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RESEARCH ARTICLE

The Hypoglycemic Effects of Ginger and Garlic Administration on Induced Diabetic Rats

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Abstract

This work was designed to investigate the possible hypoglycemic effects of ginger (*Zingiber officinal*) and garlic (*Allium sativum*) administration on type 2 diabetesinduced in rats. Seventy male adult albino rats were randomly divided into seven groups of ten animals: Normal Control (Cnt), Diabetic Control (CntD), Ginger Low (GNL), Ginger High (GNH), Garlic Low (GRL), Garlic High (GRH) and a combination group (GNH+GRH). Diabetes was induced by an intraperitoneal injection of streptozotocin (STZ, 65 mg/kg of body weight) in all groups except the Cnt group. Rats were treated with ginger and garlic powders in different doses for 2 months. At the end of experiment, glycated hemoglobin (HbA1c), serum glucose, serum insulin, cholesterol, and high density lipoprotein (HDL)concentrations, low density lipoprotein (LDL), liver glycogen and glucagon levels were estimated.Expression of Glucose-6-Phosphatase and Glucokinase genes in liver samples from each group were normalized with housekeeping gene (*ß-actin*) using reverse transcriptase real time Polymerase chain reaction. Serum insulin and HDL concentrations were significantly ($P< 0.05$) higherbutbody weight, fasting blood glucose, total cholesterol, LDLand HbA1clevels were significantly ($P< 0.05$) lower in the Cnt, GNH, GRH and GNH+GRHgroups compared to the CntD, GNL and GRL groups. Liver glycogen level was significantly ($P< 0.05$) higher and serum glucagon level was significantly ($P< 0.05$) lower in the combination group only but non significant difference was observed for the other groups. The expression of liver Glucose-6-Phosphatase gene was significantly ($P< 0.05$) downregulated but the Glucokinase gene was significantly ($P< 0.05$) upregulated in STZ diabetic rats treated withhigh doses of ginger and garlic powders. This study suggests that ginger and garlic powders can be used to ameliorate type 2 diabetes and might also help in preventing secondary diabetic complications.

Keywords: Ginger, Garlic, Type 2diabetes, Glucokinase gene.

Introduction

It has been estimated that within five years there will be an increase in the number of diabetic patients worldwide reaching 325 million [1]. This is attributed to several factors such as obesity, energy rich diets and longer life span. There are a lot of medicinal plants that provide therapeutic agents in traditional and modern medicine. The efficacy and safety doubts of the oral hypoglycemic agents have resulted in a search for safer and more effective natural drugs in the treatment of diabetes [2].

Insulin is one of the most important therapeutic agents for diabetes treatment but many researchers are making efforts to find insulin alternatives from plant or synthetic origins for the diabetes treatment. Many herbs have been used as substitutes to conventional therapy mostly in poor areas where insulin is not available [3].

Allium species (onions and garlic) are used as flavoring, folk medicine and foodstuffs. Using of garlic as hypoglycemic agents has

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been reported in Europe [4], India [5], and Middle East [6].

In modern medicine, garlic (*Allium sativum*) attracted the attention due to its global health use and they belief that it helps in giving more vigor and immunity against illnesses and thereby maintaining good health. The garlic biological responses are largely attributed to (i) stimulation of immunity, (ii) detoxification of foreign compound, (iii) reduction of cardiovascular diseases and cancer risk factors, (iv) antimicrobialt and antioxidant effects [7].

In addition, garlic contains sulfur containing compounds (cysteine derivatives and viz. S-alkyl cysteine sulfoxides) which are decomposed by allinase enzyme into volatile compounds as polysulfides and thiosulfinates during garlic extraction. These compounds have fibrinolytic, hypocholesterolaemic, antibiotic, antidiabetic and other biological effects. Garlicalso contains nonvolatile sulfur-containing peptides and proteins which have many valuable health benefits [8].

Ginger (*Zingiber offcinale*) is one of the most popular spices and many people use it all over the world. Southeast Asia is its origin and then ginger spread to Europe, it was used as a herbal medicine for several years to treat a variety of symptoms like pain, vomiting, cold-induced syndromes, and indigestion [9]. It was also reported that ginger possessed anti-clotting, anti-cancer, antidiabetic, analgesic and anti-inflammatory activities [10, 11]

To the best of our knowledge no research has approached the point of garlic and ginger combination until now which showed augmented hypo glycemic effect. The present study was conducted to investigate the anti-diabetic effects of dietary ginger and garlic and their combination in type 2 diabetes.

