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HYPOGLYCEMIC AND HYPOLIPIDEMIC EFFECTS OF GINGER IMPROVE KIDNEY FUNCTION IN OBESE MALE RATS

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Aside from being a social stigma, obesity is frequently associated with insulin resistance, in turn linked to development of type II diabetes, hypertension, hyperlipidemia, and atherosclerosis – the so-called metabolic syndrome.This study investigated the biochemical changes in serum urea and creatinine levels in obese male rats treated with aqueous ginger extract. Forty age-matched adult male wister rats (90-110) gm were divided into four groups of ten rats each: Group I, Control group; Group II: Obese group. Group III: Low ginger dose (200 mg/kg body weight) treated obese group; Group IV: High ginger dose (400 mg/kg body weight) treated obese group.The obese group exhibited hyperglycemia accompanied with increasing in serum levels of Triglycerides (TG), Low Density Lipoprotein Cholesterol (LDL-C), Total Cholesterol (TC) levels. On the other hand, there was a significant reduction in High Density Lipoprotein Cholesterol (HDL-C) level. Ginger was effective in lowering all previous mentioned biochemical parameters and HDL-C level was increased significantly. Serum urea and creatinine levels showed a significant increase in obese rats. Otherwise, obese rats treated with ginger at either dose revealed a significant decrease as compared to obese group. These results indicated that the hypoglycemic and hypolipidemic effects of aqueous ginger extract (200, 400 mg/kg/day) could ameliorate obesity related kidney dysfunction.

INTRODUCTION

The global prevalence of obesity has been approximately 3-fold higher compared to 1975[1] and is suggested to still rise in future[2]. Over the last three decades, body mass index (BMI) has increased worldwide by 0.4 $kg.m^{-2}$ per decade[3]. According to World Health Organization (WHO), Obesity is defined as a profuse accumulation of fat caused by an imbalance in intake and consumption of energy accompanied by insufficient physical activity[1].

Obesity may be associated with renal disease[4]. It increases the incidence of predisposing factors of chronic kidney disease (CKD), like hypertension and diabetes[5]. Increased renal filtration occurs in obese individuals to meet the elevated metabolic demands of raised body weight[4]. The hyper-intraglomerular pressure can destroy the kidney and increase the risk of developing CKD by time[6].

Ginger (*Zingiber officinale* family, *Zingiberacae*) is one of the most widely consumed spices worldwide. It was reported that ginger also has a therapeutic benefits in cancer, clotting, inflammation, and analgesic activities[7]. The renoprotective effects of ginger have also been reported in the animal models of ischemia/reperfusion[8], and streptozotocin[9] induced renal injuries. However, the efficacy of ginger on the metabolic syndrome-associated kidney damages in HFSD-induced obese rats remains unknown. In the present study, the impact of ginger on HFSD-induced kidney injury in rats was investigated.

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MATERIALS AND METHODS

Experimental animals

Forty age-matched adult male wister rats with initial body weights ranging from 90-110 gm were chosen as an animal model for this study. They were obtained from animal house, Faculty of Medicine, Assiut University, Assiut, Egypt. They were maintained on a balanced diet of bread with water supply till the start of experiment. The experiment ran according to Institutional Animal Ethic Committee guidelines for care and use of laboratory animals[10].

Preparation of aqueous ginger extract

Aqueous ginger extract was prepared as reported by Al-Amin *et al.*[11]. Ginger powder was purchased from Dop Organik Company for Pharmaceutical Industries, Turkey.

Induction of obesity

After two weeks of acclimatization, the rats were randomly divided into: Group I: Control group (10 rats), they were fed a standard diet throughout the experimental period. The remaining 30 rats were daily fed a high fat, sucrose diet (HFSD) which was composed of 55% standard diet, 15% beef tallow, 20% sucrose, 5% roasted peanuts, 5% milk powder, 5% egg, 3% sesame oil and 2% NaCl as reported by Ragab *et al*. (2015)[12]. After eight weeks, according to BMI, oral daily administration of aqueous ginger extract was started in concomitant with continuation of HFSD feeding for another eight weeks as follows; Group II: Obese group (10 rats), they were left untreated. Group III: Low ginger dose treated obese group (LGD, 10 rats), they were received aqueous ginger extract(200 mg/kg body weight). Group IV: High ginger dose treated obese group (HGD, 10 rats), they were received aqueous ginger extract (400 mg/kg body weight) according to Bhandari *et al.*[13].

