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AMELIORATIVE EFFECTS OF *ANACARDIUM OCCIDENTALE* METHANOLIC NUT EXTRACT IN HIGH-FAT DIET-INDUCED OBESITY, OXIDATIVE STRESS AND DISRUPTED METABOLIC HORMONES

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ABSTRACT

Background: Obesity is considered as major risk factors for development of many chronic metabolic diseases and prevention of obesity in alleviating these diseases is globally challenging. This study investigated the potential anti-obesity effect of *Anacardium occidentale* methanolic nut extract in high-fat diet induced obese rats compared to Simvastatin. **Methods:** Fifty (50) male Wistar rats weighing (180±20g) were used and obesity was induced using high-fat diet. The animals were divided into five groups (10rats/group): control, HFD, HFD+100mg/kgb.wt *Anacardium occidentale*, HFD+200100mg/kgb.wt *Anacardium occidentale* and HFD+40mg/kgb.wt Simvastatin group. Body weight and blood glucose were measured weekly. On the last day of the experiment, the animals were sacrificed and blood sample were collected for biochemical estimation of lipid profile, insulin, leptin, ghrelin, oxidative stress parameters and Markers of Kidney functions. **Results:** Treatment with *Anacardium occidentale* nut extract significantly ($p<0.05$) decrease the body weight, blood glucose, leptin, triglyceride (TG), total cholesterol (TC), low-density lipoprotein (LDL), very-low density lipoprotein (VLDL) and enhanced the high-density lipoprotein (HDL) and ghrelin levels in high-fat diet treated rats. Furthermore, Glutathione peroxidase (GPx), Superoxide dismutase (SOD), Reduced glutathione (GSH), and Catalase (CAT) levels were significantly ($p<0.05$) increases with a decrease Malondialdehyde (MDA) level in high-fat diet treated rats. Also, Markers of kidney functions urea, uric acid and creatinine level were improved in high-fat diet treated rats. **Conclusion:** From these findings, *Anacardium occidentale* nut extract has potential anti-obesity effects and it can be explored as alternative therapy in preventing obesity-related metabolic disease.

KEYWORDS: *Anacardium occidentale* nut, High-fat diet, Obesity, Oxidative stress, Metabolic hormones.

INTRODUCTION

Obesity prevalence has tripled in number since 1975, and in 2016 global estimated obese individual with a body mass index (BMI) of greater 30 was 1.9 billion and an additional 650 million are overweight (BMI>25).[1] Many factors such as dietary preference for high-fat and caloric rich diets, sedentary lifestyle, genetic susceptibility, and endocrine disorders contribute to the increasing trend of obesity. The major etiology for obesity and overweight is the energy imbalance in which energy intake exceeding the energy expenditure.[2]

Obesity is a metabolic disorder caused by abnormal or excessive body fat accumulation in adipose tissue leading to pathogenesis of numerous metabolic diseases associated with obesity includes hyperlipidemia, hypertension, atherosclerotic, cardiovascular disease and type 2 diabetes mellitus.[3,4] These diseases are frequently accompanied by insulin resistance, increased oxidative stress, and enhanced inflammatory marker expression.[5] Obesity related insulin resistance is a core factor for pathogenesis of long term diabetes complications including diabetic nephropathy.[6] Obesity is considered as peril factor for the development, spread and progression of chronic kidney disease.[7]

Furthermore, increased oxidative stress in obesity usually aggravate by high level of reactive oxygen species and decline production of body defence endogenous antioxidant enzymes (superoxide dismutase (SOD), catalase (CAT), glutathione S-transferase (GST), and glutathione peroxidases (GPx).[8] Excessive reactive molecules cause cellular damage and development of multiple diseases due to declining endogenous antioxidant system capacity to eliminate free radicals.[9] Therefore, treatment and prevention of obesity and overweight is one of the global health challenges.

Currently, the well known methods for preventing obesity and overweight involve calorie diet restriction and adequate exercise which are not properly maintained. Also, in conjunction with diet restriction and proper adequate exercise practice, the emergent interest to reduce body weight through medical therapies (drugs) has been reported to have adverse side effect.[10] Hence, there is urgent need to search for effective method and safe therapies for treatment and prevention of obesity-associated metabolic diseases.