Materials and Methods

Animals

Seventy male adult albino rats with an average body weight of 190±20gm at the beginning of the experiment were purchased from the laboratory animal farm, Faculty of Veterinary Medicine, Zagazig University. Rats were housed with a relative humidity of 55+ 10% and 12:12 h light/dark. Animals were kept under similar environmental conditions of temperature, illumination, acoustic noise, and ventilation. Food and water were kept in special open containers fixed in the walls of the cages. Cleaning and changing water and food were done for all animals twice daily.

Experimental protocol

The protocol of this study was approved by the Committee of Animal Welfare and Research Ethics, Faculty of Veterinary. After two weeks of accommodation, 10 rats were separated to be used as non diabetic control group (Cnt) that fed standard diet only.The other rats were fed garlic and ginger powdersin different doses for 4- weeks.Then type 2 diabetes was induced in overnight fasted rats using a single dose of Nicotinamide I/P (110 mg/kg BW) dissolved in normal saline 15 minutes before intraperitoneal injection of Streptozotocin (65 mg/kg of BW) dissolved in citrate buffer (pH 4.5) [12]. Blood samples were collected from overnight fasted rats from recto-orbital puncture and serum samples were analyzed for fasting blood glucose level.

Rats with fasting blood glucose ≥ 200 mg/dL were considered diabetic and used to complete the experiment. They were then divided into 6 groups (10 rats/group). The diabetic control group rats (n=10) were kept on the standard diet with no additional treatment along the experimental period G1 (Cnt): Control, while the other diabetic groups (n=50) were fed garlic and ginger powders for 4 weeks and divided into:G2 (CntD): STZ control diabetic,G3 (GNL): Diabetic treated with ginger low dose, G4 (GNH): Diabetic treated with ginger high dose(N=10), G5 (GRL): Diabetic treated with garlic high dose, G6 (GRH): Diabetic treated with garlic low dose,G7 (MIX): Diabetic treated with mixed ginger and garlic high dose.

Low dose groups were treated orally and daily with ginger or garlic powders by putting 0.5% ginger or garlic powders instead of 0.5% cornstarch in the control diet. High dose groups were treated orally and daily with ginger or garlic powders by putting 2% ginger or garlic powders instead of cornstarch in control diet and mix group treated orally and daily with garlic powder and ginger powder by

replacing the same amount of 4%cornstarch from the control diet with an equal amount of ginger powder and garlic powder for a 8-week, 4weeks before STZ injection (induction of diabetes) and 4 weeks after injection with STZ[13].

Sampling protocol

At the end of the experiment, over night fasted rats were sacrificed, and then liver and blood samples were taken for further analysis. After that, 1 ml of blood samples was collected over heparin and they have been then preserved at 4°C for analysis of glycated hemoglobin (HbA1c). Moreover, another 1 ml blood sample was collected and centrifuged at 3000 rounds per minute (rpm) for 16 minutes and then the supernatants were collected to be used for detection of serum glucose concentration and serum insulin, cholesterol, HDL, LDL, liver glycogen and glucagon levels.

Parts of collected liver were cut, washed with cold saline, wiped with filter paper, weighed, frozen and preserved in liquid nitrogen for RNA extraction. The other parts of collected liver were preserved in 10% buffered formalin for histopathological examination.

Biochemical analysis

Serum glucose concentration

It was determined calorimetrically by BioMed diagnostic kits as previously described [14].

Serum insulin level:

Plasma insulin was determined according to Finlay *et al.* [15].

Glycated Hemoglobin (HbA1c) concentration and Total cholesterol level

HbA1c and total cholesterol level were determined as previously described [16,17], respectively.

Serum HDL level

It was determined as according to Burstein *et al.* [18].

Serum LDL concentration

It was determined using the following equation LDL – cholesterol = total cholesterol – triacylglycerol/5 – HDL-cholesterol [19].

Liver glycogen level

It was determined using Rat Liver Glycogen (LGLY) ELISA kit (MyBiosource,Catalog Number: MBS731185).

Serum glucagon level

It was determined using Rat Glucagon (GC) ELISA kit (MyBiosource, Catalog Number: MBS741717).