Rats' body weight (BW) was measured at the end of experiment and BMI was calculated as follows:

BMI =body weight (kg)/length^2 (m^2).

Sample collection

At the end of this period (16 weeks), animals fasted overnight; venous blood samples (3-5ml) were taken from the retro-orbital sinus via glass capillaries under light anesthesia with diethyl ether to reduce animals' excitability[14]. These samples were put in Wassermann empty tube, left to clot at room temperature for 30 min then centrifuged at 3000 rpm for 10 min, then the serum was separated immediately and divided into aliquots for the measurement of serum fasting glucose, the lipid profile parameters, urea and creatinine levels.

RESULTS AND DISCUSSION

Results

Effect of oral daily administration of aqueous ginger extract (200, 400 mg/kg body weight) on body weight, BMI, serum glucose and parameters of lipid profile in obese male rats

Obese group showed a significant increase in body weight, BMI, and the mean serum levels of glucose, TC, TG, and LDL-C as compared to those of control group ($p< 0.001$, Table 1, Fig. 1). It also showed a significant decrease in the mean serum level of HLD-C as compared to that of control group ($p< 0.001$, Table 1, Fig. 1). Also, treatment of rats with 200 mg/kg/day ginger extract orally for 8 weeks produced a significant decrease in body weight, BMI, and the mean serum levels of glucose, TC, TG, and LDL-C as compared to those of obese group ($p< 0.001$, Table 1, Fig. 1) and a significant increase in the mean serum level of HLD-C as compared to that of obese group ($p< 0.001$, Table 1, Fig. 1). Moreover, the daily administration of 400 mg/kg ginger extract produced a significant decrease in body weight, and the mean serum levels of glucose, TC, TG, and LDL-C as compared to those of obese and LGD treated obese groups ($p< 0.001$, Table 1, Fig. 1), while, BMI showed a significant decrease as compared to that of obese group ($p< 0.001$, Table 1, Fig. 1) and no sigificant change as compared to LGD treated obese group. It also showed a highly significant increase in the mean serum level of HLD-C as compared to that of obese and LGD treated obese groups ($p< 0.001$, Table 1, Fig. 1).

Table 1: Effect of oral daily administration of aqueous ginger extract (200, 400 mg/kg) on body weight, BMI, serum glucose and parameters of lipid profile in obese male rats.

Group / Parameter	Control group n=10	Obese group n=10	LGD treated obese group n=10	HGD treated obese group n=10
Body Weight (gm)	175.3±18.54	374.9±32.49 a***	270.9±13.07 a*** b***	207.7±16.15 a*** b*** c***
BMI (Kg/m^2)	1.80±0.55	7.34±1.30 a***	2.36±0.65 a^{ns} b***	2.66±0.91 a^{ns} b*** c^{ns}
Fasting blood glucose level (mmol/l)	5.34±0.33	8.42±0.67 a***	7.28±0.48 a*** b***	6.43±0.40 a*** b*** c**
TC (mg/dl)	101.99±22.55	207.14±42.76 a***	137.80±12.98 a*** b***	109.02±6.80 a^{ns} b*** c***
TG (mg/dl)	77.35±46.43	256.93±67.47 a***	173.72±16.79 a*** b***	113.78±17.64 a*** b*** c***
HDL-C (mg/dl)	61.45±17.54	15.52±3.23 a***	29.38±6.27 a*** b***	44.26±5.64 a*** b*** c***
LDL-C (mg/dl)	25.07±28.97	140.23±32.62 a***	73.68±15.43 a*** b***	42.01±8.56 a*** b*** c***

BMI, body mass index; TC, total cholesterol; TG, triglycerides; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; LGD, low ginger dose; HGD, high ginger dose.

