

Antiobesity activity of *Zingiber officinale*

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ABSTRACT

Context: *Zingiber officinale* Roscoe (Zingiberaceae) rhizome, known commonly as ginger is extensively used in Indian traditional system of medicine for treatment of various disorders. The ethanolic *Z. officinale* extract is reported to have various activity such as antidiabetic, antihyperlipidemic and antioxidant activity in experimental animals. **Objective:** To evaluate anti-obesity effect of aqueous *Z. officinale* extract in murine model of high fat diet (HFD)- induced obesity. **Materials and Methods:** Male Wistar rats fed with HFD (20 g/day/rat, p.o) for a period of 42 days were used to induce obesity. Aqueous *Z. officinale* extract (20 mg/kg b.w.) administered orally to HFD fed rats from day 8 to 50 days for a period of 42 days. Body weight gain, serum lipids, insulin and leptin parameters were measured. **Results:** Oral feeding of the aqueous *Z. officinale* extract (20 mg/kg) to HFD-induced obese rats for a period of 42 days resulted in

significant reduction in body weight gain, insulin, leptin, lipids as compared to rats fed HFD alone. Further, the extract also showed significant increase in high density lipoprotein (HDL-C) levels. **Discussion and Conclusion:** These results show that aqueous *Z. officinale* extract possess significant anti-obesity potential.

Key words: *Zingiber officinale*, Leptin, High-fat diet, Rat, Insulin.

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INTRODUCTION

Obesity generally described as a condition of abnormal body weight resulting from an accumulation of extra adipose tissue, basically in response to a state of positive energy balance that occurs when intake exceeds energy expenditure. It is a growing global health problem in the present era. Obesity is a chronic relapsing, stigmatized neurochemical disease that is more prevalent in developing and developed countries and leading to much comorbidities.¹

Obesity, which is associated with serious morbidities including a high incidence of type 2 diabetes, hyperlipidemia, hypercholesterolemia, cardiovascular disease, osteoarthritis, and many more diseases.¹⁻² Obesity is a disorder not a disease, but, it has been recognized as a chronic disease by National Institute of health consensus conference in 1985 due to the increasing prevalence and associated risks.² This situation currently prevailing widely, anti-obesity drugs expanding rapidly in the market, but drugs are sparse in relation to need. Hence, novel anti-obesity drug is required to handle the problem.

Plants and natural products are long been recognized as an important sources for the therapeutically effective medicines. Approximately 80% of the world's population relies on plants for the natural products and medication. Of the 520 new drugs approved between 1983 and 1994, 39% were of natural origin and 60-80% of antibacterial and anticancer drugs were derived from natural products. Infact several Indian medicinal plants or extracts have been used as anti-obesity plant.³

Z. officinale, commonly known as Ginger, (family Zingiberaceae). *Z. officinale* rhizome contains 1-4% essential oil and an oleoresin. The essential oil varies as a function of geographical origin, but the chief constituent is sesquiterpene hydrocarbons. These compounds include (-)-zingiberene, (+)-ar-curcumene, (-)-β-sesquiphellandrene, and β-bisabolene. The rhizome cure tumors, ascites, bronchitis, jaundice and mental disorders, also have antidiabetic, antidyslipidemic, cardioprotective and antioxidant.⁴⁻⁶

However, aqueous extract of *Z. officinale* has not been investigated for its anti-obesity potential so far. Hence, this study was carried out to test

the hypothesis that aqueous extract of *Z. officinale* may have anti-obesity activity in high fat diet (HFD)- induced obesity in Wistar rats.

MATERIALS AND METHODS

Plant material

Dried *Z. officinale* fruits were purchased from Local market Kharibaoli, Delhi and authenticated by Dr. H. B. Singh, expert taxonomist, National Institute of Science Communication and Information Resources (NISCAIR), New Delhi, India.

Preparation of aqueous *Z. officinale* extract

All plant materials were washed; shade dried and powdered, then extracted with water in a soxhlet apparatus for 72 hours. The solvent was removed under reduced pressure to give a dry extract, 5% yield w/w with respect to the crude material and stored at - 20°C till experiment was not started. The weighed amount of aqueous extract was suspended in 1% gum acacia in normal saline for pharmacological activity. This extract was used for phytochemical analysis for standardization.

