

Comparative evaluation of the efficacy of ginger and orlistat on obesity management, pancreatic lipase and liver peroxisomal catalase enzyme in male albino rats

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Abstract. – BACKGROUND: Obesity is a disease involving body weight gain. Several synthetic drugs of better efficacy are being introduced in the modern system of medicine. Orlistat is a pharmacological agent promoting weight loss in obese subjects via inhibiting of gastric and pancreatic lipase. Ginger (*Zingiber officinale* Roscoe, Zingiberaceae) is one of the most commonly used spices around the world; it has long been used in traditional medicine as a cure for some diseases.

OBJECTIVE: To evaluate the effect of ginger and orlistat on rats fed high fat diet.

MATERIALS AND METHODS: Forty male Albino rats were either not treated (control), or fed high fat diet, or fed high fat diet with dietary orlistat supplementation (200 mg/kg diet), or fed high fat diet supplemented with 5% ginger powder. After four weeks of treatment, final body weight and food intake were determined. Blood samples were collected, lipid parameters, total bilirubin, pancreatic lipase were determined. Liver peroxisomes were isolated from rat livers and peroxisomal catalase activity was determined.

RESULTS: Treatment with both ginger and orlistat had significant effect in reducing body weight, besides, supplementing diet with orlistat increase food intake. Both ginger and orlistat had the ability to reduce lipid profile, ginger had great effect in increasing HDL-cholesterol than orlistat. When compared to the control group, ginger treatment did not alter either total bilirubin or pancreatic lipase activity while orlistat clearly reduced their concentration. Orlistat supplementation induced a significant reduction in peroxisomal catalase level, while ginger has been reported to interfere with enzyme activity increasing its level.

CONCLUSIONS: Ginger has a great ability to reduce body weight without inhibiting pancreatic lipase level, or affecting bilirubin concentration, with positive effect on increasing peroxisomal catalase level and HDL-cholesterol.

Key Words:

Obesity, Orlistat, Ginger, Pancreatic lipase, Liver peroxisomal catalase.

Introduction

The alarmingly increasing rate of unwanted weight gain and obesity in the past 20 years had become a worldwide concern. The World Health Organization estimates that there are currently more than 400 million obese and more than 1.6 billion overweight adults, a number that is expected to double by 2015¹.

Obesity is a disease involving body fat storage and body weight gain. The recent health crisis has spurred research in weight control, including studies in diet, exercise, surgery and pharmaceutical preparations. Because obesity is caused by a build-up of fat in the body due to, for example, the over-consumption of high fat food, modern therapeutic approaches are mostly focused on blocking or stimulating various biomolecules and enzymes involved in fat metabolism².

Obesity, which describes the condition of abnormal accumulation of body fat mass, is directly related to increased risk of several chronic diseases, including glucose intolerance, cardiovascular disease hypertension, hyperlipidaemia, hemostatic variables and increased insulin resistance³. It has been shown that a modest reduction (5%-10%) of body weight lowers cardiovascular disease risk factor; instigates modest improvements in blood pressure and serum cholesterol ;

and reduces the incidence of type-2 diabetes, markers of endothelial function, and inflammatory signatures⁴.

Hyperlipidaemia is the major health problem throughout the world because of its important and vital role in the pathogenesis of atherosclerosis. Atherosclerosis is responsible for the majority of the cases of coronary artery diseases, cerebral strokes and essential hypertension⁵.

The concepts of hyperlipidaemia is based on the biochemical changes in the blood, i.e. distributed lipid metabolism and as a result, therefore, increased concentration of lipids in the blood⁶. Both obesity and hyperlipidaemia are considered as two different diseases, but that there is an establishment link between these two diseases⁷. To overcome the problem of hyperlipidaemia, day-by-day several synthetic drugs of better efficacy are being introduced in the modern system of medicine. But apart from being effective most of these medications induce adverse side effects. Therefore, these potential agents could not be used for long time but hyperlipidaemia requires long term treatment, so it is important to choose lipid lowering substance that do not adversely affect their efficacy profile, or reinforce their potential negative side effects⁸.

