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# Effects of *Zingiber officinale* hydro-alcoholic extract on HMG-COA reductase level in the testis of streptozotocin-induced diabetic rats

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**ABSTRACT**

**Introduction:** *Zingiber officinale* Roscoe, commonly known as ginger, is used as a cooking spice and therapeutically for its antioxidant and androgenic activities. We investigated the effects of *Z. officinale* hydro-alcoholic extract on HMG-CoA (3-hydroxy-3-methylglutaryl coenzyme A) reductase level in the testis of streptozotocin (STZ)-induced diabetic rats.
**Methods**: The current experimental study was performed on four groups of male Wistar rats one of them was kept as a healthy control, while the others were rendered diabetic via a single intraperitoneal injection of STZ (60 mg $kg^{-1}$). One group was considered as diabetic control; while the others were given orally hydro-alcoholic extract (200 and 400 mg $kg^{-1}$) for 56 consecutive days. Body weight, blood glucose and insulin concentrations were evaluated using standard methods. The HMG-COA reductase level was determined by western blot analysis.
**Results:** Treatment with the extract resulted in a significant reduction of serum glucose concentration and HMG-COA reductase level in the rat's testis compared to diabetic controls ($P<0.01$). A significant increase in body weight was observed in treated diabetic rats. Also, serum insulin was significantly increased in diabetic rats treated with 400 mg/kg of the extract compared to diabetic controls ($P<0.05$).
**Conclusion:** Ginger has a potential influence on the regulation of cholesterol homeostasis by modulating of HMG-COA reductase level. The results provide scientific evidence to confirm the traditional use of *Z. officinale* in the treatment of diabetes mellitus.

*Implication for health policy/practice/research/medical education:*
Oral administration of ginger hydro-alcoholic extract could ameliorate hyperglycemic induced diabetic complications. Also, its potential influence in the regulation of cellular cholesterol homeostasis possibly is mediated by modulating of HMG-COA reductase level.

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## Introduction

Cholesterol is a vital constituent of mammalian cell membranes, and comprises about 30% of all animal cell membranes, it maintains membranes and modulates membrane fluidity over the range of physiological temperatures, however, excess cellular and circulating cholesterol is harmful that can be related to some diseases, including coronary artery disease and atherosclerosis (1,2). The maintenance of cellular cholesterol homeostasis is precisely regulated by several feedback mechanisms. The major regulatory targets of these feedback mechanisms are HMG-CoA reductase in cholesterol biosynthesis pathway, the low-density lipoprotein (LDL) receptor in cholesterol uptake, and cholesterol 7α-hydroxylase in cholesterol

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catabolism pathway (3-5). Diabetes mellitus has been revealed to be associated with sexual dysfunction in both sexes.

Previous studies have shown that several phyto-ingredients have a potential influence in the regulation of cholesterol homeostasis in animal models (6-8). One of these phyto-ingredients is *Zingiber officinal* Roscoe, that is traditionally widely-utilized spice in worldwide. Some properties such as anti-inflammatory, antioxidant and anti-diabetic properties have been reported for *Z. officinal* (9-11). Some studies have shown that the ethanol extract of *Z. officinale* alleviates plasma lipids in cholesterol fed hyperlipidemia rabbits (12,13) and in streptozotocin (STZ)-induced diabetic rats (14). Also, LDL oxidation in atherosclerotic mice was inhibited by ethanol extract of *Z. officinale* in some studies (15). In addition to the alcohol extract of ginger, the aqueous extract of *Z. officinale* has also been shown to reduce lipid profile in serum of normal rat (16). These reported effects of *Z. officinale* may be resulted from inhibition of cellular cholesterol biosynthesis (15) and excitation of cholesterol removal from the body (17,18). To the best of our knowledge, the effects of hydro-alcoholic extract of *Z. officinale* on the HMG-CoA reductase level in the testis of STZ-induced diabetic rats, which is the main aim of this study, have not yet been well assessed.

