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EFFECT OF EGYPTIAN PALM SEED (*Medemia argun*) ON BLOOD GLUCOSE, LIPID PROFILE, KIDNEY FUNCTIONS AND PANCREATIC TISSUE IN TYPE I DIABETIC RATS

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Received: 11/10/2020 ; Accepted: 22/11/2020

ABSTRACT: Diabetes mellitus (DM) is a metabolic disease with 2.8% incidence worldwide. Insulin dependent DM (IDDM) or type I DM, usually arising in early ages, in most cases is accompanied by complications on vital organs like, kidney and heart. *Medemia argun* (MA) is an Egyptian palm, rich in proanthocyanidins (PACs), which are beneficial against a wide variety of human ailments. Thirty male rats were classified into 5 equal groups (6 rats each). Type I DM was induced by a single intraperitoneal (IP) injection of alloxan (120mg/kg). Rats were then treated by insulin (30 U/kg, daily), MA seed ethanolic extract (100mg/kg, orally, once daily, dissolved in sterile saline) for one week. Random blood sugar (RBS), serum creatinine, urea, triglycerides, total cholesterol, both high and low density lipoprotein cholesterol (HDL-C, LDL-C) and pancreatic tissue morphology were studied. MA showed insulin-mimetic action by significant downregulation of RBS, more significantly when given with insulin. This action was accompanied by preserving the populations of pancreatic beta, alpha and delta cells, usually perturbed by DM induction. Similarly, MA protected kidney through maintaining creatinine and urea normal levels. The effect of MA on lipid profile members was conflicting, as showing increments in triglycerides, total cholesterol and LDL-C, with decreased HDL-C, compared to diabetic animals. Oral administration of MA ameliorated DM through showing preservation of pancreatic tissue and improving kidney functions. It protected DM subjects against complications on both pancreatic and kidney tissues, although it hasn't a promising value in the protection of cardiovascular system which showed disturbed lipid profile.

Key words: *Medemia argun*, type I diabetes mellitus, lipid profile, kidney functions, pancreatic tissue, rats.

INTRODUCTION

Diabetes mellitus (DM), is a metabolic disease, characterized by persistent elevated blood sugar levels. It is classified into 2 common types, I and II. The major late diabetic complications include neuropathy, vasculopathy and nephropathy and cardiopathy. The majority of the diagnosed diabetic patients belong to type II DM, less than 12% have type I DM, while about 3% have other types of the disease (Okur *et al.*, 2017). The words "Diabetes" denotes "a passer through a siphon" while "Mellitus" means "sweet", both are derived from Greek language. It is believed that Greeks used these terms in such way, due to the extensive urine

excretions produced by diabetic patients that attracted some insects (Patlak, 2002; Piero 2015; Chawla *et al.*, 2020). Diabetic kidney disease (DKD) is considered the most common cause of the end-stage renal disease. Although intensive treatments with hyperglycemic control, blood pressure control, and the use of renin-angiotensin system blockades, the incidence of DKD still high (Chen *et al.*, 2020). Both creatinine and urea are end products of protein metabolism, usually their serum values are considered as easy and cost-effective tools for assessment of kidney function (Damiati, 2019).

Recently, it was suggested that, in type I and type II diabetes, impairment of pancreatic beta cell function is an early sign of disease

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pathogenesis. This assumes that, in addition to beta cell mass activation for different therapies, the development of novel modalities for protection and recovery of beta cell function would be more promising for better diabetes treatment and prevention (Chen *et al.*, 2017). On the other hand, it was found that there is a high prevalence of dyslipidemia in patients with type I DM. Thus, drugs targeting dyslipidemia should be prescribed to prevent/delay chronic complications and cardiovascular disease (Homma *et al.*, 2015; Narindrangkura *et al.*, 2019).

Lipid profile is routinely requested to assess cardiovascular risk. It involves the assessment of serum levels of total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL). LDL measurement still plays a pivotal role in the diagnosis, prediction and monitoring both the course and treatment of lipid disorders, as well as cardiovascular diseases (Solnica *et al.*, 2020).