Macroscopical studies

The material of *Z. officinale* were subjected to macroscopical studies which comprised of organoleptic characteristics of the drug viz., size, colour, odour, taste, smell, texture, fracture etc.

Microscopical studies

Qualitative microscopic evaluation was carried out by taking powder. 5 g of the drug sample was taken, powdered. The powdered material was taken on an 85 mesh sieve and allowed in slow running water for washing away the minerals. The materials were cleared in chloral hydrate, wash with distilled water and mounted in glycerin, then observed characters.^{7,8}

Animals and Diets

The female Wistar rats (100-150 g) were procured from central animal house facility of Hamdard University, New Delhi, India. The animals

were housed in standard polypropylene cages and maintained under controlled room temperature ($22 \pm 2^\circ\text{C}$) and humidity ($55 \pm 5\%$) with 12 h light and 12 h dark cycle. All the rats in Normal group were provided with commercially available rodent chow diet (Amrut rat feed, Nav Maharashtra Chakan Oil Mills Ltd, Delhi, India) and tap water ad libitum. The guidelines of committee for the purpose of control and supervision of experiments on animals (CPCSEA), Government of India were followed and prior permission was sought from the Institutional Animal Ethics Committee, Jamia Hamdard, New Delhi for conducting the study.

HFD- induced obesity

Rats were fed a HFD (20 g/rat/day) in a pellet form and water ad libitum for the period of 6 weeks. HFD was purchased from National Centre for Laboratory Animal Science (NCLAS), National Institute of Nutrition (NIN), Hyderabad, India. Composition of HFD is shown in (Table 1).

Experimental Design

In this study, a total of 50 rats were used and divided into five groups of 6 rats each. Group 0020I: normal healthy control rats fed with rodent chow diet and administered 1% gum acacia (1 ml/kg, body weight (bw)) for the period of 42 days (NC); Group II: obesity control rats fed with HFD (20g/rat/day) for the period of 42 days (HFD); Group III: rats fed with HFD (20g/rat/day) for the period of 42 days, treated with aqueous *Z. officinale* extract (20 mg/kg, bw) for period of 42 days (HFD+ZO); Group IV: rats fed with HFD (20g/rat/day) for the period of 42 days, treated with Orlistate (5 mg/kg, bw) for period of 42 days (HFD+ ORL); Group V: rats fed with rodent chow diet for the period of 42 days + treated with aqueous *Z. officinale* extract (20 mg/kg, bw) for period of 42 days (ZO per se). All the drugs were administered orally via a standard orogastric cannula (Table 2).

Food and water intakes were measured daily for the period of 42 days at the same time. Food intake and water intake were measured on per cage basis (6 rats per cage) and the average food and water consumed were calculated. At the end of the experimental period (on 43 th day), the animals were anesthetized with ether, following overnight fasting. Blood was drawn by retro-orbital method into a tube and the serum was obtained by centrifugation. After collection of blood, rats were sacrificed; heart and perirenal, epididymal, mesenteric fat pads were excised immediately, rinsed with phosphate buffer saline and weighed. The serum and heart samples were stored at -70°C until analysis.

Anthropometric measurements

The body weights were determined once a week. Body mass index (BMI) was calculated from formula:

$$\text{BMI} = \text{Body weight (g)} / \text{length}^2 \text{ (cm}^2\text{)}$$

Biochemical serum analyses

Serum glucose, triglyceride (TG) and total cholesterol (TC) levels were determined by enzymatic methods using commercial assay kits (SPAN Diagnostics Ltd, Surat, India) according to the manufacturer's protocols. Serum High-density lipoprotein cholesterol (HDL- C) levels were determined using HDL Cholesterol Test Kit (Reckon Diagnostics P. Ltd, Baroda, India). Serum leptin and insulin levels were measured by immunoassays using a commercially available ELISA assay kit from Ray Biotech, Inc (Norcross, US) and Crystal Chem Inc (Downers Grove, IL 60515, USA) respectively. Low-density lipoprotein cholesterol (LDL-C) levels were calculated using Friedewald formula.⁹ Serum very

low density lipoprotein cholesterol fraction (VLDL-C) concentration was calculated by deduction of the sum of HDL-C and LDL-C concentrations from that of TC.