Orlistat (Xenical) is a pharmacological agent promoting weight loss in obese subjects via inhibiting of gastric and pancreatic lipase, an enzyme that is crucial for the digestion of the long chain triglycerides, which at a three daily dose of 120 mg reduces fat absorption by 30% and has been proven to be useful in facilitating both weight loss and weight maintenance⁹. Nevertheless, it is not known if orlistat has any impact on the clinical outcomes of other diseases and its long term safety is still to be determined¹⁰. Natural products and their active principles, as sources for new drug discovery and treatment of diseases, have attracted attention in recent years. Herbs and spices are generally considered safe and proved to be effective against various human ailments¹¹.

Ginger (*Zingiber officinale* Roscoe, Zingiberaceae) is one of the most commonly used spices around the world, especially in the Southern-Eastern Asian countries. The ginger plant has a long history of cultivation known to originate in China and then spread in India¹². It has long been used in traditional medicine as a cure for some diseases including inflammatory disease, and demonstrated to have various pharmacological activities such as antiemetic, antiulcer anti-

inflammatory, antioxidant, anti-platelet, glucose and lipid lowering, cardiovascular and anti-cancer activities¹³. Ginger rhizome is typically consumed as a fresh paste or dried powder; it also can be used in flavoring tea. In many countries, especially in India and China, fresh ginger is used to prepare vegetable and meat dishes and as flavoring agent in beverages and many other food preparations. Ginger contains up to 3% of an essential oil that causes the fragrance of the spice¹⁴. The sensory perception of ginger in mouth and the nose arises from two distinct groups of chemicals: *Volatile oils*: The volatile oil components in ginger consist mainly of sesquiterpene hydrocarbons, predominantly zingiberene (35%), curcumene (18%) and farnesene (10%), *Non volatile pungent compounds*: This species contains biologically active constituents such as gingerol, paradol and shogol that have many properties and zingerone that produce a hot sensation in the mouth¹⁵. Therefore, the following study was taken up to evaluate the effect of ginger and orlistat on rats fed after high fat diet.

Materials and Methods

Experimental Animals

Adult male albino rats (n=40) were included in the present study. Rats were purchased from Abou-Rawash Animal House, Giza, Egypt. The rats were 5 weeks old and weighing 150 ± 7 g each. Male rats were housed in temperature controlled rooms (25°C) with constant humidity and 12h/12h light/dark cycle prior to experimental protocols. The experiments were conducted according to Institutional Animal Ethics Committee guidelines for the care and use of laboratory animals.

Chemicals

Orlistat

Purchased from Sigma Pharmaceutical Industries, Egypt SAE, as capsules each capsule contains 120 mg.

Ginger was purchased from local market, peeled, washed, coarsely minced and allowed to air-dry. Four kilograms of air dried ginger were milled into fine powder and mixed with diet to get diets of 5% ginger¹⁶.

Experimental Designs

Animals were divided into four groups as follows:

Group (1) G1: Are control animals just received basic diets

Group (2) G2: (High fat diet), rats of this group fed high fat diet (The diet contain 30% corn oil) according to Jacobs¹⁷

Group (3) G3: (Orlistat treated), rats of this group fed high fat diet supplemented with dietary orlistat (200 mg/kg diet) according to Nishioka et al¹⁸

Group (4) G4: (Ginger treated) rats of this group fed high fat diet supplemented with 5% dried ginger powder according to Nirmala et al¹⁶.

Body Weight Gain and Food Consumption

Individual body weight gains were recorded before study initiation (Day 0), and weekly thereafter. Mean body weight gains were calculated for each group at each interval and for the overall testing interval. During the study, food consumptions were measured weekly per cage and mean food consumption by individual rat were calculated. At the end of the experimental period, animals were fasted overnight but allowed free access to water. Animals were also weight immediately prior to sacrifice (fasted body weight). Animals were sacrificed under anesthesia with diethyl ether, and then blood was collected and refrigerated for one hour to clot. Samples were then centrifuged for 5 minutes.

Peroxisomal Enzymes Analysis

Rat livers were immediately removed weighed then kept in ice. Liver peroxisomes from rats were isolated according to the method described by Mridulk and Amyia¹⁹. Catalase activity in peroxisomes was determined according to Leighton et al²⁰.