Expression of of Glucokinase and Glucose-6-Phosphatase genes using reverse transcriptase real timePCR

RNA was extracted from liver tissues using RNA extraction kit (Thermo Scientific, Fermentas, #K0731) then cDNA was synthesized using Reverse transcription kits (Thermo Scientific, Fermentas, #EP0451). Real-time PCR with SYBR Green was used to measure expression of mRNAs of target genes in the liver, with the house keeping (ß-actin) as an internal reference gene to calculate the relative gene expression or fold change in target gene. The isolated cDNA were amplified using 2X Maxima SYBR Green/ROX qPCR Master Mix following the manufacturer protocol (Thermo scientific, USA, # K0221) and gene specific primers. Primer 3 (http://www-genome.wi.mit.edu/cgi-bin/primer/ primer3_www.cgi) was used to design these primers based on published rat sequences. Glucokinase gene (F/5 GTG GTG CTT TTG AGA CCC GTT 3/), (R/5 TTC GAT GAA GGT GAT TTC GCA 3/), Glucose-6-Phosphatase(F/5 AAA GAG ACT GTC GGC ATC AAT C 3/) (R/5 AAG AGG CTG GCA AAG GGT GTA G 3/) and β-actin gene (F/5 AAG TCC CTC ACC CTC CCA AAA G 3/), (R/5 AAG CAA TGC TGT CAC CTT CCC 3/).To ensure primer sequence is unique for the template sequence; similarity to other known sequences was checked with BLAST (www.ncbi.nlm.nih.gov/blast/Blast.cgi).

The thermal cycler condition was initial denaturation at 95˚C/ 10 min, denaturation at 95˚C/ 15 sec, annealing at 60˚C/ 30 sec, extension at 72˚C/ 30 sec for 40 cycles..At the end of the last cycle temperature was increased

from 60 to 95 °C to produce a melt curve..The threshold cycle numbers (Ct) of target gene were normalized with (Ct) of housekeeping gene (*ß-actin*) by using the $2^{-\Delta\Delta Ct}$method [20].

Statistical analysis

All the data were expressed as means ±S.E. The statistical significance was evaluated by one-way analysis of variance (ANOVA) using SPSS, 18.0 software, 2011 and the individual comparisons were obtained by Duncan's multiple range test (DMRT). Values were considered statistically significant when $p<0.05$.

In this study the body weight was significantly ($P< 0.05$) increased in STZ-diabetic animals.

The body weight was significantly ($P< 0.05$) decreased after treatment with ginger and garlic powders high doses (Table 1). This result is in a complete agreement with previous results of a recent study conducted in diabetic rodents treated with ginger ethanolic extract at a dose of 100, 200, and 400 mg/kg for 45 days, the marked increase in serum glucose, body weight, total cholesterol, insulin, triglycerides, LDL cholesterol, phospholipids, and free fatty acid which induced by receiving high-fat diet significantly reduced [21].

Results & Discussion

Table 1: Body weight, fasting blood glucose level and serum insulin level in STZ diabetic rats and treated with ginger and garlic powders in different doses for 2 months

Group	Body weight (gm)	Fasting blood glucose(mg/dl)	Serum insulin (ng/ml)
G1 (Cnt)	199±5.86^{a}	107.00±4.04^{c}	4.91±0.13^{a}
G2 (CntD)	205.33±5.78^{a}	208.67±3.18^{a}	2.55±0.25^{d}
G3 (GNL)	209.67±11.26^{a}	143.00±2.08^{b}	2.85±0.13^{d}
G4 (GNH)	206.67±4.81^{a}	138.33±2.03^{b}	2.87±0.17^{d}
G5 (GRL)	195.00±8.66^{a}	143.33±2.73^{b}	3.31±0.15^{c}
G6 (GRH)	175.67±2.33^{b}	137.00±2.89^{b}	3.51±0.21^{c}
G7 (MIX)	170.33±3.18^{b}	112.00±4.36^{c}	4.10±0.14^{b}

STZ: streptozotocin. Data are presented as means± standard error. Mean values with different superscript letters in the same column are significantly different at ($P\leq0.05$). G1 (Cnt): Control, G2 (CntD): STZ control diabetic, G3 (GNL): Diabetic treated with ginger low dose, G4 (GNH): Diabetic treated with ginger high dose, G5 (GRL): Diabetic treated with garlic high dose, G6 (GRH): Diabetic treated with garlic low dose, G7 (MIX): Diabetic treated with mixed ginger and garlic high dose.