Statistical analysis

Data are expressed as the mean \pm standard error of the mean (SEM). The statistical significance of difference between the mean values for the treatment groups was analysed by ANOVA (analysis of variance) followed by Dunnett's t- test using Graph pad InStat[®] version 3.06 (Graph Pad Software, San Diego, CA, USA). Values of $p < 0.05$ were considered significant.

RESULTS

Macroscopical Studies

The *Z. officinale* are light brown colored irregular shaped rhizome, odour pleasant, Pungent taste and rough textured shown in (Figure.1). The organoleptic evaluations of *Z. officinale* were showed in (Table 3).

Microscopic study

For microscopic study, 5 g of the drug sample was taken, powdered. The powdered material was

taken on a 85 mesh sieve and allowed in slow running water for washing away the minerals. The materials were cleared in chloral hydrate, wash with distilled water and mounted in glycerin, then observed characters⁸ (Figure 2).

Effect on Food and Water intake

Negligible ($P > 0.05$) change in food and water intake was observed in HFD fed group as compared to the NC group. Administration of aqueous *Z. officinale* extract (20 mg/kg) along with HFD (HFD + ZO group) did not produce significant change in the food and water intake as compared to HFD group (Table 4).

Effect on anthropometric Parameters

In the HFD group body weight gain of rats was greater than the values for the NC. HFD supplemented with 20 mg/kg aqueous *Z. officinale* extract reduced body weight gain of the rats. However, there was no significant difference in body weight gain among the NC and ZO per se treated groups (Table 4).

Effect on organ weight and fat pad analysis

No significant changes in weights of heart, kidney, liver and spleen in drug treated albino rats as compared to control and high fat diet fed group except weight of kidney was reduced significantly ($P < 0.05$). However, drug treatment has variably restricted increase in fat pad weights compared to high fat diet group significantly ($P < 0.01$) (Table 5 & 6).

Effect on serum lipid levels

Serum TG levels were significantly higher in HFD fed group compared to that of NC group, HFD+ ZO group ($p < 0.01$). Levels of serum TC, LDL-C, VLDL-C were similar to tendency of serum triglyceride level ($p < 0.01$). However, TC, LDL-C and HDL-C were significantly ($p < 0.05$) affected in HFD+ ZO treated group Serum levels of HDL-C were higher in HFD+ ORL treated group compared to HFD fed and NC group, significant difference was recognized ($p < 0.001$) (Table 7).

Table 1: Compositions of the HFD (g/kg diet)

Ingredients	Quantity
Casein	342.0
L-Cystine	3.0
Starch	172.0
Sucrose	172.0
Cellulose	50.0
Ground nut oil	25.0
Tallow	190.0
AIN Salt mix	35.0
AIN Vitamin mix	10.0
Total (g)	999.0

Table 2: Experimental design

Groups	No. of animals
Normal control	6
Obese control (HFD)	6
HFD + <i>Z. officinale</i> (20 mg/kg)	6
HFD + Orlistat std (5 mg/kg)	6
<i>Z. officinale</i> per se	6
	30

Table 3: Organoleptic properties of *Z. officinale*

Colour	Light brown
Shape	Irregular
Odour	Pleasant
Texture	Rough
Taste	Pungent

Table 4: Effect of aqueous *Z. officinale* extract (20 mg/kg) on food intake, water intake, and body weight gain in HFD-induced obesity in wistar rats

Groups	Food intake (gm/day/rat)	Water intake (ml/day/rat)	Body weight gain (g)
NC	14.91 ± 0.26	38.34 ± 4.81	74.67 ± 1.26
HFD	20.87 ± 0.35	41.6 ± 8.87	125.33 ± 1.27
HFD+ZO	19.15 ± 0.26	38.5 ± 1.98ns	112.67 ± 1.33
HFD+ ORL	18.16 ± 0.39 ns	37.8 ± 1.91ns	91.50 ± 1.34**
ZO per s	17.89 ± 0.54	40.8 ± 2.38	103.8 ± 1.59

Data are expressed as Mean ± SD (n=6). Statistical significance in comparison to High Fat Diet group at *P<0.05, **P<0.01, ***P<0.001. One way ANOVA followed by Dunnet's t-test.

