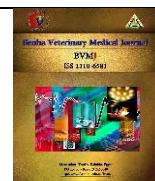




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The potential ameliorative effect of Sukkari date extract on Streptozotocin-induced diabetes in male rats

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ABSTRACT

This study evaluated the protective effect of Sukkari date extract on Streptozotocin (STZ)-induced diabetes in rats. Forty male albino rats were divided into 2 main groups: Group I (Control group, n=10): received no drugs and served as control. Group II (Diabetic group, n=30): received a single dose of STZ (50mg/kg b.wt.p.) for induction of diabetes, and 48 hours after diabetes induction, the rats were divided into 3 equal subgroups. Subgroup (a): Diabetic non-treated rats. Subgroup (b): Diabetic aqueous sukkari date extract-treated rats. Subgroup (c): Diabetic Amaryl-treated rats. Treatment with sukkari date extract (10 ml/rat/day) and Amaryl (1ml/rat/day) were given orally and daily for 60 days. Blood samples and liver tissues were collected from all animals once after 60 days of treatment for determination of serum glucose, lipids profile, insulin, L-malondialdehyde (L-MDA), superoxide dismutase (SOD) and 8-hydroxy-2-deoxyguanosine (8-OHdG) in addition to paraoxonase 1 (PONI) gene expression level in liver tissue. The obtained results showed a significant increase in serum glucose, total cholesterol, triacylglycerols, low density lipoprotein-cholesterol (LDL-c), L-MDA and 8-OHdG levels with marked decrease in serum insulin, high density lipoprotein-cholesterol (HDL-c) and SOD activity in addition to significant down-regulation of PONI gene expression level in liver in STZ-induced diabetic rats. On the other hand, treatments of diabetic rats with aqueous sukkari date extract or amaryl exhibited a significant ameliorative effect on all previous biomarkers and approximately reach to normal levels. This study suggest the ameliorative role of aqueous sukkari date extract in diabetes and its protective effect may be mediated through reduction in oxidative stress, the promising hypoglycemic and hypolipidemic activity.

1. INTRODUCTION

Diabetes mellitus is a group of metabolic alterations characterized by hyperglycemia resulting from defects in insulin secretion, action or both. Chronic hyperglycemia of diabetes is associated with long term damage, dysfunction and eventually the failure of organs, especially the eyes, kidney, nerves, heart, and blood vessels (Huang et al., 2005). In diabetic patients with vascular complications, there are significant changes such as increased lipid peroxidation, dyslipidemia, and irregularity in the metabolism of proteins, carbohydrates and lipids. Increased lipid peroxidation is accepted to be one of the main causes of diabetic complications (Gallou et al., 1994). Also, the presence of high glucose levels may affect the function of different organs such as liver, pancreas, and retina (Ramkumar et al., 2007).

It has become increasingly evident that nature has numerous medicinal plants that contain phytochemicals with potent pharmacological activities, including promising antitoxic properties (Ekor, 2014). Phoenix dactylifera is a useful traditional medicinal plant belonging to the family

Arecaceae (Sirisena et al., 2015). The protective effects of *P. dactylifera* are thought to be due to not only the fiber, vitamins, and minerals, but also to a diversity of plant secondary metabolites as flavonoids and phenolics (Benmeddour et al., 2013). Its phytochemical investigation has revealed that the fruits contain anthocyanins, phenolics, sterols, carotenoids, procyanidins, and flavonoids, compounds known to possess free radical scavenging, antioxidant, antimutagenic, antimicrobial, anti-inflammatory, antihyperlipidemic, gastroprotective, hepatoprotective, nephroprotective, anticancer and immunostimulant activities (Baliga et al., 2011). Also, the polyphenolic proanthocyanidins may act in combination with other phenolics as free radical scavengers or heavy metal chelators, and in turn, they can prevent the oxidative stress and inflammation (Blade et al., 2016). Likewise, *P. dactylifera* contains considerable amounts of water and fat-soluble vitamins origins that are very important for vitality. Moreover, it contains vitamins of powerful antioxidant potentials that are capable of chelating different radicals in the non-enzymatic reaction such as vitamin A, C, and E (Vayalil, 2012).

