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# Methanol Leaves Extract of *Zingiber officinale* (Roscoe) exhibited Anti-Obesity Effect in Wistar Rats Fed with a High Fat Diet

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## ABSTRACT

This study evaluated the anti-obesity properties of the methanol extract of *Zingiber officinale* leaves in Wistar rats. Thirty male rats were distributed into five groups, with six rats in each group, and different groups were treated with a normal fat diet (NFD), high-fat diet (HFD), HFD + orlistat (20 mg/kg) p.o, HFD + *Zingiber officinale* (200 mg/kg) p.o, and HFD + *Zingiber officinale* (400 mg/kg) p.o for fifty-six days. After all administrations, the animals were sacrificed by cervical dislocation, and various biochemical analyses were carried out. Results showed that there was a significant decrease ($p < 0.05$) in body weight and adiposity in the *Zingiber officinale*, NFD, and orlistat groups compared to the HFD control. However, there was no significant difference in the body weights of rats in the *Zingiber officinale* groups compared to the NFD control and orlistat groups. Furthermore, rats in the *Zingiber officinale* groups had normal lipid concentrations, antioxidant status, adipokines, cytokines, liver, kidney, and cardiac function parameters that were comparable to orlistat and normal control but in contrast with the HFD control. Findings from the study suggest that *Zingiber officinale* leaves have significant anti-obesity, antioxidant, and anti-inflammatory properties.

**Keywords:** *Zingiber officinale*, body weight, adipose tissues, cytokines, orlistat, adipokines, antioxidants.

## 1. INTRODUCTION

Obesity is a chronic disease involving an excess amount of body fat that develops as a result of a long-term energy imbalance, i.e., excessive caloric consumption and insufficient energy output[1]. Research has demonstrated that obesity decreases life expectancy because it raises the possibility of developing numerous medical complications, such as type 2 diabetes mellitus, dyslipidemia, cardiovascular diseases, and some types of cancer[2].

Orlistat, lorcaserin, and a combination of phentermine and topiramate are available for the management of obesity. However, they may cause gastrointestinal, kidney, and heart problems[3,4]. Presently, no drug provides continuous and reasonable weight loss with few side effects[5]. Therefore, various efforts are made to lower weight with pharmacological agents from plants that may bring minimal adverse reactions[6]. Traditionally, plants have been utilized as medicines for treating various diseases. Leaves of *Cymbopogon citratus* are used in the treatment of cold and flu[7, 8]. *Moringa oleifera* (leaves and seeds), *Momordica charantia* and *Tinospora crispa* leaves are used in the treatment of diabetes[8,9,10]. It has been reported that diarrhea is treated with *Psidium guajava* leaves[11], while indigestion and stomachache are treated with leaves of *Capraria biflora*[8]. Fruits of *Passiflora edulis* are used in the treatment of hypertension[11]. *A.*

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*falcata* and *M. aurea* leaves are used in the management of inflammation and skin irritations[12]. Research has revealed that various herbal plants have anti-obesity properties. *Curcuma longa* rhizomes have been found to reduce body weight, serum lipids, and suppress adipocyte differentiation in high-fat diet-induced rats[13]. *In vitro* study by Kim *et al.* [14] showed that a mixture of peels of *Citrus unshiu* and Diospyros kaki fruits has pancreatic lipase inhibition activity. Prunus salicina extract attenuated adipogenesis in murine 3T3-L1 adipocytes cells[15]. Findings made by Maia-Landim *et al.*[16] showed that *Garnicia cambogia* and glucomannan from Amorphophallus konjac reduced appetite and weight in obese people while findings by Nepali *et al.* [17] showed that *Chrysanthemum indicum* inhibited adipogenesis in high fat diet induced mice.

*Zingiber officinale*, commonly called 'ginger,' is a very important medicinal plant. Traditionally, ginger rhizomes are often used to cure many illnesses, such as indigestion, loss of appetite, flatulence, nausea, vomiting, allergic reactions, acute and chronic cough, common cold, fever, allergic rhinitis, sinusitis, bronchitis, respiratory troubles, headache, backache, and toothache[18]. It is also used for the treatment of primary dysmenorrhea[19]. Ginger leaves have been employed as a flavor for foods in Asian traditional medicine. They have been used to reduce toothache, promote digestion, and reduce constipation[20]. Reports have shown that ginger rhizomes possess hypoglycemic activity and ameliorate type I diabetes [21]. Al-Amin *et al.* [22] also demonstrated that ginger rhizomes possess hypolipidemic activity. Research has shown that extract of ginger rhizomes possess weight lowering, renoprotective, and antioxidant properties[23]. Ginger leaves extract have been reported to possess antioxidant activities and phytochemicals including flavonoids, tannins, saponins, and glycosides [24].

There is a paucity of information on the anti-obesity effect of *Zingiber officinale* leaves, and most studies on the plant are on the rhizomes. Therefore, this study aimed at evaluating the anti-obesity property of *Zingiber officinale* leaves in Wistar rats fed with a high-fat diet.

## 2. MATERIALS AND METHODS

### 2.1 Plants

Fresh leaves of *Zingiber officinale* were harvested from a private farm in Ondo City, Ondo State, Nigeria, and authenticated by a Botanist at the University of Benin. A specimen with voucher number UBHz 368 was deposited at the herbarium. The leaves of *Zingiber officinale* (700g) were dried in the air, pulverized, and immersed in absolute methanol (7.5mL) for 72 hours. Filtration was thereafter carried out using chiffon filter. A rotary evaporator was then used to concentrate the filtrate (temperature, 40 oC), and the resulting paste was further dried in an incubator at 40oC and stored in an airtight sterile bottle. The percentage yield of the extract was 4.8%.

### 2.2 Experimental animals

Wistar rats (male) with weights ranging from 130g to 150g were obtained from the animal house of the University of Medical Sciences (UNIMED), Ondo, Nigeria. Ethical approval for the use of animals was obtained from the UNIMED Research Ethics Committee with the number UNIMED-AREC/Apv/2022/015

The animals were housed in clean cages at room temperature (25 ± 1oC), with a 12-hour light/dark cycle, and the litter was changed every day. The experiments were carried out in compliance with internationally accepted principles for the use and care of laboratory animals[25] .

