IJBPAS, July, 2019, 8(7): 1249-1289

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

EFFECT OF CELERY (*APIUM GRAVEOLENS* L.) ON FERTILITY AND SOME BIOCHEMICAL AND HEMATOLOGICAL PARAMETERS IN ALLOXAN-INDUCED DIABETIC MALE RATS

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Received 4th Jan. 2019; Revised 23rd Jan. 2019; Accepted 4th Feb. 2019; Available online 1st July 2019

https://doi.org/10.31032/IJBPAS/2019/8.7.4750

ABSTRACT

Diabetes is a metabolic disorder characterized by hyperglycemia which has a harmful effect on all systems including the reproductive system of animals. Purpose of this study is to evaluate the effects of methanolic and aqueous extract derived from celery (Apium graveolens L.) on fertility and some hematological and biochemical parameters in alloxan-induced diabetic male rats.

This study was conducted on eighty experimental male rats (Sprague Dawly strain) weighing about 220 g each were used throughout the study and randomly assigned to eight experimental groups of 10 rats each. Group I received normal saline (0.5 ml/kg) and serves as a control. Group II and III - gavaged daily for thirty days with 1ml of the ethanol extract at doses of 213 mg/kg and 425 mg/kg body wt and served as control. Group IV group Rats were made diabetic by injecting alloxan monohydrate "B.O.H chemical LTD England" intraperitoneally at a dose of 150ml/kg (dissolved in fresh normal saline) to 18h fasted rat. Every week after injection, blood was collected from the hearts of all surviving rats and blood glucose levels were determined. Rats with blood sugar levels of 200 to 450mg/100 ml were considered as diabetic and were used in the study and considered as diabetic rats. Rats of experimental groups V, IV, IIV, and IIIV were treated intraperitoneally with 1 ml of Apium graveolens ethanol extract of celery (Apium graveolens L.) at doses of (213 and 425 mg/kg, 200mg/kg of

aqueous extract and 14.2 mg/kg of metformin body wt respectively once a day for thirty consecutive days, and the rats control groups were treated on the same manner with the vehicle. After thirty days of treatments, all rats were sacrificed and level of blood glucose, insulin, testosterone, follicle stimulating hormone (FSH) and luteinizing hormone (LH), the weight of testis, sperm count and motility were measured. Lipid profile and some hematological parameters also measured in all experimental groups. Our results show that the treatment with ethanol, aqueous extract, and metformin to diabetic rats lead to significant increased in all measured parameters of in experimental rats except the level of LH as compared to diabetic rats, control and metformin-treated groups. Effects produced by this extract were closely similar to a standard antidiabetic drug, metformin ($p<0.05$) hypoglycemic effects in alloxan-induced diabetic rats, fertility, protection against body weight loss of diabetic animals and might alleviate the diabetes-induced disturbances of some biochemical, hematological and lipid profile parameters

Keywords: Hyperglycemia, Alloxan, metformin, Apium graveolens L

INTRODUCTION

Diabetes (DM) is a complex metabolic disorder that can cause clinical complications in the body. This disorder is determined by high blood sugar, low antioxidants and abnormal metabolic pattern of fat, carbohydrates, proteins, and electrolytes **[1-3]**. An estimated 366 million people are at risk of developing diabetes in 2030 **[4,5]**. The most significant diabetes mellitus complication is the extreme elevation of blood glucose level, referred as "Diabetic Hyperglycemia", mostly induced by insulin hormone synthesis and secretion impairment, insulin function defect or a complex of these two pathological conditions **[6-7].** In 2014, the World Health Organization reported that 422 million people had diabetes, indicating a global increase of 60% over 2002 **[8]**. The World Health Organization (WHO) has previously predicted that the number will rise to about 300 million by 2025 **[9]**. Hyperglycemia has recently been implicated in the induction of oxidative stress which in turn leads to the initiation and development of complications of diabetes. Many complications of diabetes include physical disability, kidney failure, impaired vision, cardiovascular disease, and sexual dysfunction **[10,11]**. Many synthetic compounds were used as

therapeutic drugs to control DM, including metformin **[12,13,14]** Male infertility describes male inefficiency in fertilization in fertile females during a 12-month period of unprofessional and unprotected intercourse [15]. It is estimated that 56% of infertile couples of childbearing age require medical assistance **[16]**. In the middle of these couples, 10% -30% of cases of infertility were attributed exclusively to a male problem and 15% -30% of the cases showed significant anomalies in both partners **[17]**. Studies have revealed the prevalence of infertility in male partners of DM for couples who suffer from infertility to decrease sperm movement and increase morphology in abnormal sperm **[18, 19].** affecting it Fertility is considered as one of the main parts of population growth that have always been an extensive issue and continual research has been done on the factors in jordan and abroad. Measurement and recognition of the level of fertility in each class seem to be the essential component of population projections and the infrastructure of economic, social, and demographic planning for the development of a country. Also, they are considered as important and major indicators in assessing the economic and social conditions of the studied society **[20]**. Fertility sociology has great importance in discussing population transition. Experience has also shown that fertility changes play a greater role in determining the size of the population than the changes in mortality **[21]**. Fertility and infertility problems are among the complex issues in medicine. In any community, approximately 13 % of people are infertile. The most common cause of infertility in males is their inability to produce enough healthy and active sperms **[22].** Infertility can cause personal and social problems because of high spending costs for treatment which can damage the family stability. Infertility that is the inability to have children affects men and women in reproductive age and can expose people with problems. The World Health Organization has introduced infertility as an important problem of reproduction. However, infertility can cause major emotional disorders, psychological, and social consequences and side effects **[23]**. Diabetes has been shown to have adverse effects on both male and female reproductive function **[24, 25]** and its effects can be seen in increasing infertility **[26].** About 90% of diabetics suffer from sexual dysfunction,