Many physicians prescribe natural products as alternative to conventional treatment for many diseases, including DM (Cazzola and Benvenuto, 2013). A variety of herbals have been proved for their efficacy to protect against DM and its complications in many disciplines (Abdel-Hamid *et al.*, 2011; Choudhury *et al.*, 2018).

Medemia argun (MA) is an ancient palm containing proanthocyanidins (PACs) as active principles. These polyphenolic products are widely distributed in plants and are important part of the human diet (Hamed *et al.*, 2014). Few studies were published showing the medicinal value of MA. It is a fan palm, growing at the Nubian Desert Oases of South Egypt and North Sudan. The fruit has been found in the tombs from the 5th Dynasty (2500 BC) and Roman times (6–7th century AD), reportedly inside the tomb of Tut Ankh Ammon (Masullo *et al.*, 2016). The PACs derived from MA nuts are efficient protector against oxidative and nitrate stress responsible for many diseases (Hamed *et al.*, 2014).

PACs have potential antioxidant properties, which seems to be responsible for the utility of MA during ancient times, and may explain the frequent use of this fruit as a cost effective source of hydrolyzable PACs containing

afzelechin, catechin and galocatechins (Hamed *et al.*, 2014; Aldubayan, 2020).

The aim of the present works to investigate the possible insulinomimic potential of MA seed ethanolic extract against experimental type I diabetes, induced by alloxan, and the therapeutic benefit of the extract on associated disturbed kidney functions, morphology of the pancreatic tissue as well as, its effect on lipid profile, whether used alone or concomitant to insulin.

MATERIALS AND METHODS

Materials

Chemicals

Alloxan powder was purchased from Sigma Chemical Co. (St. Louis, MO, USA). Mixtard insulin (soluble insulin 30% and isophane insulin 70%), was obtained from Egyptian local market, imported from Novo Nordisk, Denmark. All other chemicals used, were of analytical grade.

Preparation of MA seed extract

Seeds of *Medemia argun* were separated from their fruits, put in a dry and clean place for 5 days, crushed into small particles by a grinder. The particles of the powdered seeds were kept for 2 days in conical flask containing 70% ethanol. The conical flask was covered with aluminum foil and kept on a shaker for 24 hr. with continuous agitation at 150 rev/min for thorough mixing and also. Dissolution of the active ingredients then, the extract was filtered by using filter paper. The solvent was removed from the extract by using rotary vacuum evaporator at temperature of 45°C in water bath. Finally, the crude extract was collected in petri dishes, kept in a dry and clean place for 2 days. Then crude extract was ready to use for the experiment by dispensing in sterile normal saline for intraperitoneal use (Nagappan, 2012; Al-Hamimi and Turner, 2020).

Animals and experimental design

The procedures of the experiment followed International Standards of Animal Ethics for Animal Care and Use.

Thirty adult male albino rats weighing 100–120 g, were randomly allocated for the study.

Table 1. Design of the experimental groups

Group	Control	Diabetic	Diabetic treated with MA	Diabetic treated with insulin	Diabetic treated with insulin and MA
Alloxan				120 mg/kg	
Treatment	Saline	Alloxan	Ethanol extract of MA	Only insulin	Insulin and MA
Dose and duration	daily, intraperitoneally (I.P), for one week	120 mg/kg, single dose	100 mg/kg, daily, orally for one week	subcutaneously (30 U/kg, daily) for one week	Insulin subcutaneously (30 U/kg, daily) + MA (100 mg/kg, daily, orally) for one week

The animals were housed in polyethylene cages in a moderately humid room under a controlled 12 hours light/dark cycle and left under constant environmental and nutritional conditions with free access to standard food and water ad libitum. Animals were kept 2 weeks for acclimatization before starting the experiment, then, randomly classified into 5 groups (6 animals each), as per Table 1 the first group was left without any treatment served as a negative control, the four remaining groups received a single intraperitoneal inject of alloxan (120 mg/kg) (Yadav *et al.*, 2008). One group of them was left without treatment served as positive control. The three remaining groups received one of the following treatment, ethanolic extract of MA 100 mg/kg, daily, orally (Abd Allah *et al.*, 2020), insulin or a mixture of (ethanolic MA+ insulin) subcutaneously (30 U/kg, daily) + MA (100 mg/kg, daily, orally). DM was confirmed 1 week after alloxan injection by measuring blood glucose levels; only animals with blood glucose more than 200 mg/dl were considered diabetic (Spadella *et al.* 2005). The treatment continued for one week, then, animals were sacrificed. The setting of the experiment was in the animal house of Faculty of Medicine, Zagazig University, Egypt.