Biochemical Analysis

Serum was used for determination of level of total lipids (TL), triglycerides (TG), total cholesterol (TC), High density lipoprotein cholesterol (HDL-C), and low density lipoprotein cholesterol (LDL-C), all the kits were provided by Greiner Diagnostic GmbH (Greiner Bio-One GmbH, Brunel Way, Business Park, UK), and purchased from Indomedix Egypt Company. Serum total bilirubin was determined according to the method by Balistreri and Shaw²¹. The determination of pancreatic lipase activity was performed according to previously described method²².

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Statistical Analysis

Data analyses were performed using SPSS software version 14.0 for windows (SPSS Inc., Chicago, IL, USA). All data were expressed as mean \pm SD. Analysis of variance was used to test for differences between the groups.

Results

Gain in Body Weight and Feed Efficiency Ratio

Table I shows the initial and final body weights (g) and food intake/week after feeding rats for 30 days with control diets, high fat diets, and high fat diet supplemented with orlistat, or ginger powder. On average, the rats of G1, G2 and G4 gained weight throughout the experimental period, when compared to the initial body weight, while insignificant increase is observed in G3. Also it is clear that, there is a significant reduction in G3 and G4 when compared to G2. Besides, there was a significant increase of food intake in orlistat treated G3 when compared to other groups, followed by ginger treated G4 group.

Serum Lipid Profiles

Table II shows the general serum lipid profile results, Parameters determined were total lipids (TL), triglycerides (TG), total cholesterol (TC), high density lipoprotein cholesterol (HDL-C) and

Table I. The Effects of ginger and orlistat treatments on final body weight and food intake changes in rats fed high fat diet.

Groups parameters	G1 (control)	G2 (high fat diet)	G3 (orlistat supplemented)	G4 (ginger supplemented)
Initial Body Weight (g)	150.6	150.5	150.4	150.6
Final Body Weight (g)	210 \pm 12	280 \pm 18	157 \pm 13	172 \pm 16
Food Intake (g/week)	187 \pm 15	200 \pm 19	243 \pm 21	212 \pm 22

All the values are means \pm SD of ten individual observations. Significant at $p < 0.05$ with respect to normal control.

Table II. The effect of ginger and orlistat treatments on lipid parameters in rats fed high fat diet.

Groups parameters	G1 (control)	G2 (high fat diet)	G3 (orlistat supplemented)	G4 (ginger supplemented)
Total lipids (TL) mg/dl	498.6 ± 40.2	806.6 ± 60.8	450.6 ± 31.7	520.61 ± 22.7
Triglycerides (TG) mg/dl	170.85 ± 15.1	260.61 ± 23.4	186.21 ± 14.61	190.61 ± 13.2
Total Cholesterol (TC) mg/dl	41.7 ± 2.2	92.6 ± 12.5	56.7 ± 10.7	48.52 ± 11.1
HDL-Cholesterol (HDL-C) mg/dl	6.3 ± 1.1	6.9 ± 2.6	5.5 ± 0.9	7.1 ± 0.93
LDL-Cholesterol (LDL-C) mg/dl	15.6 ± 2.7	18.6 ± 2.7	15.4 ± 0.76	12.1 ± 0.7

All the values are means ± SD of ten individual observations. Significant at $p < 0.05$ with respect to normal control.

low density lipoprotein cholesterol (LDL-C). Generally, higher values were seen in G2 when compared to the other groups. There was a significant ($p < 0.01$) reduction in TL, TG, TC, LDL-C levels in G3 and G4 when compared to G2, while a significant increase in HDL-C observed in G4 when compared to G2. On the other side, comparing results of HDL-C level and LDL-C level between G3 and G4, shows that there were significant ($p < 0.01$) increase in HDL-C level in G4 (7.1 vs 5.5) while opposite results seen in LDL-C level. Comparing between the tested group revealed that the lowest value of HDL-C was seen in G3. While there were a significant ($p < 0.01$) reduction in TL level (450.2 vs 520.6), TG (186.21 vs 190.61) and total cholesterol (48.1 vs 56.7) in G3 when compared to G4 respectively.