### 2.3 Experimental procedure

Obesity was induced by a high-fat diet (HFD). The diets were formulated based on the method of Cha and Jones[26]. The composition of the Normal Fat Diet (NFD) and HFD is shown in Table 1. Thirty Wistar rats were distributed into 5 groups, each comprising 6 rats. The dried extract of *Zingiber officinale* leaves was dissolved in distilled water (vehicle) according to the corresponding dose. The rats were subjected to the following for 56 days:

- Group 1: NFD + distilled water (NFD control)
- Group 2: HFD + distilled water (HFD control)
- Group 3: HFD + Orlistat (Reference anti-obesity drug; 20mg/kg, *p.o*
- Group 4: HFD + *Zingiber officinale* (200mg/kg, *p.o*)
- Group 5: HFD + *Zingiber officinale* (400mg/kg, *p.o*)

**Table 1: Content of NFD versus HFD**

| NUTRIENT | NFD(w/w) | HFD(w/w) |
|---|---|---|
| Soya beans | 15% | 15% |
| Corn starch | 60% | 40% |
| Sucrose | 10% | 10% |
| Soybean oil | 4% | 4% |
| Beef fat | - | 20% |
| Vitamins mix | 3.5% | 3.5% |
| Minerals mix | 1% | 1% |
| Cellulose | 6.5% | 6.5% |

Weights of rats were taken weekly and feed consumption was recorded daily for eight weeks (56 days).

On the 57th day, the rats were then sacrificed by cervical dislocation. The body length (nose-to-anus) was measured, and their values were used to calculate the following anthropometric parameters:

**Body mass index (BMI):** body weight (g)/length$^2$ (cm$^2$)[27].

**Lee's index:** Body weight (g) (cube root) /nose-to-anus length (cm) [27].

Epididymal fat, retroperitoneal fat were collected and weighed. Adiposity index was calculated with the formula of Boustany *et al.*[28] as follows:

$$Adiposity\ index = \frac{\text{Epididymal fat} + \text{Retroperitoneal fat}}{\text{Weight of body (g)} - (\text{Epididymal fat} + \text{Retroperitoneal fat})} \times 100$$

Blood samples were collected via cardiac puncture into sterile tubes and allowed to stand for 30 minutes at 20-25$^o$C. The clear serum was separated at 2500*g* for 15 minutes using a centrifuge.

Liver and heart samples were harvested. A sample of the liver (1g) was homogenized in 9 mL of buffer (sodium phosphate) pH 7.0, while 0.5 g of the heart was homogenized in 4.5 mL of buffer at pH 7.0. The homogenates were centrifuged at 1000 g for 15 minutes, and the supernatant was stored for subsequent analyses.

**1.4 Serum liver function tests**

Aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), bilirubin, albumin, and total protein were assayed in the serum using kits from Randox Laboratories Ltd, Crumlin, County Antrim, United Kingdom.

**1.5 Serum cardiac function tests**

Creatine kinase (CK) and lactate dehydrogenase (LDH) were assayed in the serum using kits from Randox Laboratories Ltd, Crumlin, County Antrim, United Kingdom.

**2.6 Serum kidney function tests**

Sodium, potassium, chloride, and bicarbonate ions were measured with kits from Fortress Diagnostics, Antrim, United Kingdom. Creatinine and urea were measured using kits from Randox Laboratories Ltd, Crumlin, County Antrim, United Kingdom.

**2.7 Serum lipid profile assay**

Total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-C), and triglycerides (TG) were measured in the serum using kits from Randox

Laboratories Ltd, Crumlin, County Antrim, United Kingdom.

Low-density lipoprotein cholesterol (LDL-C), very low density lipoprotein cholesterol (VLDL-C), atherogenic index (AI) and coronary risk index (CRI) were calculated using the formula of Friedewald *et al* .[29] as follows:

LDL-C = TC-(HDL-C +TG/5)

VLDL-C= TG/5

AI = (TC-HDL-C) / HDL-C

CRI = TC / HDL-C

**2.8 Serum adipokines and cytokines**

Adipokines (leptin and adiponectin) were analyzed in serum using ELISA kits by Elabscience Biotechnology Company, Houston, Texas, USA. Cytokines (tumor necrosis factor alpha (TNFα) and interleukin-6) were analyzed in serum using ELISA kits by Elabscience Biotechnology Company, Houston, Texas, USA.

**2.9 Oxidative stress indices**

Malondialdehyde (MDA)[30], reduced glutathione (GSH) [31] and glutathione peroxidase (GPx) [32] were assayed in the liver and heart homogenates of rats.

**2.10 Histological analyses**

The liver and kidney were harvested from the animals and used for histological analyses. They were immersed in 10% phosphate-buffered formalin, cut into tiny pieces, rinsed, and dehydrated in increasing grades of alcohol. The specimens were then cleaned in xylol, embedded in paraffin, sectioned at 4-6 microns thickness, and stained with Hematoxylin and Eosin for histopathological analyses[33].

**2.11 Statistical analysis**

The results obtained were depicted as mean ± SEM. One-way analysis of variance (ANOVA) was employed to ascertain the difference in mean between the groups. Tukey-Kramer test was utilized to check the significance levels at p-values less than 0.05. Statistical analysis was performed using SPSS version 23.

**2. Results**

**3.1 Anthropometric parameters of rats**

**3.1.1 Mean body weight**

From week 2 to 8, the mean body weight of rats treated with leaves extract of *Z. officinale* was significantly lower ($p < 0.05$) than the HFD control and not significantly different ($p > 0.05$) from the NFD control and orlistat group (Figure 1).