Results were expressed by Mean ± S.D.
a compared to control group.
b compared to obese group.
c compared to LGD treated obese group.
* P< 0.05, ** P< 0.01, *** P< 0.001.

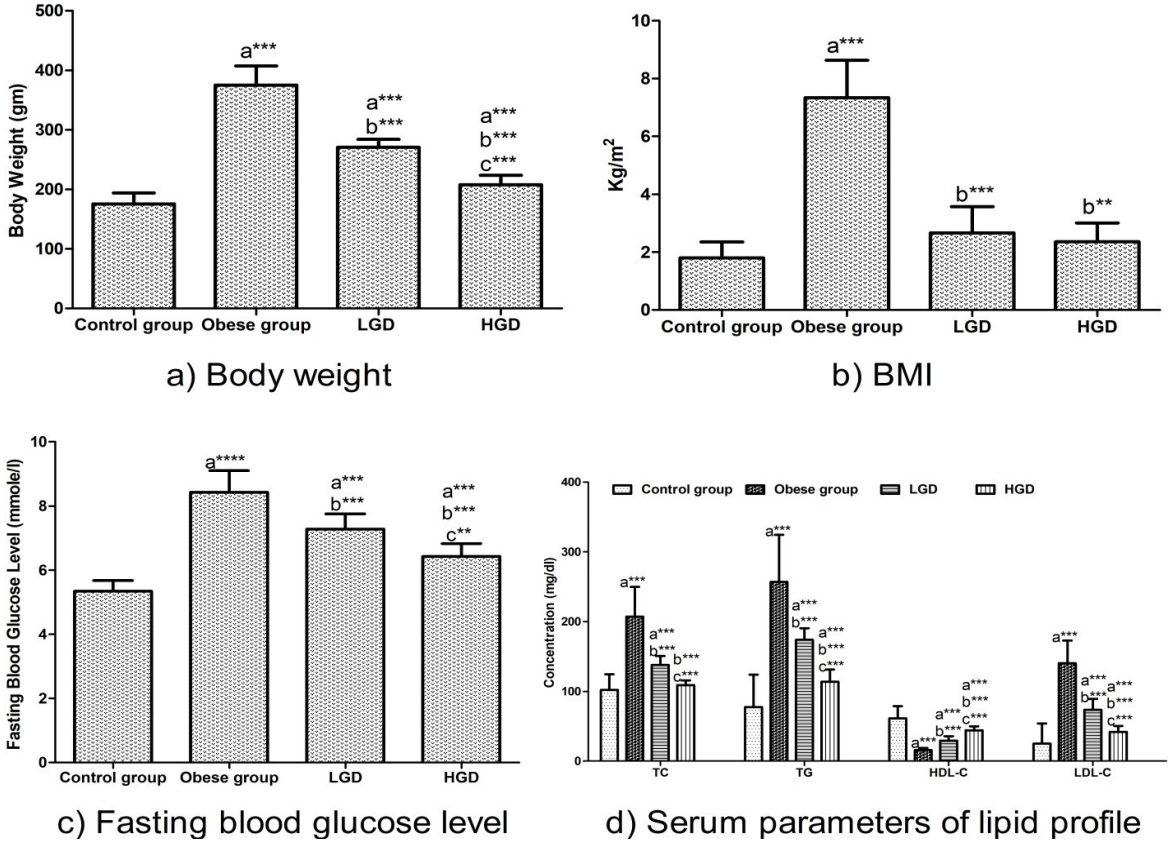

Fig. 1: Effect of oral daily administration of aqueous ginger extract (200, 400 mg/kg) on body weight, BMI, serum glucose and parameters of lipid profile in obese male rats.