Effect on serum insulin, lipase and leptin levels

It was observed after 42 days of treatment, HFD + ZO group showed serum lipase levels in HFD fed group was significantly higher than that of normal control but significant reduction observed in HFD + ZO group (p < 0.05). Result of HFD + ORL group, HFD + ZO group were mentioned in Table 8.

Histopathological studies

Results reveal that drug significantly reduced the fat accumulation in liver, heart and kidney (Figure 3, 4 & 5 respectively).

Table 5: Effect of aqueous *Z. officinale* extract (20 mg/kg) on organ weight profile in albino rats after 42 days of treatment

Groups	Organ weight (g/100g of animal weight)			
	Heart	Kidney	Liver	Spleen
NC	0.607 ± 0.091	1.020 ± 0.240	6.981 ± 0.580	0.606 ± 0.041
HFD	0.838 ± 0.034	1.493 ± .291	9.376 ± 0.195	0.805 ± 0.027
HFD+ZO	0.782 ± 0.084	1.214 ± 0.305*	7.809 ± 0.767	0.698 ± 0.097
HFD+ORL	0.725 ± 0.055*	1.088 ± 0.157**	7.171 ± 0.976**	0.643 ± 0.062
ZO per se	0.659 ± 0.54	1.179 ± 0.38	7.685 ± 0.59	0.654 ± 0.77

Data are expressed as Mean ± SD (n=6). Statistical significance in comparison to High Fat Diet group at *P<0.05, **P<0.01, ***P<0.001. One way ANOVA followed by Dunnet's t-test.

Table 6: Effect of aqueous *Z. officinale* extract (20 mg/kg) on Fat pad weight profile in albino rats after 42 days of treatment

Groups	Fat pad weights (g/100g of animal weight)		
	Mesentric	Perirenal	Uterine
NC	0.462 ± 0.076	0.74 ± 0.032	0.725 ± 0.070
HFD	0.931 ± 0.086	1.22 ± 0.288	1.035 ± 0.118
HFD+ZO	0.563 ± 0.080**	0.84 ± 0.092**	0.809 ± 0.104
HFD+ORL	0.511 ± 0.086***	0.78 ± 0.084***	0.754 ± 0.092*
ZO per se	0.559 ± 0.56	0.81 ± 0.14	0.792 ± 0.71

All values were expressed as Mean ± SEM, (n=6); ##P<0.01, ###P<0.001, #P<0.05 as compared to the NC group; one way ANOVA followed by Dunnet's t-test.

**Figure 1: Dried rhizome of *Zingiber officinale*.**

Table 7: Effect of aqueous *Z. officinale* extract (20 mg/kg) on serum TC, TG, LDL-C, VLDL-C and HDL-C levels in HFD-induced obesity in wistar rats

