD+FW demonstrated promising outcomes. These interventions effectively countered the significant increase in FBG, insulin, and HOMA-IR levels observed in the negative control group, indicating their potential in mitigating the adverse effects induced by the high fructose diet.

Atorvastatin, a commonly prescribed medication for managing cholesterol levels, exhibited a significant protective effect, maintaining levels comparable to the normal control rats. This is in line with studies indicating the potential of statins in improving insulin sensitivity and reducing insulin resistance in metabolic disorders. It obviously achieved this by preventing the dyslipidaemia which would have induced hyperglycaemia and insulin resistance (14, 15, 24).

Yoyo cleanser bitters used in the study, showcased potential in preventing the drastic increase in FBG, insulin, and HOMA-IR levels induced by the high fructose diet. Herbal remedies like this have been highlighted in various researches for its potential anti-diabetic and metabolic regulatory effects due to their phytochemical constituent and bioactive compounds (6, 7, 25, 26, 27). The ability of the Yoyo cleanser bitters of this study to achieve this preventive role, is not farfetched considering the fact that it contain plant extracts/herbs with biomolecules, phytochemical and mineral constituents which are known to have hypoglycaemic effects, as well as effects that improve insulin sensitivity, which can also be referred to as its anti-diabetic effects (6, 7, 26, 28, 29). Such biomolecules and phytochemicals include complex carbohydrates, alkaloids, flavonoids, tannins, glycopeptides, peptides and amines, terpenoids, cyanogens, steroids, lipids, coumarins, sulphur

compounds and inorganic ions, whose mechanism of action in achieving these effects is still being investigated (6, 7, 28, 29, 30). Examples of plants with known blood glucose level lowering properties, contained in the bitters of this study include *Aloe vera*, *Acinos Arvensis*, *Citrus aurantifolia,* just to mention but a few, (6, 7, 29). They act synergistically to bring down or prevent a rise in the blood glucose level (6, 7, 29, 30). The comparable effectiveness among Atorvastatin and Yoyo cleanser bitters in preventing the rise in FBG, insulin, and HOMA-IR levels induced by the high fructose diet is noteworthy. Though their possible major mechanism of action is via the antilipidaemic pathway, considering the fact that Yoyo cleanser bitters has a myriad of phytochemicals, it may also be exhibiting its effect with other possible mechanisms of action. This indicates there may be diverse avenues for addressing metabolic disturbances associated with excessive fructose intake.

Conclusion: The findings of this study contributed to the growing body of evidence supporting the therapeutic potential of herbal interventions in preventing metabolic disorders. Furthermore, the comparable effectiveness of Yoyo cleanser bitters compared to Atorvastatin, accentuates the viability of natural alternatives in addressing metabolic imbalances. This research underscored the significance of dietary interventions and natural remedies in modulating glucose and insulin homeostasis in the context of metabolic health. Further investigations and clinical trials are warranted to delve deeper into the mechanisms of action underlying the efficacy of Yoyo cleanser bitters, paving the way for their potential integration into therapeutic strategies aimed at preventing or ameliorating metabolic abnormalities associated with diet induced metabolic disturbances, especially from excessive fructose intake. Overall, this study underscores the promising role of Yoyo cleanser bitters as a potential natural supplement in preventing the adverse effects of high fructose diets on metabolic health.

Author Details: Department of Medical Biochemistry, University of Benin, Benin City, Edo State, Nigeria.

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