including decreased libido, impotence and infertility **[27]**. In addition, men with diabetes are exposed to various sexual problems, although progressive physical disorders and degraded psychological response are contributing factors. Many studies have investigated and reported on various diseases commonly experienced by men with diabetes and also highlighted subsequent reproductive defects. Some extracted results highlight the effects of DM on male reproductive functions in human and animal models. According to the WHO, regarding the preservation of public health, family planning, reproductive health, and the use of herbal products have come to the consideration as an alternative to synthetic drugs. Given that the herbs are more compatible with the human body, herbal medicines are predicted to have fewer side effects and fewer damages compared to chemical drugs **[28].** There is a lot of information available regarding the historical uses and the effectiveness of herbal products **[29]**. Currently, in many developed countries, the experimental use of medicinal plants and traditional medicine in the treatment of many diseases is common, including the treatment of wounds [30], blood pressure, diabetes, hyperlipidemia **[31],** anemia **[32]**, reproductive system functioning, and many other effects conditions **[33]**. A variety of plants in traditional medicine affect fertility. The most beneficial effect of medicinal plants on male reproductive function is related to the plants' antioxidant effects which improve spermatogenesis and steroidogenesis **[34].** Antioxidant compounds increase testosterone production, sperm count and motility which enhance male fertility **[35].** Studies have shown that some plants having androgenic, antioxidant and antiestrogen properties are influential in the treatment of infertility **[36]**. Moreover, it has been mentioned that these plants enhance male fertility by increasing sperm motility, production, and survival of motile spermatozoa **[37].** Medicinal plants also restore balance to the menstrual cycle hormones and p Studies on animals around the hyperglycemia caused some adverse effects on male reproductive function for change endocrine control **[38,39]**. Additionally, decreased Sertoli cell vacuolization **[40],** decreased sperm production **[41],** decreased fertility **[42]**, and the alteration of morphology and bulimia **[43]**. Decreased LH, FSH, and serum testosterone levels **[44]**,

decreased. The number of Leydig and Sertoli cells decreases and the number of cells Sperm **[45]** were observed in induced diabetes. Archaeology of the DM on the sperm did not appear only in the animal Models but also was presented in men. Furthermore, **[46]** reported a decrease in the Leydig cell. The number and function cells are weak in streptozosin (STZ) induced mice model of DM. The number of Leydig-associated cells in serum LH, which is partially explained by the alarm clock Effects of LH on Leydig Cells. This also indicates that Leydig Producing cells involving insulin and growth factor is similar to insulin 1 Signaling mechanisms mediated by LH **[47]**. While weak Cell function was measured by the loss of tyrosine phosphorylation, As well as decreased expression of GLUT-3 receptors, androgens Receptors and insulin-like growth factor 1 receptors **[48]**. This is the results supported by many other animal studies. WHO suggested that the practice of using traditional medicine to control fertility, rather than synthetic drugs, as cost-effective management of birth control **[49]**. Dactyloctenium aegyptium (D. aegyptium) is a common coarse herb belonging to the Poaceae family **[50]** and is commonly found all over the world. Herbal medicine is a common practice adopted in folk medicine and alternative medicine and has been used in the treatment of various disorders since ancient times [50]. According to **[51]**, about 80% of individuals from developing countries use traditional medicine to meet their primary health care needs.

Jordan is a country rich in plants with regard to the number of plant species **[52]**. It was recorded that 20% of the total plants in Jordan are medicinal plants **[53]** which are used in folk medicine and can be used in the pharmaceutical industry. Despite the lack of evidence-based safety and efficacy of herbal medicines, the use of herbal drugs is increasing in developing countries, including Jordan **[54]**. According to a survey conducted **[56]**., 92% of males with infertility problems in Jordan resort to herbalists to treat their problems. Celery (Apium graveolens L.) is a plant belonging to the Apiaceae family which originated from the Middle East and the Mediterranean, and is one of the most important vegetables worldwide **[57]**. Celery is widely cultivated owing to its low-calorie count and abundant celluloses, vitamins, and carotenes. Previous studies have found that celery

possesses numerous medicinal functions, such as inhibiting cancer cell growth and decreasing blood pressure **[58.59]**. Celery (*Apium graveolens*) is a mossy plant in the Apiaceae family that has been cultivated as a vegetable since ancient times. The celery contains a long-tailed fibrous stalk in the leaves. Depending on the location and varieties, their stems, leaves or hypocotyl are taken up and used in cooking. Celery seeds are also used as spices and their extracts are used in herbal medicines. In recent years, there has been renewed interest in plant medicine for the treatment against different diseases **[60.61].** Isolated studies screened various plants having "folk medicine reputation" by biochemical test for this antidiabetogenic effect **[62]**. A. graveolens extracts have different beneficial biological activities as reported by **[63]** concerning its antibiotic activity. The isolated compounds from the seeds exhibited antioxidant and inhibitory effects of cyclooxygenase and topoisomerase enzymes (type I and II) **[64].** Celery can have protective effects against substances such as sodium valproate, propylene glycol, and diethyl phthalate causing damages to the testicular structure and spermatogenesis **[65]** so that our study was dedicated to monitoring the fertility and some biochemical and hematological in alloxan-induced diabetic male rats under the hypoglycemic effects of celery seed extract.

2. MATERIALS AND METHODS

2.1 Plant Processing

Brown carmocarp seeds of A. graveolens were purchased from the local market (Amman). The seeds were planted in the greenhouse of the Department of Biological Sciences, Faculty of Science University of Jordan. The plant was taxonomically identified by direct comparison with authenticate sample and with the help of Prof. Dawoud Al-Eisawi, Department of Biological Sciences, University of Jordan. A voucher specimen (Number APO-05) was deposited at the Department of Pharmaceutical Sciences, Faculty of Pharmacy, University of Jordan. A. graveolen seeds (3 kg) were finely powdered and infused using hot water overnight. Plant materials were then extracted by Soxhlet apparatus using 96% ethanol for 2 h. The solvent was then distilled off under

reduced pressure below 50°C using Rotavapor. The dark brown residual extract which equals to 188 g was kept in the refrigerator at 4°C until use. The yield of the ethanol extract was 6.26%.

2.2 TLC screening

Plant extracts were applied to pre-coated TLC silica gel plates (silica gel 60 F 254, AluGram, Germany) developed in appropriate solvent systems and visualized using different reagents according to the type of secondary metabolites under investigation. Chromatograms were examined before and after spraying under UV and daylight to detect the presence of flavonoids, coumarins, alkaloids, and terpenes [Table 1].

2.3 Determination of the Median Lethal Dose (LD50)

The toxicity of the I. viscosa extract was evaluated by the calculation of intraperitoneal (i.p) LD50 which determines the dose that kills 50% of animals. The LD50 in rats was determined to evaluate the proper treatment dose to be used in this study. For the LD50 determination, BALB/c male mice (weight 20-25 g) were obtained from the Animal House of Al-Ahliyya Amman University. The LD50 for the Apium graveolens L extract was determined according to the method of Alawi and Jeryes (1982). Mice were divided into eight groups (ten mice each). The doses of the plant extract ranged from 200 mg/kg to 1000 mg/kg and were given i.p. Animal behavior was carefully observed for two hours, and the number of dead mice was counted in the experimental groups after twenty-four-hours. .