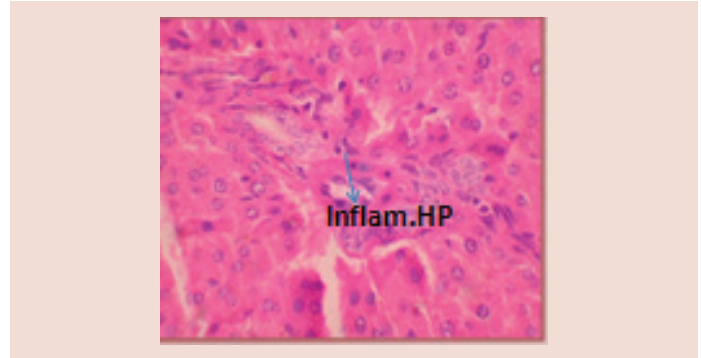
Groups	TC(mg/dl)	TG(mg/ dl)	LDL-C(mg/dl)	VLDL-C(mg/dl)	HDL-C(mg/dl)
NC	87.43 ± 3.40	69.44 ± 12.21	40.03 ± 2.26	13.89 ± 2.44	33.51 ± 6.95
HFD	164.76 ± 24.26	171.30 ± 25.17	107.28 ± 9.54	34.26 ± 5.03	23.23 ± 9.69
HFD + ZO	146.15 ± 21.39*	149.07 ± 34.19	84.35 ± 6.91*	29.81 ± 6.84	31.99 ± 7.65*
HFD + ORL	114.14 ± 13.20***	110.19 ± 20.04 ***	53.81 ± 2.58***	22.04 ± 4.01**	38.30 ± 9.44***
ZO per se	121.91 ± 0.67	132.05 ± 1.01	78.18 ± 7.01	26.10 ± 0.20	29.66 ± 0.57

Data are expressed as Mean ± SD (n=6). Statistical significance in comparison to High Fat Diet group at *P<0.05, **P<0.01, ***P<0.001. One way ANOVA followed by Dunnet's t-test.

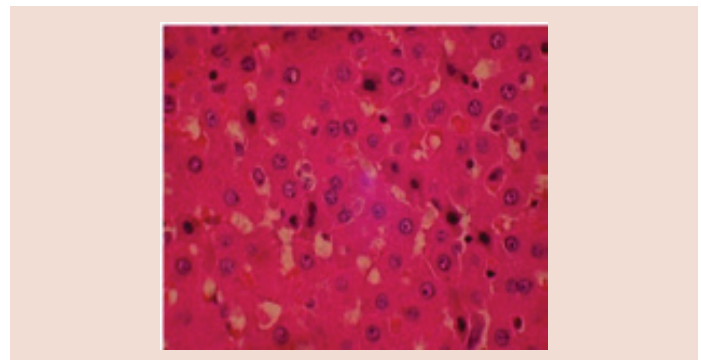
Table 8: Effect of aqueous *Z. officinale* extract (20 mg/kg) on serum Insulin and leptin levels in HFD-induced obesity in wistar rats

Groups	Insulin (ng/ml)	Leptin (ng/ml)	Lipase (U/L)
NC	0.91 ± 0.21	5.91 ± 0.96	661.32 ± 54.12
HFD	1.81 ± 0.21	19.77 ± 2.34	1109.94 ± 218. 23
HFD + ZO	1.56 ± 0.39	17.82 ± 1.93	943.67 ± 102.19*
HFD + ORL	1.12 ± 0.16***	12.58 ± 1.59***	861.11 ± 102.89***
ZO per se	1.19 ± 0.67	16.05 ± 1.01	921.12 ± 11.2

Data are expressed as Mean ± SD (n=6). Statistical significance in comparison to High Fat Diet group at *P<0.05, **P<0.01, ***P<0.001. One way ANOVA followed by Dunnet's t-test.



High power photomicrograph of liver from HFD* control group showing swelling of hepatocytes (HP) and narrowing sinusoids (H&E x 400).



High power photomicrograph of liver from *Z. officinale* treated group showing a lot of fatty change (H&E x 400).