Natural plants or fruit or nuts, rich in phenolic compounds are known for their extensive potential therapeutic effects such as anticancer, antibacterial, antioxidant, antidiabetic, and anti-inflammatory properties.[11] One of the third rank famous nutritional plant nuts in the world is cashew nut (*Anacardium occidentale L.*) which can modulate the risk of developing many metabolic diseases.[12]

Anacardium occidentale is a plant originated from Brazil that is generally consumed in nature and used in folk medicine with high value edible nut and a source of carbohydrates, proteins, phosphorous, iron, zinc, magnesium, fibers, and fatty acids.[13] The various parts of the plant are medicinally explored to treat different ailments.[14] Phytochemical analysis of *Anacardium occidentale* plant revealed the presences of many bioactive compounds and other polyphenols as well.[15] *Anacardium occidentale* nuts is rich of unsaturated fatty acids, flavonoids, anthocyanins and tannins, fiber, folate and tocopherols.[16–20] Despite various therapeutic effects of this plant parts, there had been little attention on the consumption of *Anacardium occidentale* nut for prevention and treatment of chronic metabolic diseases. Therefore, the present study aimed at investigating the potential anti-obesity effects of methanolic extract of *Anacardium occidentale* nut in high-fat diet (HFD) induced obese male Wistar rats.

MATERIALS AND METHODS

Collection of Plant Materials

Fresh *Anacardium occidentale* nuts were harvested from Plant Agricultural Research Farm, Ladoke Akintola University of Technology, Ogbomosho, Oyo State, Nigeria. The plant nut was identified, authenticated, and given a voucher specimen number LH0533 by Dr. A. T. J. Ogunkunle at Biology Department, Ladoke Akintola University of Technology, Ogbomoso, Oyo State, Nigeria.

Extraction of *Anacardium occidentale* nut

The *Anacardium occidentale* nuts were thoroughly washed and air-dried at room temperature. The outer coated was removed to obtain the nuts. Then, the nuts were grinded into fine powder form by an electric blender and stored in air-tight container. 500g of the fine powdered form was extracted in a Soxhlet apparatus with 95% methanol solvent. The methanolic extract was also kept in air-tight container and store at 4^{o}C until used.

Experimental Animals

Fifty (50) healthy male Wistar rats (180±20g) were used. The animals were obtained from the Animal Research House of Physiology Department, Ladoke Akintola University of Technology, Ogbomosho, Oyo State, Nigeria. The rats were housed in a plastic cage (10rats per each cage) under free-pathogen conditions of relative humidity (45±5%), temperature (25±5^{o}C) and 12hours light/dark cycles. The animals were acclimatized for two (2) weeks and had free access to rat pellet feed with water *add libitum* before the experiment was commence. All experimental protocols and handling of animals were performed in accordance with the guidelines of the National Institutes of Health for the Care and Use of Laboratory Animals.

Animals Grouping and Treatment

The fifty (50) rats were randomly divided into five major groups of ten rats per each group (n=10).
Group 1: Normal pellet diet (Normal control)
Group 2: High-fat diet (Obese control)
Group 3: High-fat diet + 100mg/kgb.wt *Anacardium occidentale* methanolic nut extract
Group 4: High-fat diet + 200mg/kgb.wt *Anacardium occidentale* methanolic nut extract
Group 5: High-fat diet + 40mg/kgb.wt Simvastatin

All the groups were water *add libitum* and administration of the nut extract was done via oral gavage with oral cannular. The experimental period last for six (6) weeks.

Fasting Plasma Glucose Level and Body Weight Assessment

Fasting plasma glucose levels and body weight changes of the rats were measured at weekly intervals prior and during the administration of *Anacardium occidentale* methanolic nut extract, throughout the experimental period. Plasma glucose levels were determined by glucose oxidase/peroxidase (GOD-POD) method with a glucometer and test stripes (Accu-Chek Advantage, Roche Diagnostic, Germany).

Determination of Biochemical Parameters

At the end of the period of experiment, the animals were fasted overnight (12 hours fasting), anaesthetized with intraperitoneal injection of ketamine-75mg/kg and xylazine-20mg/kg and then sacrificed by cervical dislocation. Fasting blood samples were collected from the apex beat of the rats' heart via cardiac puncture into heparinized tubes, centrifuged at 3000rpm for 5mins and supernatant plasma was retrieved for biochemical analysis.