2.4 Toxicity and Fertility

In this part of the study, nine-week male Wistar rats were used. A total of twenty-four rats were randomly divided into three groups (eight rats each): Group I (high dose group) received 82.95 mg/kg (1/10 of the LD50 of the acetone extract of I. viscosa). Group II (low dose group) rats received 41.475 mg/kg (1/20 of the LD50 of the acetone extract). Group III (control group) received the vehicle of the acetone extract (100 µL of Dimethyl sulfoxide (DMSO) per rat daily). Rats received their I.P treatments once a day, and the treatment period lasted for sixty consecutive days in accordance with the WHO protocol (1983).

2.5 Animal Model This study was conducted with eighty experimental animals. All animals were housed, fed and treated in accordance with the in house guidelines for animal protection to minimize pain and discomfort. Adult albino rats (Sprague Dawely strain) weighing about 220 g each were used throughout the study. The animals were left for a week to adapt to the room conditions (temperature, humidity, light and dark period, aeration, and caging). Food and water were provided ad libitum. Animals were described as fasted were deprived of food for at least 12 h but were allowed free access to drinking water.

2.6 Alloxan induce hyperglycemia

Rats were made diabetic by injecting alloxan monohydrate "B.O.H chemical LTD England" intraperitoneally at a dose of 150ml/kg (dissolved in fresh normal saline) to 18h fasted rat. Every week after injection, blood was collected from the hearts of all surviving rats and blood glucose levels were determined. Rats with blood sugar levels of 200 to 450mg/100 ml were considered as diabetic and were used in the study.

2.7 Experimental Design

The eighty rats were randomly assigned to 8 experimental groups of 10 rats each:

Group I received normal saline (0.5 ml/kg) and serves as a control. Group II and III - gavaged daily for thirty days with 1ml of the ethanol extract at doses of 213 mg/kg and 425 mg/kg body wt and served as control. Group IV group Rats were made diabetic by injecting alloxan monohydrate "B.O.H chemical LTD England" intraperitoneally at a dose of 150ml/kg (dissolved in fresh normal saline) to 18h fasted rat. Every week after injection, blood was collected from the hearts of all surviving rats and blood glucose levels were determined. Rats with blood sugar levels of 200 to 450mg/100 ml were considered as diabetic and were used in the study. Rats of experimental groups V, IV, IIV, IIIV were treated intraperitoneally with 1 ml of Apium graveolens ethanol extract at doses of (213 and 425 mg/kg, 200mg/kg of aqueous extract and 14.2 mg/kg of metformin body wt, respectively, once a day for thirty consecutive days.

Metformin was purchased from Bristol-Myers Squibb Company, UK. The seed extract and metformin were given daily, using an intragastric tube for 6 weeks. All rats were maintained in these treatment regimens for six weeks with free access to food and water. At the end of the experimental period, blood samples were taken from these experimental rats by cardiac puncture protocol. Rats were sacrificed by cervical dislocation under light ether anesthesia. These experiments complied with the guidelines of our animal ethics committee, which was established in accordance with the internationally accepted principles for laboratory animal use and care.

2.8 Blood Sample Collection

Blood Sample Collection By the end of each experiment, the rats were reweighed, starved for 24 hours and sacrificed under chloroform anesthesia. 5 ml of blood was Mans and Aburjai; JPRI, 26(6): 1-10, 2019; Article no.JPRI.47971 4 collected from each animal by cardiac puncture using sterile needle and syringe. Part of the blood sample was put into test tubes and allowed to clot for 30 minutes before centrifuging using a bench top centrifuge (Cenformix). The remaining blood sample was put in an EDTA bottle for hematological determinations.

2.9 Assessment of sperm motility and testes

One of caudal epidermal and testis was taken immediately and minced into two halves by a sharp blade, one half was taken and immersed in one ml of physiological saline and this solution was kept in 37°C.After gentle mixing a drop of this solution. It was taken on a neubauer chamber and then assessed for sperm motility as percent this was determined by counting both motile and nonmotile spermatozoa in different fields. All the solutions and instruments that were used in this experiment were kept in an incubator at 37°C (Ali. 2002).

2.10 Assessment of sperm count

The control and treated rats were sacrificed by cervical dislocation under light ether anesthesia and the following measurements were recorded, testicular weight, body weight, epididymis and testicular sperm count for treated and control groups. The excised left testes and

epididymis from each rat was put in 20ml of normal saline (0.9% sodium chloride) and homogenized for sperm count. The epididymis was put in 15 ml of normal saline (0.9% sodium chloride) and homogenized for epididymis sperm count. Sperm count was preformed according to the method of Amann and Lambaise, 1969 as follows: Testis and epididymis for each rat were sectioned by disposable blade in 20ml of normal saline in Petri dish, then minced using manual glass homogenize, the homogenate was placed in a hemocytometer chamber epididymis sperm count were evaluated and expressed as number of sperm per gram of epididymis, testicular sperm were calculated and expressed as a number of spermatids per gram of testis. The estimate was of daily sperm production (DSP) in testis per day, and per gram of testis each day "efficiency" estimate on calculated based on a factor of 6.1 (Amann et al., 1994) which is the duration of the somniferous cycle during which developing spermatozoa in the spermatic stage.

2.11 Hematological Analysis

The CBC was performed on an automated hematology analyzer using well mixed whole blood to which EDTA was added to prevent clotting. (ESR) determined by Wintergreen method, differential WBC count was performed on Giemsa stained blood smears. Total protein, albumin, urea, uric acid, and creatinine analyses Total protein, albumin, blood urea, uric acid, and creatinine levels were also determined by using Bio-Merieux Kit (Bio- Meraux Lab reagent and product, France). Serum Insulin determination was measured by radioimmunoassay methods (CEA-JRE-SORIN Firm, France)

2.12 Biochemical Analysis

Serum glucose and lipid profile, including total cholesterol (TC); triglycerides (TG); high-density lipoprotein cholesterol (HDL-c) and low-density lipoprotein cholesterol (LDL-c) was determined by using commercial analytical kits from Sigma (St. Louis, Mo, USA).

2.13 Hormonal Analysis

All plasma samples were assayed for hormones using enzyme-linked immunoassay methodology (ELISA) and the absorbency was read at 450 nm as described

previously . The ELISA kits were obtained from Dia Metra (Italy).

2.14 Statistical analysis

The results were expressed as mean ± standard deviation. Differences between control and experimental groups were estimated using students t-test analysis. Within-group comparisons were performed by analysis of variance using the ANOVA test. Differences were considered significant if P-value was less than 0.05.