An amazing finding was obtained in this study, fasting blood glucose levels are significantly ($P< 0.05$) reduced in STZ-diabetic rats after treatment with high doses of ginger and garlic powders.Our data agree with Jelodar *et al* [22]who reported that there was a significant reduction in serum fasting blood glucose level when alloxan-induced diabetic animals treated with garlic in diet (12.5% of their body weight) for 2 weeks. It was known that oral administration of the juice of the garlic every day 1mL/100gm of body weight) for 2 months significantly reduced the fasting blood glucose level in alloxan-induced diabetic rats [23]. (S-alkyl cysteine, sulfoxides and alliin) has a hypoglycemic benefits and also increases the level of blood insulin [24]. Ginger reduced the hyperglycaemia resulting from the diabetes which induced by STZ injection. The reduction in glucose levels in blood was due to the antidiabetic compounds (gingerols and shogaols) found in ginger[25].Also Al-Amin *et al*. [26] declared that aqueous extract of ginger when injected intraperitoneal at a dose of (500 mg/kg BW) caused reduction in blood sugar and reduction in concentrations of lipid when animals received control diet for 49 days. On the other hand, Bordia *et al*. [27] found that 10 g of ginger powder when given once to different people, there is no effect on postprandial glucose, in fasting glucose or in lipid.From these results, it is very clear that the allium species effect as hypoglycemic

agent is not the same in all conditions or in all studies.

Serum insulin concentration is a crucial factor helping to maintain normal blood glucose level.This study showed that, administration of different doses of ginger and garlic powders for 2monthes succeeded to significantly ($P< 0.05$) increase the level of the serum insulin in STZ-diabetic rats and administration of mixed ginger and garlic powders for 2monthes in high doses succeeded to nearly normalize the serum insulin level in STZ-diabetic rats when compared to diabetic control group. These results are similar to the findings of Akhani *et al*. [28] who recorded that oral administration of gingerjuice (4mL/kg) for 1.5 months the level of serum insulin was significantly induced in type 1 diabetes in rats injected with STZ. Another study found that when garlic was given orally for 2 weeks (0.25 or 0.5 g of garlic/kg), the concentration of serum insulin had significantly increased in diabetic rodents [29].Diallyl trisulfide and *S*-Allyl cysteine sulfoxide are the major active sulfur compounds found in garlic. They have insulin secretagogue activity in isolated beta-cells of normal rats pancreas when isolated *in vitro* and in *vivo* rats diabetic pancreas [8, 30].The active component of ginger called gingerol. Gingerol and gingerol-sensitive nerves may have the ability to produce insulin in GNH group and in combination (GNH+GRH) group [28].

Augusti and Sheela [8] reported that garlic acts as an insulin secretagogue in diabetic rats. Another proposed mechanism is due to spare insulin from sulfhydryl group. Inactivation of insulin by sulfhydryl group is a common phenomenon. Garlic can effectively combine with compounds like cysteine and enhance serum insulin. Bailey and Day [6] proposed that garlic can act as an antidiabetic agent by increasing either the pancreatic secretion of insulin from the beta cells or its release from bound insulin.

Gingerol showed a protective effect on pancreatic β-cells and restored the plasma insulin level. The mechanism underlying this action of ginger may involve interaction with the 5-HT3 receptor as it was found that gingerols and shogaol can act on 5-HT3 receptor- ion channel complex by binding to a modulatory site distinct from the serotonin binding site [31].The key enzymes controlling carbohydrate metabolism associated with hyperglycaemia and type2 diabetes are α-amylase and α-glucosidase. The action of ginger against these two enzymes was found to be correlated with the phenolic contents of gingerol and shogaol in these extracts [32].