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The dietary fiber content of dates enhances their suitability as ingredients for preparation of fiber-based foods and dietary supplements. Dietary fibers have important therapeutic application and protective effect against conditions such as hypertension, coronary heart disease, obesity, hyperlipidemia and diabetes. It also possesses anticancer, antioxidant, hepato-protective, anti-ulcerative, anti-inflammatory, anti-proliferative, anti-mutagenic, antibacterial, antifungal and antiviral potentials (Mallhi et al., 2014). The active principles present in medicinal plants have been reported to possess pancreatic beta cells regenerating, insulin releasing and fighting the problem of insulin resistance (Singh et al., 2009).

Glimepiride (Amaryl®) is an oral blood-glucose-lowering drug of the sulfonylurea class. Glimepiride administration can lead to increased sensitivity of peripheral tissues to insulin. These findings are consistent with the results of a long-term, randomized, placebo-controlled trial in which Amaryl therapy improved overall glycemic control (Sanofi-Aventis, 2008). Accordingly, this study aims to elucidate the hypoglycemic, hypolipidaemic and antioxidant activities of Sukkari date extract administration as a natural product on experimentally induced diabetes mellitus in male rats.

2. MATERIAL AND METHODS

2.1. Experimental Animals:

Forty-white male albino rats, 12-16 weeks old, and weighing 250-300gm were used in this study. Rats were housed in separated metal cages and kept at the same environmental and nutritional conditions throughout the period of experiment. The animals were fed on same ration and water was supplied *ad-libitum*. All animals were acclimatized for minimum period of two weeks prior to the beginning of study.

2.2. Chemicals:

Streptozotocin (STZ): It was purchased from Sigma Chemicals Co, St. Louis, MO, USA. Streptozotocin has a molecular formula of C₈H₁₅N₃O₇, molecular weight of 265 g/mol (Dolan, 1997). STZ was freshly dissolved in cold 0.01M citrate buffer pH 4.2 (Rafiq et al., 2011).

2.2.1. *Sukkari Dates*: Sukkari, Sukkari dates were collected from a commercial market, Egypt.

Preparation of date aqueous extract:

Date was suspended in 100 mL sterile distilled water for 24h, and then homogenized in a Waring blender at a maximum speed. The homogenized extract was filtered through a Millipore filter. The final volume was completed to one liter with distilled water. Freshly prepared extract was used throughout the entire periods of the experiment (Belmir et al., 2015). Date aqueous extract was given orally at a daily dose of 10 ml/day/rat at concentration of (100g/L) according to (Hasan and Mohieldein, 2016).

2.2.2. Amaryl:

Glimepiride (Amaryl®, Sanofi-Aventis U.S.) 2mg tablets. The stock solution was prepared by dissolving 2mg of Amaryl tablet (5 tablets) in 270ml of distilled water. Amaryl was given at a daily dose of (1ml/rat/day) orally (Paget and Barnes, 1964).

2.3. Diabetes induction:

Rats were fasted for 18 hours and allowed free access of water. The experimental induction of diabetes in male rats was induced by a single intraperitoneal (i.p) injection of 50 mg/kg b.wt of streptozotocin (STZ) freshly dissolved in citrate buffer, pH 4.5.

2.4. Experimental design:

Rats were randomly divided into two main groups:

Group I (Control): Consists of 10 rats, not received drugs, served as normal control.

Group II (STZ): Included 30 rats injected with a single dose of STZ (50 mg/kg b.wt; i.p) for induction of diabetes and after 24 hours of diabetes induction all rats were randomly divided into 3 subgroups (10 rats each), placed in individual cages and classified as follow:

Subgroup a: Diabetic non treated rats.

Subgroup b: Diabetic rats administrated with aqueous sukari date extract at a dose of 10 ml/rat/day orally for 60 days.

Subgroup c: Diabetic rats treated with Amaryl at a dose of 1ml/rat/day orally for 60 days.

2.5. Sampling:

Blood samples and liver tissue specimens were collected after overnight fasting from all animal groups at 60 days from the onset of treatment.

2.6. Blood samples:

Blood samples were collected from the retro-orbital venous plexus of eyes at the end of 60 days after treatment. All samples were collected in dry and clean tube without anticoagulant, allowed to clot at room temperature for 30 min and centrifuged at 4500 rpm for 10 minutes to separate the serum. The clear specimens were aspirated carefully by Pasteur pipettes and transferred into dry, clean and sterile labeled tubes, and then kept at -80 °C till used for determination of the following biochemical parameters: Glucose, total cholesterol, triacylglycerols, high-density lipoprotein-cholesterol (HDL-c), low-density lipoprotein-cholesterol (LDL-c), insulin, L-MDA, SOD and 8-OHdG.

