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Research Article
Anti-obesity and Anti-hepatosteatosis Effects of Dietary *Zingiber officinale* Extract in Male Obese Rats

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Abstract

Background and Objective: Obesity is a chronic, multifactorial disease that develops from the interaction of behavioral, physiological, metabolic, cellular and molecular factors. High fat diet produces a consistent and significant increase ($p<0.05$) in body fat content which is dependent on both the amount of fat in the diet and the duration of feeding. So, this study was aimed to investigate the effects of ginger extract on obesity and hepatosteatosis in obese rats-induced by high fat diet and its capability of antioxidants-rich ginger extract in protecting rats against obesity complications. **Materials and Methods:** The study continued for eight weeks and the animal groups consisted of 80 male Wistar rats which were distributed equally among four groups. Body and fat weight, hepatic enzymes, anti-oxidant enzymes, oxidative stress marker, lipid profile, hepatic histopathological and ultrastructure investigations were recorded. **Results:** High Fat Diet (HFD) treated group exhibited a significant decrease ($p<0.05$) in antioxidant enzymes and High-Density Lipoprotein (HDL). Also, subjects in this group exhibited a significant increase ($p<0.05$) in liver enzymes, malondialdehyde (MDA), Total Cholesterol (TC) and triglycerides (TG). Additionally, concurrent exposure to HFD and treated with ginger extract significantly showed the protective potential of ginger extract in restoring the altered antioxidants, lipid profile and other biochemical analysis. Furthermore, Rats treated with HFD and protected with ginger extract improved the histopathological changes induced in the liver by obesity and showed that the hepatocytes with normal nucleus, large number of mitochondria and well developed Rough Endoplasmic Reticulum (RER) reflected the activity of the cell to produce high amount of proteins needed for normal differentiation. **Conclusion:** The extract of ginger showed noteworthy protection from the HFD-induced metabolic disturbances by strongly suppressing the body weight gain, oxidative stress and hyperlipidemia. Thus the present findings emphasize that the rhizome of *Z. officinale* possesses potential medicinal values.

Key words: Obesity, *Zingiber officinale*, high fat diet, anti-oxidants, hepatosteatosis, hyperlipidemia

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Obesity is a chronic, multifactorial disease that develops from the interaction of behavioral, physiological, metabolic, cellular and molecular factors. it is a worldwide public health concern. Also, it is expected that the obesity epidemic will double by the year 2030 to become the major health problem of this century[1,2]. Lifestyle factors, including reduced physical exercise and a high calorie intake, are responsible for the increase of obesity in industrialized countries[3]. High fat diet produces a consistent and significant increase ($p<0.05$) in body fat content which is dependent on both the amount of fat in the diet and the duration of feeding[4].

According to the National Health and Nutrition Examination Survey (NHANES, 2007-2008)[5], the adult prevalence of obesity (BMI $\geq$30 kg m^{-2}) is approximately 33.9% and combined prevalence of obesity and overweight (BMI $\geq$25 kg m^{-2}) is 68.3%, BMI is a ratio of the weight (kg) to the height[5]. A clustering of metabolic abnormalities that are known as risk factors for cardiovascular disease and type 2 diabetes often accompany obesity[6].

Obesity prevention during infancy, childhood and adolescence is significantly important. This is due to the fact that obesity tracks into adulthood, leading to elevated risks for hypertension, osteoarthritis, coronary heart disease, congestive heart failure, stroke, breast and colon cancer and premature death[7]. Over nutrition and less physical activity are believed to the main causes of the obesity[8]. Fundamentally, there are two ways to treat obesity: Reduce energy intake or increase expenditure of energy[9].