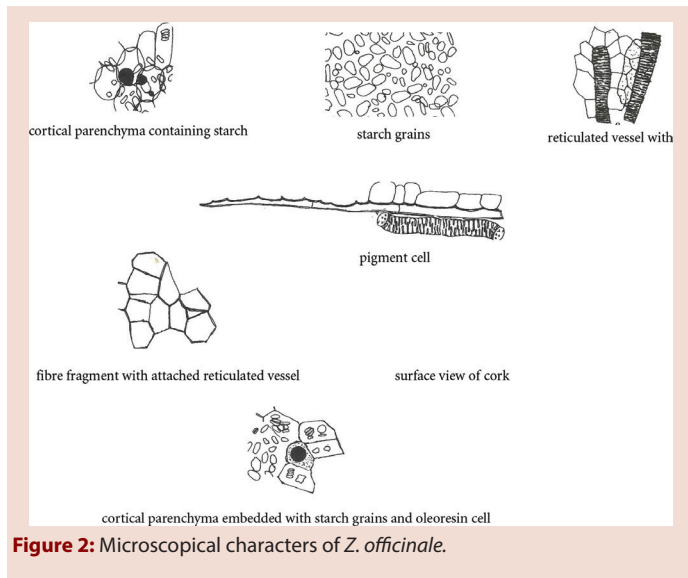
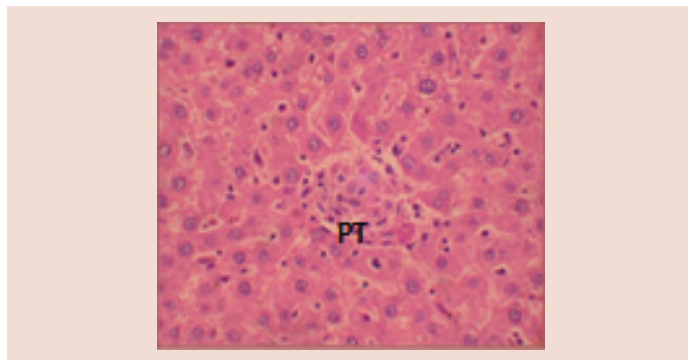
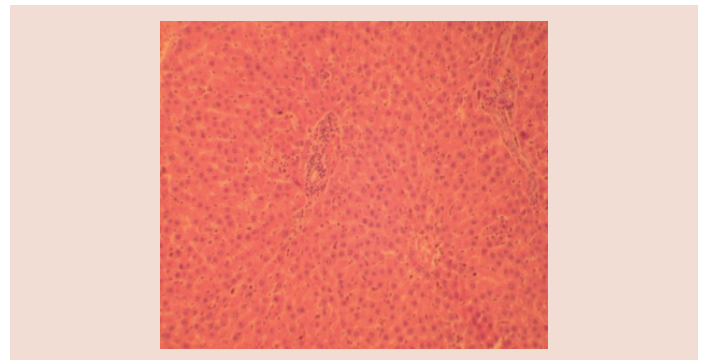


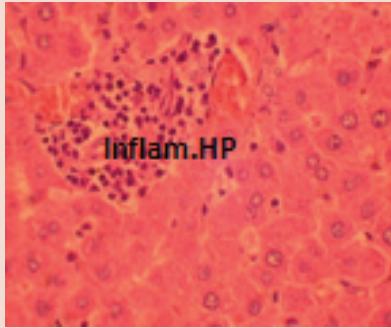
Figure 2: Microscopical characters of *Z. officinale*.



High power photomicrograph of liver from ND* control group showing a normal portal triad (PT) and hepatocytes (H&E x 400).



High power photomicrograph of liver from standard group showing no fat deposition (H&E x 400).

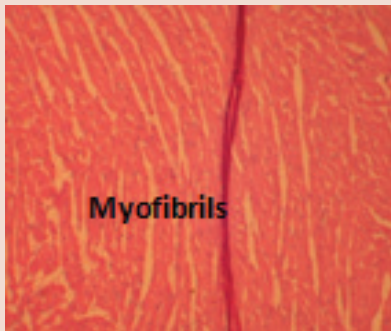


High power photomicrograph of liver from per se group showing significant inflammation of hepatocytes and damage to liver (H&E x 400).

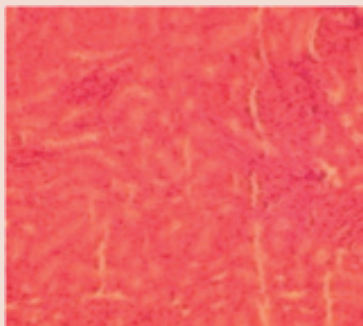
Figure 3: Changes observed in liver of different groups.



