

## The antihyperglycemic and antihyperlipidemic effect of ethanolic extract of *Apium Graveolens* (celery) in Streptozocin/ high fat diet induced hyperglycemic mice.

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### Keywords:

*Apium Graveolens*(celery), Antihyperglycemic, Antihyperlipidemic , STZ, HFD .

### ABSTRACT

In spite of the drugs available for the treatment of diabetes and high blood lipids but still accompanied by undesirable side effects, and so a wide attention and tendency for herbal and poly herbal treatment because of the lack of side effects, and low cost and accessibility.

Celery seeds, also known scientifically as *Apium graveolens* belong to the plant family Apiaceae . Analysis of the active ingredients of the ethanol extract of celery seeds proved the presence of different compounds, including terpenes and fatty acids, but fatty acids were the largest proportion of the rest of the substances that were examined through GC-MS.

The aim of the current study is to verify the effectiveness of ethanolic extract of *A. graveolens* in reducing hyperglycemia and high lipids in hyperglycemic mice .

Fourty male mice were used in the current study and mice were divided into 4 equal groups. . Group-1 (control) received distilled water (50µl ) orally and standard diet. Group-2 (drug control) orally and injected with STZ (150 mg/Kg) intraperitoneally and received distilled water (50µl per day) orally with HFD . Group-3 injected with STZ and received glyburide (p.o) 0.5 mg/kg per day as standard drug with HFD for 28 days . Group-4 injected with STZ and received ethanolic extract of celery seed (400 mg/kg) per day by gastric lavage as well as HFD.

After the treatment was completed, blood samples were collected for analysis and isolation of liver and pancreas tissue for the histological examination.

The ethanolic extract of *A. graveolens* showed a significant decreasing in the level of blood glucose, lipid profile , serum (C-peptide) , improved (GSH), and reduction

in level of MDA when compared with untreated group. The presence of variety of active constituents in *A. graveolens* like flavonoids , turbinones and unsaturated fatty acids may be the reason for the antihyperglycemic and antihyperlipidemic effects.

### الخلاصة :

على الرغم من كثرة الأدوية المتاحة لعلاج مرض السكري وارتفاع نسبة الدهون في الدم ولكن لا يزال ترافقها آثار جانبية غير مرغوب فيها لذلك كان هناك اهتماما واسعا للعلاجات العشبية ومستخلصاتها قلة الآثار جانبية لها، وانخفاض تكلفتها وسهولة الحصول عليها .

ان الهدف من الدراسة الحالية هو التحقق من فعالية المستخلص الايثانولي لبذور الكرفس في الحد من ارتفاع السكر في الدم والدهون العالية في الفئران المستحدث فيها ارتفاع مستوى سكر الدم باستخدام عقار الستربتوزوتوسين . أثبت تحليل ال (GC-MS) للمستخلص الإيثانولي لبذور الكرفس المعروفة علميا باسم (*A. graveolens*) وجود مركبات مختلفة، بما في ذلك التربينات والأحماض الدهنية، ولكن الأحماض الدهنية كانت النسبة الأكبر من بقية المواد التي تم فحصها من خلال هذا التحليل.

استخدمت أربعون من الفئران الذكور في الدراسة الحالية، وتم تقسيم الفئران إلى 4 مجموعات متساوية العدد (عشرة لكل مجموعة) . المجموعة 1 (السيطرة) جرعت نورمل سلاين ( 50 مايكرو لتر يوميا" عن طريق الفم) مع غذاء قياسي . المجموعة 2 حققت بعقار الستربتوزوتوسين (150 ملغ / كلغ) تحت البريتون وجرعت نورمل سلاين ( 50 مايكرو لتر يوميا" عن طريق الفم) مع غذاء مشبع بالدهون . المجموعة 3 حققت عقار الستربتوزوتوسين (150 ملغ / كلغ) تحت البريتون وعولجت بعقار الكلابيرايد (0.5 ملغ / كغ يوميا كدواء قياسي) مع غذاء عالي الدهون. المجموعة 4 حققت بعقار الستربتوزوتوسين (150 ملغ / كلغ) تحت البريتون مع غذاء مشبع بالدهون وجرعت المستخلص الايثانولي لبذور الكرفس (400 ملغ / كلغ) يوميا عن طريق الفم بعد الانتهاء من العلاج . بعد 28 يوم من التجربة تم جمع عينات الدم للتحليل وعزل أنسجة الكبد والبنكرياس لإجراء الفحص النسيجي. أظهر المستخلص الايثانولي لبذور الكرفس انخفاضا ملحوظا" في مستوى الجلوكوز في الدم، والدهون، وتحسن مستوى ببتيد C- ، وتحسن (GSH)، وانخفاض في مستوى (MDA) بالمقارنة مع المجموعة غير المعالجة. يمكن ان يكون وجود مجموعة متنوعة من المكونات في بذور الكرفس مثل الفلافونويدات، والتوربينات والأحماض الدهنية غير المشبعة هو السبب في التأثير المخفض للسكر والدهون في الفئران .

### Introduction:

Diabetes mellitus is a clinical syndrome characterized by inappropriate hyperglycemia that caused by a relative or absolute deficiency of insulin or by a resistance to the action of insulin at the cellular level. The drugs that available for the treatment of diabetes and high blood lipids still accompanied by undesirable side effects, and so a wide attention and tendency for herbal and poly herbal treatment because of the lack of side effects, and low cost and accessibility.