It has been reported that polyphenolic compounds, including mangiferin, catechins and tannins, may be involved in the anti-obesity effects through inhibition of lipid-metabolizing enzymes and enhanced lipolysis[10]. Ginger (*Zingiber officinale* Roscoe), the ginger rhizomes, is an herbal medicine for diabetes, cancer[11], fructose-induced fatty liver[12] and atherosclerosis[13]. Ginger root extract contains polyphenol compounds (6-gingerol and its derivatives), which have a high anti-oxidant activity. Although the digestion stimulating e ect of this spice has been known for a very long time, the stimulating effect on peptic juices, such as intestinal juice, pancreatic, bile and gastric juices, has been recently reported by Stoilova *et al*.,[13]. Ginger extract reduced the elevated expression of NFκB and TNF-α in liver cancer of rats. Also, ginger may act as an anti-inflammatory and anti-cancer agent by inactivating NFκB through the suppression of the pro-inflammatory TNF-α[14].

The aim of the present study was to assess some pharmacological effects of ginger aqueous extract on obese rat model and to elucidate the potential mechanisms for its hepatoprotective and anti-oxidant properties.

MATERIALS AND METHODS

Animal grouping: This study continued for eight weeks and the sample consisted of 80 rats (Sprague-Dawley strain), the average weight of each was about 150-200 g. The rats were divided into 4 equal groups as follows: in group (1), animals were fed on *ad libitum*, a standard laboratory diet (control group), in group (2), animals were fed on *ad libitum* and ginger extract (95%)[15] in group (3), animals were fed on *ad libitum* a high-fat diet as shown in Table 1[16] and in group (4), animals were supplied with the high-fat diet and they were orally given the ginger extract.

Clinical observations were routinely performed and body weight gain was weekly measured. At the time of scarifying the liver and visceral (intra-abdominal), fat mass including peri-renal, peri-metrial and mesenteric fat were weighed and excised.

The complications of obesity and the effects of the ginger extract were monitored by estimating the extent of the changes in biochemical parameters in blood serum and liver histopathology.

Biochemical assays: Assay kit for determination of malondialdehyde (MDA) in hepatic tissues was obtained from NWLSS (USA, Cat. No. NWK-MDA01). Determination of Superoxide dismutase (SOD) and catalase (CAT) levels in hepatic tissues were performed using assay kits from Cayman Chemicals (USA, Cat. No. 706002). Also, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were assessed according to Huang *et al*.[17]. Serum lipids including total triglycerides (TG), Total Cholesterol (TC), High Density Lipoproteins (HDL) and Low Density Lipoprotein (LDL) were determined using colorimetric assay kits from Human Company (Germany).

Histopathological investigation: The animals were fasted overnight, sacrificed in the morning and dissected to obtain

Table 1: Ingredients and nutrient composition of rat high-fat diet

Ingredients	Standard diet (g kg^{-1})	High-fat diet (g kg^{-1})
Casein	200.0	200.0
Starch	615.0	145.0
Sucrose	000.0	150.0
Corn oil	080.0	000.0
Beef tallow	000.0	400.0
Cellulose	050.0	050.0
Vitamin-mineral premix	050.0	050.0
DL-Methionine	003.0	003.0
Choline chloride	002.0	002.0

the liver which fixed in 10% buffered formalin for histopathology and 5% buffered glutaraldehyde for Transmission electron microscope (JEM-1011, Jeol Co., Japan) investigations.

Transmission electron microscope: Small pieces of the liver tissues from animals in all groups (1.0-2.0 mm^3) were fixed by immersion in 5% glutaraldehyde buffered in 0.1 M sodium cacodylate buffer (pH 7.2) at 4°C for 3 h and soaked overnight in the buffer at 4°C. This was followed by post osmofication in 1% cold osmium tetraoxide in 0.1 M sodium cacodylate at pH 7.2, for 2 h. Then the tissues were allowed to warm up to room temperature. Samples were then briefly washed in the buffer, dehydrated through a graded series of ethanol and taken through propylene oxide, then left overnight in a freshly prepared mixture of resin. After infiltration in the resin mixture at room temperature on tumbler for 24 h, the tissues were placed in suitable moulds containing the resin mixture. The polymerization was carried out in an oven at 58-60°C for about 40 h. After trimming the blocks, 1 µm thick sections were cut with LKB ultramicrotome (Spain) using glass knives. The ultrathin sections were occurring. The sections which showed silver pale gold interference colors were cut and mounted on copper grids that had been previously covered with formvar membrane. Sections were stained for 60 min in 1% uranyl acetate in 25% ethyl alcohol. The stain was freshly prepared just before use from a stock solution of saturated uranyl acetate and lead carbonate. After staining, the grids were washed first in 0.01 N NaOH and then in distilled water and dried in desiccators. The double stained sections were examined in Joel Electron Microscope (JEM-1011 M, Jeol Co., Japan) operating at 60 kv[18].