BMI, body mass index; TC, total cholesterol; TG, triglycerides; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; LGD, low ginger dose; HGD, high ginger dose.
Results were expressed by Mean ± S.D.
a compared to control group.
b compared to obese group.
c compared to LGD treated obese group.
* P< 0.05, ** P< 0.01, *** P< 0.001.

Effect of oral daily administration of aqueous ginger extract (200,400 mg/kg body weight) on serum levels of urea and creatinine in obese male rats

Obese group showed a highly significant increase in the mean serum levels of urea and creatinine as compared to those of control group (p< 0.001, Table 2, Fig. 2). Treatment of rats with 200 mg/kg/day ginger extract orally for 8 weeks produced a highly significant decrease in the mean serum level of creatinine as compared to those of obese group (p< 0.001, Table 2, Fig. 2), while, the mean serum level of urea was showed no significant difference as compared to that of obese group. Also, administration of 400 mg/kg ginger extract produced a significant decrease in the mean serum levels of urea and creatinine as compared to those of obese and LGD treated obese groups (p< 0.01, Table 2, Fig. 2).

Table 2: Effect of oral daily administration of aqueous ginger extract (200, 400 mg/kg) on serum levels of urea and creatinine in obese male rats.

Group / Parameter	Control group n=10	Obese group n=10	LGD treated obese group n=10	HGD treated obese group n=10
Urea (mg/dl)	31. ± 5.48	46.31±9.21 a***	47.50±7.46 a*** b^{ns}	35.40±4.18 a^{ns} b** c**
Creatinine (mg/dl)	0.52±0.10	0.84±0.05 a***	0.74±0.05 a*** b**	0.62±0.04 a** b** c**

LGD, low ginger dose; HGD, high ginger dose.
Results were expressed by Mean ± S.D.
a compared to control group.
b compared to obese group.
c compared to LGD treated obese group.
* P< 0.05, ** P< 0.01, *** P< 0.001.

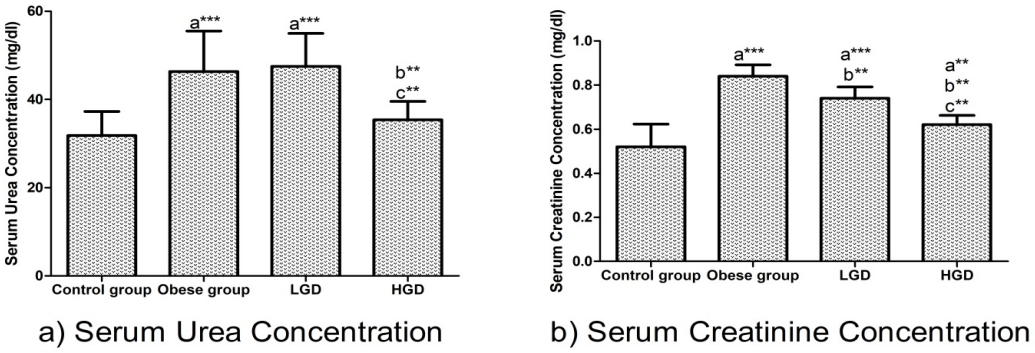

Fig. 2: Effect of oral daily administration of aqueous ginger extract (200, 400 mg/kg) on serum levels of urea and creatinine in obese male rats.

Results were expressed by Mean ± S.D.
a compared to control group.
b compared to obese group.
c compared to LGD treated obese group.
* P< 0.05, ** P< 0.01, *** P< 0.001.

Discussion

Obesity is a serious nutritional problem, as it increases the risk of morbidity from several pathologies[15]. Obesity, especially the central or visceral type, is a predisposing factor for the development of type II diabetes mellitus, hypertension, and cardiovascular disease (CVD)[16]. Recently, dietary polyphenols and their roles in the prevention of obesity and obesity-related chronic and metabolic diseases have received research attention. Whether a spice, vegetable, or traditional medicine, ginger is well-known for its therapeutic effects on obesity[17]. In the present study, the effect of aqueous ginger extract on some biochemical parameters in obese male rats was investigated.