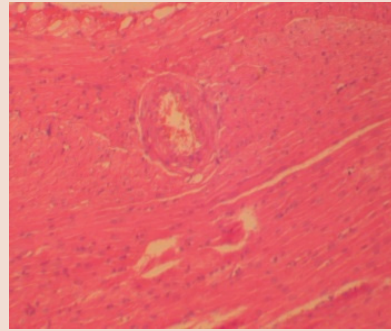
High power photomicrograph of Heart from ND* control group showing normal arteriole (A) and muscles (M-myofibrils) (H&E x 400).



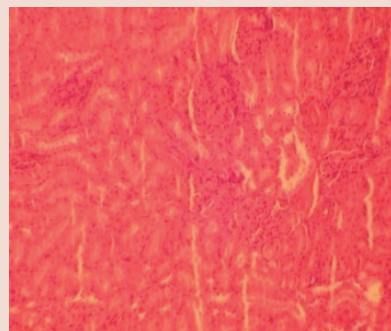
High power photomicrograph of Heart from HFD* control group showing edema (E) and change in colour of heart from pink-red to yellowish pink (H&E x 400).



High power photomicrograph of Heart from *Z. officinale* treated group showing without any significant change with normal arteriole (H&E x 400).

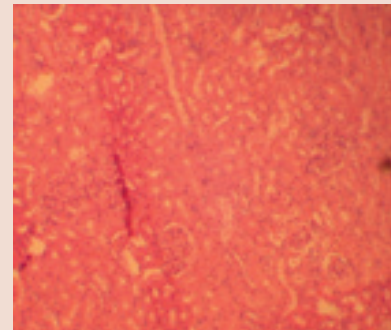


High power photomicrograph of Heart standard group showing normal arteriole (H&E x 400).



High power photomicrograph of Heart from per se group without any significant change with normal arteriole (H&E x 400).

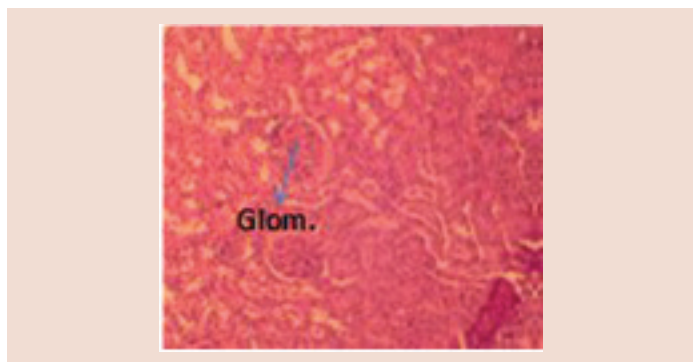
Figure 4: Changes observed in heart of different groups



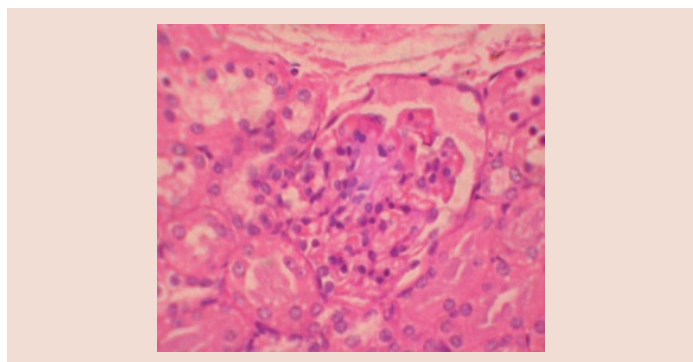
Low power photomicrograph of Kidney from ND* control group showing normal glomerulus (H&E x 100).



High power photomicrograph of Kidney from HFD* control group showing normal glomerulus (G) (H&E x 400).



High power photomicrograph of Kidney from *Z. officinale* treated group showing normal glomeruli (G). (H&E x 400).



High power photomicrograph of Kidney from standard group showing normal glomerulus (G) (H&E x 400).



Low power photomicrograph of Kidney from per se group showing normal glomeruli (G) (H&E x 100).