## Materials and Methods

### Animals

In this experimental study a total 16 male Wistar rats with the average weight of 200-250 g were assessed. The rats were purchased from Research Center and Experimental Animal House of Ahvaz Jundishapur University of Medical Sciences (Ahvaz, Iran). Upon entrance, all the animals were accommodated in a well-ventilated room with a comparative temperature of 22±2˚C and photoperiod of 12-hour light-dark cycle. During the experiment, all animals were given free access to standard food pellet and tap water.

### Experimental design

For induction of diabetes, after one-week adaptation and following an overnight fasting, the rats were given a single intraperitoneal (ip) injection of STZ (Purchase from Sigma-Aldrich, USA) 60 mg/kg that was freshly dissolved in 0.1 M cold citrate buffer in pH 4.5. Also, the healthy control rats were injected alone with the same volume of sodium citrate buffer solution. After three days of STZ induction, blood specimens were collected from the nicked tail-vein, and the blood glucose levels were measured. The blood glucose more than 350 mg/dL was considered as diabetes. Two weeks after STZ injection, oral gavage of *Z. officinale* extract was initiated and continued for a period of 8 weeks. The rats were randomly categorized into four experimental groups, each group consisted of four rats, and assessed as follows:

Group 1: Healthy control was orally gavaged with 1.5 mL/kg distilled water once daily.

Group 2: Diabetic control was orally gavaged with 1.5 mL/kg distilled water once daily.

Group 3: Diabetic rats were orally gavaged with 200 mg/kg of the extract once daily.

Group 4: Diabetic rats were orally gavaged with 400 mg/kg of the extract once daily.

### Sample collection

The fasted rats in all groups at the end of eight-week treatment were weighed and then sacrificed after anesthetizing. By using not heparinized syringes, fresh blood samples were directly obtained via cardiac puncture and sera were separated by centrifugation for biochemical measurements. The testis was immediately isolated and washed with cold normal saline solution, then stored at -80˚C for later assays.

### Preparation of Zingiber officinale hydro-alcoholic extract

Dried roots of *Z. officinale* were purchased from a local company, Gol Darou, Isfahan, Iran. For extraction, 200 g of dry roots were grounded using an electric blender, and soaked in 1400 mL of 70% methanol solution (v/v) for 3 days. The extract was filtered through the Whatman filter paper, concentrated in a rotoevaporator, and dried with Freeze Dryer. The obtained extract, dry powder, was calculated 12.5%.

### Western blot analysis

Western blot Analysis was performed on the supernatant fraction of homogenized rat's testis. By Bradford method, concentrations of total protein on the supernatant were measured. Seventy micrograms of protein were loaded onto 8% sodium dodecyl sulfate (SDS)–polyacrylamide gel for electrophoresis (SDS-PAGE). After SDS-PAGE, by BIO-RAD transfer system (USA), Protein blots transferred to a methanol pre-activated polyvinylidene difluoride (PVDF) membrane. After blotting, the membrane was blocked with skimmed milk 5% for 1.5 hours with gradually shakes. Subsequently, blots were probed with antibody specific for HMG-CoA reductase (1:5000 dilution) (Santa Cruz Biotechnology), and reprobed for β-actin (1:4000 dilution) (sc-130656; Santa Cruz Biotechnology) to serve as a loading control. Bound antibody was probed with secondary antibody, goat anti-rabbit IgG-HRP (horse radish peroxidase) (sc-2030; Santa Cruz) diluted 1:10000 in 3% BSA (bovine serum albumin) for 1h at room temperature. After each step membranes were washed thrice with Tris-buffered saline–Tween (TBST) 0.1%. Finally, the blots were visualized with Chemi-Doc gel documentation system (Bio-Rad, Hercules, CA) using enhanced chemi luminescence (ECL) western blot detection kit according to the manufacturer's protocol. By using ImageJ software optical densities of bands were measured and quantified as ratio to β-actin.