The levels of plasma triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) were determined using enzymatic colorimetric methods with a commercial Diagnostic kit (Genzyme Diagnostics, MA. USA). Plasma levels of very-density lipoprotein (VLDL-C) were estimated according to Friedewald formula.[21]

$$\text{VLDL-C} = \frac{\text{Triglyceride (TG)}}{5}$$

The Plasma insulin, leptin and ghrelin levels were measured by an enzyme link immunosorbent assay (ELISA) methods using ELISA kits respectively. Also, superoxide dismutase (SOD), glutathione (GSH), glutathione peroxidase (GPx) and catalase (CAT) antioxidant activities were estimated by enzyme linked immunosorbent assay (ELISA) methods using Rat SOD, GSH GPx and CAT ELISA Kits as described by Sigma-Aldrich Kit. Malondialdehyde (MDA) was measured following the manufacturer's instructions (Oxford Biomedical Research, USA).

Markers of kidney function (blood urea nitrogen (BUN), plasma creatinine, and uric acid) were determined using the commercially kits from Siemens Health Care Diagnostics.

Statistical Analysis

Statistical Package for Social Sciences (SPSS), version 20.0 software was used for the experimental data analysis. Data were expressed as mean ± SEM (n=10). Mean differences between groups were tested for statistical significance using one-way analysis of variance (ANOVA) followed by Bonferroni post hoc test. P-value less than 0.05 ($P<0.05$) were considered statistical significant for all data analysis.

RESULTS

Effects of *Anacardium occidentale* nut extract on Body Weight in HFD-induced obese rats

The body weight of high-fat diet induced obese group rats was significantly ($p<0.05$) increased compared with the rats fed with normal diet (control group). Treatment with 100mg/kg and 200mg/kg of *Anacardium occidentale* nut extract and 40mg/kg of Simvastatin respectively reduced the body weight in groups 3, 4 and 5 compared to the untreated obese group (Fig. 1).

Effects of *Anacardium occidentale* nut extract on Plasma Blood Glucose and Insulin Concentration Levels in HFD-induced obese rats

Plasma blood glucose level and insulin concentration were significantly ($p<0.05$) increases in high-fat diet untreated group compared with the control group. Oral administration of 100mg/kg and 200mg/kg of *Anacardium occidentale* nut extract and 40mg/kg of Simvastatin attenuates the blood glucose and insulin concentration levels in groups 3, 4, and 5 when compared with untreated obese group (Fig 2. a, b).

Effects of *Anacardium occidentale* nut extract on Lipid Profile Parameters in HFD-induced obese rats

Untreated obese group rats showed significant ($p<0.05$) increases in total cholesterol (TC,) triglyceride (TG), low-density lipoprotein-cholesterol (LDL-c), very-low density lipoprotein-cholesterol (VLDL-c), levels while high-density lipoprotein-cholesterol (HDL-c) level decreased significantly when compared with the control. Administration of 100mg/kg and 200mg/kg of *Anacardium occidentale* nut extract and 40mg/kg of Simvastatin markedly reversed the levels of TC, TG, LDL-c, and VLDL-c with improve HDL-c level in groups 3, 4, and 5 when compared with the untreated obese group (Fig. 3a). Also, atherogenic index (AI) and Cardiac risk index (CRI) were significantly ($p<0.05$) higher in untreated obese group rats when compared to the control group and treatment with both doses of *Anacardium occidentale* nut extract and Simvastatin lower these levels in groups 3, 4, and 5 (Fig 3. b, c).

Effects of *Anacardium occidentale* nut extract on Plasma Leptin and Ghrelin Concentration Levels in HFD-induced obese rats

The rats fed with high-fat diet exhibit significant ($p<0.05$) increase in leptin and decrease ghrelin concentration levels compared with the control group. Supplement of 100mg/kg and 200mg/kg of *Anacardium occidentale* nut extract and 40mg/kg of Simvastatin decrease the leptin and alleviate the ghrelin concentration levels in groups 3, 4 and 5 when compared with the untreated obese group (Fig 4. a, b).

Effects of *Anacardium occidentale* nut extract on Antioxidant Enzymes, Oxidative Stress Parameters, and Markers of Renal Function in HFD-induced obese rats.

There were significant ($p<0.05$) decreased in the activity of reduced glutathione (GSH), glutathione peroxidase (GPx), superoxide dismutase (SOD) and Catalase (CAT) level in untreated obese group rats while the levels of malondialdehyde (MDA) was significantly increased in comparison to the control group. Administration of 100mg/kg and 200mg/kg of *Anacardium occidentale* nut extract and 40mg/kg of Simvastatin ameliorates the activity of GSH, GPx, SOD and CAT compared to the untreated obese group rats. However, the level MDA activity significantly reduced after treatment with 100mg/kg and 200mg/kg of *Anacardium occidentale* nut extract compared to the 40mg/kg of Simvastatin (table 1).