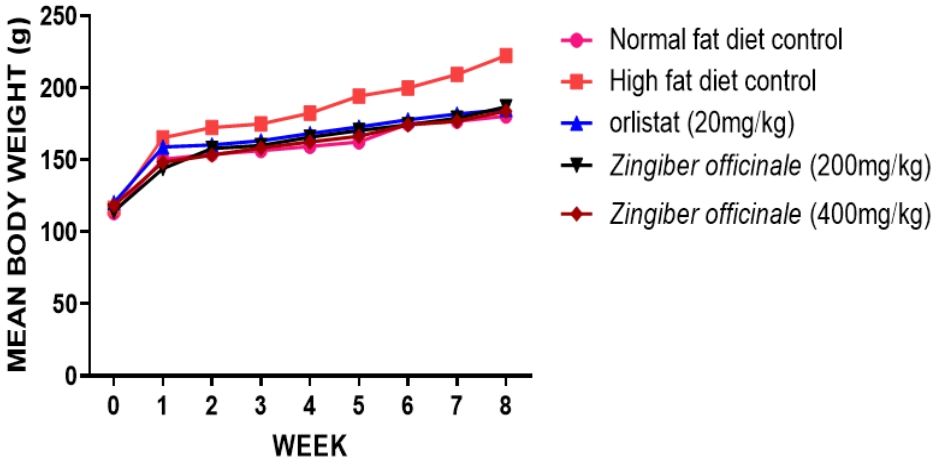


**Fig 1: Weekly mean body weight of rats**

Results are shown as mean±SEM (n = 6)

### 3.1.2 Body mass index and Lee's index

Body mass index and Lee's index of rats treated with leaves extract of *Z. officinale* were significantly lower ($p < 0.05$) than the HFD control but were not significantly different ($p > 0.05$) from the normal control and orlistat group (Table 2).

**Table 2 Body mass index (BMI) and Lee's index of rats**

| | BMI (g/cm$^2$) | Lee's index |
|---|---|---|
| **NFD control** | 0.42±0.008$^a$ | 0.26 ±0.003$^a$ |
| **HFD control** | 0.54 ±0.004$^b$ | 0.35 ±0.003$^b$ |
| **Orlistat (20mg/kg)** | 0.47 ±0.003$^c$ | 0.28 ±0.002$^a$ |
| ***Z. officinale* (200mg/kg)** | 0.43 ±0.003$^{ac}$ | 0.26 ±0.003$^a$ |
| ***Z. officinale* (400mg/kg)** | 0.43 ±0.004 $^{ac}$ | 0.28 ±0.003$^a$ |

Results are shown as mean±SEM (n = 6). Different alphabets in same column signifies significant difference between means ($p < 0.05$)

### 3.2 Feed consumption of rats

Daily feed consumed by rats treated with leaves extract of *Z. officinale* was not significantly different *($p > 0.05$)* from, orlistat, NFD control and HFD control (Figure 2).

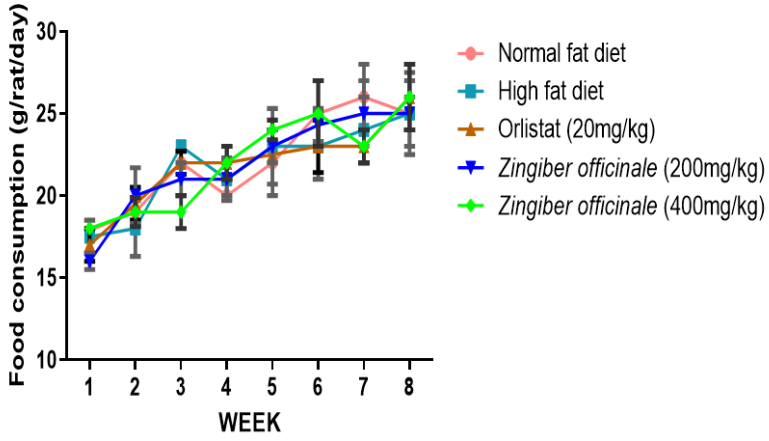


**Fig 2: Food consumption of rats**

Results are shown as mean±SEM (n = 6)

### 3.3 Serum lipid profile of rats

The *Zingiber officinale* leaves extract group had significantly lower ($p < 0.05$) total cholesterol, triglycerides, LDLC, VLDLC, AI, and CRI than the HFD control but was not significantly different ($p > 0.05$) from the normal control and orlistat group. However, HDLC was significantly higher ($p < 0.05$) in the *Zingiber officinale* leaves extract group than the HFD control, and no significant difference was seen in HDLC of the leaves extract group compared to the normal control/orlistat group (Tables 3 and 4).

**Table 3: Serum lipid profile of rats**

| | Total cholesterol (mg/dl) | Triglycerides (mg/dl) | HDL-C (mg/dl) | LDL-C (mg/dl) | VLDL-C (mg/dl) |
|---|---|---|---|---|---|
| **NFD control** | 79.34 ±1.60[a] | 76.50 ± 1.07[a] | 29.20 ±1.62[a] | 34.74 ±0.22[a] | 15.40 ±0.40[a] |
| **HFD control** | 108.57±1.00[b] | 106.30 ±1.08[b] | 18.02 ±1.05[b] | 69.20 ±0.20[b] | 21.25 ±0.10[b] |
| **Orlistat (20mg/kg)** | 80.00 ± 1.47[a] | 86.21 ±0.50[a] | 29.00 ±1.20[a] | 33.73±1.28[a] | 17.25± 0.51[a] |
| ***Z. officinale* (200mg/kg)** | 81.40±3.00[a] | 75.70 ± 1.50[a] | 29.90 ±1.20[a] | 36.35 ±1.05[a] | 15.15 ±1.22[a] |
| ***Z. officinale* (400mg/kg)** | 82.50 ± 1.25[a] | 82.25 ± 2.50[a] | 28.20 ±1.03[a] | 37.07 ±1.08[a] | 16.21 ±0.85[a] |

Results are shown as mean±SEM (n = 6). Different alphabets in same column signifies significant difference between means ($p < 0.05$)

**Table 4: Atherogenic index and coronary risk index of rats**

| | Atherogenic index | Coronary risk index |
|---|---|---|
| NFD control | 1.72±0.20[a] | 2.72±0.82[a] |
| HFD control | 5.05±0.32[b] | 6.03±0.50[b] |
| Orlistat (20mg/kg) | 1.76±0.28[a] | 2.76±0.78[a] |
| *Z. officinale* (200mg/kg) | 1.73±0.50[a] | 2.70±0.65[a] |
| *Z. officinale* (400mg/kg) | 1.90±0.25[a] | 2.91±0.55[a] |

Results are shown as mean±SEM (n = 6). Different alphabets in same column signifies significant difference between means ($p < 0.05$)

### 3.4 Adiposity of rats

The *Zingiber officinale* leaves extract group had significantly lower ($p < 0.05$) epididymal fat than the HFD control, significantly higher ($p < 0.05$) than the NFD control but was not significantly different ($p > 0.05$) from the orlistat group (Table 5).