Blood sample collection

At the end of the experiment, rats were decapitated, blood samples were obtained directly after decapitation of animals, centrifuged at 2500 rpm for 10 min. after standing for 30 minutes at 4°C. The obtained serum were kept at -80°C till biochemical analyses.

Pancreatic tissue sampling

Pancreatic tissues were dissected out, washed by cold saline, blotted by tissue paper, kept in a solution of formalin and saline (10% V/V) for histological examination.

Serum biochemical investigations

Random blood glucose levels (Thompson, 1966), serum creatinine (Heinegard and Tiderstrom, 1973), urea (With *et al.*, 1961), triglycerides (TG) (Siedel *et al.*, 1993), total cholesterol (TC) (Allain *et al.*, 1974), HDLC (Warnick *et al.*, 2001) were investigated. Then, LDLC was calculated from Friedewald formula, using determined TC, HDL-C and TG levels as follows:

$LDLC = TC - HDLC - TG/5$ (mg/dl) (Martin *et al.*, 2013)

All variables were spectrophotometrically analyzed, using available locally manufactured kits in Egyptian market and manufacturer's instructions were followed.

Histopathological investigation

Fixation and tissue processing: Formalin preserved pancreatic tissues were processed in an automated tissue processor. The processing consisted of an initial 2 step fixation and dehydration. Fixation comprised tissue immersion in 10% buffered formalin for 48 hours, followed by removal of fixative in distilled water for 30 minutes. Dehydration was then carried out by running the tissues through a graded series of alcohol (70%, 90% and 100%). The tissue was initially exposed to 70% alcohol for 120 minutes, followed by 90% alcohol for 90 minutes and then two cycles of absolute alcohol, each for one hour. Dehydration was then followed by clearing the samples in several changes of xylene. It consisted of tissue immersion for one hour in a mixture comprising 50% alcohol and 50% xylene, followed by pure xylene for one and half hour. Samples were then impregnated with molten paraffin wax, then embedded and blocked out. Paraffin sections (4–5 μ m) were stained with hematoxylin and eosin (Suvarna

and Bancroft, 2018). Stained sections were examined for inflammation, degenerations, necrosis and other pathological changes.

Statistical Analysis

Data were statistically analyzed using SPSS, USA, all data of control and treated groups were expressed as mean values \pm SE. Two-Tail ANOVA and unpaired t-test were carried out to find if there was any significant difference among control and treated groups. P values <0.05 , were considered significant.

RESULTS AND DISCUSSION

The results in Table 2 show that, alloxan administration to rats, induced type I diabetes mellitus (DM), within 10 days, as confirmed by a significant increase in random blood sugar (RBS). Serum creatinine was also significantly elevated, compared to normoglycemic control after alloxan treatment (4.8 ± 0.6 , 1.3 ± 0.17 , mg/dl, respectively). Treatment of DM animals with MA seed extract, significantly lowered creatinine than untreated DM animals (0.5 ± 0.1 , 4.8 ± 0.6 , mg/dl, respectively). The same effects were observed with insulin treatment (0.3 ± 0.01 , 4.8 ± 0.6 , respectively) and with (insulin + MA) (1.1 ± 0.1 , 4.8 ± 0.6 , mg/dl, respectively) than untreated DM animals. Serum urea was significantly elevated in DM group (87.2 ± 2.5 mg/dl), compared to negative control (36.3 ± 2.3 mg/dl). Treatment of DM animals with MA seed extract, significantly lowered urea than DM members (46.6 ± 3.8 , 87.2 ± 2.5 mg/dl, respectively). Same effects were observed with insulin (43 ± 3.6 , 87.2 ± 2.5 mg/dl, respectively) and with insulin plus MA (43 ± 3.6 , 87.2 ± 2.5 mg/dl, respectively) compared to untreated DM animals. Induction of DM significantly decreased serum triglycerides (TG) than control (91.2 ± 14.1 , 142.3 ± 16.7 , mg/dl, respectively), but MA treatment to DM rats significantly elevated TG level (173 ± 18.4 , 91.2 ± 14.1 , mg/dl, respectively) than untreated DM animals. Both insulin alone (124.3 ± 24.3 , 91.2 ± 14.1 , mg/dl, respectively) and insulin plus MA (130 ± 14 , 91.2 ± 14.1 , mg/dl, respectively) significantly increased serum TG than DM group. Also, induction of DM significantly decreased serum total cholesterol (TC) than control (133.3 ± 12 , 183.1 ± 8.4 , mg/dl, respectively), but MA treatment to DM rats significantly elevated TC level than untreated