Statistical analysis: Data was expressed in terms of frequency, percentage and Mean+SD. One-way analysis of variance (ANOVA) was used to test significance and p-value <0.05 was considered statistically significant[15].

RESULTS

The final body weight (B.wt.) and fat weight (F.wt.) of rats feeding on High Fat Diet (HFD) for 8 weeks were significantly increased ($p<0.05$) in comparison to animals in the control and other experimental groups. Oral administration of Ginger Extract (GE) to obese rats for 8 weeks caused significant decreases ($p<0.05$) in B.wt and F.wt. when compared to positive obese rats (Table 2).

The hepatic enzymes AST and ALT in the blood serum, the antioxidant enzyme activities (SOD and CAT) and oxidative stress agent (MDA) of both control and tested groups were measured. In HFD group, a significant increase ($p<0.05$) of AST, ALT and MDA and also a significant decrease of SOD and CAT activities were observed, as compared with control group ($p<0.05$). Diet supplemented with ginger extract improved levels of AST, ALT, MDA, SOD and CAT activities in animals of group 4 (HFD+Ginger), when compared with animals of HFD group. These changes, which revealed a failure of defense against obesity effects, largely were corrected in animals treated with ginger as shown in (Table 3).

Rats feeding on High Fat-Diet (HFD) for 8 weeks increased significantly ($p<0.05$) levels of Total Cholesterol (TC) and triglycerides (TG) when compared to rats fed on basal diet. Oral administration of ginger extract to obese rats for 8 weeks decreased significantly ($p<0.05$) the elevated levels of serum TC and TG, compared to obese rats. Also, serum analysis revealed that rats fed on High Fat-Diet (HFD) for 8 weeks had a significant decrease ($p<0.05$) in High Density Lipoprotein (HDL) and a significant increase in Low Density Lipoprotein (LDL), compared to the control group. Oral administration of ginger extract to obese rats increased serum HDL and decreased LDL when compared with the obese rats group as shown in (Table 4).

The normal structural unit of control rat's liver is the hepatic lobule which is made up of radiating strands, cord or plates of cells forming a network around a central vein (Fig. 1a). Animals administered with Ginger Extract (GE) daily for 5 weeks showed the same histological observations as in the liver of control animals (Fig. 1b). The extremely infiltrate of inflammatory cell and fat vacuolation were associated with HFD-treated animal group (Fig. 1c-e). Also, the microscopic examination of liver sections taken from rat of HFD group has display apparent signs of degenerative change. In these specimens, severe damages were observed in the liver architecture, the normal arrangement of the hepatocytes wasn't easily recognized. In addition, leukocyte infiltration and cytoplasmic vacuolation of the hepatocytes with pyknotic nuclei were observed. The ginger extract reduced the severity of all obesity-induced hepatic responses, but the degree of reduction in obese rats treated with ginger extract was incomplete, where the dilated and congested central vein and some blood sinusoids were present in animals of group 4 (Fig. 1f).