The *Zingiber officinale* leaves extract group had significantly lower ($p < 0.05$) retroperitoneal fat and adiposity index than the HFD control but significantly higher ($p < 0.05$) than the NFD control. *Zingiber officinale* (200mg/kg) had significantly lower ($p < 0.05$) retroperitoneal fat and adiposity index than *Zingiber officinale* (400mg/kg) and the orlistat group (Table 5).

**Table 5: Epididymal fat, retroperitoneal fat and adiposity index of rats**

| | Epididymal fat (g) | Retroperitoneal fat (g) | Adiposity index (%) |
|---|---|---|---|
| NFD control | 0.73±0.10[a] | 0.58±0.01[a] | 0.73±0.01[a] |
| HFD control | 3.02±0.20[b] | 1.90±0.020[b] | 2.26±0.05[b] |
| Orlistat (20mg/kg) | 1.68±0.15[c] | 1.35±0.03[c] | 1.67±0.01[c] |
| *Z. officinale* (200mg/kg) | 1.40±0.20[c] | 1.25±0.01[d] | 1.44±0.01[d] |
| *Z. officinale* (400mg/kg) | 1.60±0.10[c] | 1.40±0.01[c] | 1.66±0.01[c] |

Results are shown as mean±SEM (n = 6). Different alphabets in same column signifies significant difference between means ($p < 0.05$)

### 3.5 Kidney function parameters of rats

There was no significant difference ($p > 0.05$) in sodium, potassium, and chloride concentrations of the *Zingiber officinale* leaves extract groups compared to HFD control, orlistat, and NFD control. However, bicarbonate concentration in *Zingiber officinale* leaves extract groups

was significantly higher ($p < 0.05$) than HFD control, orlistat, and NFD control (Table 6).

The concentration of urea in *Zingiber officinale* leaves extract groups was significantly lower ($p < 0.05$) than HFD control but not significantly different ($p > 0.05$) from orlistat and NFD control (Table 7).

The concentration of creatinine in *Zingiber officinale* leaves extract groups was significantly lower ($p < 0.05$) than HFD control but significantly higher ($p < 0.05$) than orlistat and NFD control (Table 7). *Zingiber officinale* (200mg/kg) had significantly lower ($p < 0.05$) creatinine concentration than the *Zingiber officinale* (400mg/kg) group (Table 7).

**Table 6: Serum electrolytes concentration of rats**

| | $Na^+$(mmol/L) | $K^+$(mmol/L) | $Cl^-$(mmol/L) | $HCO_3^-$ (mmol/L) |
|---|---|---|---|---|
| **NFD control** | 115.17±.148[a] | 16.08±0.92[a] | 83.45±1.89[a] | 142.78±0.94[ac] |
| **HFD control** | 117.83± 1.60[a] | 13.73±1.50[ab] | 92.97±4.68[a] | 79.00±3.33[b] |
| **Orlistat (20mg/kg)** | 118.17±2.01[a] | 13.89±0.37[ab] | 93.03±2.26[a] | 135.94±1.19[c] |
| ***Z. officinale* (200mg/kg)** | 111.5±1.95[ab] | 11.21±0.69[ab] | 93.08±2.67[a] | 154.39±2.30[d] |
| ***Z. officinale* (400mg/kg)** | 117.00±1.68[a] | 12.46±0.52[ab] | 89.72±2.22[a] | 151.38±3.68[d] |

Results are shown as mean±SEM (n = 6). Different alphabets in same column signifies significant difference between means ($p < 0.05$)

**Table 7: Urea and creatinine concentration of rats**

| | Urea (mg/dL) | Creatinine (mg/dL) |
|---|---|---|
| **NFD control** | 27.34±1.31[a] | 27.68±1.06[a] |
| **HFD control** | 38.14±0.35[b] | 155.03±1.50[b] |
| **Orlistat (20mg/kg)** | 26.32±0.42[a] | 89.69±1.71[c] |
| ***Z. officinale* (200mg/kg)** | 26.23±0.38[a] | 124.56±1.72[d] |
| ***Z. officinale* (400mg/kg)** | 25.31±0.46[a] | 134.41±0.81[e] |

Results are shown as mean±SEM (n = 6). Different alphabets in same column signifies significant difference between means ($p < 0.05$)

**3.6 Effect of leaf extract of *Zingiber officinale* on liver function parameters of rats**

The activity of ALT in *Zingiber officinale* leaves extract groups was significantly lower ($p < 0.05$) than HFD control but significantly higher ($p < 0.05$) than orlistat and NFD control (Table 8).

The activity of AST in *Zingiber officinale* leaves extract groups was significantly lower ($p < 0.05$) than HFD control. *Zingiber officinale* (200mg/kg) had significantly lower ($p < 0.05$) AST activity than *Zingiber officinale* (400mg/kg) and NFD control but was not significantly different from the orlistat group (Table 8).

The activity of ALP in *Zingiber officinale* leaves extract groups was significantly lower ($p < 0.05$) than HFD control. *Zingiber officinale* (200mg/kg) had significantly lower ($p < 0.05$) ALP activity than *Zingiber officinale* (400mg/kg) and orlistat group but was not significantly different from NFD control (Table 8).

The concentration of bilirubin in *Zingiber officinale* leaves extract groups was significantly lower ($p < 0.05$) than orlistat and HFD control. *Zingiber officinale* (400mg/kg) had significantly lower ($p < 0.05$) bilirubin concentration than *Zingiber officinale* (200mg/kg) and NFD control (Table 9).

The concentration of total protein in *Zingiber officinale* leaves extract groups was significantly greater ($p < 0.05$) than

HFD control but not significantly different from NFD control. *Zingiber officinale* (200mg/kg) had significantly greater ($p < 0.05$) total protein than the orlistat group (Table 9).

The concentration of albumin in *Zingiber officinale* leaves extract groups was significantly greater ($p < 0.05$) than HFD control, significantly lower than NFD control, but not significantly different from the orlistat group (Table 9).