DM animals (191 ± 25 , 133.3 ± 12 , mg/dl, respectively). Both insulin alone (110 ± 6.7 , 133.3 ± 12 , mg/dl, respectively) and insulin plus MA (101 ± 3.0 , 133.3 ± 12 , mg/dl, respectively) significantly decreased serum TC than untreated DM group. HDLC was significantly decreased in DM animals than untreated control (57.6 ± 5.4 , 100.1 ± 6.7 , mg/dl, respectively). Treatment of DM animals by MA alone (20 ± 1.8 , 57.6 ± 5.4 , mg/dl, respectively), or insulin alone (37.7 ± 2.8 , 57.6 ± 5.4 , mg/dl, respectively), or their combination (22.5 ± 0.7 , 57.6 ± 5.4 , mg/dl, respectively), in comparison to DM animals. LDLC was significantly increased after induction of DM, in comparison to control (56.5 ± 6.7 , 54.5 ± 9.5 , mg/dl, respectively) and treatment with MA to diabetic rats (126.2 ± 22 , 56.5 ± 6.7 , mg/dl, respectively), in comparison to DM control. Insulin treatment for diabetic rats, whether given alone (46.5 ± 12.2 , 56.5 ± 6.7 , mg/dl, respectively) or combined with MA (52.3 ± 4.5 , 56.5 ± 6.7 , mg/dl, respectively) non significantly decreased LDLC of DM group near untreated DM animals (Table 2).

Examination of pancreatic tissue (Fig.1) showed that induction of DM caused decreased size and population of the islets. The beta-cell islets revealed degenerative and early necrotic changes with compensatory increase of the alpha and delta cells. Besides, the exocrine pancreas revealed congestion, peri-ductal, interstitial lymphocytic infiltration and cystic dilatation of the pancreatic ducts and moderate proliferation of their lining epithelium (Plate 2), in comparison to control tissue, that showed normal structures of both exocrine, endocrine parts and the islet cells beta, alpha and delta (Plate 1).

Treatment of DM rats with MA alone also preserved normal islet cells with preserved population of beta, alpha and delta cells (Plate 3). Insulin treatment to DM group showed that pancreatic islets appeared comparatively smaller in size with few cells had decreased population of cellular contents and the exocrine pancreatic ducts appeared cystically dilated (Plate 4). Co-treatment of MA to insulin for diabetic rats showed normal pancreatic tissue of both exocrine and endocrine parts. The islet cells including beta, alpha and delta cells were normal and healthy with active secretory activity. Only few parts of beta cells showed degenerative changes, mostly vacuolation and apoptotic changes in other cells (Plate 5).

Table 2. Variations in serum random blood glucose, renal functions and lipid profile among experimental groups, (Values are expressed as Mean \pm SEM, n = 6)

Parameter (mg/dl)	Negative control (Saline)	Positive control diabetic	MA treated DM rats	Insulin treated diabetic group	Insulin + MA treated diabetic group
Random blood glucose	104.1 \pm 12.6	230.1 \pm 5.5 ^a	109.4 \pm 6.6 ^b	113.2 \pm 4.1 ^b	100.6 \pm 5.1 ^b
Creatinine	1.3 \pm 0.17	4.8 \pm 0.6 ^a	0.5 \pm 0.1 ^b	0.3 \pm 0.01 ^b	1.1 \pm 0.1 ^b
Urea	36.3 \pm 2.3	87.2 \pm 2.5 ^a	46.6 \pm 3.8 ^b	43 \pm 3.6 ^b	46.6 \pm 3.8 ^b
Triglycerides	142.3 \pm 16.7	91.2 \pm 14.1 ^a	173 \pm 18.4 ^b	124.3 \pm 24.3 ^b	130 \pm 14 ^b
Total cholesterol	183.1 \pm 8.4	133.3 \pm 12 ^a	191 \pm 25	110 \pm 6.7 ^b	101 \pm 3.0 ^b
HDLC	100.1 \pm 6.7	57.6 \pm 5.4 ^a	20 \pm 1.8 ^b	37.7 \pm 2.8 ^b	22.5 \pm 0.7 ^b
LDLC	54.5 \pm 9.5	56.5 \pm 6.7 ^a	126.2 \pm 22 ^b	46.5 \pm 12.2	52.3 \pm 4.5