Additionally, the makers of kidney function urea, uric acid and creatinine levels in the untreated obese group rats significantly ($p<0.05$) increased compared to the control. The Simvastatin treatment group showed a markedly reduction in urea and uric acid levels when compared with the extract groups. However, rats administered with 200mg/kg of *Anacardium occidentale* nut extract obviously lower the creatinine level compared to the rats received 100mg/kg *Anacardium occidentale* nut extract and 40mg/kg Simvastatin (table 1).

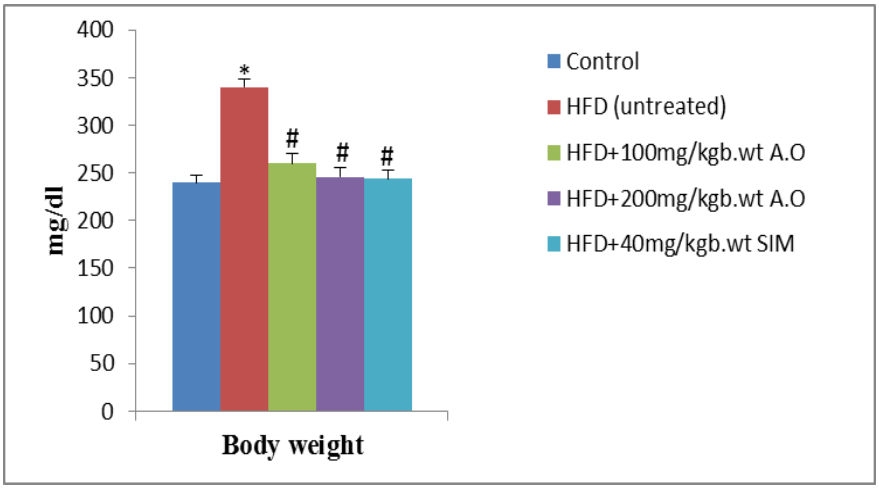
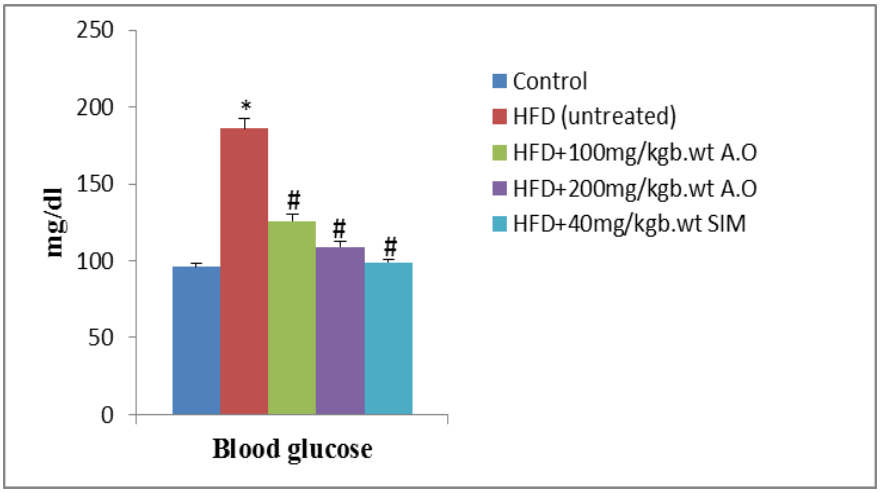
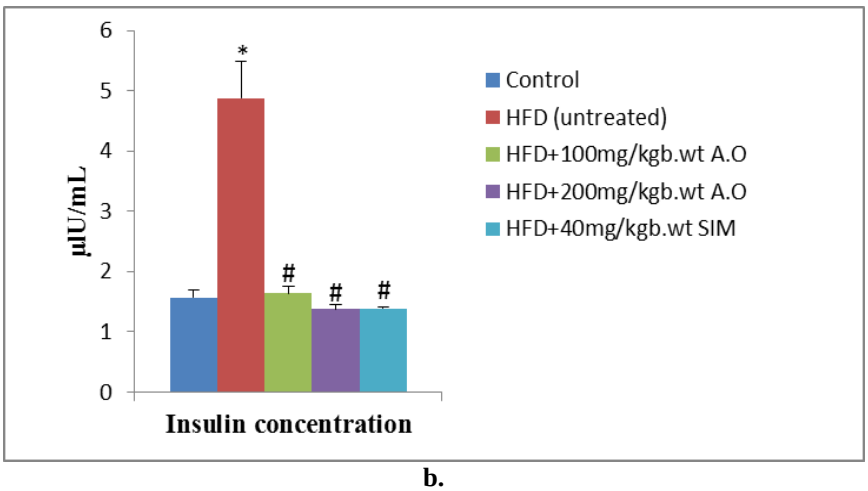