In the present study, the potent DNA alkylating antibiotic streptozotocin (STZ) was used to induce experimentally hyperglycemia in mice [1] . STZ is a glucosamine–nitrosourea compound derived from *Streptomyces achromogenes* that is used clinically as a chemotherapeutic agent in the treatment of pancreatic  $\beta$  cell carcinoma [2] . The results showed that STZ is effective in inducing hyperglycemia and the mechanism of induction involves destruction of  $\beta$ -cells in islets of Langerhans via DNA methylation and subsequent damage after being accumulated inside pancreatic  $\beta$  cell due to its analogue characteristic to glucose molecule [3].

High fat diet is used to induce hyperlipidemia in mice [4]. Celery seeds, also known scientifically as *Apium graveolens*, belong to the plant family Apiaceae, which has long been used for medicinal purposes. Analysis of the active ingredients of the ethanol extract of celery seeds proved the presence of different compounds, including terpenes and fatty acids, but fatty acids were the largest proportion of the rest of the substances that were examined through GC-MS. It is used as appetizer and laxative and in case of cystic kidney [5]. Antihypertensive [6]. Diuretic accelerate excretion of urinary calcium [7]. Decreasing in hepatotoxicity by Paracetamol and thioacetamide [8]. Celery contains active compounds called phthalides, which can help to relax arteries and allow those vessels to dilate, thus the blood can flow at a lower pressure [9]. The phenolic compounds which present in celery considered a strong antioxidants [10]. *Apium graveolens* is cultivated in different countries of the world.

#### **Aim of study:**

The present study was designed to determine the antihyperglycemic and antihyperlipidemic effect of ethanolic extract of *Apium Graveolens* (celery), in Streptozocin/ high fat diet induced hyperglycemic mice.

#### **MATERIALS AND METHODS:**

##### **MATERIALS AND METHODS:**

##### **Chemicals:**

All chemicals used in the present study were of analytical grade. STZ was procured from Fluke, England. Glyburide from Actavis, England. Cholesterol powder from BDH, England. The kits for estimation of serum C-peptide, MDA, GSH were purchased from Mybiosource, USA.

##### **Plant extraction :**

*A. graveolens* (apiaceae) seeds were collected from local herbal apothecary in Baghdad and were authenticated by Botanic Department, Al-Mustansiriya University, Iraq). Then 500 mg. freshly collected seed were shade-dried and washed with tap water then washed with distilled water then it was been dried in an incubator at 37 c until water droplets completely evaporated then the dried seed were coarsely powdered in mixer grinder. Powdered dried seeds 500 g. were soaked for 15 hrs. in 1.5 liters of 95 % ethanol. Suspension was filtered and the residue was soaked again in equal amount of ethanol for 48 hr. and filtered again. The two filtrates obtained were evaporated and dried by distillation under reduced pressure at 40 to 50°C in rotary evaporator. Complete dryness was done by vacuum pumping. Dried extract was weighted and stored in freezer. The extraction mass (brown colour) so obtained (42g.) was suspended in distilled water in the required amount at the time of administration of experimental animals [11]. GC-MS analysis of ethanolic extract of AG was done.

##### **Animals:**

The normal blood values of glucose were determined in 40 healthy male mice before Streptozocin/ high fat diet induction & at three occasions 7,14,28 day after

induction by Streptozocin/ high fat diet and treatment with ethanolic extract of *Apium Graveolens* for 28 days, also serum C- peptide, MDA, GSH, cholesterol ,triglyceride ,VLDL, LDL, HDL are measured at end of experiment .

**Hyperlipidemia induction:**

Was done by adding high fat diet (2% cholesterol and 1% peanut butter) to the standard diet in order to induce hyperlipidemia in all groups except control group for 30 days and as in table (1.1).

Table (1.1) : Composition of High fat diet.

Standard diet	High fat diet
Seeds (sunflower, groundnut)	Seeds (sunflower, groundnut)
Cereals	Cereals
Fruits (grapes, apple)	Fruits (grapes, apple)
Vegetables	Vegetables
Vitamin A	Vitamin A
Vitamin D3	Vitamin D3
Vitamin E	Vitamin E
	Cholesterol powder
	Peanut butter

Fourty healthy male albino mice weighing 25-40 g. were used in the present study, they were supplied by animal house of college of Medicine at Al- Nahrain University. Animals were housed under good conditions at 28 C° in separated cages and were fed high fat diet except control group & were given water (standard diet only) .

Streptozotocin induces diabetes within 3-5 days by destroying the beta cells of Langerhans islets in the pancreas [12]. [Prepare the citrate buffer prior to injection] dissolve the STZ in the 50 mM sodium citrate buffer (pH 4.5) to a final concentration of 4 mg/ml. Because STZ degrades within 15 to 20 min after dissolving in the citrate buffer, the STZ solution should be prepared immediately before use [13].

The mice were randomly allocated to four groups (each contains ten mice) they were given a single daily dose of the followings at 9:00 a.m. for 28 successive days. Group-1 (control) received distilled water (50µl) orally. Group-2 (drug control) received distilled water (50µl) orally and injected with STZ (150 mg/Kg) intraperitoneal with HFD. Group-3 received glyburide (p.o) 0.5 mg per kg as standard drug with HFD for 28 days. Group-4 received ethanolic extract of celery seed (400 mg/kg) per day orally as well as HFD.

The doses of celery & had been chosen using many doses in pilot study. At 10:00 a.m. of the first day group 2,3 and 4 the animals were injected by streptozotocin (150 mg/kg i.p).