P value represents the difference between all groups, ^a represents differences from negative control group, ^b represents differences from diabetic control group. P values <0.05, were considered significant. Results were computed by Two-tail ANOVA.

Negative control

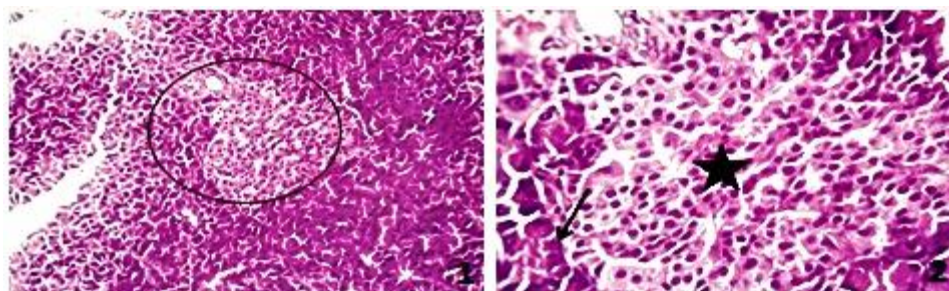


Plate 1. Photomicrographs of pancreatic tissue showing normal structures of both exocrine (arrow) and endocrine parts (1: circle and 2: star). The islet cells including beta, alpha and delta were apparently normal. (1) X100, (2) X400

Diabetic control

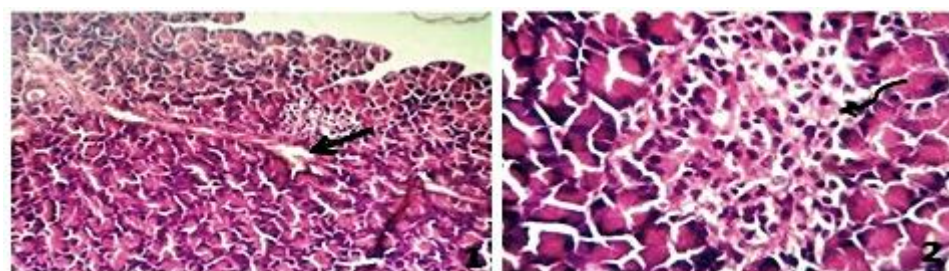


Plate 2. Photomicrograph of pancreatic tissue showed decreased size and population of the islets. The beta-cell islets revealed degenerative and early necrotic changes with compensatory increase of the alpha and delta cells (2: curved arrow). The exocrine pancreas revealed congestion, peri-ductal and interstitial lymphocytic infiltration and cystic dilatation of the pancreatic ducts, some of them showed moderate proliferation of their lining epithelium (1: open arrow). (1) X100, (2) X400

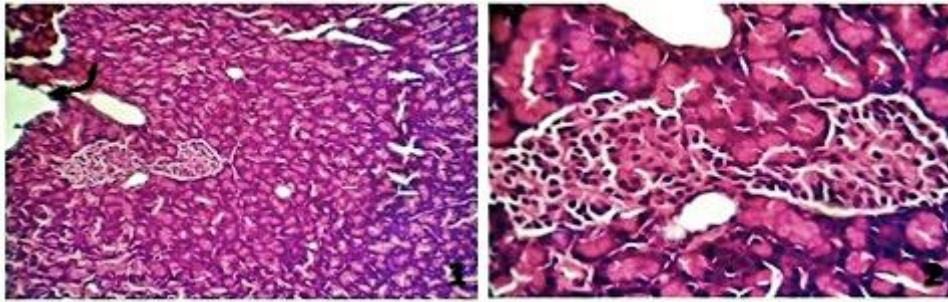
Diabetic group treated with MA

Plate 3. Photomicrographs of pancreatic tissue showed apparently normal islet cells with preserved population of beta, alpha and delta cells. The pancreatic ducts of the exocrine pancreas appeared mildly dilated (1: curved arrow). (1) X100, (2) X400