Serum Total Bilirubin and Pancreatic Lipase Activity

From Table III it is noticed that after 30 days of the treatment, the total bile content of rats were different, G3 was significantly ($p < 0.01$) lower than all experimental groups. Although not

significant ($p > 0.05$) total bilirubin of rats in G1 is higher than G1 and G4. Ginger treatment didn't alter total bilirubin. Results of serum pancreatic lipase levels showed that high fat content in diet increased the enzyme level. On the basis of the present data and the results of others, it would be appeared that levels of pancreatic lipase are increased when the fat content of the diet raised from about 5% to 15-22%. There was a significant ($p < 0.01$) reduction in the enzyme level noticed in G3 when compared to all other groups. On the other hand, no significant difference between the enzyme levels recorded in G4 when compared to the control group G1.

Liver Peroxisomal Catalase Activity

Analysis of peroxisomal catalase activity (pCAT) in crude liver homogenates revealed that, the total activity of this enzyme was higher in G4 when compared to the other tested groups. High fat diet did not alter the enzyme level significantly when compared to the control. Orlistat supplementation clearly induced a significant reduction in the enzyme level recording lowest

Table III. The effect of ginger and orlistat treatments on Total Bilirubin, Pancreatic Lipase and Peroxisomal Catalase (p CAT) in rats fed high fat diet.

Groups parameters	G1 (control)	G2 (high fat diet)	G3 (orlistat supplemented)	G4 (ginger supplemented)
Total Bilirubin mg/dL	1.90 ± 0.04	2.20 ± 0.09	0.60 ± 0.074	1.85 ± 0.043
Pancreatic Lipase	22.8 ± 1.9	42.2 ± 2.6	12.6 ± 0.9	22.9 ± 1.3
Peroxisomal Catalase (p CAT)	436 ± 16	432 ± 12	210 ± 21	450 ± 18

All the values are means ± SD of ten individual observations. Significant at $p < 0.05$ with respect to normal control.

value of the enzyme level, while ginger has been reported to interfere with enzyme activity increasing its level.

Discussion

In this study, orlistat and ginger were added to the animal diet, and tested for their ability to reduce body weight gain and preventing obesity; also their effect on peroxisomal liver catalase activity was studied. It has been reported that orlistat is highly efficient when given in conjugation with a high fat diet or by gavage with an important loading of lipid²³. Indeed, higher doses of orlistat provided to rats led to 54% reduction in fat absorption, whereas, in humans, the expected reduction is 30%²⁴. Epidemiological studies identified a positive correlation between average dietary fat intake and the incidence of obesity. To determine the effect of orlistat and ginger treatment on obesity, a high fat diet-induced obese rat model was used. Rats were fed with a high-fat diet (HFD) containing 20 g fat/100 g diet²⁵. Ginger was added to the diet as 5% dried ginger powder. It has been reported that treatment with dried rhizomes of ginger produced a significant reduction in elevated lipid levels, body weight, hyperglycemia and hyperinsulinemia. It is well known that both dried and fresh are considered as medicinal products in some countries; on the other hand, dehydration process keeps the physical and chemical properties of ginger active compounds²⁶. Several reviews have appeared in the literature about this plant, and this may reflect the popularity of the subject and its common use as a spice and a medicinal plant²⁷. Ginger is considered as a safe herbal medicine, acute experimental study suggested that a patented extract (25-100 mg/kg) with a high content of gingerols and shogaols did not induce significant changes in blood glucose, blood coagulation and heart rate in normal male rats²⁸.

Results obtained from this study showed that, the rats of G1, G2 and G4 gained weight throughout the experimental period, when compared to the initial body weight. Ginger treated rats G4 and orlistat treated showed announced reduction in body weight when compared to G1 and G2. More importantly, the reduced body weight in G3 mainly due to a selective reduction in body fat, leaving lean mass unchanged as the effect of orlistat drug. Orlistat reduced the attrac-