Blood samples were collected from tail vein of the mice of all groups for analysis of fasting blood glucose by glucometer, while blood samples collected from cardiac puncture for biochemical analysis of serum C-peptide, MDA, GSH at the end of experiment using Eliza, while estimation of serum lipid profile using autoanalyzer. Later on, all the mice were sacrificed under light anesthesia of chloroform to take pancreas specimen. Histopathological examination was performed to check the microscopic changes of the pancreas tissue using polarized microscope after fixating the section in 10% formalin for 48 hours and staining with hematoxylin & eosin.

#### STATISTICAL ANALYSIS:

All the obtained results were expressed as mean  $\pm$  SD. The difference among means had been analyzed by student's test using SPSS version12, p values less than 0.05 were considered to be statistically significant.

#### Results :

##### 1. Gas Chromatography – Mass Spectroscopy (GC-MS) analysis of *Apium graveolens* seeds:

The results obtained from GC-MS analysis for *Apium graveolens* seeds extract are shown in the table (1.1) and figure (1.2):

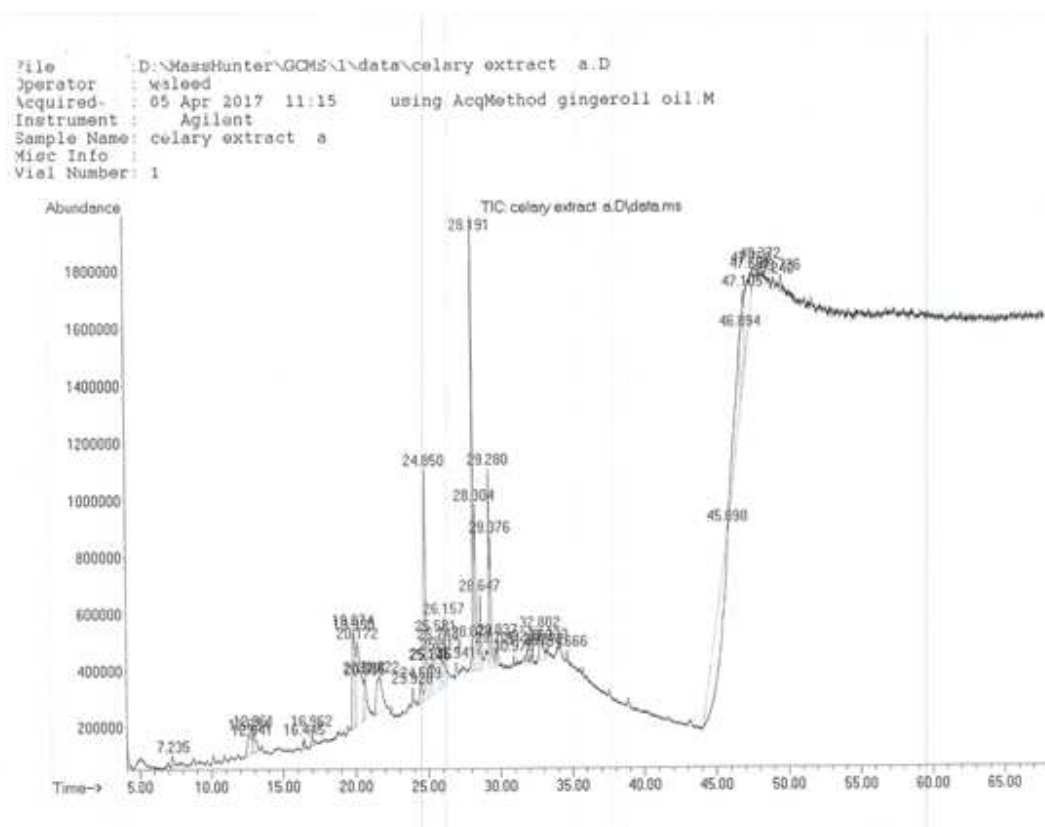


Figure (1.1): The chromatogram chart of GC-MS for *Apium graveolens* seeds .

Table (1-2): The phytochemical constituents detected by GC-MS for *A. graveolens* seeds with their molecular formula and weight.

NO.	Compound name	Molecular formula	Molecular weight
1	Methyl salicylate	C <sub>8</sub> H <sub>8</sub> O <sub>3</sub>	152
2	Naphthalene,	C <sub>10</sub> H <sub>8</sub>	204
3	Phenol, 2,4-bis 1,1-dimethylethyl	C <sub>14</sub> H <sub>22</sub> O	206
4	Diethyl Phthalate C <sub>12</sub> H <sub>14</sub> O <sub>4</sub> 222		
5	Oxalic acid, isobutyl nonyl ester	C <sub>2</sub> H <sub>2</sub> O <sub>4</sub>	272
6	2-Furanethanol, .alpha.-methyl-, acetate	C <sub>3</sub> H <sub>6</sub> O <sub>2</sub>	168

7	4-Cyclopropylcarbonyloxy tridecane	C17H32O2	268
8	Cyclopropanoic acid, 2-[[2-[(2-ethylcyclopropyl)methyl]	C8H16O6	296
9	6-Octadecenoic acid, methyl ester	C19H34O2	296
10	3-Trifluoro Acetoxypentadecane	C17H31F3O2	324

### Blood glucose concentration and C-peptide level in control and study groups:

Before of induction, blood samples were withdrawn from all groups in order to measure blood glucose concentration which were proved to have no significant variation in control and study groups ( $P>0.05$ ), as shown in table (1-3) .

