Cinnamon Extract Regulates Gene Expression of Lipid and Carbohydrate Metabolism in Streptozotocin Induced Diabetic Wistar Rats

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ABSTRACT

Cinnamon is a herbal medication plant used widely for many diseases in the Middle East and ancient countries. Cinnamon Extract (CE) contains many active substances that modulate insulin sensitivity and acts as anti-diabetic medication. Diabetes mellitus is a disease characterized by disturbance in carbohydrate and lipid metabolism. The aim of this study was to examine the effect of Cinnamon Extract (CE, 200 mg kg^{-1} body weight) on genes expression of lipid and carbohydrate metabolism in Streptozotocin (STZ) induced diabetes in Wistar rats. Administration of CE to STZ diabetic rats for 2 months normalized TG, cholesterol, VLDL, HDL and glucose levels. CE administration increased FAS and STREB-1c gene expressions that were inhibited in diabetic rats. Moreover, CE inhibited significantly the increase in LPL, HSL and resistin expression. In parallel, CE increased the expression of PPECK and GLUT2 and inhibited the decrement in IGF and PK expression. In conclusion, CE regulates the expression of genes related to lipid and carbohydrate metabolism in a way to control the metabolic disorders occur during diabetes.

Keywords: Cinnamon, Diabetes, Carbohydrates, Lipids, Metabolism

1. INTRODUCTION

Diabetes is a chronic metabolic disease occurred due to either destruction of β cells of pancreas or insulin resistance occurred during obesity and its related metabolic disorders (Hall, 2003; Havel, 2004). Diabetes is associated with an increased risk of coronary heart disease, stroke, hypertension, renal failure, type 2 diabetes, dyslipidemia and all cause mortality (Trayhurn and Beattie, 2001). Clinically diabetic patients characterized by marked increase in blood glucose levels followed by mild hyperlipidemia (Reddy *et al.*, 2009). Traditional herbal medicine has been widely used for diabetes treatment and is recognized as an interesting alternative to conventional medicine (Kameswara-Rao *et al.*, 1997) especially in the third world countries and therefore represent new avenues in the search for alternative hypoglycemic drugs (Day, 1998). Diabetes treatment depends mainly on regulation of genes related to glucose and/or carbohydrate metabolism. Glucose transport is the rate limiting step in carbohydrate metabolism (Maughana, 2009) which is facilitated by Glucose Transporters (GLUT) across the cell membrane (Anand *et al.*, 2010).

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So, drugs facilitate GLUT4 translocation and improve insulin sensitivity together with carbohydrate and lipid metabolism could be beneficial for the treatment of diabetes (Kipmen-Korgun *et al*., 2009; Shepherd and Kahn, 1999). Usage of natural products as cinnamon and other dietary modulators with anti-diabetic activity are the first choice of diabetic patients. This tendency is because insulin, to date, cannot be used orally and its repeated injections have many undesirable adverse effects. In addition, most of hypoglycemic agents or drugs are not effective to decrease blood glucose levels in chronic diabetic patients (Cheng and Fantus, 2005).

Cinnamon contains active components as cinnamic aldehyde, cinnamic acid, tannin and methyl-hydroxychalcone polymer with insulin-mimetic properties (Kim *et al*., 2006). CE has hypoglycemic and hypolipidemic effect in rats (Qin *et al*., 2003) and increases insulin sensitivity and glucose uptake in adipocytes (Khan *et al*., 2003; Jarvull-Taylor *et al*., 2001; Yaghmoor and Khoja, 2010). The mechanism of hypoglycemic effect of CE are reported *In vitro* and *in vivo* studies through enhancement of glucose uptake by activating insulin receptor kinase activity, autophosphorylation of insulin receptor and glycogen synthase activity (Kannappan *et al*., 2006). CE reduces lipid profiles in fructose-fed rats and affects immune responses by regulating anti-, proinflammatory and glucose transporter gene expressions in mouse macrophages (Cao *et al*., 2008) but CE effects on genes of carbohydrate and lipids have not been examined yet. Cinnamon has a hepatoprotective effect against carbon tetrachloride induced oxidative stress and liver injury in rats (Moselhy and Ali, 2009). Clinical and animal studies have confirmed a strong relationship between obesity and hypertension with diabetes (Mohamed-Ali *et al*., 1998). During diabetes there is alteration in lipid and carbohydrate metabolism. As lipolysis, glycolysis and gluconeogenesis enhanced to overcome metabolic needs. Those processes are regulated by variable enzymes as Lipoprotein Lipase (LPL), Hormone Sensitive Lipase (HSL), Fatty Acids Synthase (FAS), Sterol Responsible Binding Protein-1c (SREBP-1c), Pyruvate Kinase (PK), Phosphoenol Pyruvate Carboxy Kinase (PEPCK) and Glucose Transporter 2 (GLUT-2) in liver. Therefore, the aim of present work is to speculate the interaction between cinnamon and diabetes through alteration in the expression of enzymes which regulate both lipid (FAS, LPL, HSL and SREBP1c) and carbohydrate metabolism (PK, PEPCK and GLUT2) in STZ Wistar rats.

2. MATERIAL AND METHODS

2.1. Materials

Streptozotocin (STZ) was obtained from sigma Aldrich, USA. The Wistar albino rats were from Egyptian Co. for Experimental Animals Import, Helwan, Egypt. Vehicles and related materials were from ADWIA pharmaceutical company, Egypt. Oligo dT, chloroform, ethanol and cytokines primers were from Wako pure chemicals, Osaka, Japan. TriZol reagent was from Invitrogen, Carlsbad, CA.

2.2. Cinnamon Extract Preparation

Cinnamon extract was extracted based on the method of (Sheng *et al*., 2008; Soliman *et al*., 2012). Briefly, cinnamon powder (100 g) was dissolved in 1000 mL double distilled water then subjected for revolving evaporator in vacuum state using vacuum pump till the volume of water reduced to 50%. The supernatant was filtered through Whatman paper no. 1 to obtain cinnamon water extract. The final CE concentration was measured by Lowry method for protein concentration.