RESULTS

Chromatograms were examined before and after spraying under UV and daylight to detect the presence of flavonoids, coumarins, alkaloids, and terpenes **(Table 1)**. Upon gavaging the animals in control and vehicle groups with one ml of the solutions, the number of survived animals were recorded after 24 h of treatment. Animals were gavaged with one ml of the prepared doses; 30, 40, 50, 60, 70, 80, 85, 90, 95, 100 mg/20 g. After 24 h of injection, the dead and survived animals were recorded. Changes in body weight in all groups are shown in **(Table 2).** Significant ($P \leq 0.05$) weight loss was observed in treated diabetic rats than untreated normal rats. Treatment with 1ml of the extract at doses of 213, 425 mg/kg body wt, 200 mg/kg of aqueous extract and 14.2 mg/kg of metformin respectively improved the weight of Apium graveolens L ht gain compared to untreated diabetic rats. The treatment effect of Apium graveolens L extract on body weight in the alloxan induced diabetic rats; all rats were monitored for gain in body weight. The control group (I) gained weight over the four weeks of the experimental period, with the mean body weight increasing by 40g after 4 weeks **(Table 3**). In contrast, the untreated diabetic group (II) lost an average of 20 g after 4 weeks ($p<0.05$). Treatment with methanolic resulted in significant weight gain to levels approaching the control group. Water and food intake in untreated diabetic group was significantly higher than that of the control group **(Table 4).** On the other hand, there were significant decreases in water and food intake in treated diabetic groups compared to the untreated diabetic group during the entire period of the experiment ($p<0.05$). The sexual

hormones FSH, Testosterone and LH levels, the sperm count and motility were significantly reduced in all diabetic groups in **table 5** ($p<0.05$). The Administration of alloxan to male rats induced diabetes and significantly increased the glucose and reduced the insulin **(Table 6).** Treating diabetic with ethanol seed extract and metformin had significantly ($p < 0.05$) increased the levels of insulin, FSH, and testosterone, but no significant increase in the levels of LH. Similarly, significant increase in testis and testes weights, sperm count and motility were also indicated and shown in **tables (6 and 7)**. Significant increase in testis and epididymis weights, sperm count and motility were also indicated and shown in Table (4). The administration of the extract at a dose of 425 mg/kg body wt indicates a significant decrease ($p<0.05$) of blood glucose concentration and the increase of serum insulin was found to be antidiabetic. None of the animals treated with extract showed any visible serious symptoms of toxicity; however, there were mild signs of respiratory distress, diarrhea, and convulsions. This indicates that A. graveolens seed extract may not cause any toxic effect on the body. It was also found that the RBC and WBC count, PCV, and neutrophil percentage significantly decreased (p**<0.05) (Table 6)**. The oral administration of 213 and 425 mg/kg of methanolic extract, 200mg/kg of aqueous extract and 14.2 mg/kg of metformin body wt respectively significantly increased (p**<0.05)** RBC, PCV, ESR, and neutrophil percentage in diabetic rats. However, the WBC count of the A. graveolens seed extract - treated diabetic group was still lower than those of control values (Table 6). In this study, it has also been observed that there is a significant decrease in the concentration of total cholesterol, triglycerides, LDL cholesterol and a significant increase in HDL cholesterol in the treated groups with 213 and 425 mg/kg of methanolic extract, 200mg/kg of aqueous extract and 14.2 mg/kg of metformin body wt **(Table 8).**

Table 1: Phytochemical screening of ethanol extracts of *Apium graveolens L*

Compound	Ethanol Extract
Flavonoids	+++
Coumarins	++
Alkaloids	-
Tetranoides	+++

Table 2: Table 2: Result of the LD50 experiment

Dose (mg/20g)	30	40	50	60	70	80	85	90	95	100
Total number of the group	7	7	7	7	7	7	7	7	7	7
Number of animals died	0	1	2	1	3	1	1	6	6	7
Number of animals survived	7	6	5	6	4	6	6	1	1	0
Sg	42	35	29	24	18	14	8	2	1	0
Ds	0	1	3	4	7	8	9	15	21	28
Sg + DS	42	36	32	28	15	22	17	17	22	28
Mortality= DS/(Sg+Ds)X 100%	0	3	9	14	28	36	53	88	95	100

Sg: Number of mice survived at this dose and higher doses; Ds: Number of mice died at this dose and lower doses

Table 3: Effect of oral administration of *Apium graveolens L* extract for four weeks on body weight (g) in Alloxan-induced diabetic male rats

Group	Treatment	Initial (g)	2 weeks (g)	4 weeks (g)	Gain in body weight (g)
I	(Control)	220 ± 4.6	240 ± 3.25**	264 ± 4.55**	44 ± 0.1
II	ethanol extract at dose of 213 mg/kg	218 ± 5.3	229 ±4.8 **	254 ±5.65**	36 ± 0.4
III	ethanol extract at doses of 425 mg/kg	215 ± 6.8	232 ± 4.8 5**	256 ± 7.2 5**	41 ± 0.4
IV	(Diabetic Rats)	218± 5.75	198 ±6.2 **	176 ±5.9**	-42± 0.2
V	(Diabetic group treated with methanol extract dose of 213 mg/kg	186±6.2	198 ±4.6**	211 ±7.6**	25 ± 1.4
VI	(Diabetic group treated with methanol extract dose of 425 mg/kg	182 ± 4.5	202 ±6.4 **	216 ± 6.3 **	34± 1.8
VII	(Diabetic group treated with 200mg/kg of aqueous extract dose of 200 mg/kg	178 ± 5.8	192 ± 6.2 **	208 ± 6.4**	30 ± 0.6
VIII	(Diabetic group treated with 14.2 mg/kg of metformin body wt	182 ±4.8	200 ± 4.6 **	216 ± 5.6 **	34± 0.8

Values are the mean values ± standard deviation of 10 rats; **: Statistically significant when compared to untreated diabetic group (II) at ($p<0.05$).

Table 4: Effect of oral administration of *Apium graveolens L* extract for four weeks on food intake (g) and water intake (ml) in Alloxan-induced diabetic male rats

Group	Treatment	Water intake (ml) / day	Food intake (g) / day
I	(Control)	26.6 ±4.2	14.6±2.2
II	ethanol extract at dose of 213 mg/kg	28.2 ±2.6	16.2 ±2.8
III	ethanol extract at doses of 425 mg/kg	24.7± 1.9	17.4± 3.1
IV	(Diabetic Rats)	68 .6± 18.3	21.6± 4.2
V	(Diabetic group treated with methanol extract dose of 213 mg/kg	37 .4± 8.9	16.9±1.6
VI	(Diabetic group treated with methanol extract dose of 425 mg/kg	42.3±9.4	18.6 ±2.5
VI	(Diabetic group treated with 200mg/kg of aqueous extract dose of 200 mg/kg	38.4±6.6	20 .7±3.7
VI	(Diabetic group treated with 14.2 mg/kg of metformin body wt	34.2 ±5.4	16.8 ± 1.4

Values are the mean values ± standard deviation of 10 rats; **: Statistically significant when compared to untreated diabetic group (II) at ($p<0.05$).