Following induction, serial measurements of blood glucose were done on day 7, 14 and 28. In the control group, it was noticed that blood glucose level remained at nearly steady level within normal range, whereas significant changes were reported in study groups as following: in group (STZ), blood glucose became significantly high on day 7

And continue as such till the end of the experiment within diabetic range. In other groups, glyburide, AG seed, it was noticed that glucose level started at high level and then became significantly lower on day 14 and further significant reduction was observed on day 28; however the rate of reduction in blood glucose level, the more reduction was marked in glyburide group followed by AG group, as shown in table (1-4) .

**Table (1-3):** Mean  $\pm$  SD blood glucose in control and study groups before induction of DM.

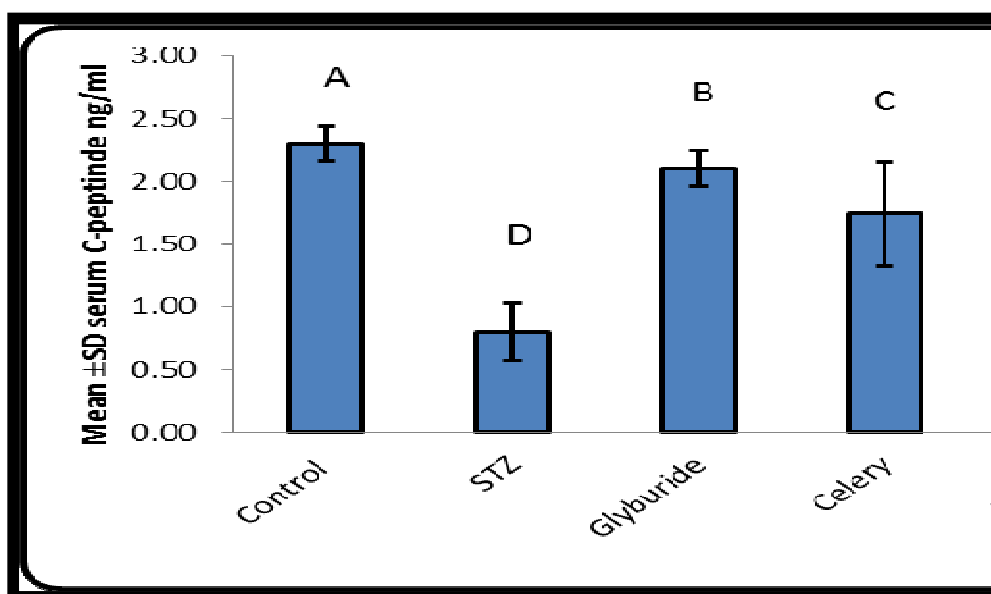
Groups	Mean	P
Control	106.25 $\pm$ 5.51	0.368
STZ	107.73 $\pm$ 5.88	
Glyburide	106.75 $\pm$ 4.79	
Celery seed	107.46 $\pm$ 6.51	

**Table (1-4):** Mean  $\pm$  SD blood glucose in control and study groups at different intervals .

Groups	Day 7	Day 14	Day 28
	Control	106.25 $\pm$ 1.51 B, b	114.75 $\pm$ 1.99 A, f
STZ	231.50 $\pm$ 12.06 C, a	259.50 $\pm$ 3.03 A, a	243.85 $\pm$ 3.39 B, a
Glyburide	230.01 $\pm$ 10.88 A, a	169.50 $\pm$ 3.03 B, e	120.50 $\pm$ 3.03 C, e
Celery seed	233.90 $\pm$ 15.45 A, a	215.00 $\pm$ 30.28 B, b	160.50 $\pm$ 3.03 C, b

Capital letters for comparison among days; small letters for comparison among groups; similar letters for no difference; A and a for the highest value; SD: Standard deviation.