tiveness of dietary fat, although it did not make the fat aversive. In clinical use, lipase inhibitors may be effectiveness in reducing dietary fat intake by reducing both the consumption and absorption of fat²⁹. The effect of ginger in reducing body weight is highly significance in G4 as this may most likely be due to the inhibitory action of ginger on absorption of dietary fats by inhibiting its hydrolysis and as a result may decrease the adipose tissue weight³⁰. The slight increase in food intake in orlistat treated group G3, may due to the effect of orlistat on salivary glands structure and function. Interestingly, the orlistat treated animals tended to eat slightly more the succeeded to reach similar amounts of food intake as control rats. Furthermore, Bryer³¹ showed that, Tetrahydrolipstatin (Orlistat) accelerates gastric emptying, reduces pyloric pressure, and enhances duodenal motility. On the other hand, several scientific investigations aimed at the role of ginger in treatment of constipation and indigestion. The increase in food intake observed in G4 fed ginger may also due to its importance as an appetite stimulant³². Ginger has a gastro protective activity and the ability to protect gastric mucosa against any necrotizing agent suggesting increased digestion. It also significantly reduced ethanol- and indomethacin-induced gastric mucosa damage in rats, promoted gastric secretion and inhibited gastric emptying³³. A study by Xi-anglo et al³⁴ indicated the potential of ginger in improving symptoms such as abdominal discomfort and bloating, which may accompany several gastrointestinal illnesses. It has been recorded as being useful in preventing post operative nausea and vomiting without significant effect on gastric emptying. It also stimulates digestion beneficially, enhancing the digestive activities like the intestinal lipase, the disaccharides, sucrase and maltase.

After the completion of 30 days of treatment there was an increase in lipid parameters in G2. A significant reduction observed in TL, TC, TG and LDL-C concentrations in G3 and G4 when compared to the high fat diet G2, on the other hand, comparing between G3 and G4 showed that the effect of orlistat treatment on reducing levels of TL, TC and TG was more apparent than that of ginger. Orlistat inhibits acylglycerols digestion and not lipid absorption in the small intestine. Therefore, it can be inferred that the transfer rate of dietary fatty acids from the lumen of the small intestine to the brush border cells and then the lymph will be affected by the

reduction of the dietary lipid hydrolysis³⁵. Before being incorporated into cell membranes, fatty acids are transported to the lymph, metabolized in the liver and then transported in the plasma³⁶. The effectiveness of orlistat in obesity is conferred by the ability of the drug to inhibit pancreatic lipase in the gastrointestinal tract, thereby preventing uptake of dietary fat³⁷. These findings explain the reduction of lipid parameters levels in orlistat fed group G3. A study by Ellrichmann et al³⁸ used a liquid emulsion of orlistat powder with the different test meals. This mixing of orlistat presumably resulted in an insufficient lipase inhibition. They concluded that a premixed liquid meal stabilizes the TG in form of an emulsion that provides a much better substrate for gastric and pancreatic lipase. Since half the inhibition time of the pancreatic lipase is about 5 minutes, most of the TG are hydrolyzed before the lipases are significantly inhibited by orlistat³⁹.

The lowering effect of ginger on cholesterol seen in G4 was in consistent with previous reports demonstrating the hypocholesterolemic and anti-atherosclerotic effects of ginger⁴⁰⁻⁴². This effect may be due to the presence of some chemical constituents in ginger, which inhibit the absorption of dietary fat by inhibiting its hydrolysis, it also stimulate the activity of hepatic enzyme cholesterol-7- α hydroxylase, which in turn stimulates the conversion of cholesterol to bile acids, an important pathway of elimination of cholesterol from the body.

Treatment with orlistat (G3) is found to decrease the HDL-C level when compared to the control group (G1); the effect of ginger in increasing the level of HDL-cholesterol is also significant as seen in G4. HDL-cholesterol is considered as protective against atherosclerosis because it moves cholesterol from peripheral tissues to the liver reverse cholesterol or good transport of plasma cholesterol⁴³. Evaluating the results of pancreatic lipase showed that no significant difference in the enzyme level in G4 (ginger treated) when compared to G1 (control group). There was a highly significant reduction in the pancreatic lipase level in G3 (orlistat treatment) when compared to other groups. Orlistat is chemically synthesized derivative of the natural product Lipstatin and specifically inhibits lipase at their catalytic triad serine 153-histidine 264-aspartate 177 by covalent binding to serine residue. The catalytic triad is a highly conserved feature of many biological lipases; the lipases in

the gastrointestinal tract, which are gastric lipase, pancreatic lipase and carboxyl ester lipase⁴⁴. Reduction of the enzymatic activity is mediated through the covalent binding of orlistat to the serine residue of the lipase active site⁴⁵.