Rats fed a HFSD showed visceral adiposity, hyperglycemia, dyslipidemia,

hyperinsulinemia, oxidative stress, meta-inflammation, hepatic and renal dysfunction, which are distinctly linked with human obesity[18]. Excessive growth of adipose tissue results in obesity, which includes two growth mechanisms: hyperplastic (an increase in cell number) and hypertrophic (an increase in cell size)[19]. In the present study, obese rats showed a significant increase in body weight and body mass index. The increased in body weight and body mass index found in HFSD fed rats might be due to the consumption of a diet rich in energy. These findings are in agreement with Liu *et al.* and Lomba *et al.*[20&21] who stated that HFSD induced weight gain and obesity.

In the present study, treatment with ginger showed a significant decrease in body weight and BMI. These results are in consistence with Ebrahimzadeh *et al*., Saravanan *et al.* and Lu *et al.*[22-24]. Ginger suppresses body weight gain induced by HFD feeding via the regulation of fatty acid metabolism[25] and inhibiting adipocyte differentiation[26&27]. In adipocytes, PPAR-γ and C/EBP-α are the key transcription regulator genes involved in adipogenesis[28&29]. Recent studies indicated that PPARs are the major mediators of the anti-obesity and anti-diabetic effects of ginger and its constituent compounds[30&31]. 6-Shogaol reduced the expression of PPAR-γ-associated genes and reduced adipogenesis in the cell line[32]. However, 6-gingerol could inhibit adipocyte differentiation by attenuating the Akt/GSK-3β pathway[33] and activating the Wnt/β-catenin signaling pathway[34].

In the present study, the obese rats showed mild hyperglycemia as compared to control group. HFSD has been shown to induce mild hyperglycemia by different mechanisms but considered mainly through the Randle or glucose–fatty acid cycle which is a biochemical mechanism involving the competition between glucose and fatty acids for their oxidation and uptake in muscle and adipose tissue[35]. Inflammation also contributes to the insulin signaling activity in adipocytes and hepatocytes through inhibition of insulin binding to its receptor, receptor phosphorylation, tyrosine kinase activity, and phosphorylation of IRSs[36]. These findings are in agreement with Liang *et al.*[37] and Kothari *et al.*[38].

In the present study, ginger treated obese group showed a significant decrease in fasting blood glucose as compared to obese group. These finding could by explained by the study of Zhu *et al.* who found that ginger promotes insulin sensitivity[39], thus lowering insulin resistance in obese rats, possibly by regulating the cell energy metabolism or reducing free fatty acids[23]. Ginger has been reported to increase the activity of hepatic glycolytic enzymes, including glucokinase, phosphofructokinase and pyruvate kinase. Ginger increased peripheral glucose utilization and decreased gluconeogenesis in the liver through its insulin mimetic effect[40]. These results are in consistence with Maharlouei *et al.,* Iranloye *et al.* and Silveira *et al*.[41-43].

HFSD supplementation resulted in dyslipidemic changes; increasing in serum TG, TC and LDL-C levels and decreasing in serum level of HDL-C[44]. High levels of TC, TG, LDL-C are the risk factor for CVD[45]. The alteration of lipid profile induced by HFSD might be caused by the activation of gastric lipases, intestinal fat absorption and the lipolysis. Also, impaired insulin action is associated with an over-supply of lipids. Diminished hepatic and muscular uptake of glucose produced hyperlipidemia due to increased fat mobilization from adipose tissue and resistance to the anti-lipolytic actions of insulin[46]. In the present study, supplementation of HFSD increased the lipid profile in plasma of experimental rats. These findings are in agreement withYamamoto *et al*.[47].

In the current study, ginger treated obese rats showed a significant reduction TG, TC and LDL-C levels and increase in serum level of HDL-C as compared to obese group. The suppression of plasma lipids by ginger may result from the reduction of the absorption of fat and cholesterol by inhibiting the activity of pancreatic lipase[23]. Consistent with this study, studies reported that the ginger extracts produced a significant reduction of TC, TG, and LDL-C levels when compared to different models of obese rats[11&48-50].