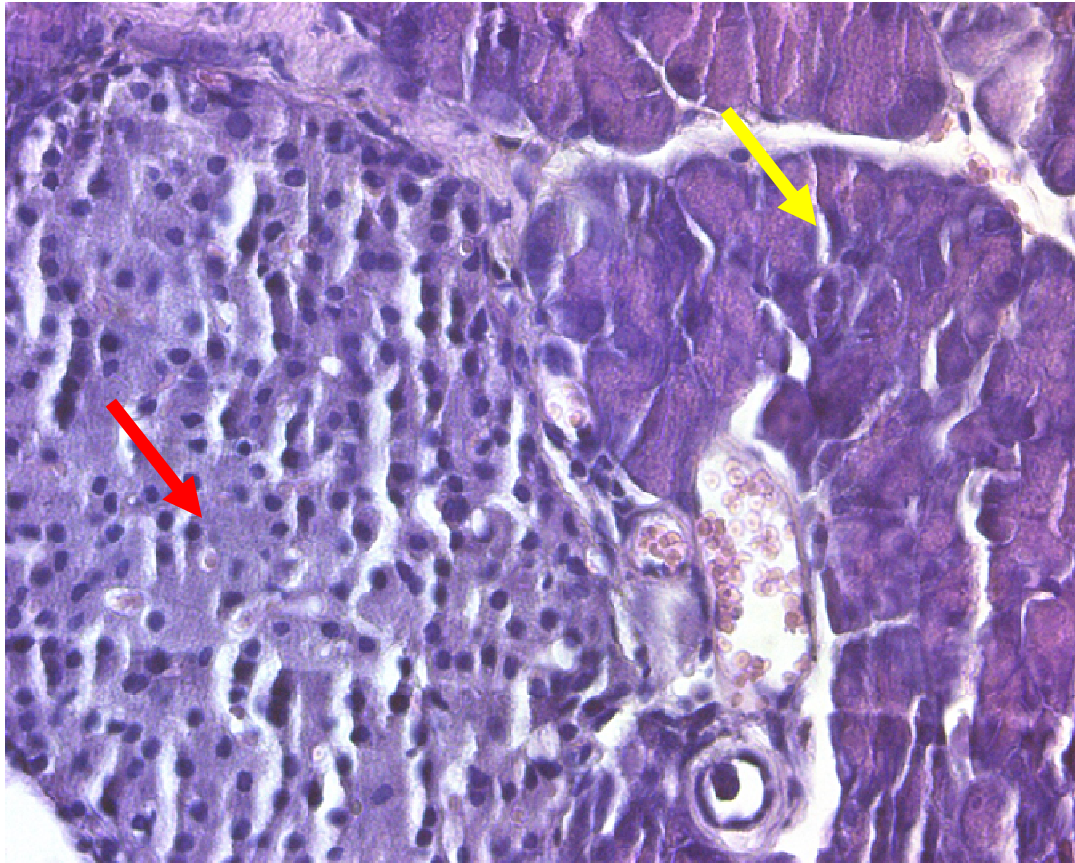
At the end of the experiment, C-peptide serum level was estimated for all groups and the results are shown in figure (1-2). Regarding study groups, the lowest concentration was reported in STZ group (0.80  $\pm$ 0.23) ng/ml and the highest level was recorded in the control group (2.30  $\pm$ 0.14) ng/ml, then glyburide group (2.10  $\pm$  0.14) Then followed by AG group as in figure (1.2) .



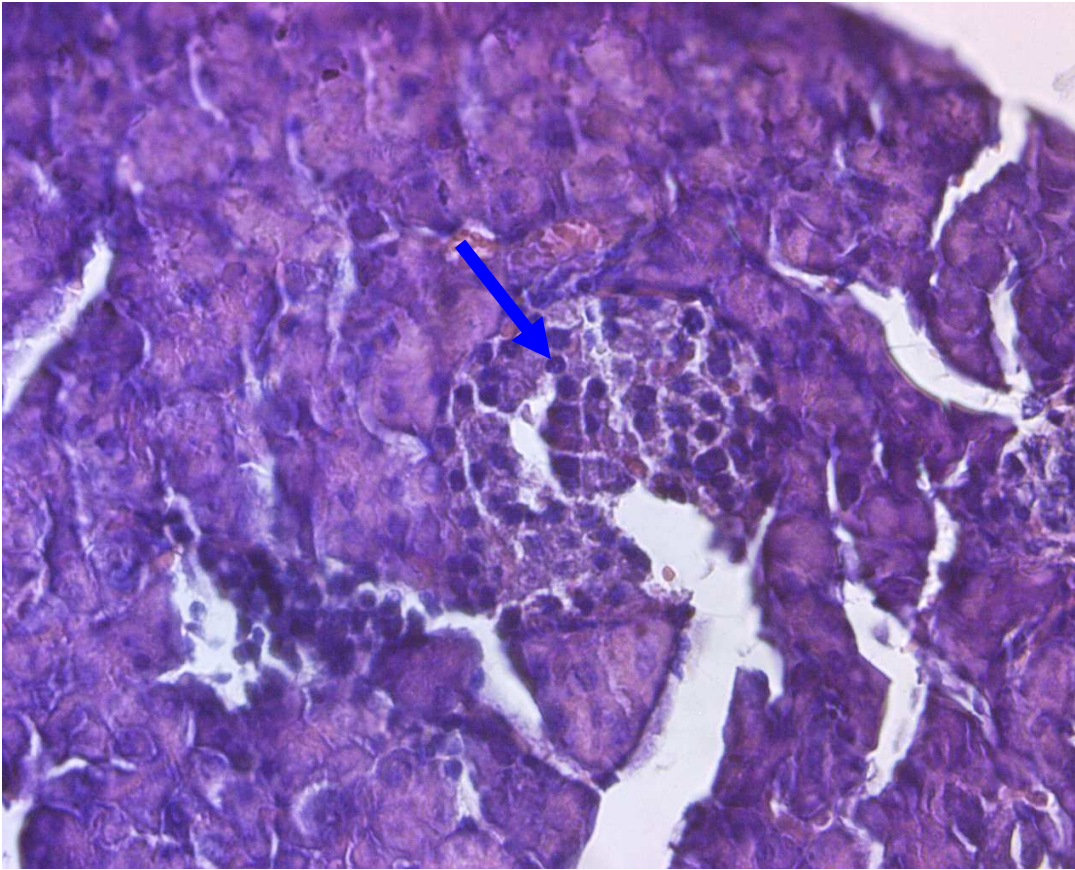
**Figure (1-2):** serum C-peptide concentration in control and study groups. Capital letters for comparison among groups; similar letters for no difference; (A) for the highest value.