Glycation of the hemoglobin is formed through the erythrocytes circulatory life, simply by addition of glucose to the end of the β-chain of hemoglobin. This is a non-enzymatic process andit gives an indication about the average of hemoglobin exposure to glucose through and an extended period. Glycated hemoglobin which is a good monitor used as an indicator for the blood glucose level over the proceeding weeks, while a single glucose determination gives a value which is true only at the time when the blood sample was collected [33].Results revealed that treatment of diabetic rats with garlic powder in different doses and treatment with mixed high doses of ginger and garlic powders help to significantly ($P< 0.05$) decreased the $HbA_{1c}$when compared to diabetic control group (Table 2).This data agrees with Mahluji *et al*. [34]who recorded that daily intake of 2g of ginger powder in type 2 diabetic patients for 2 months significantly decreased HbA1C, TG and LDL. Moreover Sathibabu and Saravanan[35] found that diabetic rats treated with garlic, SAC and Gliclazide showed a noteworthy diminish in glycosylated Hemoglobin levels that might be due to the anti hyperglycemic effect of garlic.

Table 2: HbA_{1c}, Cholesterol and HDL in STZ diabetic rats and treated with ginger and garlic powder in different doses for 2 months

Group	HbA_{1c} (ng/ml)	Cholesterol (mg/dl)	HDL (mg/dl)
G1 (Cnt)	11.87 ± 0.32^{c}	105.70 ± 3.18^{e}	53.39 ± 0.83^{a}
G2 (CntD)	20.03 ± 0.33^{a}	196.03 ± 3.12^{a}	39.93 ± 0.73^{e}
G3 (GNL)	15.71 ± 0.37^{b}	148.15 ± 2.70^{b}	43.69 ± 0.42^{d}
G4 (GNH)	15.33 ± 0.32^{b}	137.55 ± 3.74^{c}	46.08 ± 0.61^{c}
G5 (GRL)	12.60 ± 0.30^{c}	145.87 ± 2.91^{b}	43.54 ± 0.79^{d}
G6 (GRH)	12.04 ± 0.42^{c}	134.90 ± 1.91^{c}	46.47 ± 0.41^{c}
G7 (MIX)	11.98 ± 0.35^{c}	114.00 ± 3.09^{d}	51.05 ± 0.34^{b}

HbA1c: glycated hemoglobin, HDL: high density lipoprotein, STZ: streptozotocin. Data are presented as means± standard error. Mean values with different superscript letters in the same column are significantly different at ($P\leq0.05$).G1 (Cnt): Control, G2 (CntD): STZ control diabetic, G3 (GNL): Diabetic treated with ginger low dose, G4 (GNH): Diabetic treated with ginger high dose, G5 (GRL): Diabetic treated with garlic high dose, G6 (GRH): Diabetic treated with garlic low dose, G7 (MIX): Diabetic treated with mixed ginger and garlic high dose.

This study stated that daily treatment with ginger and garlic powders in high doses to STZ diabetic rats for 2 months significantly ($P< 0.05$) decreased the level of cholesterol when compared to diabetic control group (Table 2).This data agrees with Ashraf *et al*. [36]who stated that garlic tablets (300 mg) when given twice daily for 3 months, it reduced cholesterol in type 2 diabetic patients and also agrees with Eidi *et al*. [29] who recorded that the ethanolic extract of garlic (0.25, 0.5 and 0.1 gm per kg BW) when given once daily for 2 weeks, it helped in reducing serum sugar, triglyceride, and total cholesterol levels in diabetic animals. It is also agree with Akhani *et al.* [27] who recorded that *Z. Officinale* ethanolic extract (200 mg/ kg BW) administration every day for 20 days led to both triglycerides and cholesterol had reduced, and when ginger juice was given (4 ml / kg BW) orally and daily for one month and 15 days to type 1 diabetic patients maintained with a standard rodent diet, the same results observed. On the other hand, this data disagrees with Bordia *et al.*[27] who stated that there is no change in either glucose or lipid in the blood of patients suffering from coronary artery diseases after consumption of ginger (4 gm) for 90 days also Gardner *et al*. [37] found that, there is no effect of any form of garlic like powder, adult or raw garlic when we fed to the adult patients only 6 days in the week for 24 weeks on lipid effect but it may lower the lipid on patients suffering from mild hyperlipidemia .

This study showed that after daily administration of garlic and ginger powders in low doses, HDL level significantly ($P< 0.05$) decreased, but in rate less efficient than ginger and garlic powders high doses groups when compared to diabetic control group. This data agrees withAshraf*et al*.[36] who reported that type 2 diabetes mellitus patients when treated with 2 tablets of garlic the dose of each tablet is 300 mg for 84days, increased HDL level. Ethanolic *Z. officinale* extract helps in increasing the level of high density lipoprotein and lower the amount of triglycerides, cholesterol, and thiobarbituric acid-reactive substances in liver and pancreas in rats suffering from diabetes [38].