Table 2: Body and fat weights in different experimental animals groups

	Groups			
Parameters	Control	GE	HFD	HFD+GE
Body weight (g)	279.11±12.2	243.64±10.1	344.35±13.5*	290.34±12.3
Fat weight (g)	12.08±1.02	10±0.09	20.11±1.23*	15.05±0.10

Data are expressed as Mean+SD, *: Significantly different from the control group

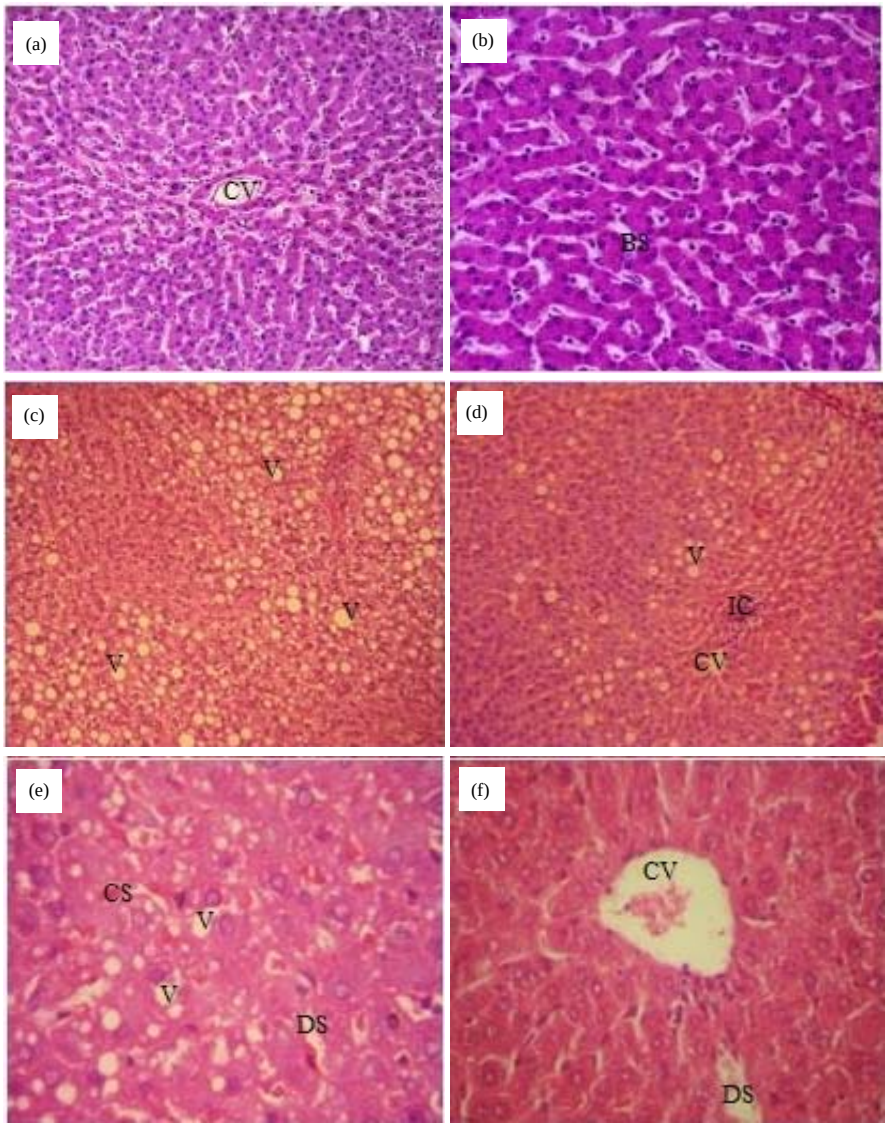

Fig. 1(a-f): Liver sections of (a) Control rats, (b) GE treated rats, (c-e) HFD-induced obesity rats, (f) HFD treated with GE rats, (×400)

CV: Central vein, BS: Blood sinusoid, IC: Infiltration cells, V: Fat vacuoles, CS: Congested sinusoid, DS: Dilated sinusoid

Table 3: Liver enzymes level of Aspartate (AST and ALT), (MDA) and anti-oxidative enzymes (SOD and CAT) in different experimental animals groups