In addition, recent studies have identified oxidative stress as a key player in obesity associated kidney dysfunction[51]. Rosas-Villegas *et al*., indicated that the exposure to HFSD, rats promotes the antioxidant system depression due to the increase of lipid peroxidation and decrease of GSH amount in the kidneys[52]. In the present study, obese rats

showed a significant increase in serum creatinine and urea levels. Increased creatinine and urea levels indicate a lower degree of pore shrinkage due to cell proliferation and fibrosis of renal tubules[53]. The mechanism through which HFSD induced cell proliferation and fibrosis is not fully understood.

Accordingly, if HFSD consumption induces some functional abnormalities in kidneys through hyperglycemia and hyperlipidemia, as confirmed by present study and some previous ones, the effect of ginger supplementation on these abnormalities will be decreased. In the present study, Ginger treated obese rats showed a significant reduction in serum urea and creatinine. In agreement with Tzang *et al.,* Gabr *et al*. and Mehradad *et al.*[9&54&55] who stated that ginger and its active component improves obesity associated kidney dysfunction.

In Conclusion, The current study has demonstrated that ginger has protective effects on obesity and obesity-related chronic kidney diseases through its hypoglycemic and hypolipidemic effects.

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نشرة العلوم الصيدلية
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خفض مستويي الجلوكوز والدهون بواسطة الزنجبيل يحسن وظائف الكلى في ذكور الجرذان المسمنة

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ترتبط السمنة في كثير من الأحيان بمقاومة الأنسولين، وبدورها بتطور مرض السكري من النوع الثاني وارتفاع ضغط الدم وفرط شحميات الدم وتصلب الشرايين – ما يسمى متلازمة التمثيل الغذائي الي جانب كونها وصمة عار مجتمعية. تعين هذه الدراسة التغيرات البيوكيميائية في مستويات اليوريا والكرياتينين في دم ذكور الجرذان المسمنة المعالجة بمستخلص الزنجبيل المائي. تم تقسيم أربعين جرذا من الذكور المتطابقة في العمر بأوزان مبدئية (٩٠-١١٠) جم إلى أربع مجموعات في كل مجموعة عشر جرذان: المجموعة الأولى ، المجموعة الجرذان الضابطة ؛ المجموعة الثانية: مجموعة جرذان المسمنة. المجموعة الثالثة: مجموعة جرذان المسمنة والمعالجة بجرعة زنجبيل منخفضة (٢٠٠ ملجم / كجم من وزن الجسم)؛ المجموعة الرابعة: مجموعة جرذان المسمنة والمعالجة بجرعة زنجبيل عالية (٤٠٠ ملجم / كجم من وزن الجسم). اوضحت نتائج الجرذان المسمنة ارتفاع مستوي السكر في الدم مصحوبة بزيادة في مستويات الدهون الثلاثية (TG) ، كوليسترول البروتين الدهني منخفض الكثافة (LDL-C) ، والكوليسترول الكلي (TC). من ناحية أخرى ، كان هناك انخفاض في مستوي كوليسترول البروتين الدهني عالي الكثافة (HDL-C). كان الزنجبيل فعالاً في خفض جميع قياسات البيوكيميائية المذكورة سابقًا ، بينما زاد من مستوى كوليسترول البروتين الدهني عالي الكثافة (HDL-C) بشكل كبير. كشفت مستويات اليوريا والكرياتينين في دم الجرذان المسمنة التي عولجت بالزنجبيل بأي من الجرعتين انخفاضا كبيرا بالمقارنة مع مجموعة المسمنة. وتشير هذه النتائج إلى أن تأثير انقاص السكر والدهون في الدم ب (٢٠٠ ، ٤٠٠ ملجم / كجم من وزن الجسم/ يوم) من مستخلص الزنجبيل المائي يمكن أن يخفف من اختلال وظائف الكلى المرتبط بالسمنة.