Our study stated that daily low doses of ginger and garlic powders succeeded to significantly ($P< 0.05$) decrease the level of LDL, but in rate less efficient than ginger and garlic powders high doses groups and treatment of STZ diabetic rats with mixed high doses of ginger and garlic powders succeeded to nearly normalize LDL level when compared with diabetic control group. This data agrees with Nammi *et al*. [21] who reported that treatment of type 2 diabetic rats fed on high fat diet with an ethanolic *Z. officinale* at doses of (400, 200, and 100 mg per kg body weight) for 45 days helps in decreasing body weight, cholesterol, LDL, triglycerides, phospholipids, and free fatty acids, which rises as a result of high fat diet. There is a lot of studies conducted hoping to detect the beneficial effects of *Z. officinal* in patients. Consumption of divided doses of three grams dry powder of ginger for one month caused reduction in blood triglyceride, glucose, total cholesterol, and very low

density lipoprotein in patients suffering from diabetes [39]. Another study conducted by Al-Amin *et al*. [26] stated that aqueous ginger extract has hypocholesterolemic, hypolipidemic, and hypoglycemic effects after a single dose when given intraperitoneally.

The liver plays an important role in the synthesis of glycogen and in decrease postprandial hyperglycemia.Glucose is stored intracellular in the form of glycogen. Its level in tissues gives a direct indication of the activity of insulin, because insulin stimulates glycogen synthase and inhibits glycogen phosphorylase so it increases intracellular glycogen. Streptozotocin causes β-cells destruction, so insulin concentration decreased, it is rational that glycogen levels in insulin- dependent tissues (skeletal muscle & liver) decrease as they depend on insulin [40,41]

The present study showed that the liver glycogen level in diabetic control groupsignificantly ($P< 0.05$) decreased, but after treatment with mixed high doses of ginger and garlic powders, liver glycogen level was significantly ($P <0.05$) increased. On the other hand, there is no significant change in liver glycogen level after treatment of STZ diabetic rats with different doses of ginger and garlic powders. These data are in agreement with Hikino *et al*. [42] who found that liver glycogen content decreased drastically in diabetic rats by approximately three- quarters of their basal levels, but liver glycogen level showed non significant increase after treatment with an aqueous extract of ginger. And also agrees with Abdulrazaq *et al*. [43] who stated that when rodents suffering from diabetes treated with an aqueous ginger extract, glycogen content in kidney was increased, but there is no significantly increase in the glycogen in skeletal muscle and liver. Also Sheela *et al*. [44] found that the allicin supplements increased the liver glycogen phosphorylase activity in STZ-diabetic rats.

In our study the serum glucagon level significantly ($P< 0.05$) increased in STZ diabetic rats. STZ diabetic rats receiving different doses of garlic and mixed high doses of ginger and garlic powders succeeded to significantly ($P< 0.05$) decrease serum glucagon level.

The present study showed significant ($P< 0.05$) upregulation of glucose 6phosphatase gene expression level in hepatic tissues of diabetic rats, but this expression was significantly ($P< 0.05$) downregulated in combination (GNH+GRH) group as shown in Figure 1.This data agrees with Spence[45]who reported that the gluconeogenic enzymes in hepatic tissue (fructose-1, 6-bisphosphatase & glucose-6-phosphatase) were increased in diabetic animals.