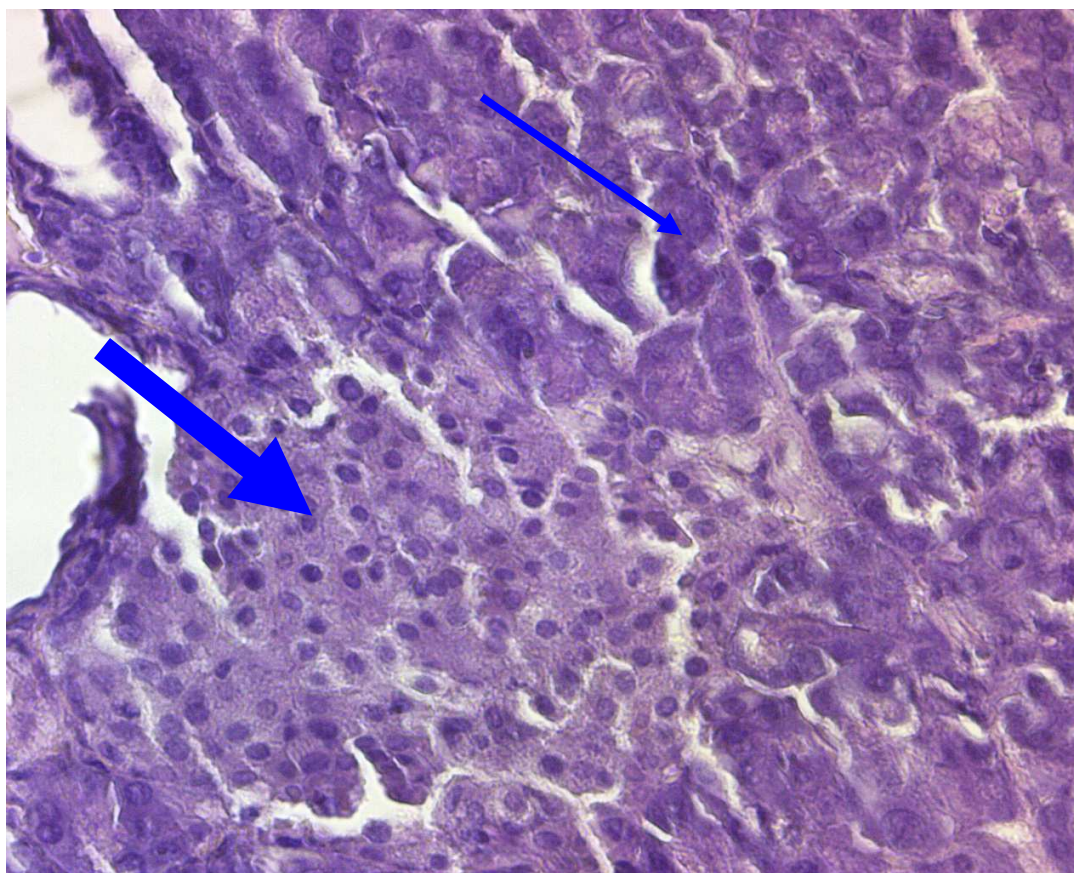
The improved serum C-peptide level in groups receiving treatment reflected the improvement in  $\beta$ -cell mass as shown in histological sections (figures 1- 3 to 1- 6).



**Figure (1-3):**section of the pancreatic tissue of Control group shows normal pancreatic islets (red arrow) and normal pancreatic acini (yellow arrow) 40X.