Fig 1. Effect of *Anacardium occidental* methanolic nut extract on body weight in HFD-induced obese rats. ***Values are expressed as mean ± SEM (n=10). *significant at p<0.05 compared with control; #significant at p<0.05 compared with HFD group.***

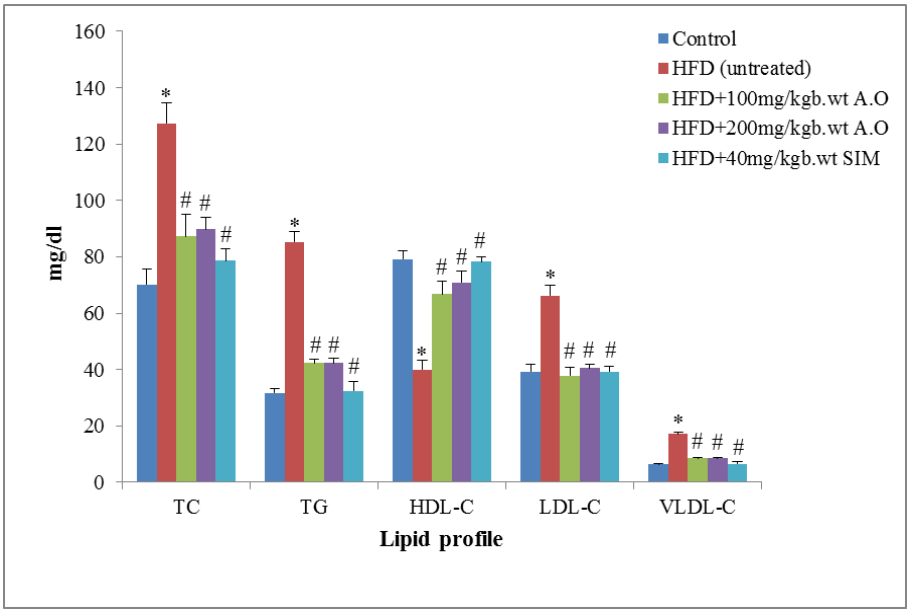


a.



b.

Fig. 2: Effects of *Anacardium occidental* methanolic nut extract on (a) blood glucose (b) insulin concentrations in HFD-induced obese rats. ***Values are expressed as mean ± SEM (n=10). *significant at p<0.05 compared with control; #significant at p<0.05 compared with HFD group.***