2.3. Induction of Diabetes in Wistar Rats and Experimental Procedures

Adult Wistar rats weighting 200-250 g (90 days old) were used for conducting the experiment. A group of rats were injected intraperitoneally (ip) with STZ at the dose of 60 mg kg^{-1} body weight. The other group injected with water and received water orally and daily for 2 months and considered as a control group. STZ induced diabetes within 3 days after injection as confirmed by the increase in blood glucose levels. Rats with glucose levels over 200 mg dL^{-1} were considered as diabetic rats and were used for experiments. Next, diabetic rats were divided into control diabetic group received water and cinnamon diabetic treated group received cinnamon extract at a dose of 200 mg kg^{-1} body weight (Kim *et al*., 2006; Kim and Choung, 2010) orally and daily for 2 months. At the end of the experiment, rats were killed by decapitation and blood was collected to get plasma. Liver samples were immediately immersed in TriZol reagent and kept at -70°C until RNA extraction.

2.4. RT-PCR Analysis and Gene Expression

Homogenization of 50 mg of frozen tissue samples was carried after addition of 1 mL TriZol (Invitrogen, Carlsbad, CA) using a Polytron 300 D homogenizer (Brinkman Instruments, Westbury, NY).

Table 1. PCR conditions for genes of carbohydrate and lipid metabolism

gene & product size	Forward primer	Reverse primer	Annealing temperature
HSL313bp	5'-TGCCCAGGAGTGTGTCTGAG-3'	5'AGGACACCTTGGCTTGAGCG-3'	40 cycles, 61°C 1 min
LPL 269 bp	5'-CCTGATGACGCTGATTTTGT-3'	5'TATGCTTTGCTGGGGTTTTC-3'	24 cycle, 60°C 45 sec
PK 229 bp	5'ATTGCTGTGACTGGATCTGC-3'	5'CCCGCATGATGTTGGTATAG-3'	30 cycle, 52°C 1 min
PEPCK 236 bp	5'TTTACTGGGAAGGCATCGAT-3'	5'-TCGTAGACAAGGGGGCAC-3'	30 cycle, 52°C 1 min
GLUT-2 330 bp	5'-AAGGATCAAAGCCATGTTGG-3'	5'-GGAGACCTTCTGCTCAGTGG-3'	30 cycle, 55°C 1 min
FAS 345 bp	5'-CCAGAGCCCAGACAGAGAAG-3'	5'-GACGCCAGTGTTCGTTCC-3'	30 cycle, 56°C 1 min
IGF 376 bp	5'GTAGGTCTTGTTTCCTGCAC-3'	5'CACATCTCTTCTACCTGCC-3'	40 cycles, 58°C 1 min
SREBP-1c 191 bp	5'GGAGCCATGGATTGCACATT-3'	5'-AGGAAGGCTTCCAGAGAGGA-3'	33 cycle, 58°C 1 min
Resistin 220 bp	5'-CCTCCTTTTCCTTTTCTTCC-3'	5'-TGAGGACGGTTGATTGAGAA-3'	30 cycles, 58°C 1 min
GAPDH (309 bP)	5'-AGATCCACAACGGATACATT-3	5-TCCCTCAAGATTGTCAGCAA-3'	25 cycles, 52°C 1 min

PCR cycle of respective genes are shown, while temperature and time of denaturation and elongation steps of each PCR cycle are 94°C, 30 s and 72°C, 60 s, respectively

Table 2. Changes in insulin, glucose and lipid profiles in normal, diabetic and diabetic plus cinnamon extract administered Wistar rats

Parameter	Control	Diabetic	Diabetic plus cinnamon extract
Glucose (mg/dL)	90.7±8.53	320.1±20.5[*]	108.5±6.2[#]
Insulin (mIU/mL)	5.2±0.4	2.7±0.07[*]	8±1.01[#]
Triglycerids (mg/dL)	70.4±2.1	120.8±2.6[*]	71.5±1.5[#]
Cholesterol (mg/dL)	95.5±9.1	147.4±12.6[*]	90.5±9.7[#]
VLDL (mg/dL)	25.7±2.9	32.6±2.7[*]	29.2±1.9[#]
HDL (mg/dL)	35.4±3.9	28.2±3.5[*]	33.1±2.5[#]

Data are presented as (means ± S.E.). S.E = Standard error for 5 rats per each group. *$p < 0.05$ Vs control and #$p < 0.05$ Vs diabetic rats

Total RNA was extracted from tissue homogenate via chloroform extraction followed by nucleic acid precipitation with isopropanol. The pellet was washed with 75% ethanol and resuspended in molecular biology grade water. Nucleic acid concentration was determined spectrophotometrically by measuring O.D at 260 nm (Smart-Spec; Bio-Rad Laboratories, Hercules, CA) and RNA integrity was evaluated using an Agilent bioanalyzer (model 2100; Agilent Technologies, Foster City, CA).