	Groups			
Parameters	Control	GE	HFD	HFD+GE
AST (U L^{-1})	60.12±10.1	56.53±10.4	170.43±26.18*	83.3±9.09
ALT (U L^{-1})	45.44±3.4	40.34±4.09	105.1±12.30*	64.55±9.91
MDA (nmol mg^{-1})	9.15±0.76	7.23±0.65	18.22±1.28*	11.43±0.93
SOD (U mg^{-1})	90.27±17.21	150.82±5.67*	62.09±5.88*	144.64±7.89*
CAT (nmol min^{-1} mg^{-1})	55.71±4.03	65.65±2.65	38.99±2.65*	53.87±3.89

GE: Ginger extract, HFD: High fat diet, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase. MDA: Malondialdehyde, SOD: Superoxide dismutase, CAT: Catalase, Data are expressed as Mean+SD, *Significantly different from the control group

The electron microscopic investigation of the control rats showed that the liver cells are delimited by a well-defined plasma membrane, the cytoplasm of the hepatocytes embodies numerous scattered rounded or elongated

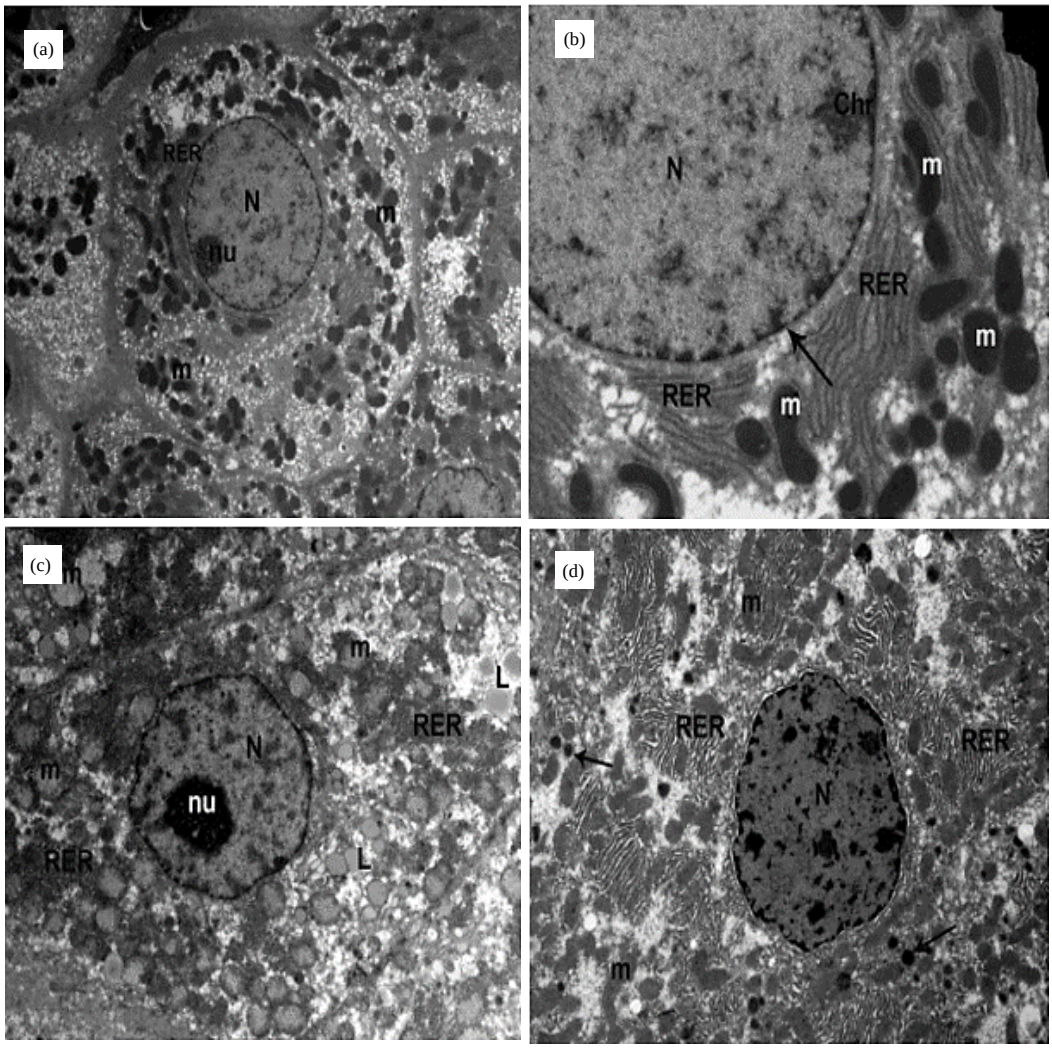

Fig. 2(a-d): (a, b) Transmission electron micrographs of the hepatic tissue of the control and GE groups (X: 5000 and 10000, respectively), (c): Electron micrograph of liver of HFD treated animal group (X: 5000), (d) A hepatocyte of obese rat treated with GE (X5000)

N: Nuclei, Nu: Nucleoli, M: Mitochondria, RER: Rough endoplasmic reticulum, Chr: Chromatin masses, L: Lipid droplets

Table 4: Lipid profile in different experimental animals groups

	Groups			
Parameters mg dL^{-1}	Control	GE	HFD	HFD+GE
TC	100.33±2.83	70.38±1.69	130.83±9.87*	109.44±234
TG	22.51±2.71	17.45±3.01	70.37±3.76*	25.17±2.06
HDL	46.35±4.1	44.17±3.09	37.38±1.06*	42.94±4.11
LDL	27.27±3.01	21.09±3.83	50.74±7.43*	33.08±4.18

TC: Total cholesterol, TG: Triglyceride, HDL: High density lipoprotein, LDL: Low density lipoprotein, GE: Ginger extract, HFD: High fat diet, Data are expressed as Mean±SD, *Significantly different from the control group

mitochondria, normal Rough Endoplasmic Reticulum (RER) and nucleus (N) with nucleolus (nu) (Fig. 2a). The same features were present in the electron microscopic examination in the rats of the GE group (Fig. 2b). In animals of HFD group, some hepatocytes showed effect of moderate severity with more or less normal cytoplasm and nuclei. The cytoplasm revealed aggregations of density profiles of RER, many lipid droplets of different sizes. Many small vesicles and some