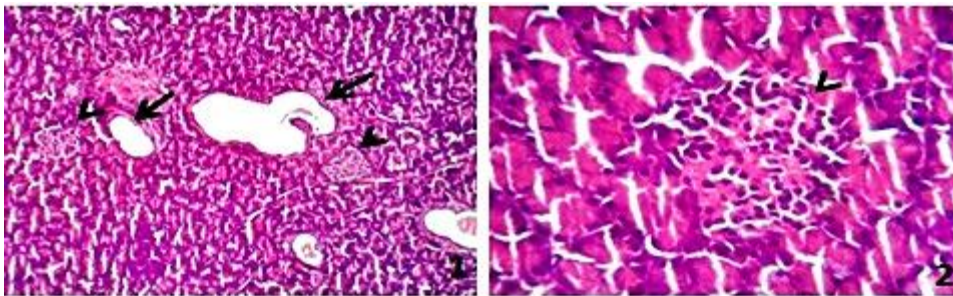
Diabetic group treated with insulin

Plate 4. Photomicrographs of pancreatic tissue revealed that islets appeared comparatively smaller in size (1, 2: arrow heads), and few number with decreased population of cellular contents and the exocrine pancreatic ducts appeared cystically dilated (1, open arrows). (1) X100, (2) X400

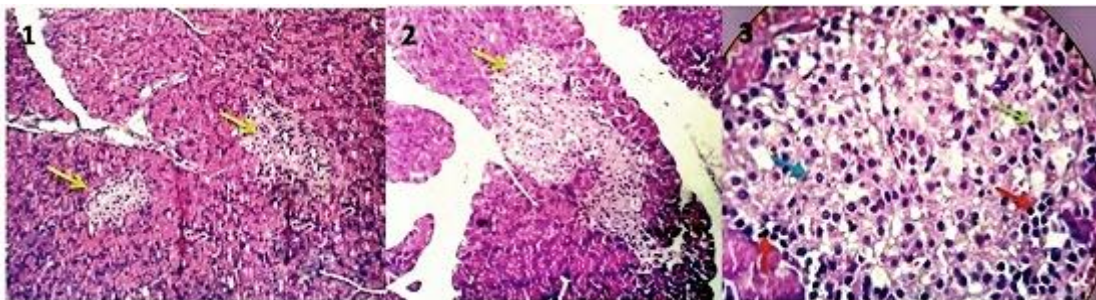
Diabetic group treated with MA and insulin

Plate 5. Photomicrographs of pancreatic tissue revealed normal structures of both exocrine and endocrine parts. The islet cells including beta(3, blue arrow) ,alpha (3, red arrow)and delta cells(3, green arrow) were apparently normal and in a good healthy condition with active secretory activity. Few parts of beta cells showed degenerative changes, mostly vacuolation (3, orange arrow head) and apoptotic changes in other cells (3, black arrow head). (1) X100, (2) X400

Fig. 1. It shows histopathologic findings among studied groups (all were stained with H and E)

Diabetes mellitus is caused by deficiency or decreased utilisation from available insulin, leading to an increase in glucose levels in the blood. It negatively affects many body systems, particularly blood vessels, eyes, kidney, heart and nerves (Ismail, 2009). Type I diabetes is believed to be an autoimmune disease characterized by a local inflammatory reaction in and around islets that is followed by destruction of B cells, whereas Type II diabetes is characterized by peripheral insulin resistance and impaired insulin secretion (Arora *et al.*, 2009). In this work, administration of alloxan induced DM in the treated rats, this is well known reported model (Lee and Lee, 2008). Alloxan also showed decreased size and population of the pancreatic islets, degenerated beta-cell islets, early necrotic changes with compensatory increase of alpha and delta cells. The exocrine pancreas showed congestion, periductal and interstitial lymphocytic infiltration and cystic dilatation of the pancreatic ducts, an effect which directly led to DM (Abdul-Hamid and Moustafa, 2014). This action was reported before as well (Collard *et al.*, 2018). The histological changes were somewhat corrected by insulin, but MA whether used alone or added to insulin significantly restored these changes. These actions of MA were observed for the first time. Alloxan significantly up regulated serum creatinine level and significantly elevated urea level, these consequences were also reported earlier (Das and Sil, 2012).