For cDNA synthesis, total RNA (1 μg) was denatured at 72°C for 5 min and then reverse transcribed using 100 units of Moloney Murine Leukemia virus reverse transcriptase (Gibco), 50 pmol of oligo (dT) primer and 20 nmol of dNTPs in a total volume of 10 μL at 37°C for 1 h followed by heating at 94°C for 5 min, PCR amplification was performed with 2.5 units Taq DNA polymerase (Perkin-Elmer, Foster City, CA, USA), 3 mM MgCl2 and 50 pmol of forward and reverse primers specific for respective genes in a total volume of 50 μL. The PCR conditions and primers sequence for different examined genes are listed in **Table 1**. PCR products were electrophoresed in 1.5% agarose gel stained with ethidium bromide and visualized under UV lamp.
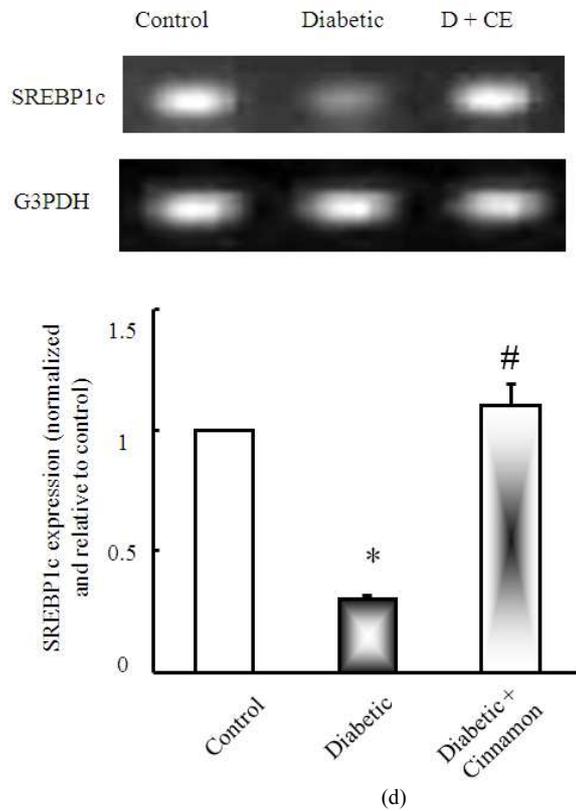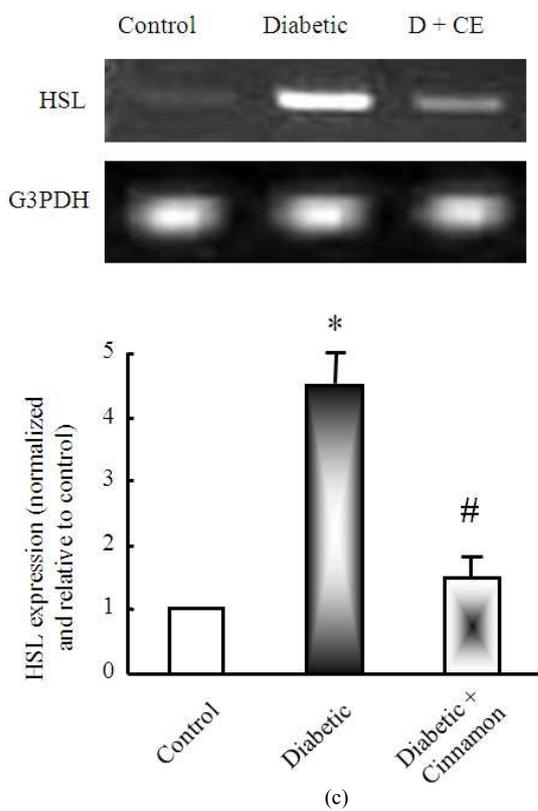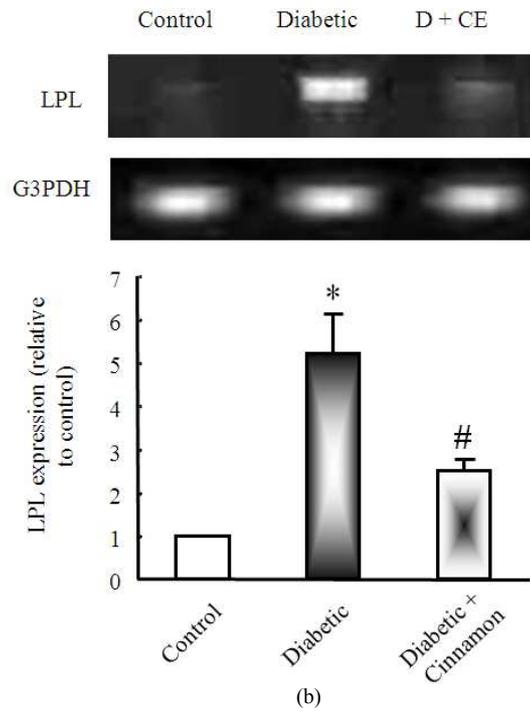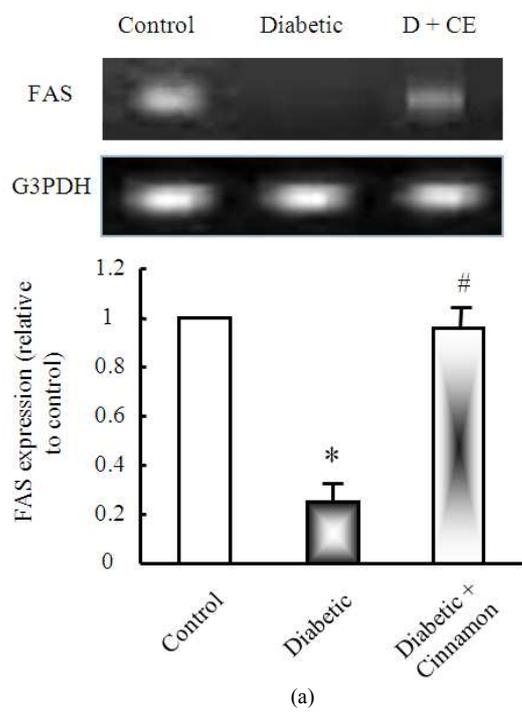
2.5. Statistical Analysis

Results are expressed as means ± S.E. of independent experiments. Statistical analysis was done using ANOVA and Fischer's post hoc test, with $p < 0.05$ being considered as statistically significant.

3. RESULTS

3.1. Effect of CE Administration on Lipid Parameters and Glucose Levels in Diabetic Wistar Rats

STZ induced diabetic rats showed significant increase in cholesterol, TG, VLDL and decrease in HDL compared to normal rats. Meanwhile, administration of CE significantly ($p < 0.05$) restored their levels to normal (**Table 2**). Concerning plasma insulin level in STZ diabetic rats, there was a decrement due to destruction of β-cells. Meanwhile, CE administration increased insulin and even higher than control. Results of insulin was reflected on glucose level which was higher in diabetic rats and normalized in CE administered rats compared to control (**Table 2**).
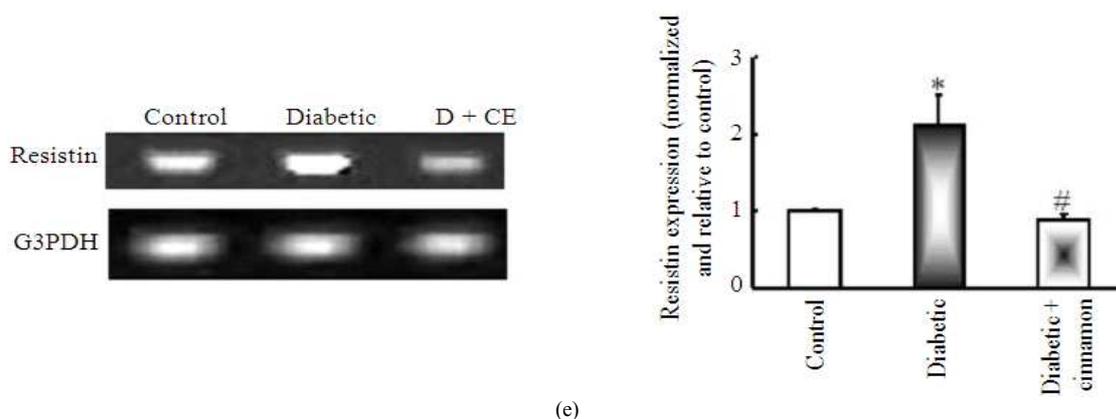
(a)