**Table 8: Liver function enzymes of rats**

| | ALT (U/L) | AST (U/L) | ALP (U/L) |
|---|---|---|---|
| **NFD control** | 21.89±0.29[a] | 19.17±0.12[a] | 48.38±0.11[a] |
| **HFD control** | 30.60±1.40[b] | 27.57±0.22[b] | 53.60±0.02[b] |
| **Orlistat (20mg/kg)** | 21.20±0.34[a] | 14.82±0.23[c] | 50.42±0.09[c] |
| ***Z. officinale* (200mg/kg)** | 23.68±0.26[c] | 14.68±0.29[c] | 48.33±0.12[a] |
| ***Z. officinale* (400mg/kg)** | 24.80±0.33[c] | 19.30±0.24[a] | 50.35±0.10[c] |

Results are shown as mean±SEM (n = 6). Different alphabets in same column signifies significant difference between means ($p < 0.05$)

**Table 9: Bilirubin, total protein and albumin concentrations of rats**

| | Bilirubin(µmol/L) | Total protein (g/dL) | Albumin (g/dL) |
|---|---|---|---|
| **NFD control** | 18.24±0.73[a] | 7.17±0.35[ac] | 4.14±0.02[a] |
| **HFD control** | 34.73±0.81[b] | 6.01±0.06[b] | 2.74±0.01[b] |
| **Orlistat (20mg/kg)** | 21.83±0.42[c] | 7.03±0.01[c] | 3.94±0.02[c] |
| ***Z. officinale* (200mg/kg)** | 18.37±0.79[a] | 7.42±0.08[a] | 3.80±0.03[c] |
| ***Z. officinale* (400mg/kg)** | 15.41±0.41[d] | 7.28±0.12[ac] | 3.72±0.06[c] |

Results are shown as mean±SEM (n = 6). Different alphabets in same column signifies significant difference between means ($p < 0.05$)

**3.7 Cardiac function tests**

The activity of creatine kinase in *Zingiber officinale* leaves extract groups was significantly lower ($p < 0.05$) than HFD control and the orlistat group but not significantly different from NFD control (Table 10).

The activity of lactate dehydrogenase in *Zingiber officinale* leaves extract groups was significantly lower ($p < 0.05$) than HFD control but significantly higher ($p < 0.05$) than NFD control. Lactate dehydrogenase of *Zingiber officinale* (200mg/kg) was significantly lower ($p < 0.05$) than *Zingiber officinale* (400mg/kg) but was not significantly different from the orlistat group (Table 10).

**Table 10: Cardiac function enzymes of rats**

| | Creatinine kinase (U/L) | Lactate dehydrogenase (U/L) |
|---|---|---|
| **NFD control** | 10.47±0.19[a] | 23.25±1.42[a] |
| **HFD control** | 16.56±0.18[b] | 84.93±0.80[b] |
| **Orlistat (20mg/kg)** | 12.62±0.03[c] | 58.74±0.65[c] |
| ***Z. officinale* (200mg/kg)** | 10.60±0.27[a] | 58.87±0.43[c] |
| ***Z. officinale* (400mg/kg)** | 11.26±0.18[a] | 75.48±0.23[d] |

Results are shown as mean±SEM (n = 6). Different alphabets in same column signifies significant difference between means ($p < 0.05$)

**3.8 In vivo antioxidant parameters of rats**

For both the liver and heart, GSH concentration in *Zingiber officinale* leaves extract groups was significantly higher ($p < 0.05$) than HFD control but significantly lower ($p < 0.05$) than NFD control. However, GSH concentration of *Zingiber officinale* (400mg/kg) was significantly higher ($p < 0.05$) than *Zingiber officinale* (200mg/kg) and the orlistat group (Tables 11 and 12).

For liver MDA concentration, *Zingiber officinale* leaves extract groups were significantly lower ($p < 0.05$) than HFD control, while *Zingiber officinale* (200mg/kg) had significantly lower ($p < 0.05$) MDA concentration than *Zingiber officinale* (400mg/kg), NFD control, and the orlistat group (Table 11).

In the heart, MDA concentration of *Zingiber officinale* leaves extract groups was significantly lower ($p < 0.05$) than HFD control but significantly higher ($p < 0.05$) than NFD control and the orlistat group. Also, *Zingiber officinale* (400mg/kg) had significantly lower ($p < 0.05$) MDA concentration than *Zingiber officinale* (200mg/kg) (Table 12).

Liver GPx activities in *Zingiber officinale* leaves extract groups were significantly higher ($p < 0.05$) than HFD control but not significantly different from NFD control. GPx activity of *Zingiber officinale* (400mg/kg) was significantly higher ($p < 0.05$) than *Zingiber officinale* (200mg/kg) and the orlistat group (Table 11).

Heart GPx activities in *Zingiber officinale* leaves extract groups were significantly higher ($p < 0.05$) than HFD control, significantly lower ($p < 0.05$) than NFD control but not significantly different from the orlistat group (Table 12).

**Table 11: Antioxidant parameters in liver of rats**

| | GSH (ng/mg protein) | MDA (nmoles /mg protein) | GPx (nmoles/ min/ mg protein) |
|---|---|---|---|
| **NFD control** | $1.94\pm0.01^{a}$ | $0.89\pm0.01^{a}$ | $0.81\pm0.02^{ad}$ |
| **HFD control** | $0.82\pm0.01^{b}$ | $2.53\pm0.13^{b}$ | $0.24\pm0.02^{b}$ |
| **Orlistat (20mg/kg)** | $1.67\pm0.01^{c}$ | $0.64\pm0.02^{c}$ | $0.73\pm0.02^{ac}$ |
| ***Z. officinale* (200mg/kg)** | $1.44\pm0.01^{d}$ | $0.45\pm0.03^{d}$ | $0.76\pm0.01^{ac}$ |
| ***Z. officinale* (400mg/kg)** | $1.74\pm0.02^{e}$ | $0.90\pm0.01^{a}$ | $0.87\pm0.01^{d}$ |

Results are shown as mean±SEM (n = 6). Different alphabets in same column signifies significant difference between means ($p < 0.05$)