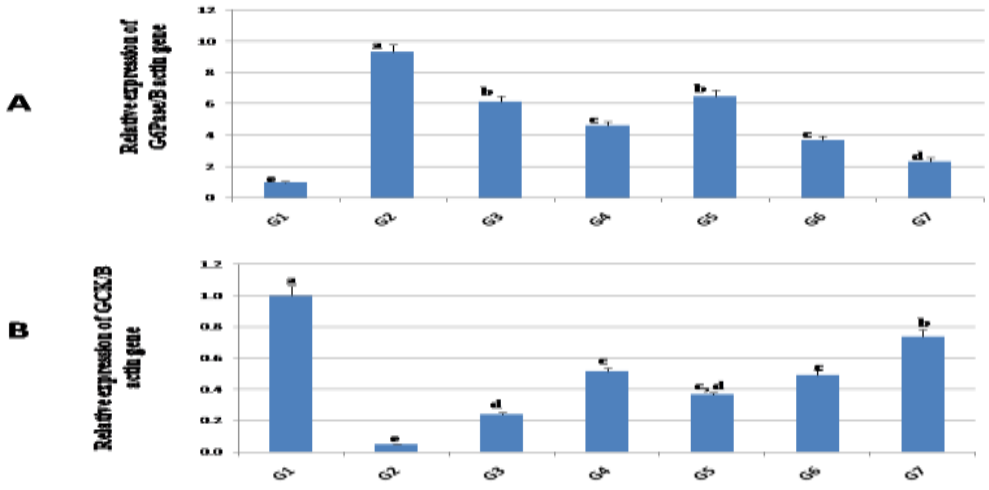

Figure (4): Change in relative gene expression of Glucose-6-phosphatase (a) and Glucokinase (b) in STZ diabetic rats and treated with ginger and garlic powder in different doses for 2 months. G1 (Cnt): Control, G2 (CntD): STZ control diabetic, G3 (GNL): Diabetic treated with ginger low dose, G4 (GNH): Diabetic treated with ginger high dose, G5 (GRL): Diabetic treated with garlic high dose, G6 (GRH): Diabetic treated with garlic low dose, G7 (MIX): Diabetic treated with mixed ginger and garlic high dose.Columns carrying different superscripts are significantly different at *p*<0.05. Bars represent means± S.E.

A previous study demonstrated that the gene expression of some key enzymes of glucose metabolism, including glucose 6 phosphatase in liver tissue. This enzyme plays a vital role in gluconeogenesis and stimulates liver to produce glucose in the blood [46].Increased G6Pase activity was observed in a lot of diabetic models [47].

The activities of the glucose-6-phosphatase were found to be increased significantly in STZ-NAD induced diabetic rats. The diminishment in the activities of this gluconeogenic enzyme can bring about diminished concentration of glucose in blood by the supplementation of garlic, SAC and Gliclazide [35].The allicin supplement stimulates the liver glycogen phosphorylase activity and it inhibits glucose-6-phosphatase activity. So, they proposed the possibility that garlic enhances endogenous insulin action [44].

Glucokinase, one of the key enzymes of the metabolism of glucose are distinctly changed to produce hyperglycemia, which lead to complications of diabetes. Glucokinase, the first regulatory enzyme of glycolysis, is an insulin-sensitive enzyme and is almost entirely introverted in diabetic hepatic tissue in the insulin deficiency [48].The present study showed significant($P< 0.05$) down regulation of glucokinase gene expression level in diabetic hepatic tissue, but this expression was significantly ($P < 0.05$) up regulated in GNH, GRH, and mix (GNH+GRH) groups. The obtained results are in agreement with Sathibabu and Saravanan[35]who observed a decrease in hepatic gluokinase activity in STZ-NAD induced diabetic patients. Administration of SAC, Gliclazide, and garlic to streptozotozin-NAD treated animals lead to an increase in hexokinase activity in liver.

Table 3: LDL level, liver glycogen level and serum glucagon level in STZ diabetic rats and treated with ginger and garlic powder in different doses for 2 months

Group	LDL (mg/dl)	Liver glycogen(umol/g)	Serum glucagon(pg/ml)
G1 (Cnt)	42.48±0.37^{e}	235.71±2.77^{a}	83.03±0.96^{d}
G2 (CntD)	80.09±0.59^{a}	81.56±4.60^{c}	189.98±2.03^{a}
G3 (GNL)	61.07±0.45^{b}	78.82±3.45^{c}	184.25±3.10^{a}
G4 (GNH)	57.10±0.51^{c}	80.47±1.48^{a}	184.68±1.85^{a}
G5 (GRL)	61.68±0.22^{b}	82.42±1.28^{c}	145.16±2.50^{b}
G6 (GRH)	58.58±0.34^{b,c}	83.24±2.05^{c}	143.68±3.02^{b}
G7 (MIX)	45.90±0.49^{d}	135.61±2.56^{b}	102.16±1.94^{c}

LDL: low density lipoprotein, STZ: streptozotocin. Data are presented as means± standard error.Mean values with different superscript letters in the same column aresignificantly different at ($P \leq 0.05$).G1 (Cnt): Control, G2 (CntD): STZ control diabetic, G3 (GNL): Diabetic treated with ginger low dose, G4 (GNH): Diabetic treated with ginger high dose, G5 (GRL): Diabetic treated with garlic high dose, G6 (GRH): Diabetic treated with garlic low dose, G7 (MIX): Diabetic treated with mixed ginger and garlic high dose.