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### Statistical analysis

All statistical analysis was carried out with SPSS software (SPSS Inc., Chicago, IL). Statistical significance was determined by one-way analysis of variance (ANOVA) followed by Tukey post hoc test. The comparison of data with normal distribution including blood glucose and body weight was done by ANOVA test. And, the data with no normal distribution were analyzed by Kruskal-Wallis test. The results were reported as means ± standard deviation (SD). A $P$ value < 0.05 was considered statistically significant difference.

## Results

### Effects of *Zingiber* officinale extract on the biochemical parameters

Before induction of diabetes, the mean of body weight was similar between groups and there was no significant difference in fasting blood glucose concentration. The effect of *Z. officinale* extract on the body weight, insulin level, and fasting blood glucose concentrations were assessed and the results are presented elsewhere (19).

### Effects of *Zingiber* officinale extract on the rats' testis HMG-COA reductase level

As illustrated in Figure 1, at the end of the experimental period in western blot analysis, a significant decrease in HMG-COA reductase protein level was observed in diabetic rats treated with 200 and 400 mg/kg of *Z. officinale* extract compared to controls ($P<0.01$). No statistically significant difference for HMG-COA reductase protein level was observed between healthy controls and diabetic controls ($P=0.208$).

## Discussion

Hypercholesterolemia is common in diabetic patients and is a risk factor for coronary heart disease (CHD) according to reported by numerous studies (20-22). Some diabetic medications have troublesome side-effects, so there is increasing tendency to use of natural therapies. In traditional medicine, herbs are rich sources of therapeutic compounds for relieving symptoms of illness such as diabetes and hyperglycemia. *Z. officinale* is used as an important herbal remedy which has a reducing effect on blood glucose and cholesterol according to the results from previous studies (9-11,23) However, no studies have been done about the effects of *Z. officinale* hydro-alcoholic extract on the HMG-COA reductase expression in testis of diabetic rats. In the present study we have investigated this issue.

Our results showed that in STZ-induced diabetic rats' body weight was significantly decreased compared to healthy control. Based on a study conducted by Kusari et al, in STZ-induced diabetes loss of body weight was observed. This reduction was related to loss of skeletal muscle resulting from hyperglycemia or high urine excretion and dehydration (24). Also, Eleazu et al showed that the reason for the loss of body weight was resulted from the degradation of muscle proteins similar to the results of our study (25). According to the present study, *Z. officinale* extract can prevent weight loss in rats with STZ-induced diabetic and this effect may be related to its hypoglycemic properties. Furthermore, this result is consistent with the

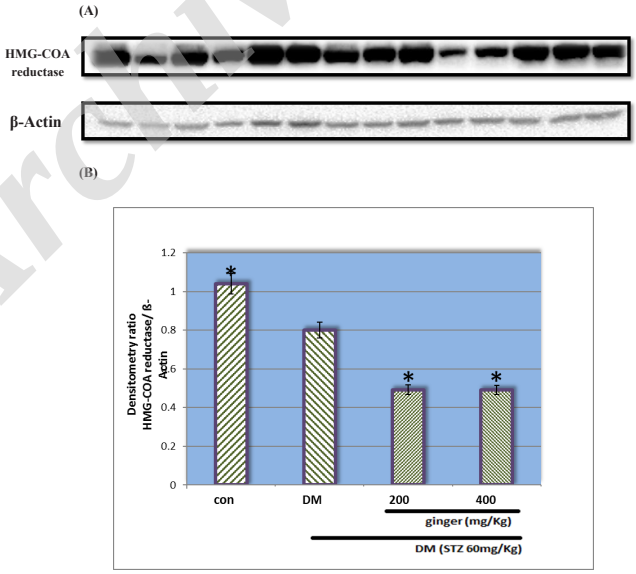


**Figure 1** Effect of *Z. officinal* extract at the end of 8 weeks intervention on the HMG-COA reductase expression. (A) Representative of immune-blots demonstrating specific bands for HMG-COA reductase (B) Graphical presentation of data obtained from four independent experiments from western blot analysis. The mean value of HMG-COA reductase is expressed as ratio of HMG-COA reductase to β-actin in each column. β-actin was applied as an internal control. Error bars show S.D. *$P$ < 0.01 vs. healthy control and diabetic controls. con=Healthy control; DM=Diabetic control; 200= Diabetic treated with 200 mg/kg of the extract; 400=Diabetic treated with 400 mg/kg of the extract. In Figure 1A from left to right, lanes 1,2,3,4 related to con ; lanes 5,6,7,8 related to DM; lanes 9,10,11 related to 200; and lanes 12,13,14 related to 400, respectively.