Figure 5: Changes observed in kidney of different groups

DISCUSSION

Present study was carried out to investigate the anti-obesity effects of aqueous *Z. officinale* extract in HFD-induced obesity in Wistar rats. Obesity, which affects up to 30% of the adult population in developed countries. Obesity is associated with serious mortalities including high incidence of type 2 diabetes, hyperlipidemia, hypercholesterolemia, cardiovascular disease and many more. HFD is thought to be one of the main factors for development of obesity. We selected a rat model of diet induced obesity based on numerous experimental studies indicated that consumption of HFD leads to increased body weight and fat mass, induce alterations in carbohydrate and lipid metabolism, lead to insulin resistance, increase production and release of leptin in laboratory animals and humans.¹⁰⁻¹³

In the present study, we found that the body weight was markedly reduced in the animal groups treated by *Z. officinale* to vehicle-treated control. The inhibition of body weight gain did not depend upon a decreased food or energy intake, because there was no significant correlation in diet intake between the control and experimental groups, but was caused by preventing and/or delaying of fat absorption. Similarly, we found that the feeding of *Z. officinale* for 6 weeks suppressed the increases in organ weights of the heart kidney, liver, spleen and adipose tissue weights of mesenteric, perirenal and uterine fat pad weights induced by a HFD. On the other hand, it is reported that feeding with a high fat diet in wistar rats leads to increase in weight of body organs such as liver, heart, spleen and both kidneys. It is also reported that high fat diet induces substantial increase in deposition of fat in the mesenteric, perirenal and uterine region in wistar rats.

The present study results showed that compared to that of NC, Serum TG, TC, LDL-C, VLDL-C levels were significantly elevated in HFD fed rats (HFD group) decreased in HFD+ ZO treated group more than that of HFD fed group; indicating potential lipid lowering activity of the test drug.

Among various fat deposits, visceral fat mass correlated to insulin resistance in animal model.¹⁴ Individuals with visceral by obesity have impaired insulin action,¹⁵ and prevents insulin resistance by removing visceral fat mass¹⁶ From adipose tissue, two groups of inflammatory proteins are produced (i) IL-6 and TNF- α [inflammatory mediators], (ii) leptin, adiponectin and resistin [adipocytokines].¹⁷ Human obesity is characterized by variable degrees of hyperleptinemia and leptin resistance.¹⁸ The result of the present study indicates insulin sensitivity improved in rat fed with the drug. The drug induced melioration of insulin resistance which is supported by down regulation of leptin. Thus, visceral fat accumulation and improved insulin resistance in rat model with HFD induced obesity may possibly be through down regulation of leptin, TNF- α , SREBP1 γ , and PPAR γ 2 gene expression. Uygun et al reported that leptin might contribute to hepatic steatosis by promoting insulin resistance and also by altering insulin signaling in hepatocytes, which consequently promote increased intracellular fatty acid.¹⁹ Hence, drug treatment to rats with HFD prevents increase of these levels due to decrease of the body fat content. The *Z. officinale* administration also showed significant activity against lipase activity.

Conclusively, observed reduction in body weight gain, serum lipids, insulin, leptin levels suggests that aqueous extract of *Z. officinale* possess significant anti-obesity potential.

ABBREVIATIONS USED

ZO: Zingiber officinale; **HFD:** High Fat Diet; **TC:** Triglycerides; **LDL-C:** Low Density Lipoprotein; **VLDL-C:** Very Low Density Lipoprotein; **HDL-C:** High Density Lipoprotein; **ORL:** Orlistate.

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SUMMARY

- On compared to NC, Serum TG, TC, LDL-C, VLDL-C levels were significantly elevated in HFD fed rats (HFD group) decreased in HFD+ ZO treated group, indicating potential lipid lowering activity of the test drug.
- *Z. officinale* extract causes visceral fat accumulation and improved insulin resistance in rat model with HFD induced obesity through down regulation of leptin, TNF- α , SREBP1 γ , and PPAR γ 2 gene expression.
- *Z. officinale* administration also showed significant activity against lipase activity by decrease of the body fat content.
- Reduction in body weight gain, serum lipids, insulin, leptin levels suggests that aqueous extract of *Z. officinale* possess significant anti-obesity potential.



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