(b)

(c)

(d)

(e)

Fig. 1. RT-PCR analysis of FAS, LPL, HSL, SREBP-1c and resistin in liver and epididymal fat tissue of rats. Cinnamon was administrerd for STZ rats for 2 months as described in materials and methods. RNA was extracted and reverse transcribed (1 µg) and RT-PCR analysis was carried out for FAS, LPL, HSL, SREBP-1c and resistin genes
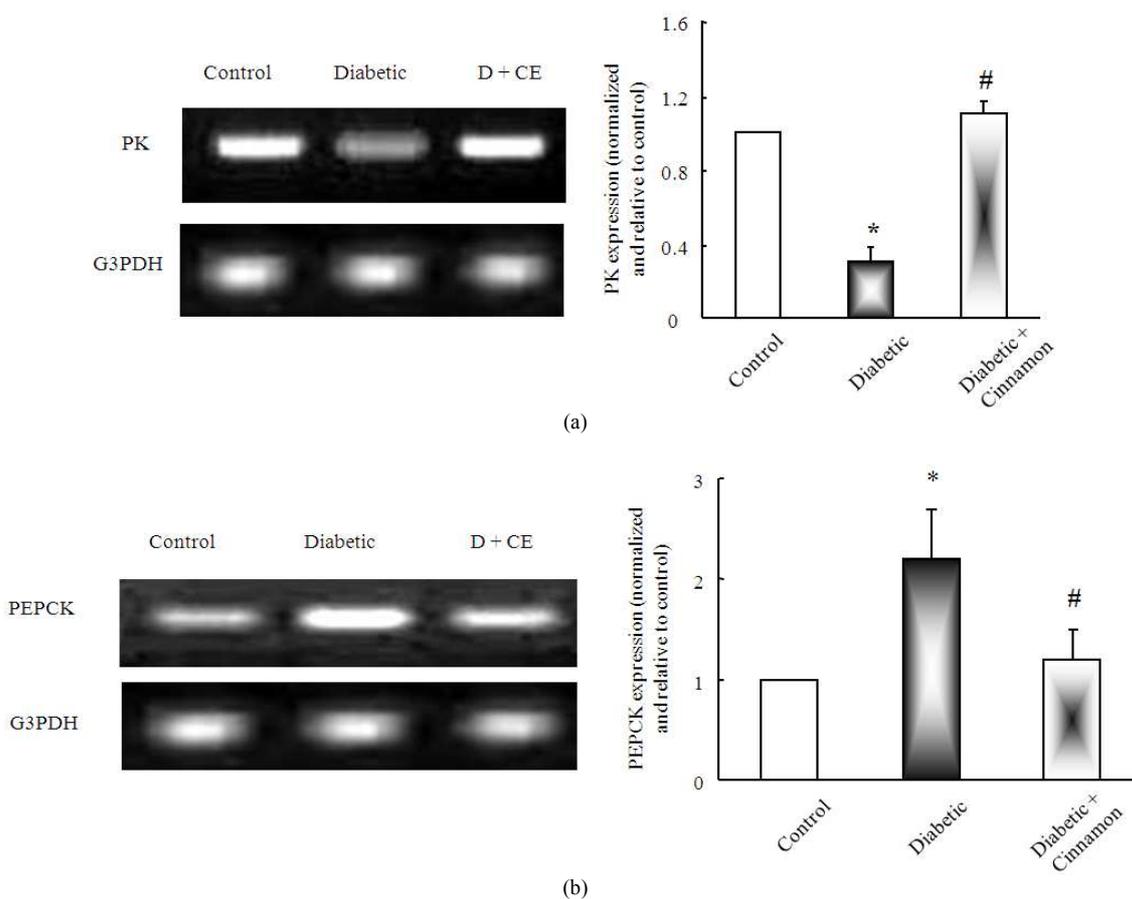

(a)

(b)