**Table 12: Antioxidant parameters in heart of rats**

| | GSH (ng/mg protein) | MDA (nmoles /mg protein) | GPx (nmoles/ min/ mg protein) |
|---|---|---|---|
| **NFD control** | $1.49\pm0.02^{a}$ | $0.46\pm0.03^{a}$ | $1.73\pm0.07^{a}$ |
| **HFD control** | $0.65\pm0.02^{b}$ | $1.80\pm0.01^{b}$ | $0.56\pm0.02^{b}$ |
| **Orlistat (20mg/kg)** | $1.16\pm0.01^{c}$ | $0.42\pm0.01^{a}$ | $1.21\pm0.04^{c}$ |
| ***Z. officinale* (200mg/kg)** | $1.05\pm0.01^{d}$ | $0.64\pm0.01^{c}$ | $1.04\pm0.01^{c}$ |
| ***Z. officinale* (400mg/kg)** | $1.31\pm0.02^{e}$ | $0.55\pm0.01^{d}$ | $0.96\pm0.02^{c}$ |

Results are shown as mean±SEM (n = 6). Different alphabets in same column signifies significant difference between means ($p < 0.05$)

**3.9 Adipokines and cytokines concentrations**

There was no significant difference ($p > 0.05$) in leptin concentration of *Zingiber officinale* leaves extract groups, NFD control, HFD control, and the orlistat group. The concentration of adiponectin in *Zingiber officinale* leaves extract groups was significantly higher ($p < 0.05$) than HFD control and the orlistat group but significantly lower than NFD control. Also, adiponectin concentration of *Zingiber officinale* (400mg/kg) was significantly higher ($p < 0.05$) than *Zingiber officinale* (200mg/kg) (Table 13).

The concentration of TNFα in *Zingiber officinale* leaves extract groups was significantly lower ($p < 0.05$) than HFD control, NFD control, and the orlistat group. Also, TNFα of *Zingiber officinale* (400mg/kg) was significantly higher ($p < 0.05$) than *Zingiber officinale* (200mg/kg) (Table 13).

The concentration of IL-6 in *Zingiber officinale* leaves extract groups was significantly lower ($p < 0.05$) than HFD control, not significantly different from the orlistat group, but significantly higher than NFD control.

**Table 13: Adipokines and cytokines concentrations of rats**

| | Leptin (pg/mL) | Adiponectin (ng/mL) | TNFα (ng/mL) | IL-6 (ng/mL) |
|---|---|---|---|---|
| **NFD control** | 213.83±4.12[a] | 2.63±0.01[a] | 179.94±1.37[a] | 264.86±0.74[a] |
| **HFD control** | 213.51±2.19[a] | 0.63±0.01[b] | 296.09±1.41[b] | 395.43±1.08[b] |
| **Orlistat (20mg/kg)** | 222.02±2.52[a] | 1.93±0.04[c] | 206.85±1.32[c] | 301.35±0.38[c] |
| ***Z. officinale* (200mg/kg)** | 223.60±3.34[a] | 2.28±0.08[d] | 151.29±2.05[d] | 302.67±0.89[c] |
| ***Z. officinale* (400mg/kg)** | 222.77±0.58[a] | 2.49±0.01[e] | 167.50±1.12[e] | 300.18±2.31[c] |

Results are shown as mean±SEM (n = 6). Different alphabets in same column signifies significant difference between means ($p < 0.05$)

### 3.10 Liver and kidney histology of rats

#### 3.10.1 Liver histology

NFD control showed normal hepatic histology with clearly delineated portal triads, central veins, and spirally arranged hepatocytes. Hepatocytes featured large nuclei with conspicuous nucleoli. No obvious pathological changes or hepatocyte degeneration were observed in other groups (Plate 1).

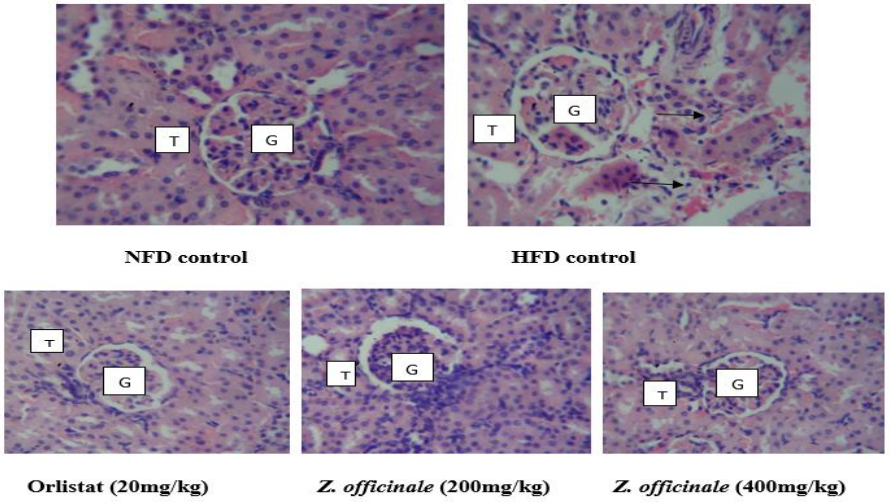


**Plate 1: Histological changes in liver of experimental groups. H&E; Magnification = x400. Black arrow– hepatic nuclei; white arrow– portal triad**

#### 3.10.2 Kidney histology

NFD control showed normal renal histology with distinct renal corpuscles consisting of intact glomeruli and narrow Bowman spaces surrounding the glomeruli. Additionally, numerous intact tubules (proximal and distal tubules) were seen in the kidney cortex. Extract and orlistat treated groups also showed mostly intact renal histology. However, HFD control showed mild hemorrhage into the tissue parenchyma with mild inflammatory infiltrate (Plate 2).