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findings reported in previous studies (26,27).

In the present study, serum insulin level was significantly reduced in diabetic control in comparison with healthy control, ones after 10 weeks of diabetes induction. It has been demonstrated the diabetogenic effect of STZ is resulted from the permanent destruction of the β-cells and deficiency of insulin secretion (28), so this finding can verify our result. On the other hand, serum insulin level was significantly higher in diabetic rats treated with 400 mg/kg of Z. *officinale* extract than diabetic controls (29,30). *Z. officinale* extract may be stimulating β cells to secrete insulin or releases this hormone of insulin-granule complex. This finding is in agreement with our results (29,30). In diabetic controls compared to healthy control ones, following decreased insulin secretion, the fasting blood glucose concentration was significantly increased. Some other animal studies have reported similar findings (11,28,29).

We observed that decrease of fasting blood glucose in diabetic rats treated with *Z. officinale* extract was dose dependent which is in agreement with other findings reported by other studies (11,23,27). Hypoglycemic property of *Z. officinal* is probably related to certain plant components such as polyphenol constituents and flavonoids (9). Flavonoids may decrease plasma and hepatic cholesterol level due to the decrease hepatic HMG-CoA reductase level (31). Raw ginger extract can decrease serum cholesterol and triacylglycerol levels in diabetic rats and it has the great effect for controlling of diabetic complications (32). Our results indicated there was a significant reduction in HMG-CoA reductase level after treatment with both doses of *Z. officinal* extract. Cholesterol is a precursor to testicular androgens production in Leydig cells. It was assumed that decrease of total cholesterol level by reduction of HMG-CoA reductase with *Z. officinal* may create sexual hormone dysfunction and it is a side effect to use for diabetes disease. But Kamtchouing et al reported that the aqueous extract of *Z. officinal* significantly increases the serum testosterone level (33) that is in contrast with its cholesterol-lowering effect. The mechanism of action of ginger for increasing the level of testosterone is unknown. However, it has been suggested that ginger may stimulate the production of luteinizing hormone (LH) which in turn more stimulate Leydig cells to produce testosterone (34). The effect of *Z. officinal* roots on fertility in diabetic male rats has been reported previously. It can enhance the serum testosterone and improve the sperm motility (35). In a study ginger which was added to semen fluid could induce toxic effects on sperm motility and morphology. The result was dose and time-dependent, but in several studies, ginger showed useful effects on the semen parameters (36).

## Conclusion

The oral administration of *Z. officinale* hydro-alcoholic extract has been shown to increases body weight, reduce blood glucose concentration and improve serum insulin levels in STZ-induced diabetic rats. However, the extract significantly decreased HMG-COA reductase level in diabetic rat's testis. In general, ginger shows effective glycaemic control properties, and, has a potential influence in the regulation of cholesterol homeostasis through modulation of HMG-COA reductase level in testis of diabetic rats.

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## Authors' contributions

GM coordinated, designed, analyzed the data and revised the manuscript. AK provided assistance for study design and western blot analysis. SAP and NLD participated in plant extraction and all animal intervention. BMP and FA participated in the draft preparation and carried out western blot analysis. The paper has been read and approved by all authors.

## Conflict of interests

The authors declared no conflict of interests exist.

## Ethical considerations

The study was approved and conducted in accordance with the Ethical Committee of Animal Breeding and Research of Jundishapur University of Medical Sciences (Ethical Code: IR.AJUMS.REC.1395.25). thical issues have been observed by the authors.

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