Fig. 2. RT-PCR analysis of PEPCK and PK expression in liver of rats. Cinnamon was administrerd for STZ rats for 2 months as described in materials and methods. RNA was extracted and reverse transcribed (1 µg) and RT-PCR analysis was carried out for PEPCK and PK genes
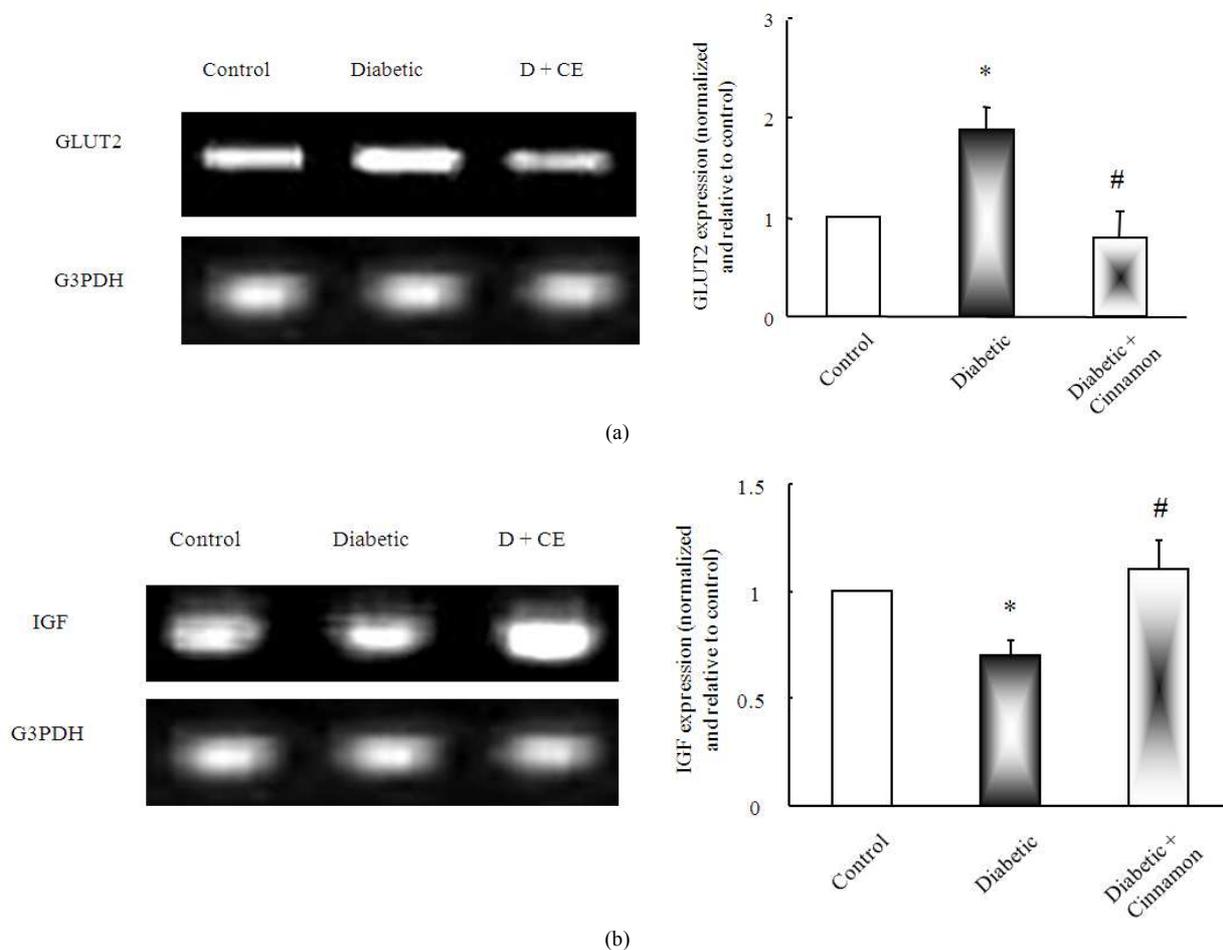
(a)

(b)

Fig. 3. RT-PCR analysis of GLUT-2 and IGF expression in liver of rats. Cinnamon was administrerd for STZ rats for 2 months as described in materials and methods. RNA was extracted and reverse transcribed (1 µg) and RT-PCR analysis was carried out for GLUT-2 and IGF genes

3.2. Effect of CE Administration on Gene Expression of Lipid Metabolism in Liver Tissues

To investigate the alteration in lipid metabolism by CE, mRNA from liver tissue was subjected for RT-PCR analysis. As shown in **Fig. 1a**, diabetes inhibited FAS mRNA expression and CE administration for 2 months normalized FAS expression to the normal control level. Moreover, there was an increase in mRNA expression of both LPL and HSL in diabetic rats. These increments were inhibited by administration of CE (**Fig. 1b and c**). Concerning SREBP1c mRNA expression in liver tissues, diabetic rats show decrement in mRNA expression. CE administration normalized SREBP1c expression compared

to diabetic group (**Fig. 1d and e**). Resistin expression increased in diabetic rats and CE administration returned that increase to normal control expression.

3.3. Effect of CE Administration on PK and PEPCK Gene Expression in Liver Tissues

Next, we investigated the alteration in some enzymes regulating glucose metabolism including Pyruvate Kinase (PK) that is responsible for glycolysis and Phosphoenol Pyruvate Carboxykinase (PEPCK) that is involved in gluconeogenesis. The expression of hepatic PK mRNA as estimated by RT-PCR analysis was significantly decreased in diabetic rats (**Fig. 2a**). Administration of CE to diabetic rats resulted in reversal PK expression. Parallel to those findings, there was an increase in

hepatic PEPCK mRNA expression in diabetic rats compared to control rats (**Fig. 2b**) and administration of CE for 2 months normalized the PEPCK mRNA levels of CE administered diabetic rats.

3.4. Effect of CE Administration on GLUT2 and IGF Gene Expression in Liver Tissues

Since insulin was decreased in diabetic rats and CE administration normalized the increase in glucose, we tested the physiological importance of insulin dependent GLUT2 translocation. As shown in **Fig. 3a**, diabetic rats showed an increase in GLUT2 mRNA expression and that increase was inhibited after CE administration in a way to regulate the excessive hepatic glucose utilization. Finally, we tested the changes in Insulin like Growth Factor (IGF) mRNA expression. As shown in **Fig. 3b**, IGF expression was significantly decreased in diabetic rats and normalized and increased after CE administration for 2 months to react with hyperglycemia of diabetic rats.

4. DISCUSSION

Diabetes is a chronic metabolic disorder that affects approximately 3% of population worldwide (Kim *et al.*, 2006). Gaster and Hirsch (1998) reported that sustained reductions in hyperglycemia will decrease the risk of developing microvascular diseases and reduce diabetes complications. Usage of oral hypoglycemic drugs to treat diabetes has several limitations, such as adverse effects and high rates of secondary failure (Kim *et al.*, 2006). Those adverse effects forced the diabetic patients to use herbal medication that has a similar degree of efficiency without side effects and that is the purpose of this study. We have shown in this study that administration of cinnamon extract to STZ diabetic rats induced insulin mimetic effects. The results showed that, insulin deficiency is strongly associated with metabolic dyslipidemia in diabetes and obesity. Moreover, Qin *et al.* (2010) reported that the use of water-soluble CE improved the metabolic syndrome by regulating the circulating adipose-derived factors and multiple genes related to carbohydrate metabolism and lipogenesis. Our findings have shown the anti-diabetic activity of CE in STZ diabetic rats. CE administration not only reduced blood glucose levels (320.1±20.5 for diabetic rats Vs. 108.5±6.2 for CE plus Diabetes) after 2 months but also normalized and restored insulin levels in diabetic rats

(2.7±0.07, 8±1.01 for diabetic and CE plus diabetes respectively) compared to initial insulin control values. Parallel findings were reported by Anand *et al.* (2010) and Subash Babu *et al.* (2007) who reported that 45 days treatment of cinnamaldehyde increases serum insulin levels in STZ induced diabetic rats. This finding was explained that the over insulin secretion from still working β cell in a way to overcome hyperglycemia of diabetic rats (Kim *et al.*, 2006).