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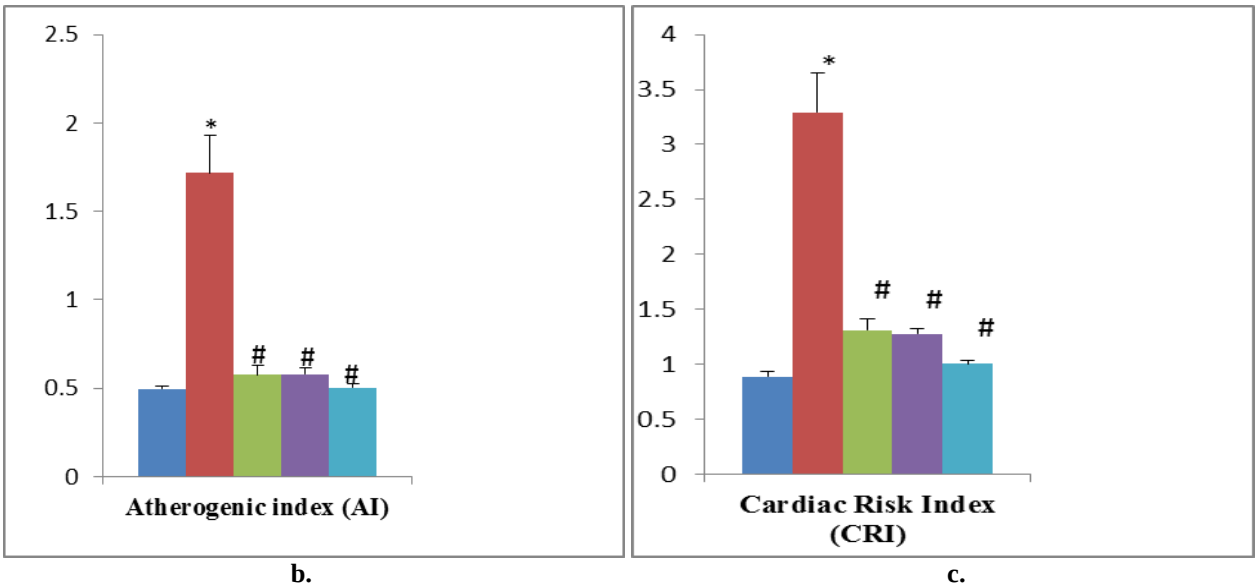
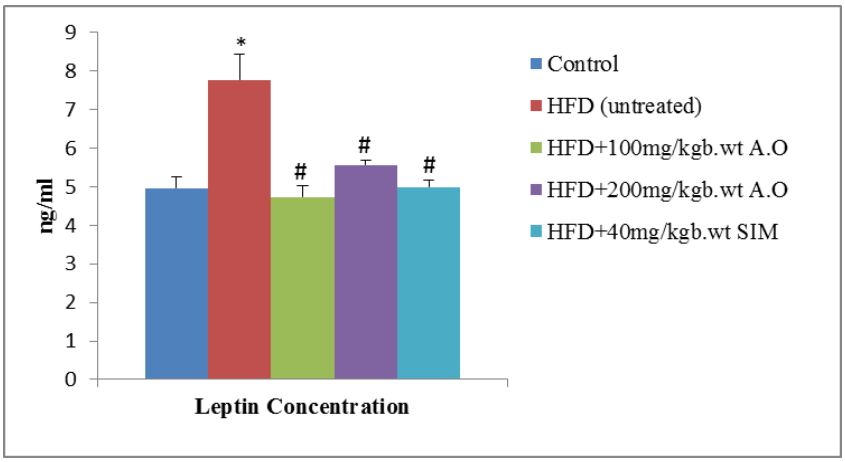
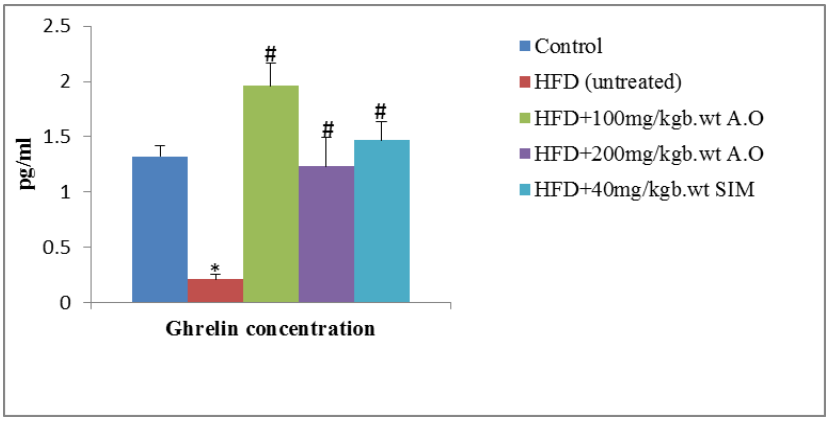


b. **c.**

Fig. 3: Effects of *Anacardium occidental* methanolic nut extract on (a) lipid profile (b)Atherogenic index (c) Cardiac risk index in HFD-induced obese rats *Values are expressed as mean ± SEM (n=10). *significant at p<0.05 compared with control; #significant at p<0.05 compared with HFD group.*



a.



b.

Fig. 4: Effects of *Anacardium occidental* methanolic nut extract on (a) Leptin (b) Ghrelin concentrations in HFD-induced obese rats. *Values are expressed as mean ± SEM (n=10). *significant at p<0.05 compared with control; #significant at p<0.05 compared with HFD group.*

Table 1: Effects of *Anacardium occidentale* nut extract on Antioxidant Enzymes, Oxidative Stress Parameters, and Markers of Kideny Function in HFD-induced obese rats.