2.7. Biochemical analysis:

Serum glucose, total cholesterol, triacylglycerols, HDL-c, LDL-c, insulin, L-MDA, SOD and 8-OHdG were determined according to the methods described by Trinder (1969), Allain et al. (1974), Fossati and Prencipe (1982), Burnstein et al. (1970), Falholt et al. (1973), Mesbah et al. (2004), Mesbah et al. (2004), Kakkar et al. (1984) and Nadja et al. (2001), respectively.

2.8. Liver tissue for molecular analysis:

At the end of the experiment, rats of each group were sacrificed by cervical decapitation. The abdomen was opened and the liver specimen was quickly removed and cleaned by rinsing with ice-cold isotonic saline to remove any blood cells and clots, then blotted between 2 filter papers and quickly stored in a deep freezer at (-80 °C) for the determination of PON1 by PCR (Hussein et al., 2016).

2.9. Liver tissues for molecular analysis:

About 0.5 g of liver tissues were collected from all animals' groups, put in Eppendorf tubes and were immediately kept in liquid nitrogen and stored at -80°C till RNA extraction. The Molecular analysis of the relative gene expression in

liver tissues evaluated by reverse transcription polymerase chain reaction (RT-PCR) was paraoxonase 1 (PON1).

2.10. Molecular analysis:

Total RNA was isolated from liver tissue of rats using RNeasy Mini Kit (Thermo Qiagen, #74104) according to the manufacturer's protocol. Following determination of RNA concentration and purity by Quawellnanodrop Q5000 (USA), 5 mg of total RNA from each sample was reverse transcribed using Quantiscript reverse transcriptase. The produced cDNA was used as a template to determine the relative expression of paraoxonase 1 genes.

Table 1 Forward and reverse primers sequence for real time PCR.

Gene	Forward primer (5'-----/3')	Reverse primer (5'-----/3')
PON1	TGAGAGCTTCTATGCCACAAAT G	CCATGACAGGCCCAAGTAC A
β -actin	ACCCACACTGTGCCATCTA	CGTCACACTTCATGATG

2.11. Statistical analysis:

The obtained data were analyzed using the statistical package for social science (SPSS,13.0 software,2009),for obtaining mean and standard error. The data were analyzed

using one-way ANOVA to determine the statistical significance differences between groups. Duncan's test was used for making a multiple comparisons among the groups for testing the inter-grouping.

3. RESULTS

The obtained results presented in table (2)revealed that rats injected with STZ showed a significant increase in serum glucose, TC, TAG, LDL-c, L-MDAand 8-hydroxy-2-deoxyguanosine(8-OHdG). While a significant decrease in serum insulin, HDL-c and SOD with significant down-regulation of PON1 gene expression level in liverwere observed in STZ-induced diabetic rats when compared with the normal control group. Treatment with Sukkari date extract or Amaryl to diabetic rats exhibited a significant decrease in serum glucose, TC, TAG, LDL-c, L-MDA and 8-hydroxy-2-deoxyguanosine(8-OHdG) levels. In addition to marked increase in serum insulin, HDL-c and SOD with significant up-regulation in PON1 gene expression in liver tissue when compared with STZ non-treated group.

Table 2 Effect of Sukkari date extract or Amaryl treatment on some blood serum parameters and liver PON1 gene expression level in STZ-induced diabetic male rats