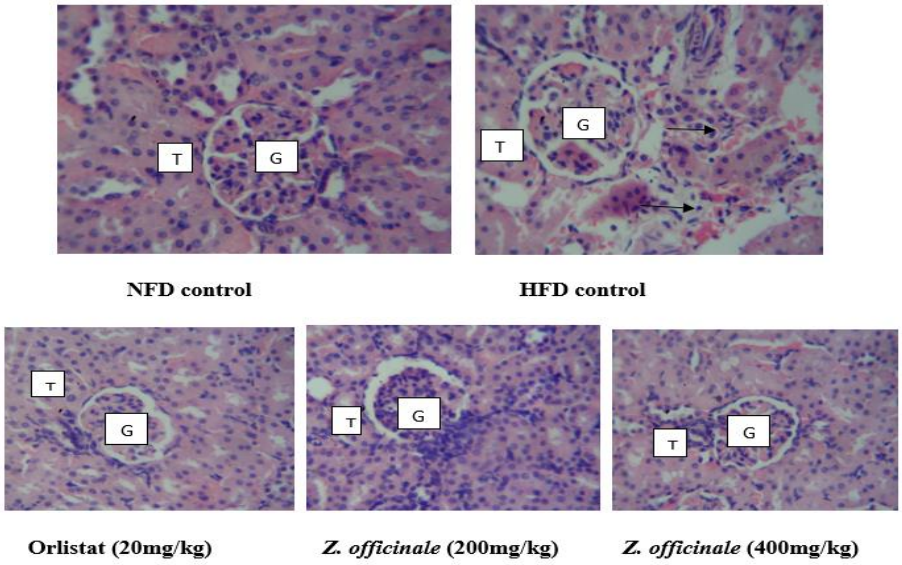


**Plate 2: Histological changes in kidney of experimental groups. H&E; Magnification = x400. G – glomerulus; T – renal tubules; arrows – mild haemorrhage with inflammatory infiltrate**

## DISCUSSION

This study was conducted to evaluate the anti-obesity effect of methanol leaves extract of *Zingiber officinale* in Wistar rats fed with HFD. HFD-induced obesity in rats is regarded as a reliable technique for studying anti-obesity activity[34].

In this research, consumption of calorically dense HFD led to an increase in body weight, weights of epididymal and retroperitoneal fats. However, *Z. officinale* leaves extract-treated groups had significantly lower ($p < 0.05$) body weights than HFD control but were not significantly different from NFD control and the orlistat group. There was also a significant decline ($p < 0.05$) in adiposity of *Z. officinale* leaves extract groups compared to HFD control, which was comparable to that of the reference drug, Orlistat. Orlistat is a derivative of lipstatin that inhibits the activity of pancreatic lipase, resulting in reduced dietary fat absorption[35]. Similarly, Nazish *et al.* [36] reported a significant decrease in body weights and adiposity of rats fed with HFD and treated with *Z. officinale* rhizomes compared to HFD control. The ability of methanol leaves extracts of *Z. officinale* to decrease body weight and adiposity of rats might be attributed to singular or synergistic activities of the phytochemicals in it. Leaves of *Z. officinale* have been reported to be rich in flavonoids, tannins, saponins, and glycosides[24]. Some of these compounds have anti-obesity properties. Specifically, flavonoids have been found to possess anti-obesity effects by inhibiting adipogenesis and lipogenesis[37]. In addition, saponins have been found to exhibit anti-obesity effects by inhibiting adipocyte hypertrophy[38].

Lipid profile, CRI, and AI have been shown to be significant determinants of metabolic disturbances such as atherosclerosis, cardiovascular diseases, hypertension, and dyslipidemia. Any increase in concentrations of lipids raises the risk for atherosclerotic plaques, cardiovascular diseases, and endothelial dysfunction[39]. In this study, methanol leaves extract of *Z. officinale* demonstrated an anti-dyslipidemic effect by restoring the lipid profile, lowering AI and CRI in the rats. These results support those of Ramadan *et al.*[40] in which *Z. officinale* rhizomes produced anti-dyslipidaemic effect in HFD induced rats.

A reliable and fast method for the determination of obesity in rats was described by Lee [41] and was named "Lee index". Lee index and fat mass have a positive correlation. Rats with Lee's index equal to or greater than 0.3 are considered obese, according to Malafaia *et al.*[42] BMI is another anthropometric parameter that can be used to estimate obesity in rats[43]. Results obtained indicated that *Z. officinale* leaves extract-treated groups had significantly lower ($p < 0.05$) BMI and Lee's index than HFD control but were not significantly different from NFD control and the orlistat group. Furthermore, *Z. officinale* leaves extract, orlistat, and NFD groups had Lee's index below 0.3 and can be regarded as non-obese, whereas HFD control had Lee's index higher than 0.3 and may be regarded as obese rats based on the explanation by Malafaia *et al.*[42].

Results from this study showed that the extract of *Z. officinale* leaves exhibited anti-obesity activity in rats without affecting feed consumption. This is because there was no significant difference in daily feed consumption of *Z. officinale* (methanol leaves extract) groups compared to HFD control. Research by Nazish *et al.* [36] also showed that *Z. officinale* rhizomes also produced anti-obesity effect in rats fed with HFD without altering feed consumption of the rats.

HFD is known to affect liver metabolism, causing steatosis, which is a complicated disorder related to mitochondrial changes and increased formation of reactive oxygen species[44]. This concept explains the significant reduction ($p < 0.05$) in AST, ALT, ALP, bilirubin with an increase in the concentration of albumin and total proteins of the *Z. officinale* leaves extract, NFD control, and orlistat groups compared to HFD control. AST activity and albumin concentration of *Z. officinale* leaves extract groups were not significantly different from the orlistat group, and *Z. officinale* leaves extract groups had significantly higher ($p < 0.05$) ALT than NFD control. Similar findings were made by Vanissa *et al.* [45] where treatment of HFD fed rats with *Z. officinale* rhizomes extract restored liver function of rats to normal.

Obesity and dyslipidaemia are risk factors for cardiovascular diseases[46]. This research showed that there was a significant reduction ($p < 0.05$) in the activities of cardiac function enzymes (creatine kinase and lactate dehydrogenase) in *Z. officinale* leaves extract, NFD control, and orlistat groups in comparison with HFD control. Creatine kinase of *Z. officinale* leaves extract groups was significantly lower than the orlistat group but was not significantly different from NFD control. Cardioprotective effects of *Z. officinale* rhizomes extract in rats have been reported by Ojo *et al.*[47].

HFD induced obesity may cause renal injury and inflammation [48]. In this study, renal injury of rats induced by HFD was ameliorated by the methanol leaves extract of *Z. officinale* and orlistat in their respective groups. This explains the observed significant decrease ($p < 0.05$) in kidney function markers (urea and creatinine) in the leaves extract of *Z. officinale*, NFD control, and orlistat groups in comparison with HFD control. Urea levels for the methanol leaves extract of *Z. officinale* groups were not significantly different from orlistat and NFD control, whereas creatinine levels for the methanol leaves extract of *Z. officinale* groups were significantly higher than orlistat and NFD control. Low bicarbonate concentration is synonymous with metabolic acidosis, which indicates kidney failure[49]. The result from this study also revealed that bicarbonate concentrations in *Zingiber officinale* leaves extract groups were significantly higher ($p < 0.05$) than HFD control, orlistat, and NFD control. Furthermore, renal histology revealed that the methanol leaves extract of *Z. officinale* and orlistat groups had normal kidney histology similar to NFD control, whereas HFD control had inflammation and mild hemorrhage. These findings are in agreement with those of Vanissa *et al.*, in which the extract of *Z. officinale* rhizomes protected the kidney of rats fed with HFD.