Parameters	Control	High-fat diet (untreated)	High-fat diet +100mg/kgb.wt A.O	High-fat diet +200mg/kgb.wt A.O	High-fat diet +40mg/kgb.wt SIM
GSH (mM)	1.93 ± 0.07	0.88 ± 0.03*	1.70 ± 0.08#	1.85 ± 0.08#	1.61 ± 0.14#
GPx (u/L)	603.43 ± 10.99	388.95 ± 5.95*	515.79 ± 13.12#	546.73 ± 12.96#	581.12 ± 11.08#
SOD (µ/ml)	1.89 ± 0.10	0.91 ± 0.05*	1.54 ± 0.10#	1.51 ± 0.10#	1.71 ± 0.15#
CAT (mol/ml/min)	16.40 ± 0.98	10.17 ± 0.41*	15.27 ± 0.39#	13.44 ± 0.79#	16.69 ± 0.99#
MDA (µM)	7.80 ± 0.63	11.92 ± 0.63*	8.33 ± 0.44#	8.09 ± 0.24#	8.49 ± 0.25#
Urea (mg/dl)	51.98 ± 4.42	86.09 ± 18.06*	66.40 ± 5.05#	72.89 ± 7.97#	59.90 ± 4.55#
Uric Acid (mg/dl)	2.89 ± 0.37	7.69 ± 0.63*	2.70 ± 0.58#	2.21 ± 0.31#	1.49 ± 0.54#
Creatinine (umol/L)	52.00 ± 7.07	208.0 ± 22.72*	79.50 ± 4.87#	59.50 ± 6.61#	62.00 ± 3.16#

*Values are expressed as mean ± SEM (n=10). *significant at p<0.05 compared with control; #significant at p<0.05 compared with HFD group.*

DISCUSSION

Obesity is a serious global health problem. It is characterized by elevated lipid accumulation in an expanded adipose tissue mass.[22] The imbalance between calorie intake and energy expenditure cause obesity. Natural plant compounds and their derivatives have been used as alternative and complementary therapies for treating obesity without mortality or obvious adverse effects.[23] In this study, we investigate the potential therapeutic anti-obesity effects of *Anacardium occidentale* methanolic nut extract in high-fat diet induced obese rats.

Intakes of high-fat diet responsible for body weight gain due to its high energy and fat contents. Rats fed with high-fat diet in this study exhibited significantly higher body weight gain indicative obesity state, which supports the previous studies.[24,25] Treatment with both doses of *Anacardium occidentale* nut extract markedly reduced their bodyweights compared to the weight of untreated obese rats.

Obesity is closely related to the development of metabolic disorders, including dyslipidemia, insulin resistance, and hepatic steatosis.[26] High-fat diets are known to produce significant negative effects on the lipid panel.[27] These effects are suggested to be mediated through increased lipids absorption from the gastrointestinal tract (GIT) and a reduction of cholesterol metabolism. In this present study, animals fed with high-fat diet showed obesity related dyslipidemia with elevated TG, TC, LDL and VLDL levels and decreased in HDL level. Also, TC/HDL ratio is used to predict the risk of cardiovascular disease. This ratio is called cardiac risk index.[28] High total cholesterol levels and low HDL level will increase the cardiac risk index.[29,30] Our results show that animals fed with HFD has the highest TC/HDL ratio, indicating a high risk of cardiovascular disease. Treatments with 100mg/kgb.wt and 200mg/kgb.wt *Anacardium occidentale* nut extract showed decreased levels of TC, TG, LDL and VLDL along with significant increase in HDL level and lower cardiac risk index. The present results are consistent with a report in which treatment with *Moringa* crude extract

improve blood HDL level and lower levels of triglycerides, cholesterol, and LDL.[31] These suggest that *Anacardium occidentale* nut alleviating dyslipidemia, atherogenic index, and provide protection from development of hypertension and cardiovascular diseases.

In addition, alterations in lipid profile have been considered as contributory factors to oxidative stress in obesity.[32] Obesity increased production of reactive oxygen species through lipid peroxidation as well as reduced biological antioxidant defense mechanism.[33] The results of the current study demonstrated that obesity increased lipid peroxidation as expressed by increased tissue levels of MDA and decreased endogenous antioxidant enzymes activity of GSH, GPx, SOD, and CAT levels in HFD induced obese group compared with normal normal group, showing decrease capacity of free radical scavenge and development of oxidative stress in HFD induced obese groups. Our findings are in basic agreement with the results of Vincent, et al.,[34], Olusi et al.,[35], and Amirkhizi et al.,[36] who showed that, obesity is an independent risk factor for increasing lipid peroxidation and decreased activity of cytoprotective enzymes. *Anacardium occidentale* nut extract administration enhanced the endogenous antioxidant defense enzymes activity and decreased the MDA level in HFD induced obese groups which indicate the anti-oxidative and antioxidant amelioration ability of the Anacardium occidentale nut.