Animal Groups	Glucose (mg/dl)	T C (mg/dl)	TAG (mg/dl)	HDL-c (mg/dl)	LDL-c (mg/dl)	Insulin (nmol/ml)	L-MDA (nM/ml)	SOD (IU/ml)	8-OHdG (pg/ml)	PON1 Fold change
Group I (control)	90.60±3.11 ^c	96.20±3.11 ^c	92.40±3.85 ^b	43.10±2.30 ^a	34.62±3.18 ^c	5.24±0.26 ^a	31.27±1.88 ^{cd}	17.36±0.92 ^b	7.39±0.58 ^d	1.00±0.02 ^a
Subgroupa (Diabetic)	487.00±26.14 ^a	179.60±7.13 ^a	159.20±5.24 ^a	21.80±1.93 ^c	125.96±6.99 ^a	1.18±0.13 ^d	80.34±5.55 ^a	5.53±0.64 ^d	31.99±1.18 ^a	0.18±0.03 ^d
Subgroupb (Diabetic+Sukkari date extract)	138.00±8.99 ^b	115.40±5.99 ^b	80.40±4.73 ^b	34.60±1.28 ^b	64.72±3.64 ^b	3.45±0.25 ^b	39.85±3.08 ^c	14.78±1.57 ^{bc}	12.99±1.03 ^c	0.65±0.04 ^b
Subgroupc (Diabetic+Amaryl)	124.00±7.15 ^b	109.40±4.15 ^b	85.60±4.11 ^b	37.40±1.72 ^b	54.88±2.78 ^b	2.42±0.27 ^c	51.81±4.06 ^b	12.78±1.46 ^c	20.52±1.42 ^b	0.39±0.02 ^c

Data are presented as(Mean ±S.E). Mean values with different superscript letters in the same column are significantly different at (P>0.05).

4. DISCUSSION

Diabetes mellitus is a syndrome, which is characterized by hyperglycemia, lipoprotein abnormalities, raised basal metabolic rate, defect in enzymes and high oxidative stress induced damage to pancreatic beta cells (Sharma et al., 2010). Moreover, Diabetes mellitus is a frequent metabolic syndrome initially characterized by loss of glucose homeostasis. The disease is progressive and is associated with a high risk of atherosclerosis (Wakabayashi and Masuda, 2004).A significant increase in serum glucose level was observed in STZ-induced diabetic rats.These results were nearly similar to those reported by (Adaramoye et al.,2012) who indicated that fasting blood glucose level (FBG) was significantly increased in diabetic rats injected with streptozotocin (STZ) (35 mg/kg; i.p).This may be due to STZ causes pancreatic β -cell death and thus reduces the population of these cells. Effect of STZ on β -cells leads to development of insufficient production of insulin and consequently, the elevation of blood glucose level occurs (Rossetti et al ., 1990).

The obtained results showed that, treatment of hyperglycemic rats with Sukkari date extract or Amaryl yield a significant decrease in serum glucose level ,and the hypoglycemic effect may be due to its minerals, phenolics and phytoestrogens constituents. The minerals that are present in Phoenix dactylifera have a vital role in diabetes mellitus (DM) management such as magnesium that plays a

key role in regulation of insulin action and insulin-mediated-glucose uptake. Zinc induces the insulin formation and release, while chromium potentiates the insulin action, and selenium, which has been shown to stimulate glucose uptake, regulates glycolysis and pentose phosphate pathways. Phenolics present in P. dactylifera are considered to be a potent inhibitor of alpha glycosidase and alpha amylase, leading to reduction of carbohydrates digestion and absorption that may counteract the hyperglycemia present in DM(Ranilla et al., 2008) .

The hypoglycemic effect of Sukkari Date extract is in agreement with (Abdelaziz et al., 2015)who demonstrated that daily oral administration of aqueous Phoenix dactylifera seed aqPDS(1 g/kg/day) for 4 weeks, decreased the blood glucose level compared with diabetic group. This effect could be explained by the good glycemic control achieved by aqPDS as shown by significant reduction in the blood glucose level compared with the untreated diabetic group. On the other hand, the hypoglycemic effect of Amaryl (Glimepiride) may be due to the drug binds to specific receptors on pancreatic beta cells which lead to closure of potassium ATP channels and subsequent opening of calcium channels leading to an increase in cytoplasmic calcium and stimulation of insulin release (Muller, 2005).