To understand the molecular mechanism of CE actions, we examined the mRNA expression of genes involved in lipid and glucose metabolism in liver of diabetic rats. Administration of STZ diabetic rats with CE induced significant decrease in LPL, HSL and a significant increase in resistin. Also, the normalization in lipid parameters in blood is associated with the increase in lipids synthesizing enzymes expression in diabetic treated with CE. Because resistin is known to be a potent lipolytic protein and increased peripheral glucose utilization (Ahima and Flier, 2000; Kim and Choung, 2010; Wanders *et al.*, 2010). CE administration decreased glucose levels in STZ diabetic rats with stimulation of insulin production like effects and that confirmed by increase in plasma insulin levels. The possible mechanism may be through increasing either the pancreatic secretion of insulin from the existing beta cells or its release from the bound form (Kim *et al.*, 2006). CE might improve diabetes by normalizing the fasting blood glucose level as well as postprandial plasma glucose level (Kim *et al.*, 2009). In turn, in hyperinsulinemia, cinnamon increases insulin sensitivity for effective glucose disposal in rats although in humans cinnamon does not appear to improve fasting blood glucose levels and lipid parameters in patients with type 1 or type 2 diabetes (Baker *et al.*, 2008). Here, CE improved and normalized the changes in lipid parameters as TG, cholesterol and HDL and that was parallel with results of Khan *et al.* (2003); Kim and Choung (2010) and Qin *et al.* (2003) and improved insulin resistance induced by feeding high fat diet (Thorens, 1996). CE ameliorates hyperglycemia *in vitro* as insulin secretion studies were carried out using isolated rat primary islet culture. CE acts by enhancing release of insulin through β cells stimulation as CE exerts a direct insulin releasing effect (Sharma *et al.*, 2006; Rokeya *et al.*, 1999; Bolkent *et al.*, 2000).

For our knowledge, cinnamon effects on gene expression of lipogenesis and fatty acids biosynthesis not widly examined. SREBP-1c preferentially enhances transcription of genes required for fatty acid

synthesis but not cholesterol synthesis (Horton *et al.*, 2002). Huang *et al.* (2011) suggested that CE exerts antiadipogenic effects through modulation of the PPAR-γ and AMPK signaling pathways. Our results are in accordance with those of Khan *et al.* (2003), CE induced lowering glucose, total cholesterol, VLDL and triglyceride levels in diabetic subjects. During diabetes the expression of FAS and SREBP-1c (**Fig. 1**) decreased because lipogenesis is impaired due to disturbance in insulin levels but CE administration re-increased and normalized their expression level confirming CE role in regulation of lipogenesis. In parallel, the expression of LPL and HSL increased during diabetes in a way to support body with source for energy through fatty acids oxidation (Shimano *et al.*, 1999). But the CE administration to diabetic rats normalized significantly that increases (LPL and HSL) to normal non diabetic rats confirming the antilipolytic activity of CE. Sheng *et al.* (2008) reported an increase in LPL and GLUT4 expression and cinnamon in its water extract form can act as a dual activator of PPAR gamma and alpha and may be an alternative to PPAR gamma activator in managing obesity-related diabetes and hyperlipidemia. Moreover, Lee *et al.* (2003), reported that dietary cinnamate inhibits hepatic HMG-CoA reductase activity, resulting in lower hepatic cholesterol content and suppresses lipid peroxidation via enhancement of hepatic antioxidant enzyme activities and that is coincided with our results.

Glycogen is the storable form of glucose inside cells especially in liver and skeletal muscles and its accumulation indicates direct reflection of insulin activity since it regulates glycogen deposition by stimulating glycogen synthase and inhibiting glycogen phosphorylase (Kruszynska *et al.*, 1998; Kruszynska and Olefsky, 1996; Thorburn *et al.*, 1991). STZ causes destruction of β cells of pancreas resulting in marked decrease in insulin levels, it could be predicted that glycogen levels in tissues (muscle and liver) decrease as the influx of glucose in liver is inhibited in the absence of insulin and recovers on insulin treatment (Vats *et al.*, 2004). Our findings showed that administration of diabetic rats with CE induced significant increase in PK and a decrease in PEPCK expression in diabetic rats. That means in diabetic rats CE improved PK and PEPCK enzyme expression levels, both are the major enzymes contributed to glucose homeostasis. PEPCK, which catalyzes a regulatory step in gluconeogenesis, is one of

the key enzymes of hepatic carbohydrate metabolism and insulin deficiency is clearly associated with changes in hepatic metabolism including increased expression of PEPCK (Jomain-Baum and Schramm, 1978). In our study, CE reversed the increase of hepatic PEPCK mRNA expression in STZ diabetic rats and this attenuation of the hepatic PEPCK mRNA expression was associated with plasma glucose-lowering activity of CE (Anand *et al.*, 2010). So we conclude that CE exerts its glucose-lowering effect mainly through an enhancement of glucose utilization of skeletal muscle and a reduction of hepatic gluconeogenesis. Several potential herbal plant extract and purified compounds have been shown to improve the diabetic condition (Sharma *et al.*, 2008). The PK activity decreases as the result of diabetes and increases by the administration of insulin to diabetic rats in the liver tissues (Yamada and Noguchi, 1999). The altered activity during diabetic conditions could be expected to diminish the metabolism of glucose and ATP production. The decrease in activity of PK in the liver tissue of streptozotocin diabetic rats is the cause of reduced glycolysis and amplified gluconeogenesis as indicated by PEPCK expression (Taylor and Agius, 1988). Parallel with PK and PEPCK, is the pattern of IGF and GLUT2 expression. GLUT2 is a trans-membrane carrier protein that enables passive glucose movement across cell membranes. It is the principal transporter for transfer of glucose between liver and blood and for renal glucose reabsorption (Freitas *et al.*, 2005). IGFs are proteins with high sequence similarity to insulin. IGFs are part of a complex system that cells use to communicate with their physiologic environment, since at high concentrations is capable of activating the insulin receptor, it can also complement for the effects of insulin (Scarth, 2006). In our study, the normalization of GLUT2 expression after CE administration may be a reflect pathway to reverse the glucose uptake in liver cells while CE administration increases IGF expression to induce insulin like effects.