Table 5; Effect of ethanol extract of *A. graveolens seeds* on levels of blood testosterone, FSH and LH of rats in experimental and control groups

Groups and Treatments	Treatments	Testosterone (ng/ml)	FSH([ng/mL)	LH levels [ng/mL]
I	(Control)	1.44 ± 0.53	21.64± 2.65	1.61± 0.43
II	ethanol extract at dose of 213 mg/kg	1.53± 0.72	22.43± 1.18	1.63± 0.54
III	ethanol extract at doses of 425 mg/kg	1.55± 0.68	21.92 ± 2.22	1.62± 0.19
IV	Diabetic Rats Alloxan (150 mg/kg)	1.18** ± 0.34	18.37 ± 1.52**	1.38 ± 0.13**
V	Diabetic group treated with methanol extract dose of 213 mg/kg	1.29** ± 0.51	20.66± 1. 77**	1.44± 0.116
V1	VI(Diabetic group treated with methanol extract dose of 425 mg/kg	1.31** ± 0.62	19.86± 1.36**	1.45 ± 0.126
VI1	Diabetic group treated with 200mg/kg of aqueous extract dose of 200 mg/kg	1.34** ± 0.42	19.76± 1.74**	1.41 ± 0.67
VI11	Diabetic group treated with 14.2 mg/kg of metformin body wt	1.46** ± 0.79	20.65± 1.35**	1.42 ± 0.25

Values are the mean values ± standard deviation of 10 rats; **: Statistically significant when compared to untreated diabetic group (II) at ($p<0.05$)

Table 6: Effects of ethanol extract of *A. graveolens seeds* on levels on levels of blood glucose and insulin of rats in experimental and control groups

Groups and Treatments	Treatments	Glucose level (mg/dL)	Insulin level (µU/ml)
I	Control	86.4 ± 5.3	6.82 ± 1.7
II	ethanol extract at dose of 213 mg/kg	92.6 ± 7.3	6.45 ± 1.8
III	ethanol extract at doses of 425 mg/kg	91.8 ± 9.2	6.66± 1.5
IV	Diabetic Rats Allegan (150 mg/kg)	238.55** ± 18.34	3.63** ± 1.5
V	Diabetic group treated with methanol extract dose of 213 mg/kg	202.55** ± 11.23	4.78 * ± 1.5
V1	VI(Diabetic group treated with methanol extract dose of 425 mg/kg	198.67** ± 11.46	5.15** ± 1.3
VI1	Diabetic group treated with 200mg/kg of aqueous extract dose of 200 mg/kg	208.44** ± 13.8	4.92** ± 1.2
VI11	Diabetic group treated with 14.2 mg/kg of metformin body wt	212.65* ± 9. 8	4.68 ± 1.9

Values are the mean values ± standard deviation of 10 rats; **: Statistically significant when compared to untreated diabetic group (II) at ($p<0.05$)

Table 7: Effect of ethanol extracts of A. graveolens seeds on weight of testis, sperm count and motility of rats in experimental and control groups

Group	Treatment	Testis weight (Gram)	Sperm count million/mL	Sperm Motility
I	Control	1.38 ± 0.12	26.66± 4.45	1.56± 0.14
II	ethanol extract at a dose of 213 mg/kg	1.42± 0.18	24.72± 4.77	1.62± 0.13
III	ethanol extract at doses of 425 mg/kg	1.39± 0.7	22.62± 3.88	1.60± 0.16
IV	Diabetic Rats Allegan (150 mg/kg)	1.13** ± 0.27	16.24 ± 44 **	1.34 ± 0.15**
V	Diabetic group treated with methanol extract dose of 213 mg/kg	1.34 ± 0.18	20.45± 4.67	1.41 ± 0.126
VI	VI(Diabetic group treated with methanol extract dose of 425 mg/kg	1.32 ± 0.55	19.77± 4.66	1..39 ± 0.91
VII	Diabetic group treated with 200mg/kg of aqueous extract dose of	1.34 ± 0.18	18.85± 2.77	1.40 ± 0.156
VIII	Diabetic group treated with 14.2 mg/kg of metformin body wt	1.30 ± 0.41	19.57± 4.87	1.38 ± 0.176

Table 8: Effect of ethanol and aqueous extracts of A. graveolens seeds on some hematological parameters of rats in experimental and control groups

Groups	Treatment	RBC (x 106 µ)	Hb (g/dL)	Neutrophils %	Lymphocytes %
I	(Control)	7.3±1. 5	15.3±1.2	46 ±4.6	48±6.4
II	ethanol extract at dose of 213 mg/kg	6.9±0.8	15.6±1.4	48 ±4.5	46±5.9
III	ethanol extract at doses of 425 mg/kg	4.8±0.4	15.7±1.9	45 ±6.6	46±2.5
IV	Diabetic Rats Alloxan (150 mg/kg)	5.2±0.6	11.4±1.8	38 ± 3.2	37±4.2
V	Diabetic group treated with methanol extract dose of 213 mg/kg	6.6±0.7	14.2±1.6	39 ± 5.9	47±6.3
VI	Diabetic group treated with methanol extract dose of 425 mg/kg	6.4±0.4	14.4±1.7	41.94± 7.3	51±9.5
VII	Diabetic group treated with 200mg/kg of aqueous extract dose of 200 mg/kg	5.9±0.3	13.9±1.5	42.82± 8.2	44±3.8
VII	Diabetic group treated with 14.2 mg/kg of metformin body	5.7±0.5	13.2±1.4	40.45± 6.8	42±6.4

Table 9: Effect of ethanol extract of *A. graveolens seeds* on levels of serum cholesterol, triglycerides, LDL and HDL of rats in experimental and control groups

Groups and Treatments	Treatments	Serum Cholesterol mg/dl	Serum triglycerides mg/dl	Serum H DL mg/dl	Serum LDL mg/dl
I	(Control)	162.45± 5.92	74.66 ± 9.65	33.62± 2.43	67.33± 8.66
II	ethanol extract at dose of 213 mg/kg	158.55± 4.65	88,76. ± 6.18	32.82± 8.24	63.76± 4.54
III	ethanol extract at doses of 425 mg/kg	160.72± 6.42	78 1.92 ± 7.22	30.47± 3.65	72.75± 6.77
IV	Diabetic Rats Alloxan (150 mg/kg)	262.88 ±16.56	133,76. ± 6.18	28.33± 4.78	122.63± 16.58
V	Diabetic group treated with methanol extract dose of 213 mg/kg	221.76**±12.87	100.77± 9.45	31.51± 4.46	88.95± 8.19
V1	VI(Diabetic group treated with methanol extract dose of 425 mg/kg	218.59**±14.88	104.65± 11.32	30.22± 5.91	84.43± 11.47
VI1	Diabetic group treated with 200mg/kg of aqueous extract dose of 200 mg/kg	228,.63**±12.67	108.92± 14.84	32.44± 6.55	80.82± 12.34
VI11	Diabetic group treated with 14.2 mg/kg of metformin body wt	212,.56**±14.77	92.88. ± 12.45	29.66± 6.55	102..78± 16.33

Values are the mean values ± standard deviation of 10 rats; **: Statistically significant when compared to untreated diabetic group (II) at ($p<0.05$).