degenerated mitochondria were found in the cytoplasm. In addition, ill-defined and slightly degenerated hepatocytes were identified with very electron-dense cytoplasmic organoids (Fig. 2c). In GE treated animals in group 4, the protective potential of GE in restoring the altered hepatic histoarchitecture was close to the histoarchitecture of normal hepatic animals (Fig. 2d).

DISCUSSION

Since the synthetic chemical drugs prescribed for treating obesity have many adverse side effects, there is an impelling need to search for alternative safe natural agents from medicinal plants, herbs and spices. Ginger rhizomes (*Z. officinale)* are commonly used as culinary spice and have a long history of health benefits. In this study, obesity has been experimentally induced by feeding rat's high fat-diet for 8 weeks according to Bhatt *et al.*[19]. This model of obesity in rats closely resembles the reality of obesity in humans.

Amin and Nagy[20] reported that feeding rats on HFD significantly increased ($p<0.05$) the final body and fat weights when compared to the rats fed on basal diet. The dietary ginger is known to stimulate digestion and absorption of dietary fat in high-fat fed situation by enhancing the secretion of bile salts and increasing the activity of pancreatic lipase[21]. Therefore, this spice is at the time efficacious in suppressing body's accumulation of lipids in body and hence will aid in weight loss and management[21,22].

The liver protective effects of Ginger Extract (GE) against HFD-induced obesity was reported in this study as there was significant decreases ($p<0.05$) in the elevated serum levels of AST and ALT liver enzymes in obese rats treated with Ginger Extract (GE). Many previous studies investigated the protective effects of GE against liver toxicity induced by different agents with significant decrease ($p<0.05$) in the levels of ALT and AST[23,24]. Also, the hepatoprotective effect could be attributed to the antioxidant activity of ginger.