Regarding serum lipids profile , the obtained results revealed a significant increase in serum total cholesterol(TC), triacylglycerols (TAG), low density lipoprotein-cholesterol (LDL-c), While high density lipoprotein-cholesterol (HDL-

c) was significantly decreased in diabetic rats when compared with the normal control group. These results are in agreement with Almeida et al. (2012), who recorded that the levels of total cholesterol, LDL-cholesterol and triacylglycerols were significantly increased while HDL-cholesterol level was statistically decreased in diabetic rats received a single intraperitoneal injection of STZ (60 mg/kg b.w.) compared with the normal animals. The increase in serum lipids levels such as cholesterol and triglycerides in STZ induced diabetic rats may be due to the fact that under normal circumstances, insulin activates lipoprotein lipase and hydrolyses triglycerides. Insulin increases uptake of fatty acids into adipose tissue and increases triglyceride synthesis. Moreover, insulin inhibits lipolysis. In case of insulin deficiency, lipolysis is not inhibited but an increased lipolysis which finally leads to hyperlipidemia. In diabetic condition, the concentration of serum free acids is elevated as a result of free fatty acid outflow from fat deposited, where the balance of the free fatty acid esterification-triglyceride lipolysis cycle is displaced in increase of lipolysis (Sirwalkar et al., 2004).

On the other hand, both hypercholesterolemia, hypertriglyceridemia are high risk factors for atherosclerosis. A long old established theory suggested that the higher the circulating levels of lipoprotein the more likely they enter into arterial wall. Chemically modified or oxidized lipoprotein produced in hyperlipidemic disorders like Diabetes Mellitus, enter into the scavenger arterial wall macrophages leading to formation of foam cells. Oxidized LDL promote the following changes. Chemotactic activity of monocytes facilitate the recruitment of circulating monocytes, inhibition of migration of macrophages within artery back to plasma compartment, increased uptake of LDL by macrophages through acetyl receptor leading to generation of foam cells and Atheroma formation (Indirakumari et al., 2015).

Treatment of hyperlipidemic rats with Sukkari date extract or Amaryl produce a significant decrease in serum total cholesterol, triacylglycerols, and LDL-c levels with increase HDL-c when compared with diabetic control group. The hypolipidemic effect of Sukkari date may be due to the potential of the extract to potentiate the pancreatic secretion of insulin from β -cells of islets which enables insulin to activate lipoprotein lipase for the breakdown of lipids. Moreover, flavonoids in the seed might also play a role in boosting the activity of lecithin cholesterol acyl transferase (LCAT), which regulates blood lipids (Senecha et al., 2012). In addition, *P. dactylifera* seeds contain high amounts of fiber. Adequate intake of dietary fiber can lower the serum cholesterol level, risk of coronary heart disease, hypertension, constipation, diabetes, colon and breast cancer (Ishida et al., 2000). This is in agreement with Hasan et al. (2010), who recorded that supplementation with date palm fruit reduced the concentrations of total cholesterol (TC), TAG, and LDL-c while caused elevation in levels of HDL-c in hypercholesterolemic hamsters and rabbits. Treatment with Amaryl to diabetic rats showed a significant decrease in serum TC, TAG, LDL-c, with significant increase in HDL-c all over the periods of the experiments, and that may be due to Glimepiride influence on the lipid profile a significant feature associated with hypoglycemic effect.

The obtained data revealed a significant decrease in serum insulin level was observed in diabetic rats when compared

with the normal control group. These results are in agreement with (Sheweita et al., 2016) who stated that insulin level was significantly decreased in rats injected with (STZ). Treatment of hypoinsulinemic rats with Sukkari date extract or Amaryl produce a significant increase in serum Insulin level. Administration of Sukkari date extract showed a significant increase in serum insulin level and that may be due to Magnesium and zinc in dates stimulate the synthesis and secretion of insulin. Manganese also mimics insulin properties, which lead to hypoglycemic effect (Mokhtari et al., 2008). Moreover, Mard et al., (2010) demonstrated that sub-acute administration of PDE at 200 and 400 mg/kg and its fractions (aqueous, chloroform, and ethyl acetate) at 200 mg/kg increased plasma insulin levels in treated diabetic rats compared with diabetic non-treated group. Also, treatment of hyperglycemic rats with Amaryl produce a significant increase in serum insulin level, and this may be due to Glimepiride is a hypoglycemic factor which causes an increase in the level of insulin. It causes an intensification of the insulin secretion by beta cells of the pancreas by closing up the potassium channels and depolarizing the cell membrane, and in consequence it initiates metabolic processes which lead to the release of insulin (Lebovitz and Melander, 1997). This is in agreement with Mwafy and Yassin (2011), who demonstrated that treatment with glimepiride 0.1 mg/kg body weight/day for 4 weeks cause significant increase in serum insulin level in (STZ 50 mg/kg b. wt.) induced diabetic rats.