DISCUSSION

A variety of plants in traditional medicine affect fertility. The most beneficial effect of medicinal plants on male reproductive function is related to the plants' antioxidant effects which improve spermatogenesis and steroidogenesis [66]. Antioxidant compounds increase testosterone production, sperm count and motility which enhance male fertility **[67].** Studies have shown that some plants having androgenic, antioxidant and antiestrogen properties are influential in the treatment of infertility **[68].** Moreover, it has been mentioned that these plants enhance male fertility by increasing sperm motility, production, and survival of motile spermatozoa **[69].** Medicinal plants also restore balance to the menstrual cycle hormones and provide an appropriate environment to facilitate a durable pregnancy and thus promoting fertility in females **[70].** This study aimed to assess the effects of an ethanol extract derived from the seed of A. graveolens L. on the fertility of male diabetic rats by measuring various parameters of fertility. After injection of alloxan in male rats, our results showed that blood glucose level, significantly increased, but body weight gain decreased as compared with that in the control groups. These changes are the normal effect of diabetes mellitus. Furthermore, results also showed that administration of 1ml of the extract at doses of 213 or 425 mg/kg in alloxan - diabetic rats resulted in lowering of blood glucose levels and improving body weight gaining with no apparent side effect. These data may support the hypothesis that a component of ethanol and aqueous extracts derived from the seed of A. graveolens L. (Apiaceae) might improve the diabetic status by reversing the action of alloxan and thus restoring β-cells integrity and metabolic function that are responsible for the synthesis of insulin. In our study, the decrease in serum insulin was related to the destruction of β-cells by alloxan necrotic effect. Alloxan liberates toxic amounts of nitric oxide that inhibit aconitase activity and participates in DNA damage of pancreatic cells thus inducing diabetes mellitus in rats **[71].** It is

well known that diabetes is positively associated with lowered male fertility and sexual dysfunction. **[72]** concluded that the neuropathy and vascular abnormality caused by diabetes may be related to sexual dysfunction. In our study, we measured the levels of male sexual hormones FSH, testosterone, and Luteinizing hormone (LH) in 8 groups in the study. The obtained results showed that the administration of alloxan to male rats induced diabetes and significantly reduced the sex organ weights, testosterone levels, FSH and LH. In contrast, the ethanol and aqueous seed extract and metformin-treated rats had significantly ($p < 0.05$) improved levels of insulin, FSH, testosterone levels, with no significant increase in the levels of Luteinizing hormone (LH). The seed extract and metformin can cause a significant recovery in blood glucose level and regeneration of beta cells as proposed earlier by previous study [73] (Golalipour et al., 2007; Karou et al., 2011[74]). The other possible mechanism is related to oxidative stress. The oxidative stress is widely accepted as playing a key direct role in the pathogenesis of various diabetic complications [75] Baynes, J et al., 1999; Gautama, D.K et al., 2006; ([76).

Diabetes-induced alterations of Leydig cell functions include a decrease in androgen synthesis and in the total number of these cells (K ongkanand A et al. 2000 ([77]) The alterations of Leydig cells in diabetes are related to mechanisms that modulate the proliferation, differentiation and overall Leydig cell functions **[78].** Furthermore, diabetes-related alterations in Leydig cells are also related to changes in the pituitary–testicular axis **[79].** The decrease in serum levels of luteinizing hormone (LH) that is responsible for normal Leydig cell function **[80].** These are in agreement with recent published report which indicated that the induction of diabetes by high doses of STZ in adult male rats decreased testosterone production, suggesting a decrease in the total number of Leydig cells **[81].** Ethanol extract-treated and metformin-treated diabetic rats exhibited significant ($p < 0.05$) improvement in the levels

of insulin, FSH, testosterone levels, with no significant increase in the levels of Luteinizing hormone (LH). The improvement of reproductive functions in male rats by ethanol seed extract and metformin is linked to its antioxidant, androgenic and antidiabetic activity evidenced by hypoglycemia and hyperinsulinemia.

Celery suppresses overproduction of stomach secretions. Other compounds in celery such as flavonoids, tannins, volatile oils, alkaloids, sterols, and triterpenes have protective effects against diseases-induced gastric damage **[82].** It has been shown that celery contains ingredients which reduce blood pressure and increase heart rate in patients with hypertension **[83].** Studies have demonstrated that the celery leaf extract can be effective in reducing hyperthyroidism by adjusting the level of thyroid hormones such as T3, T4, and TSH. Coumarin compounds in the celery reduce thyroid activity by blocking the conversion of T4 into T3 outside the thyroid gland and increase TSH secretion **[84].** Kooti et al **[85].** study on the effect of hydroalcoholic extract of celery seeds at doses of 200, 400, and 800 mg/kg showed that the extract injection at a dose of 400 mg/kg significantly increases the testosterone levels (p0.05). The results of this study showed that the consumption of this plant causes no hormonal disorders in males Modarresi et al **[86].** examined the effect of celery leaf extract on sex hormones in the male mice. The impact of hydroalcoholic extract of the celery leaf on the pituitary-gonadal axis was investigated in the male rats. The extract was administered for 20 days in different doses of 50, 100, and 150 mg/kg. The findings suggested that the concentration of FSH in the group receiving the extract with doses of 100 and 150 mg/kg reduced, while the concentration of LH and testosterone decreased in all experimental groups ((p<0.05). The results of this study showed that the consumption of celery seeds in appropriate doses can have a positive effect on spermatogenesis **[87].** Hala et al. 2011 **[88]** examined the protective effect of the seeds oil of three plants of