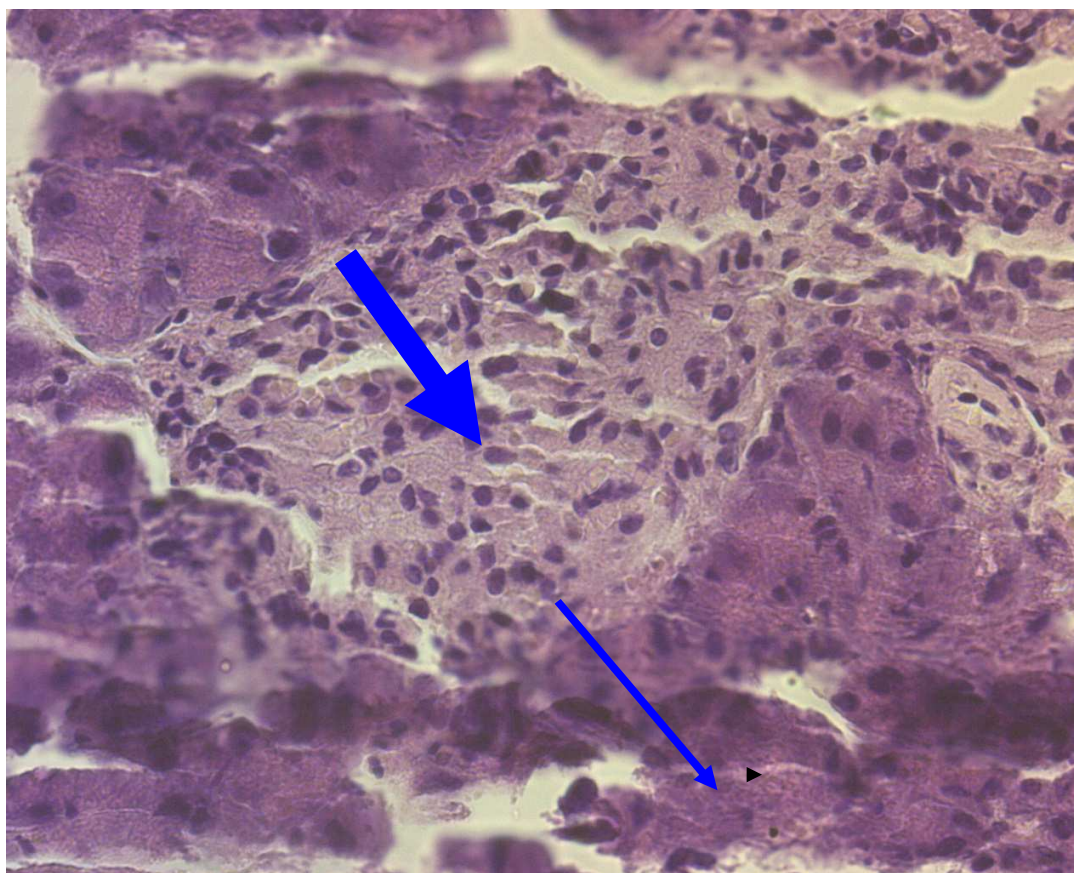


**Figure (1-4 ):** STZ group pancreas :Section of the pancreatic tissue shows shrinking of the pancreatic islet and decreases in overall number of pancreatic islet (red arrow) and dilatation of acini 40X .



**Figure (1-5):** Glyburide group Section of the pancreatic tissue shows improvement in the structure of the pancreatic islet and acini 40X.





**Figure (1-6):** pancreatic section of celery seed group the pancreatic tissue shows improvement in the structure of the pancreatic islet and acini 40 X.

## 1.2. Fatty liver changes and serum lipid concentration in control and study groups:

Mean serum lipid profile is shown in table (1-3). The highest level of cholesterol, triglyceride, LDL, VLDL, HDL and phospholipid were seen in the STZ group which was significantly higher than other groups ( $P < 0.05$ ). The serum concentrations of cholesterol, triglyceride, LDL, VLDL, HDL and phospholipid in glyburide, AG groups were not significantly different ( $P > 0.05$ ); however, these levels were significantly higher than that of the control group ( $P < 0.05$ ).

**Table (1-4):** Mean  $\pm$  SD serum lipids in control and study groups.

Characteristic	Control group	STZ group	Glyburide group	A.G	N.S	Combination
Cholesterol (mg/dl)	96.40 $\pm$ 5.30 C	115.67 $\pm$ 6.70 A	104.70 $\pm$ 4.30 B	105.80 $\pm$ 8.10 B	103.15 $\pm$ 8.70 B	106.55 $\pm$ 4.50 B
Triglyceride (mg/dl)	40.81 $\pm$ 7.80 C	89.97 $\pm$ 9.40 A	45.90 $\pm$ 8.30 C	81.10 $\pm$ 6.60 B	79.98 $\pm$ 5.90 B	78.50 $\pm$ 8.22 B
LDL (mg/dl)	32.34 $\pm$ 8.90 C	37.61 $\pm$ 7.60 A	34.50 $\pm$ 5.40 B	35.90 $\pm$ 3.20 A	33.60 $\pm$ 5.20 B	34.65 $\pm$ 6.90 A
VLDL (mg/dl)	8.25 $\pm$ 3.40 E	30.33 $\pm$ 2.40 A	10.25 $\pm$ 3.60 D	16.08 $\pm$ 3.70 B	15.79 $\pm$ 2.68 B	12.65 $\pm$ 3.22 C
HDL (mg/dl)	59.85 $\pm$ 5.66 A	18.11 $\pm$ 7.43 C	53.80 $\pm$ 6.33 B	18.89 $\pm$ 8.57 C	44.90 $\pm$ 3.77 C	48.15 $\pm$ 9.44 B
Phospholipid (mg/dl)	70.13 $\pm$ 6.77 C	88.99 $\pm$ 7.34 A	75.50 $\pm$ 8.35 B	87.63 $\pm$ 6.29 A	80.60 $\pm$ 3.03 B	82.50 $\pm$ 8.28 B

Capital letters for comparison among groups; similar letters for no difference; A for the highest value; SD: Standard deviation.

### 1.3. Serum markers of oxidative stress:

Mean serum MDA was highest in STZ group (30.48  $\pm$  2.40) and lowest in control group (20.78  $\pm$  2.16). Glyburide reduce mean serum MDA to (23.56  $\pm$  1.59) which was significantly lower than that of STZ group (P<0.05) and significantly higher than that of control group (P<0.05). AG reduced mean serum MDA to (24.85  $\pm$  1.51), however they were significantly lower than that of STZ group (P<0.05) and significantly higher than that of glyburide group, as shown in table (1-4).

Mean serum GSH was lowest in STZ group (40.40  $\pm$  3.22) and highest in control group (48.55  $\pm$  5.44). glyburide increased mean serum GSH to (46.92  $\pm$  7.22) which was significantly higher than that of STZ group (P<0.05) and significantly lower than that of control group (P<0.05). AG increased mean serum GSH to (43.55  $\pm$  6.12), however they were significantly higher than that of STZ group (P<0.05) and significantly lower than that of glyburide group, as shown in table (1-4).

**Table (1-4):** Mean  $\pm$  SD serum MDA and GSH in control and study groups :

Serum marker	Control	STZ	Glyburide	Celery seed	Nigella Sativa	Combination
MDA	20.78 $\pm$ 2.16 D	30.48 $\pm$ 2.40 A	23.56 $\pm$ 1.59 C	24.85 $\pm$ 1.51 B	24.90 $\pm$ 1.49 B	23.77 $\pm$ 1.76 C
GSH	48.55 $\pm$ 5.44 A	40.40 $\pm$ 3.22 D	46.92 $\pm$ 7.22 B	43.55 $\pm$ 6.12 C	43.04 $\pm$ 4.13 C	44.30 $\pm$ 7.19 C

Capital letters for comparison among groups; similar letters for no difference; A for the highest value; SD: Standard deviation.