Research has shown that the consumption of HFD causes oxidative stress because it attenuates the hepatic antioxidant enzyme system and increases the levels of products of lipid peroxidation in the liver and plasma[50]. Methanol leaves extract of *Z. officinale* protected against oxidative damage

caused by HFD in rats by significantly ($p < 0.05$) raising the activity of an antioxidant enzyme, GPx, and the concentration of GSH (a powerful antioxidant that directly quenches ROS), thus leading to lowered concentration of MDA (a product of lipid peroxidation) in the liver and heart of rats when compared to HFD control. Liver and heart GSH levels of *Z. officinale* leaves extract groups were significantly lower ($p < 0.05$) than NFD control. Heart MDA levels for *Z. officinale* leaves extract groups were significantly higher ($p < 0.05$) than orlistat and NFD control. No significant difference was observed in the liver GPx activities of *Z. officinale* leaves extract groups and NFD control. These results support that of Ramadan *et al.* [40] where *Z. officinale* rhizomes led to a reduction in oxidative stress of rats fed with HFD.

Methanol leaves extract of *Z. officinale* also showed a protective effect against inflammation induced by HFD. This is seen from the significant reduction ($p < 0.05$) in the concentration of proinflammatory cytokines (TNFα and IL-6) in comparison with HFD control. TNFα levels of *Z. officinale* leaves extract groups were significantly lower ($p < 0.05$) than orlistat and NFD control. However, IL-6 levels of *Z. officinale* leaves extract groups were significantly higher ($p < 0.05$) than NFD control but not significantly different from the orlistat group.

Leptin (an appetite-suppressing hormone) is synthesized by adipocytes, and it acts on the hypothalamus, resulting in reduced food intake[51]. There was no significant difference ($p > 0.05$) in leptin concentrations of all groups. This could justify why feed consumption of rats (appetite) in various groups did not differ significantly. This result supports that of Hussain *et al.* [52] whose work also showed no significant difference in leptin levels of HFD- obese control rats and other non-obese rats. Adiponectin is produced largely in adipocytes. One of its major physiological effects is that it decreases gluconeogenesis and lipogenesis in the liver, thereby resulting in decreased blood glucose and fat concentrations[53]. Unlike leptin, adiponectin levels are lowered in obesity. There is an inverse relationship between adiponectin levels and the percentage of body fat[54]. Thus, in this study, adiponectin levels of *Z. officinale* leaves extract groups were significantly higher ($p < 0.05$) than HFD control. Also, adiponectin levels of *Z. officinale* leaves extract groups were significantly lower ($p < 0.05$) than NFD control but significantly higher ($p < 0.05$) than the orlistat group.

## CONCLUSION

This study has shown that the methanol leaves extract of *Z. officinale* possesses significant anti-obesity properties that are similar to orlistat (a reference anti-obesity drug). This anti-obesity effect might be mediated through the regulation of fat metabolism. Additionally, the methanol leaves extract of *Z. officinale* protected rats against oxidative damage, inflammation, liver, kidney, and cardiac toxicity induced by HFD. However, further study to characterize the active compounds in the extract is recommended.

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## AUTHOR CONTRIBUTIONS

OI contributed to conceptualization, methodology, data interpretation and writing a draft of the manuscript. ESU contributed to investigation, methodology, supervision and revision of the manuscript. IOA contributed to methodology and revision of the manuscript. NEO participated in methodology, data analysis and interpretation. OLA contributed to methodology and data analysis. All the authors read and approved the final copy of the manuscript.

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## COMPETING INTERESTS

No competing interests were declared by the authors

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# أظهر مستخلص أوراق الميثانول من (ginger) *Zingiber officinale* تأثيرًا مضادًا للسمنة في فئران Wistar التي تتغذى على نظام غذائي عالي الدهون

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## ملخص

قيمت هذه الدراسة خاصية مكافحة السمنة لمستخلص الميثانول من أوراق *Zingiber officinale* في فئران Wistar. تم توزيع ثلاثين من ذكور الجرذان في خمس مجموعات مع ستة فئران في كل مجموعة وعولجت مجموعات مختلفة بنظام غذائي طبيعي للدهون ( NFD، نظام غذائي عالي الدهون 20 ) HFD + orlistat ( HFD ), مجم / كجم ) p.o، HFD + 200 ) *Zingiber officinale* مجم / كجم ) p.o و HFD + *Zingiber officinale*). بعد جميع الإدارات ، تم التضحية بالحيوانات عن طريق خلع عنق الرحم وأجريت تحليلات كيميائية حيوية مختلفة. أظهرت النتائج أنه كان هناك انخفاض كبير ( p ug 0.05) في وزن الجسم والسمعة في مجموعات *Zingiber officinale* و NFD و orlistat مقارنة مع التحكم في HFD. ومع ذلك، لم يكن هناك فرق كبير في أوزان الجسم للفئران في مجموعات *Zingiber officinale* مقارنة مع مجموعات NFD للتحكم و orlistat. علاوة على ذلك، كان لدى الفئران في مجموعات *Zingiber officinale* تركيزات دهنية طبيعية، وحالة مضادة للأكسدة، والأدييوكينات، والسيتوكينات، والكبد، معلمات وظائف الكلى والقلب التي يمكن مقارنتها مع أورليستات والتحكم الطبيعي ولكن على النقيض من التحكم HFD. تشير نتائج الدراسة إلى أن أوراق *Zingiber officinale* لها خصائص كبيرة مضادة للسمنة ومضادات الأكسدة ومضادة للالتهابات.

**الكلمات الدالة:** نبات الزنجبيل، وزن الجسم، الأنسجة الدهنية، السيتوكينات، أورليستات، الأدييوكينات، مضادات الأكسدة.

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