Results revealed that there is a significant increase in serum MDA, (8-OHdG), While SOD, and PON1 show different behavioral pattern, where it were detectably significant decrease in diabetic rats all-over the periods of the experiments when compared with the normal control group. These results are in agreement with (Sadri et al., 2017) who observed that, Plasma levels of MDA were significantly increased While antioxidant enzymes such as SOD and PON1 activities were significantly decreased in diabetic rats received an intraperitoneal injection of STZ (55 mg/kg; i.p.) in comparison with normal control rats. In addition, Christijanti et al. (2017) reported that the 8-oxo-dG levels were significantly increased in diabetic rats received an intraperitoneal injection of STZ (65 mg/kg; i.p.).

In the current study administration of diabetic rats with Sukkari date extract or Amaryl produce a significant decrease in serum L-MDA and 8-OHdG levels with significant increase in serum SOD activity and liver tissue PON1 gene expression level. This probable beneficial effect of Sukkari date extract may be due to its antioxidant potential via its phenolics, flavonoids and small molecules such as vitamin C, vitamin E and GSH. These antioxidant constituents of Sukkari date extract may directly react with reactive oxygen species (ROS) to destroy them by accepting or donating electrons to eliminate the unpaired condition of ROS, or indirectly decrease the cellular free radicals by enhancing the activities and expressions of antioxidant enzymes that lead to prevention of lipid peroxidation, DNA damage and protein modification. Aqueous extracts of dates were shown to have potent antioxidant activity, because they inhibit in vitro lipid and protein oxidation and possess free radical scavenging capacity (Vayalil, 2002). Moreover, Sabbah et al. (2018) stated that oral administration of Ajwa date aqueous extract (0.75 & 1.5 g/kg b.wt.) for 4 weeks reduced the urinary 8OHdG level, significantly reduced the increased serum levels of MDA and significantly increased

the enzymatic activities of SOD in cardiac tissue of the AJDAE protected rats. Additionally, Takaiedi et al. (2014) revealed that oral administration of DSE at the doses of (500 and 1000 mg/kg b. wt.) significantly increased serum paraoxonase activity compared to the untreated group.

Treatment of diabetic rats with Amaryl showed a significant decrease in serum L- MDA and 8-OHdG, increase in SOD and PON1 activity and that may be due to two possible explanations for antioxidant capacity of glimepiride, firstly through inhibition of cellular cyclooxygenase pathways (Qi et al., 1995) and the second possible mechanism may be related to the fact that glimepiride has the property to upregulate antioxidant enzyme genes like paraoxonase and superoxide dismutase gene through reducing the activation of the redox sensitive nuclear factor kappa- β (NF- κ B), or through that glimepiride possessed agonistic activities for peroxisome proliferator activator receptor gamma (PPAR γ) (Fan et al., 2008; Fukuen et al., 2005). Moreover, glimepiride significantly decreased MDA level while it significantly increased SOD activity in erythrocytes of STZ-induced diabetic rats. The antioxidant activity of glimepiride could be explained through normalization of elevated hyperglycemia as glucose auto-oxidation is the major source of free radicals and peroxides production in diabetes (Krauss et al., 2003). Similarly, Mohamed et al. (2012) stated that diabetic rats injected with STZ (50 mg/kg i.p.) and treated with glimepiride (10 mg/kg/p.o.) significantly reduced serum MDA level. While significantly increased SOD activity in diabetic rats. Also, Nagayama et al. (2010) demonstrated that treatment with glimepiride 1.5 mg/day for 6 months decreased urinary 8-hydroxy-2-deoxyguanosine (8-OHdG). Moreover, Wójcicka et al. (2010) demonstrated that Glimepiride administered (0.1 mg/kg b.wt.) daily caused an increase in PON1 activity in liver of STZ (50 mg/kg i.p.) induced -diabetic rats.

5. CONCLUSIONS

These results suggest that, Sukkari date extract is a potential antidiabetic natural product and may be effective in controlling glycemic status, improving dyslipidemia and reducing cardiovascular complications due to diabetes mellitus. In addition, treatment with Sukkari date extract attenuates the oxidative stress produced by diabetes mellitus

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