*Apium Graveolens* seed extract was showed decreasing in blood glucose, serum cholesterol ,triglyceride, vLDL, LDL, also increase in serum C-peptide and serum HDL level compared with glyburide group also, there is improvement in MDA and GSH serum levels.

## Discussion :

In the current study, the blood glucose level was increased gradually in STZ group and the level of blood glucose was reduced followed by administration of AG . For purpose of comparison, glyburide was administered to a group of mice [14] . Celery seeds contains the flavonoid (luteolin) which was found to enhance insulin release in uric acid-damaged pancreatic  $\beta$ -cells by suppressing the reduction of MAFA, principally via the NF- $\kappa$ B and inducible nitric oxide synthase–nitric oxide (iNOS–NO) signaling pathways [15] . Another possible mechanism is that celery seeds contain flavonoid like apigenin and luteolin which are capable of inhibiting the sodium glucose transporter-2 (SGT-2) at the kidney and by this way reducing blood glucose level [16] .

On the other hand kanter proposed that extra-pancreatic mechanism might be involved in reducing blood glucose concentration via enhanced glucose transport into the cells and increased utilization of glucose by the liver for glycogen synthesis. Flavonoids, important components of AG, were found to regulate the phosphorylation of AMPK to upregulate the fatty acid oxidation and increase glucose uptake via GLUT4 translocation [18]. Another possible mechanism is the regeneration of pancreatic  $\beta$ -cells[17] . Another proposed mechanism is the inhibitory effect of celery seed for further damage of already existing pancreatic cells [17] . In clonal  $\beta$ -cells, apigenin treatment attenuated 2-deoxy-d-ribose-induced apoptosis through its antioxidant effect by controlling the mitochondrial membrane potential [19] .

The present study showed that the oral administration of *A. graveolens* to experimental animals resulted in significant reduction in the level of serum cholesterol, triglyceride, LDL and VLDL and also resulted in significant rise in the level of HDL. These results agrees with the findings of [20] . The depressing of total cholesterol concentration in serum by *A. graveolens* may results from the different (inhibitory and stimulatory) effects on many enzymes at the absorption, production and elimination of cholesterol itself or its containing composites. At the absorption level, the effect of the extract may be on the Acyl-CoA-cholesterol esterase enzyme that responsible for the absorption of cholesterol in the small intestine [21] . *A. graveolens* extract may accelerate the cholesterol elimination by its stimulatory effect on 7- $\alpha$ -hydroxylase which responsible for the transformation of cholesterol into bile acid in the liver [22].

Alternatively, the present results may be attributed to the effect of *A. graveolens* extract on cholesterol production through decreasing the activity of HMG -CoA reductase enzyme which responsible for the construction of cholesterol in the liver and other body tissues, by converting it into mevalonic acid, as a result this inhibition may decrease of the inhibitory effect of cholesterol on protein kinase and the phosphoprotein phosphatase enzymes that responsible for binding of sterol-regulatory element binding protein; SREPS with the DNA[22].

The lowering effect of the *A. graveolens* extract on Serum triglycerides may attributed to the decrement of lipid peroxidation, mainly lipid hydroperoxidase enzyme, and to the decrement of fatty acids biosynthesis (stearic, olic, and palmitic acids), as well as the raising of poly unsaturated fatty acids. These alterations can be explained by the stimulatory effect of the extract on delta-6-desaturase that responsible for the insaturation of fatty acids. This enzyme act to convert the linoleic acid into gamma linoleic, as a result there is in decreasing the levels of linoleic and arachidonic acids [23].

On the other hand, the *A. graveolens* extract may causes its triglycerides dropping effect by elevating the level of lipoprotein lipase that responsible for the converting of triglycerides into fatty acids and glycerol. There is significant increase of HDL-cholesterol and significant decrease of LDL-cholesterol and VLDL-cholesterol levels compared with the baseline values in our study, states the positive efficient role of *A. graveolens* ethanolic extract as antihyperlipidemic agent. monoterpenoids and sequiterpenoids from the seed extract may be responsible for antihyperlipidemic effects [24].

Alternatively, the antihyperlipidemic effect of the *A. graveolens* extract may attributed to the creation of new receptors for the LDL, decrease intestinal absorption of cholesterol, and increase its conversion to bile acid in order to increase its excretion [25]. *A. graveolens* extract may increase lipoprotein lipase activity. Consequently, that will reduction in level of serum chylomicrones and LDL-cholesterol [26]. These results were agreed with that of [27]. Mansi and his coworkers suggest that the lipid lowering action of *A. graveolens* may be mediated through inhibition of hepatic cholesterol biosynthesis, increased bile acids excretion, and enhanced cholesterol acyltransferase activity. Administration of *A. graveolens* extract increased the activity of (GSH) enzyme and may help to control free radical, as extract has been reported to be rich in flavonoids, well known antioxidant which scavenge the free radical generated during diabetes [28].

The flavonoid apigenin, apiin which are constituents of *A. graveolens* was shown to have strong antioxidant effects by increasing scavenging activity on MDA and significantly enhanced the activities of GSH and thereby decreasing the oxidative damage to tissues [29].

#### **conclusion:**

Ethanolic extract of celery seed possess mild Antihyperglycemic, Antihyperlipidemic effect. The histopathological examination showed improvement in the sections of the pancreas tissue that support the effect of extract on the pancreas.

#### **Acknowledgment:**

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