Conclusion

This study showed that treatment of STZ diabetic rats fed on high fat diet with ginger and garlic powders for 2 months significantly reduced the marked rises in fasting blood glucose, body weight, total cholesterol, HbA1c, serum glucagon and serum LDL. Also ginger and garlic powders help to increase insulin, HDL and liver glycogen levels. The expression of liver G6Phosphatase gene was downregulated in STZ diabetic rats treated with ginger and garlic powder. On the other hand, the expression of liver Glucokinase gene was up regulated in STZ diabetic rats treated with ginger and garlic powder. Our study suggests that *Zingiber officinale* and *Allium satvium* have beneficial effects in diabetes that hold the hope of a new generation of antidiabetogenic drugs. The present study suggested that ginger and garlic help in both protection and prevention against the complications of diabetes.

Conflict of interest

The authors have no conflict of interest to declare.

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الملخص العربي

دراسة تاثير تناول كلا من الزنجبيل والثوم على الفئران المصابة بالسكري

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تم تصميم هذا العمل لدراسة الآثار المحتملة لنقص السكر في الدم من إدارة الزنجبيل (*Zingiber officinal*) والثوم (*Allium sativum*) على داء السكري من النوع ٢ في الفئران. تم إطعام سبعين من ذكور الفئران البيضاء البالغة وتم تقسيمهم بشكل عشوائي إلى سبع مجموعات من عشرة حيوانات: التحكم الطبيعي (Cnt) ، التحكم في مرض السكري (CntD) ، الزنجبيل المنخفض (GNL) ، الزنجبيل العالي (GNH) ، الثوم منخفضة (GRL) ، والثوم عالية (GRH) ومجموعة مجموعة (GNH + GRH). تم إحداث مرض السكري عن طريق الحقن داخل الصفاق من الستربتوزوتوسين (STZ، 65 ملغ / كلغ من وزن الجسم) في جميع المجموعات باستثناء مجموعة Cnt. تم علاج الجرذان بمساحيق الزنجبيل والثوم بجرعات مختلفة لمدة شهرين. في نهاية التجربة ، تم تقدير نسبة الهيموغلوبين السكري (HbA1c) ، الجلوكوز في الدم ، الأنسولين في الدم ، الكولسترول ، والبروتينات الدهنية عالية الكثافة (HDL) ، البروتينات الدهنية منخفضة الكثافة (LDL) ، مستويات الجليكوجين في الكبد والجلوكاجون في الكبد. تم تطبيع الفوسفاتيز والجلوكوكيناز في عينات الكبد من كل مجموعة مع جين (ß-actin) باستخدام تفاعل البلمرة المتسلسل النسخى العكسى الكمى. تفاعل الأنسولين في المصل و HDL كانت أقل بشكل ملحوظ (P<٠.٠٥) في مجموعات Cnt و GNH و GRH و GNH + GRH group مقارنة بمجموعات CntD و GNL و GRL. كان مستوى جليكوجين الكبد أعلى بشكل ملحوظ (P<٠.٠٥) وكان مستوى الجلوكاجون في الدم أقل بشكل ملحوظ (P<٠.٠٥) في مجموعة المجموعة فقط ولكن لوحظ عدم وجود فرق كبير للمجموعات الأخرى. كان التعبير عن جينات جلوكوز ٦ فوسفاتاز الكبد (P<٠.٠٥) أقل أهمية ، ولكن تم تنظيم جين الجلوكوكيناز بشكل كبير (P<٠.٠٥) في فئران السكري STZ التي عولجت بجرعات عالية من مساحيق الزنجبيل والثوم. تشير هذه الدراسة إلى أنه يمكن استخدام مساحيق الزنجبيل والثوم لتخفيف داء السكري من النوع ٢ وقد تساعد أيضًا في الوقاية من المضاعفات السكري الثانوية