5. CONCLUSION

We can conclude that cinnamon extract induce beneficial effects in STZ diabetic rats and affect the genes related to carbohydrate (PPECK, PK, GLUT-2 and IGF) and lipid metabolism (FAS, LPL. HSL and SREBP-1c) in a way to control the metabolic biohazards

accompanied diabetes. Moreover, CE is a good herbal medication with insulin mimetic activity.

6. AKNOWLEDGMENT

7. REFERENCES

Ahima, R.S. and J.S. Flier, 2000. Leptin. Rev. Physiol., 62: 413-437. PMID: 10845097

Anand, P., K.Y. Murali, V. Tandon, P.S. Murthy and R. Chandra, 2010. Insulinotropic effect of cinnamaldehyde on transcriptional regulation of pyruvate kinase, phosphoenolpyruvate carboxykinase and GLUT4 translocation in experimental diabetic rats. Chem. Biol. Interact., 186: 72-81. DOI: 10.1016/j.cbi.2010.03.044

Baker, L., J. Kluger, G. Williams, C. Coleman and M. White, 2008. Effect of cinnamon on glucose control and lipid parameters. Diabetes Care, 31: 41-43. PMID: 17909085

Bolkent, S., R. Yamardag, A. Tabakogluoguz and O. Ozsoy-Sacon, 2000. Effects of chord (B. *vulgaris* L. var. cicla) extract on pancreatic B cells in streptozotocin-diabetic rats: A morphologic and biochemical study. J. Ethnopharmacol., 73: 251-259.

Cao, H., J.F. Jr. Urban and R.A. Anderson, 2008. Cinnamon polyphenol extract affects immune responses by regulating anti- and proinflammatory and glucose transporter gene expression in mouse macrophages. J. Nutr., 138: 833-840. PMID: 18424588

Cheng, A and I. Fantus, 2005. Oral antihyperglycemic therapy for type 2 diabetes mellitus. CMAJ, 172: 213-226. PMID: 15655244

Day, C., 1998. Traditional plant treatments for diabetes mellitus: pharmaceutical foods. Br. J. Nutr., 80: 5-6. PMID: 9797638

Freitas, H.S., B.D. Schaan, P.M. Seraphim, M.T. Nunes and U.F. Machado, 2005. Acute and short-term insulin-induced molecular adaptations of GLUT2 gene expression in the renal cortex of diabetic rats. Mol. Cell. Endocrinol., 237: 49-57. PMID: 15869838

Gaster, B. and I.B. Hirsch, 1998. The effects of improved glycemic control on complications in type 2 diabetes. Arch. Int. Med., 158: 134-140. PMID: 9448551

Hall, J.E., 2003. The kidney, hypertension and obesity. Hypertension, 41: 625-633. PMID: 12623970

Havel, J.P., 2004. Update on adipocyte hormones: Regulation of energy balance and carbohydrate/lipid metabolism. Diabetes, 53: 143-151. PMID: 14749280

Horton, J.D., L. Joseph, D. Goldstein and M.S. Bown, 2002. SREBPs: Activators of the complete program of cholesterol and fatty acid synthesis in the liver. J. Clin. Invest., 109: 1125-1131. DOI: 10.1172/JCI0215593

Huang, B., H.D. Yuan, Y. Kim Do, H.Y. Quan and S.H. Chung, 2011. Cinnamaldehyde prevents adipocyte differentiation and adipogenesis via regulation of Peroxisome Proliferator-Activated Receptor-γ (PPARγ) and AMP-activated protein kinase (AMPK) pathways. J. Agric. Food Chem., 59: 3666-3673. PMID: 21401097

Jarvull-Taylor, K.J., R.A. Anderson and D.J. Graves, 2001. A hydroxychalcone derived from cinnamon functions as a mimetic for insulin in 3T3-L1 adipocytes. J. Am. Coll. Nutr., 20: 327-336. PMID: 11506060

Jomain-Baum, M. and V.L. Schramm, 1978. Kinetic mechanism of phosphoenol pyruvate carboxykinase (GTP) from rat liver cytosol. Product inhibition, isotope exchange at equilibrium and partial reactions. J. Biol. Chem., 253: 3648-3659. PMID: 649593

Kameswara-Rao, B., R. Giri, M.M. Kesavulu and C. Apparao, 1997. Herbal medicine: In the management of diabetes mellitus. Manphar Vaidhya Patrika I.

Kannappan, S., T. Jayaraman, P. Rajasekar, M.K. Ravichandran and C.V. Anuradha, 2006. Cinnamon bark extract improves glucose metabolism and lipid profile in the fructose-fed rat. Singapore Med. J., 47: 858-863. PMID: 16990960

Khan, A., M. Safdar, M.M. Alikhan, K.N. Khattak and R.A. Anderson, 2003. Cinnamon improves glucose and lipids of people with type 2 diabetes. Diabetes Care, 26: 3215-3218. DOI: 10.2337/diacare.26.12.3215

Kim, O.J., D.G. Lee, H.J. Kwon and S.K. Kim, 2009. Anti-diabetic effects of new herbal formula in neonatally streptozotocin-induced diabetic rats. Biol. Pharm. Bull., 32: 421-426. PMID: 19252289

Kim, S.H and S.Y. Choung, 2010. Antihyperglycemic and antihyperlipidemic action of Cinnamomi Cassiae (Cinnamon bark) extract in C57BL/Ks db/db mice. Arch. Pharm. Res., 33: 325-333. DOI: 10.1007/s12272-010-0219-0

Kim, S.H., S.H. Hyun and S.Y. Choung, 2006. Anti-diabetic effect of cinnamon extract on blood glucose in db/db mice. J. Ethnopharmacol., 8: 119-23. PMID: 16213119

Kipmen-Korgun, D., S. Bilmen-Sarikcioglu, H. Altunbas, R. Demir and E. Korgun, 2009. Type-2 diabetes down-regulates glucose transporter proteins and genes of the human blood leukocytes. Scand. J. Clin. Lab. Invest., 69: 350-358. PMID: 19110659

Kruszynska, Y.T and J.M. Olefsky, 1996. Cellular and molecular mechanisms of non-insulin dependent diabetes mellitus. J. Invest. Med., 44: 413-428. PMID: 8952222

Kruszynska, Y.T., M.I. Mulford, J. Baloga, J.G. Yu and J.M. Olefsky, 1998. Regulation of skeletal muscle hexokinase II by insulin in nondiabetic and NIDDM subjects. Diabetes, 47: 1107-1113. PMID: 9648835

Lee, J.S., S.M. Jeon, E.M. Park, T.L. Huh and O.S. Kwon *et al*., 2003. Cinnamate supplementation enhances hepatic lipid metabolism and antioxidant defense systems in high cholesterol-fed rats. J. Med. Food, 6: 183-191. PMID: 14585184

Maughana, R., 2009. Carbohydrate metabolism. Surgery, 27: 6-10.