celery, fennel, and flax in rats exposed to sodium valproate. The results showed a significant increase in testicular weight, increased sperm number and motility, and decreased abnormal sperms in the treated group ($p<0.01$). Also, it increased serum testosterone levels and reduced testicular lipid peroxides such as malondialdehyde (MDA), and increased glutathione content was reported in the treatment group (($p>0.05$). It was also reported that in both groups receiving doses of 100 and 200 mg/kg compared to the controls, the number of primary spermatocytes and sperms greatly increased, while the lumen diameter decreased. However, the number of Sertoli cells only significantly increased in the group receiving the extract with a dose of 200 mg/kg compared with the control group ($p<0.05$). In Hardani et al. study, the effects of administrating doses of 100 and 200 mg/kg of the aqueous extract of celery leaf on spermatogenesis were examined and studied for 1 month in healthy male rats. In addition, it was observed that the weight of the testicles, the tail of the epididymis, and vas deferens increased in both groups, while only the weight of the epididymis in the high-dose group was statistically significant ($p\leq0.05$). However, the testicular volumes in both groups significantly increased compared with the control group ($p\leq0.001$). The study results showed that the injection of this extract may improve the spermatogenesis process and will be useful for some of the parameters of sperm fertility **[89].** To examine the protective effects of celery against sodium valproate toxicity, Hamza et al. injected a dose of 200 mg/kg of the extract to the rats within 23 days. It was observed that the herb increases sperm motility with no obvious impact on the increased sperm count. It was also reported that the plant reduced the FSH levels, but had no effect on testosterone levels. Because of having antioxidant properties, the plant has protective effects against damage caused by oxidative stress in the testicles through normalization of SOD and increasing MDA and GSH levels. As a result, we can say that the extract derived from the celery

leaves significantly reduces the intensity of reproductive toxicity of sodium valproate in male rats [90].

This study suggested that [1] celery extract makes significant changes in the experimental groups when compared with control group, so that oral administration of 100 and 200 mg/kg of extract to male rats for 30 days, caused a significant increase in the diameter of the tubules, the number of spermatogonia, spermatocytes, and spermatozoids as well as testis volume. However, significant increases in the number of spermatids and the weight of cauda epididymis were observed in rats fed by gavage at a dose of 200 mg/kg of celery extract. According to the present study, oral administration of leaf extract of celery can increase the fertility of male rats. These results are compatible with the traditional medicine concepts, indicating that the enhanced sexual performance is achieved by taking the celery extract, in men. Therefore, the increase in testis weight and size in groups administered the extract could be attributed to the increase in the number of cells in the testis. Moreover, with the increase of these cells, it could be concluded that these extracts cause an increase in the metabolism of male reproductive tissues. On the other hand, given that the weight of sexual organs can also be affected by sex hormones [91]., this extract may be effective by affecting the pituitary gland and increasing the sex hormones. Moreover, given that the process of spermatogenesis and the function of reproductive organs are related to sex hormone secretion, the absorptive and secretory functions of the testes and epididymis could be enhanced **[92, 93].** This may explain the increased number of spermatozoids in the cauda epididymis and the increase in epididymal weight at a high dose of the extract, in addition to increases in size and number of cells in the testes **[94].** Thus, the sperm count is influenced by any change in the absorptive and secretory functions of the testis and epididymis. The finding that ethanol extract derived from seed of A. graveolens improves the diabetic status of alloxan diabetic male rats in comparison with untreated diabetic male rats favors

the contention that the antioxidant pathway is a key player in enhancing ß-cell function and growth. In addition, we cannot exclude that this extract might also directly improve the functional and structural integrity of testicular tissues by removing free radicals and enhancing antioxidant defense capacity of these cells. Sperm counts were significantly decreased ($P < 0.05$) in diabetic rats. In contrast, sperm counts significantly increased ($P < 0.05$) in diabetic rats treated with ethanol extract and metformin compared with those of diabetic rats who sustained a significant reduction of caudal sperm count. The reduction of sperm count in diabetic rats appeared through oxidative stress and overproduction of reactive oxygen species generated due to hyperglycemia **[95, 96].** **[97]** reported that the decrease in sperm count can be attributed to the influence of hyperglycemia on late stages of spermatogenesis, possibly through an increase of reactive oxygen species**.** **[98]** indicated that the increased hydroperoxide level can affect the spermatogenesis process since germ cells are more susceptible to peroxidative damage. The promotion of the production of testosterone in treated rats reported to play a vital role in the regulation of fluid dynamics of the testis, commencing with blood flow and vasomotion and ending with the production of somniferous tubular fluid **[99]** . In conclusion, our study indicates that alloxan administration induces hyperglycemia in addition to defects in fertility and in productive organs in male diabetic rats. In contrast, treatment with ethanol extracts of Apium graveolens and metformin exhibit antihyperglycemic and spermatogenic activities in alloxan-induced diabetic male rats. Another factor of this study was its sole reliance on celery leaf without a comparison with celery seed. Celery seed extract can lead to decreased blood glucose levels and increased serum insulin levels in diabetic rats **[100].** Celery seeds contain the flavonoids apigenin, luteolin, and phenolics **[101**]. Apigenin inhibits the aldose reductase enzyme **[102].** This enzyme is a key enzyme in the

polyol pathway (sorbitol-aldose-reductase pathway). The polyol pathway is a process that converts glucose to sorbitol. Increased levels of sorbitol in diabetic patients will lead to complications such as cataracts, retinopathy, and neuropathy. Therefore, celery can be used as an anti-diabetic to prevent diabetic complications **[103].** Celery seeds possess anti-diabetic properties, and they stimulate increased insulin secretion by pancreatic beta cells as well as decreased gluconeogenesis in the liver **[104].** The present study indicated that ethanol extract of A. graveolens or metformin treatment might ameliorate some disturbed hematological parameters of diabetic rats. It has been suggested that anemia occurrence in DM is due to the increased non-enzymatic glycosylation of RBC membrane proteins, which correlates with hyperglycemia **[105].** Oxidation of these glycosylated membrane proteins and hyperglycemia in DM caused an increase in the production of lipid peroxides causing the hemolysis of RBC. In this study, the RBC membrane lipid peroxide levels in diabetic rats were not measured. However, **[106]** demonstrated that serum lipid peroxide level increased in diabetic rabbits. Thus, increased RBC count of ethanol extract of A. graveolens or metformin treatment rats could be due to the lowered lipid peroxide level in RBC membrane leading to decreased susceptibility of RBC to hemolysis. Since non-enzymatic glycosylations of membrane proteins correlate with hyperglycemia **[107]** it might be suggested that ethanol extract of A. graveolens or metformin produced its effect by decreasing the elevated glucose. However, more studies by measuring the RBC fragility, and serum folic acid, iron, cobalt, vitamin B12, and calcium levels are needed to demonstrate the exact mechanism of action of ethanol extract of A. graveolens or metformin on increased RBC count of diabetic rats. Neutrophils ingest and kill bacteria and have been called the body's first line of defense against bacterial infections **[108].** It has been postulated that the body's defense mechanism against infections was disturbed due to the disturbed neutrophil