There was a great relation between lipases and plasma TG levels, in that the triacylglycerols absorption efficiency is one of the main factors contributing to the plasma TG level; however, the dietary TG are not absorbed as much until hydrolyzed to fatty acids by triacylglycerol lipases. Pancreatic lipase is involved in the TG absorption from the small intestine to the enterocytes and if somehow this initial movement of TG from the small intestinal lumen is blocked, hyperlipidemia can be prevented⁴⁶. Thus, an inhibitor of digestive lipase that helps to limit intestinal fat absorption could be proved as useful medication for the treatment of hyperlipidemia and holds great promise as an anti obesity agent. Ginger treatment did not induce any significant effect on pancreatic lipase level as observed in G4. The presence of lipase inhibitors have been reported in some natural sources and aqueous extracts of some medicinal herbs⁷. A study by Sharma et al⁴⁷ used 75 medicinal plants belonging to different families among them was ginger (*Z. officinale*), plants were screened for their antilipase activity using radioactive method, the study found that *Z. officinale* did not possess any lipase inhibitor effect. This means that ginger was able to reduce lipid profile without alterations in pancreatic lipase level.

It is noticed that after 30 days of the treatment, the biliary secretion of rats were different, G3 (orlistat fed) was significantly ($p < 0.5$) lower than all experimental groups. Although not significant ($p > 0.5$), total bilirubin of rats in G1 is higher than the other groups. There is a great relation between the reduction in cholesterol level in orlistat treated rats and the reduction in serum total bilirubin in the same group. Cholesterol synthesis from acetate is regulated by hydroxymethyl-glutaryl-coenzyme A (HMG-CoA) reductase. In obesity, cholesterol synthesis is increased, mediated largely by an increased activation of the (HMG-CoA) reductase⁴⁸. Hafkamp et al⁴⁹ hypothesized that orlistat treatment decreases plasma bilirubin concentration in rats by increasing turnover and fecal excretion of bilirubin. Clearly, ginger treatment did not induce any significant effect in total bilirubin in G4 when compared to control group G1.

Results showed that, in crude liver homogenates of G3, the peroxisomal activity of catalase (*p* CAT) enzyme was significantly lower than the other tested groups, while no significant difference in the enzyme level in G4 when compared to either G1 or G2. Peroxisomes are oval, sac-like organelles that exist in many cells in the body but are most abundant in the liver cells, or hepatocytes. These microscopic cellular structures are so named because they generate hydrogen peroxide in detoxification reactions; peroxisomes also contain several enzymes to speed up specific cellular reactions. Liver is a primary organ that filters and detoxifies the blood and also produces some digestive enzymes. For these reasons, it contains a large number of peroxisomes that assist in many biological reactions including formation of bile acids, cholesterol and other substances in the liver. Meanwhile, peroxisomes contain enzymes that convert hydrogen peroxide into water by removing a single oxygen atom from each molecule of hydrogen peroxide. The harmless water and oxygen are then released safely back into the cells and tissues. Peroxisomes produce an enzyme called catalase for this reaction⁵⁰. Lowest value of catalase enzyme obtained in orlistat treated group, while ginger has been reported to interfere with enzyme activity increasing its level. It is clear that, all major active ingredients of ginger such as zingerone, gingeriol, zingibrene, gengerols and shogaols have antioxidant activity⁵¹. Besides, other researchers showed that ginger oils have dominative protective effect on DNA damage induced by H₂O₂ and might act as a scavenger of oxygen radicals and might be used as an antioxidant⁵². Since orlistat reduces fat absorption from intestinal system, it may have including vitamins A and E which contributes to the antioxidative capacity of the body⁵³.

Oxidants and antioxidants have attracted widespread interest in nutrition research, biology and medicine. It was clear that constant generation of prooxidants, including oxygen free radicals, is an essential attribute of aerobic life⁵⁵. The high level of oxidative stress associated with the increased lipid peroxidation may be one of the reasons why those who are overweight are at greater risk for developing heart disease⁵⁵. In conclusion, ginger has a great ability to reduce body weight without inhibiting pancreatic lipase level, or affecting bilirubin concentration, with positive effect on increasing peroxisomal catalase level and HDL-cholesterol.

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