Obesity can be characterized as a chronic inflammatory disease[25] and associated with an unbalanced rate of Reactive Oxygen Species (ROS) production compared to their removal. Obesity was linked to an increase in free radical generation through lipid oxidative stress or lipid peroxidation[26] which can have downstream effects on cell biological functions. The results of current study showed that the activity of antioxidant enzymes (SOD and CAT) decreased and the production of MDA in rats of HFD group increased, compared to control and ginger extracted groups, indicating the reduced the ability for free radical scavenging in obese rats group and subsequent development of oxidative stress. The MDA content of the group treated with GE was significantly decreased ($p<0.05$)[27]. This finding can be explained by hyperlipidemia due to obesity injection that causes hepatic oxidative stress. Moreover, in accordance with other studies, ginger extract when given to obese rats induced antioxidant effects that are evident by the increased activity of SOD and CAT antioxidant enzymes in hepatic tissue, compared to obese rats that have significant decreased ($p<0.05$) in SOD and CAT[28].

In concordance with earlier reports, ginger extract administration along with the HFD effectively reduced the serum Total Cholesterol (TC) and LDL in addition to marked reduction in serum triglycerides (TG)[13]. This reduction could be due to prevention of the suppressive action of HFD on the LDL-receptor site. The serum HDL increased concentration is not altered by the high-fat diet or by ginger treatment groups as reported by Al-Amin *et al.*[29]. In the present study, HFD treatment markedly increased the serum triglycerides (TG). Presumably, these changes may be in part due to enhanced cholesterol biosynthesis during high intake of fatty diet[30]. The increase in LDL may be due to the reduced expression or activity of the LDL-receptor sites in response to high-fat diet treatment. Therefore, lowering the LDL level may be an important factor in lowering the serum total cholesterol level in rats fed HFD[31].

The present study indicated that the ginger extract treated group showed the liver sections nearly with normal architectures and normal hepatocytes. However, concerning the liver of HFD rats, the microscopic examination showed many lesions which manifested the characteristic of obesity, severe damaged hepatocytes with extensive cytoplasmic vacuolization, inflammatory cells and fat vacuoles. Similar findings have been reported by Oh *et al.*[32] and Omoregie *et al.*,[33] who described that ginger extract ameliorated the histological structures of liver, modulated the elevated values of biochemical parameters: ALT, AST and MDA. The findings showed that treating rats with HFD and ginger extract improved the biochemical changes and histopathological induced in the liver by obesity. This indicated the effectiveness of ginger extract in prevention of HFD hepatotoxicity.

In the ultrastructural investigation, the most striking feature in the HFD rats group was the appearance of hepatocyte with abnormal nuclei, elongated and spherical mitochondria (polymorphism), aggregation of lipid vacuoles. Rats treated with HFD and protected with ginger extract, showed hepatocytes with normal nucleus, large number of mitochondria and well developed RER indicating liver regeneration, extensive RER reflected the activity of the cell to produce high amount of proteins needed for normal differentiation. These observations were in agreement with

the findings of Srinivasan[34] who studied the multiple health beneficial potentials of ginger rhizomes (*Zingiber officinale*).

CONCLUSION

The extract of ginger showed noteworthy protection from the HFD-induced metabolic disturbances by strongly suppressing the body weight gain, oxidative stress and hyperlipidemia. Thus the present findings emphasize that the rhizome of *Z. officinale* possesses potential medicinal value and hence its traditional consumption in foods as a spice is beneficial in the prevention of metabolic disorders caused by high-fat diet. Further studies are being undertaken to explain fully the mechanism(s) of the glucose and lipid metabolism-regulating activities of ginger.

SIGNIFICANCE STATEMENT

The liver protective effects of Ginger Extract (GE) against HFD-induced obesity was discovered from this study as there was significant decreases ($p<0.05$) in the elevated serum levels of AST and ALT liver enzymes and MDA and increase the anti-oxidants superoxide dismutase (SOD) and catalase (CAT) levels in obese rats treated with ginger extract. Also, the ginger extract treated group showed the liver sections nearly with normal architectures and normal hepatocytes in histological and ultrastructural investigations.

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