function in diabetes **[109].** In this study, we demonstrated that ethanol extract of A. graveolens or metformin treatment increased the lowered neutrophil percentage of WBC to the level of control. This result indicated that ethanol extract of A. graveolens or metformin treatment might also increase the defense mechanism of the body against infections. In diabetic rats, Alloxan-induced diabetes increased the heart rate while ethanol extract of A. graveolens or metformin treatment decreased it to control level. The increased heart rate in diabetic rats was probably due to the increased sympathetic output produced by diabetes-induced anemia. In the present study, it was found that the heart rate decreased and also RBC count increased to control level in ethanol. Extract of A. graveolens or metformin-treated rats. Therefore, the decreased heart rate could also be due to a normalized RBC count in these rats. We have noticed elevated serum lipids in alloxan-diabetic rats. Lipids play an important role in the pathogenesis of diabetes mellitus. The level of serum lipids is usually raised in diabetes and such an elevation represents a risk factor for coronary heart disease **[110].** Lowering of serum lipids levels through dietary or drugs therapy seems to be associated with a decrease in the risk of vascular disease **[111].** The abnormal high concentration of serum lipids in diabetes is mainly due to the increase in the mobilization of fatty acids from the peripheral depots since insulin inhibits the hormone-sensitive lipase. On the other hand, glucagon, catecholamine, and other hormones enhance lipolysis. The marked hyperlipidemia that characterizes the diabetic state may, therefore, be regarded as a consequence of the uninhibited actions of lipolytic hormones on the fat depots **[112].** In addition to marked hyperglycemia, our result revealed that the alloxan-induced diabetic rats developed notable hyperlipidaemia. Diabetes-induced hyperlipidaemia was observed in diabetic experimental animal models, and it is associated with an increase of mobilization of fat from fat cells and lipid metabolism due to the inability to utilize glucose properly **[113].** This is very important since elevated

concentrations of cholesterol, triglyceride, and LDL-C are important risk factors in the development of arterioscleroses in diabetes mellitus. In our study, we have also observed an increase in the concentration of total cholesterol, triglycerides, LDL cholesterol and TC/HDL-C in alloxan untreated diabetic rats. Hyperlipidemia is a recognized consequence of diabetes mellitus **[114].** Administration of ethanol extract of A. graveolens or metformin normalized serum lipids, secondary to the diabetic state. Diabetes-induced hyperlipidemia is attributable to the excess mobilization of fat from the adipose due to the underutilization of glucose **[115].** The ability of ethanol extract of A. graveolens or metformin reduces the levels of plasma lipids in diabetic rats by increasing the utilization of glucose, thereby depressing the mobilization of fat. Our findings are consistent with a recent study by Pepato et al. **[116]** who reported that leaves of Leucas cephalotes lowered both plasma and hepatic lipid profiles (total lipid, triglycerides, and cholesterol) and LDL-C while elevating the HDL-C levels. They suggest that these improvements in lipid profiles are most likely due to the insulin-like actions of the leaves extract. Similarly, a previous study done by Pepato et al. **[116]** reported that DM patients taking insulin injection showed not only the elevation of lipoprotein lipase activity but also lowers the plasma triglyceride concentrations. Thus, it can be concluded that the enhancement of insulin secretion or level is accompanied by the enhancement of glucose utilization as well as a reduction of lipid level in diabetic rats. It is possible to suggest that the mechanism(s) of the antihyperlipidemic effect of the ethanol extract of A. graveolens might be similar to some of those suggested for anti-diabetic plants exhibiting antihyperlipidemic activity, such as activation of lipoprotein lipase, insulin-mediated lipolytic activity or inhibition of lipogenic enzymes or hormone-sensitive lipase **[117].** Similar results were observed in the effect of ethanol extract of Iris germanica L. rhizomes (Iridaceous), they indicated that ethanol extract of Iris

germanica has remarkably lowered the lipid components, particularly, the cholesterol and triglycerides **[118].** Other researchers showed also that celery seed extract helped in the support of healthy blood pressure and cholesterol levels because of its beneficial effect on prostaglandin levels. Le and Elliott **[119]** at the University of Chicago Medical Center identified it as the factor in celery responsible for the blood pressure lowering effect of celery. The results suggest that the lipid-lowering action of this natural product may be mediated through inhibition of hepatic cholesterol biosynthesis, increased faucal bile acids excretion, and enhanced plasma lecithin: cholesterol acyltransferase activity, and reduction of lipid absorption in the intestine. Our study also showed a significant decrease in serum total protein and albumin in untreated diabetic rats, whereas total protein and albumin significantly increased after the administration of this extract. The total protein and albumin levels in the blood can also be used as an indicator of liver function. Similar results were obtained when the metformin was administered orally in alloxan diabetic. These results suggest that this extract can improve some biochemical parameters that are related to liver functions. Hyperglycemia has also been recently implicated in the initiation and development of various types of diabetic complications. Nephropathy is one of these serious microvascular complications that have been observed in diabetic individuals **[119].** In addition, blood urea and creatinine concentrations were increased among uncontrolled diabetic individuals and this increase could be a result of impaired renal function due to an increased blood glucose level **[120].** Our results revealed for the first time that the mean values of these end products in that serum increased in untreated diabetic rats, while they significantly decreased after the administration of extracts. Thus, this extract might improve renal function which, in turn, leads to a reduction in these end products. It was reported that diabetic individuals had lower serum albumin concentrations as well as higher serum uric acid and urea

levels than nondiabetic individuals **[121, 122].** Thus, the reduction in urea and creatinine levels probably can be explained by a reduction in blood glucose level. In conclusion, the present study indicates that the ethanol extract of A. graveolens appears to exhibit hypoglycemic and hypolipidemic activities in alloxan-induced diabetic rats. In conclusion, our study indicates that alloxan administration induces hyperglycemia in addition to defects in fertility and in productive organs in male diabetic rats. In contrast, treatment with ethanol extracts of Apium graveolens and metformin exhibit antihyperglycemic and spermatogenic activities in alloxan-induced diabetic male rats.

CONCLUSION

The ethanol extracts of A. graveolens seeds displayed hypoglycemic and spermatogenic activities and may have the potentials of being developed into a male fertility enhancing drug.

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