Obesity is associated with leptin and insulin resistance leading to hyperinsulinemia and hyperleptinemia, which are further linked with excessive body weight, especially central obesity.[37,38] Therefore, improvement in glucose and fat metabolism by enhancement of both the insulin and leptin sensitivity and decreasing their levels is considered to be emphatic treatment strategy for obese patients. HFD has been reported to increase the insulin level, causing insulin resistance and hyperinsulinemia in rats.[39] In the present study, it was revealed that treatment with *Anacardium occidentale* nut suppressed increase in insulin level in HFD fed rats.

Leptin and ghrelin involve in the regulation of the feed intake and energy expenditure. HFD has also been reported to elevate leptin concentrations and cause leptin resistance in rats.[40] Kim et al.[41] and Lee et al.[42] reported that treatment with *Coix lachrymajobi var. mayeun* (seed) and *Diospyros kaki* (leaf) extracts exhibited reduction in body weight gain of HFD-fed Sprague dawley rats through modulation of leptin. In this study, plasma leptin levels in the low and high dose of extract treated groups were considerably lower with the decrease in body weight. Insulin has been well recognized to play a role in regulating the leptin level.[43] The significant decrease in the plasma leptin levels observed in the present study may have resulted in the suppression of body weight gain, and plasma insulin concentration.

Ghrelin has been recognized to influence feeding behavior, energy homeostasis and also gastrointestinal functions.[44] Several studies showed that body weight loss was accompanied with the increase in concentration of ghrelin.[45,46] Our results showed that treatment with *Anacardium occidentale* nut increases ghrelin levels. The observation was consistent with the results of Hsu et al.[47] that reported the effects of green tea extracts in increasing the concentration of ghrelin and adiponectin in obese women.

Obesity is known as an independent risk factor for renal injury.[48] There were elevation in creatinine, urea and uric acid levels in high-fat diet untreated rats. This result is agreed with Khan et al.[49] who reported that obesity causes a decline or loss of renal function and elevation of serum urea, creatinine and uric acid levels. In this present investigation, *Anacardium occidentale* nut extract exhibit renal protective effects against HFD-induced obesity as there were significant decreases in the elevated creatinine, urea and uric acid in obese treated rats.

CONCLUSION

In view of these findings, Administration of *Anacardium occidentale* methanolic nut extract prevents increase in body weight gain and improves dyslipidemia, blood glucose, metabolic hormones, and lower oxidative stress and enhanced kidney functions, which indicates anti-obesity effects. The presences of polyphenols compound with strong antioxidant properties in *Anacardium occidentale* nut responsible for this ameliorative effect. Therefore, consumption of this *Anacardium occidentale* nut as part of diet may be a good alternative strategy for preventing obesity and its associated metabolic disease.

Abbreviations

AO: *Anacardium Occidentale*; SIM: Simvastatin; HFD: High-fat diet; TG: Triglycerides; TC: Total cholesterol; HDL: High density lipoprotein; LDL: Low-density lipoprotein; VLDL: Very low density lipoprotein; AI: Atherogenic index; CRI: Cardiac risk index; GPx: Glutathione peroxidase; SOD: Superoxide dismutase; GSH: Reduced glutathione; CAT: Catalase; MDA: Malondialdehyde; BUN: Blood urea nitrogen; BMI: Body mass index; ELISA: Enzyme-linked immunosorbent assay; SEM: Standard error of the mean.

DECLARATIONS

Authors' Contributions

All authors have made considerable contribution to the work and approved the final version of the manuscript. FO conceived the original idea, supervised the researched work and corrected the manuscript. MO analyzed the data and wrote the manuscript. OR, NO, OJ and AP carried out the research work.

Ethics Approval

All procedures were approved by the Animal care committee of the Ladoke Akintola University of Technology and conducted according to the "Principles

of Laboratory Animal Care" and specific national laws where applicable.

Consent for Publication
All authors agreed to publish the article.

Availability of Data and Materials
All data generated and analyzed during this study are included in this article.

Competing Interests
No competing interests.

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