In addition, induction of diabetes significantly resulted in dyslipidemia, disrupting serum TG, TC, HDLC and LDLC. This action was reported as a result of alloxan injection (Rahimi-Madiseh *et al.* 2017).

In the present study, treatment with MA for diabetic rats, significantly lowered blood glucose levels than DM group. This extract wasn't reported to have anti diabetic activity up to our knowledge, however, the principal components of the extract, PACs, were reported to lower blood glucose levels significantly, which is in accordance with our work results (Salahuddin, 2017). MA treatment also, didn't affect normal pancreatic morphology. It showed normal islet cells with preserved population of beta, alpha and delta cells. Only, the pancreatic ducts of the exocrine pancreas appeared mildly

dilated. MA extract, whether given alone or concomitant with insulin, significantly down regulated disturbed kidney functions (creatinine and urea). PACs, which are the main constituents of the palm seeds were reported to have the same effect (El-Sayed *et al.*, 2017). The efficacy of PACs on modulating serum lipid profile in diabetic rats was also registered elsewhere (Vega *et al.*, 2017). The effect of PACs, as an adjuvant to insulin was reported elsewhere to have better insulinomimic activity on insulin-sensitive cell line (Pinent *et al.*, 2004) and on diabetic mice, through improving insulin sensitivity (Zhang *et al.*, 2009). As well as, dietary polyphenols have been widely investigated as antidiabetic agents in cell, animals, human study, and clinical trial (Sun *et al.* 2020).

Conclusion and Recommendations

Diabetes mellitus type I, which is principally, a degenerative pancreatic disease has common complications on kidney and lipid metabolism. The administration of MA seed extract, which is rich in PACs, could potentiate the inulinic efficacy among diabetic subjects, through preservation of normal pancreatic tissue. This regime could improve kidney functions. Thus, MA can protect DM patients against diabetic complications on both pancreatic and kidney tissues, although it hasn't a promising value in protection of cardiovascular system affected by disturbed lipid profile.

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تأثير بذور النخيل المصرية (ميديميا أرجون) على جلوكوز الدم، والتشكيلات الدهنية، ووظائف الكلى وأنسجة البنكرياس في سكر النوع الأول في الجرذان

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يعد مرض السكري مرض أبيض بنسبة حدوث ٢.٨% في جميع أنحاء العالم، عادةً ما يظهر النوع المعتمد على الأنسولين (النوع الأول) في الأعمار المبكرة، وفي معظم الحالات يكون مصحوباً بمضاعفات على الأعضاء الحيوية مثل الكلى والقلب. نخيل الزينة (الأرجون) هو نخيل مصري، غني بالبروانثوسيانيدين (PACs)، وهي مفيدة ضد مجموعة واسعة من الأمراض البشرية، أظهر تناول المستخلص الكحولي لبذرة نخيل الزينة تأثيراً مشابهاً للإنسولين، وبشكل أكثر أهمية عند إعطائه مع الأنسولين وكان مصحوباً بالحفاظ على تجمعات خلايا بيتا ألفا ودلتا في البنكرياس، التي أضرها السكري التجريبي، وبالمثل، يحمي المستخلص الكلى من خلال الحفاظ على مستويات الكرياتينين واليوريا الطبيعية، وكان تأثيره على الدهون متضارباً، حيث كانت الزيادات في الدهون الثلاثية والكوليسترول الكلي ومنخفض الكثافة، مع نقص الكوليسترول مرتفع الكثافة، مقارنة بالحيوانات المصابة بداء السكري، على الرغم من أنه ليس له قيمة واعدة في حماية نظام القلب والأوعية الدموية الذي يظهر من خلال اضطراب الدهون.

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