Mohamed-Ali, V., J.H. Pinkney and S.W. Coppack, 1998. Adipose tissue as an endocrine and paracrine organ. Int. J. Obesity, 22: 1145-1158. PMID: 9877249

Moselhy, S. and H. Ali, 2009. Hepatoprotective effect of cinnamon extracts against carbon tetrachloride induced oxidative stress and liver injury in rats. Biol. Res., 42: 93-98. PMID: 19621136

Qin, B., M. Nagasaki, M. Ren, G. Bajotto and Y. Oshida *et al*., 2003. Cinnamon extract (traditional herb) potentiates in vivo insulin-regulated glucose utilization via enhancing insulin signaling in rats. Diabetes Res. and Clin. Pract., 62: 139-148. PMID: 14625128

Qin, B., M.M., Polansky and R.A. Anderson, 2010. Cinnamon extract regulates plasma levels of adipose-derived factors and expression of multiple genes related to carbohydrate metabolism and lipogenesis in adipose tissue of fructose-fed rats. Horm. Metab. Res., 42: 187-193. PMID: 19937569

Reddy, P.K., B.A. Singh, A. Puri, K.A. Srivastava and T. Narender, 2009. Synthesis of novel triterpenoid (lupeol) derivatives and their in vivo antihyperglycemic and antidyslipidemic activity. Bio. Med. Chem. Lett., 19: 4463-4466. DOI: 10.1016/j.bmcl.2009.05.034

Rokeya, B., N. Nahar, L. Ali, Z. Hassan and M. Nure-E-Alam *et al*., 1999. Effects of five medicinal plants on blood glucose levels in non diabetic and diabetic model rats. Diabetes Res., 34: 219-228.

Scarth, J.P., 2006. Modulation of the Growth Hormone-Insulin-like Growth Factor (GH-IGF) axis by pharmaceutical, nutraceutical and environmental xenobiotics: An emerging role for xenobiotic-metabolizing enzymes and the transcription factors regulating their expression. A review. Xenobiotica, 36: 119-218. PMID: 16702112

Sharma, B., C. Balomajumder and P. Roy, 2008. Hypoglycemic and hypolipidemic effects of flavonoid rich extract from Eugenia jambolana seeds on streptozotocin induced diabetic rats. Food Chem. Toxicol., 46: 2376-2383. PMID: 18474411

Sharma, S.B., A. Nasir., K.M. Prabhu and P.S. Murthy, 2006. Antihyperglycemic effect of the fruit-pulp of Eugenia jambolana in experimental diabetes mellitus. J. Ethnopharmacol., 104: 367-373. PMID: 16386863

Sheng, X., Y. Zhang, Z. Gong, C. Huang and Y.Q. Zang, 2008. Improved insulin resistance and lipid metabolism by cinnamon extract through Activation of peroxisome proliferator-activated receptors. PPAR Res. PMID: 19096709

Shepherd, P.R and B.B. Kahn, 1999. Glucose transporters and insulin action-implications for insulin resistance and diabetes mellitus. N. Engl. J. Med., 341: 248-257. PMID: 10413738

Shimano, H., N. Yahagi, M. Amemiya-Kudo and A.H. Hasty *et al*., 1999. Sterol regulatory element-binding protein-1 as a key transcription factor for nutritional induction of lipogenic enzyme genes. J. Biol. Chem., 274: 35832-3589. PMID: 10585467

Soliman, M.M., H.F. Attia, S.A. El-Shazly and O.M. Saleh, 2012. Biomedical effects of cinnamon extract on obesity and diabetes relevance in Wistar rats. Am. J. Biochem. Mol. Biol., 2: 133-145.

Subash Babu, P., S. Prabuseenivasan and S. Ignacimuthu, 2007. Cinnamaldehyde--a potential antidiabetic agent. Phytomedicine, 14: 15-22. PMID: 17140783

Taylor, R. and L. Agius, 1988. The biochemistry of diabetes. Biochem. J. 250: 625-640. PMCID: 1148905

Thorburn, A.W., B. Gumbiner, F. Bulacan, G. Brechtel and R.R. Henry, 1991. Multiple defects in muscle glycogen synthase activity contribute to reduced glycogen synthesis in non-insulin dependent diabetes mellitus. J. Clin. Invest., 87: 489-495. PMID: 1899428

Thorens, B., 1996. Glucose transporters in the regulation of intestinal, renal and liver glucose efluxes. Am. J. Physiol., 270: 541-553. PMID: 8928783

Trayhurn, P.J. and H. Beattie, 2001. Physiological role of adipose tissue: White adipose tissue as an endocrine and secretory organ. Proc. Nutr. Soc., 60: 329-339. PMID: 11681807

Vats, V., S.P. Yadav and J.K. Grover, 2004. Ethanolic extract of Ocimum sanctum leaves partially attenuates streptozotocin-induced alterations in glycogen content and carbohydrate metabolism in rats. J. Ethnopharmacol., 90: 155-160. PMID: 14698524

Wanders, S., E.P. Plaisance and R.L. Judd, 2010. Pharmacological effects of lipid-lowering drugs on circulating adipokines. World J. Diabetes, 15: 116-128. PMID: 21537437

Yaghmoor, S.S. and S.M. Khoja, 2010. Effect of cinnamon on plasma glucose concentration and the regulation of 6-phosphofructo-1-kinase activity from the liver and small intestine of streptozotocin induced diabetic rats. J. Biol. Sci., 10: 761-766.

Yamada, K. and T. Noguchi, 1999. Nutrient and hormonal regulation of pyruvate kinase gene expression. Biochem. J., 337: 1-11. PMID: 9854017