

## Hypoglycemic and hypolipidemic effects of dietary supplementation of *plantago psyllium* seeds on diabetic and/ or hyperlipidemic albino rats

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### Abstract

This study was designed to investigate the hypoglycemic and hypolipidemic effects of *plantago psyllium* seeds added to diet in two different doses (0.5% and 1.0% w\w) on streptozotocin (STZ) induced diabetic rats and/or hyperlipidemic rats. Eighty male adult albino rats were used in this study, divided into 10 groups 8 rats each. G (1): served as healthy control, G (2) was diabetic control. G (3) was hyperlipidemic control. G (4) was diabetic fed on high fat high cholesterol diet (HFHC). Gs: (5-6) diabetic rats fed on diet supplemented with *plantago psyllium* seeds (0.5% & 1% w\w).Gs (7-8) hyperlipidemic rats fed on HFHC diet supplemented with *plantago psyllium* seeds (0.5% & 1% w\w).Gs (9-10) diabetic rats fed on HFHC diet supplemented with psyllium seeds (0.5% & 1% w\w). After 6 weeks, rats were sacrificed under diethyl ether anesthesia. Serum and tissue samples were collected to perform the biochemical analysis. Serum glucose, insulin, insulin resistance (HOMA-IR) and beta cell function index (HOMA- $\beta$ ) were measured. Moreover, Serum lipids profile including total lipid (TL), phospholipids (PL), total cholesterol (TC), triacylglycerols (TAGs), low density lipoprotein cholesterol (LDL-C), very low density lipoprotein cholesterol (VLDL-C), as well as LDL-C/ HDL-C, TC/HDL-C, TAGs/HDL-C ratios and atherogenic index (AI) were measured. Also, antioxidant status was evaluated by measuring total antioxidants capacity (TAC) level, glutathione peroxidase (GPx), glucose 6 phosphate dehydrogenase (G6PD) activities, malondialdehyde (MDA) and oxidative stress index (OSI). The results were supported with microscopic examination of pancreatic tissues. The results of this study revealed that administration of *plantago psyllium* seeds improve glucose homeostasis by decreasing blood glucose, increasing  $\beta$ -cell function, increasing serum insulin level and insulin sensitivity in STZ-induced diabetic rats. Also, *plantago psyllium* seeds ameliorate insulin resistance in hyperlipidemic groups by decreasing insulin level. The result of this study approved that psyllium seeds improve dyslipidemia relevant to HFHC diet and diabetes mainly through decreasing TL, PL, TC, TAGs, LDL-C, VLDL-C and increasing HDL-C. Furthermore, *plantago psyllium* seeds showed an important cardio protective effect through decreasing AI, TC/HDL-C, TAGs/HDL-C and LDL-C/ HDL-C ratios as a risk for coronary heart disease (CHD). The study revealed that *plantago psyllium* seeds has a significant antioxidant activity and can be used to protect tissue from oxidative stress as indicated in microscopic examination of pancreatic tissue showed amelioration in the appearance of cells. The result showed a significant decrease in serum MDA and OSI and a significant increase in TAC level, GPx and G6PD activities. The protective effect of *plantago psyllium* seeds is due to their antioxidant potential which represented by their rich content of dietary fibers, flavonoids, poly unsaturated fatty acids, and some polyphenols that appears to protect against reactive oxygen species (ROS).

**Key Words:** STZ, Psyllium, hyperlipidemia, fiber, antioxidants, oxidative stress, lipids profile.

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## 1. Introduction:

Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term tissue and organ damage, as well as, dysfunction involving the eyes, kidneys, nerves, heart, and blood vessels (**American Diabetes Association, 2014**). The presence of chronic hyperglycemia in DM is accompanied by greater or lesser impairment in the metabolism of carbohydrates, lipids and proteins. Also, hyperlipidemia is the most common complication of diabetes mellitus and it predisposes them to premature atherosclerosis and macrovascular complications. Diabetes and hyperlipidemia are two major factors involved in the development of cardiovascular disease (CVD) (**Uttra et al., 2011**).

Plants are well known in traditional herbal medicine for their hypoglycemic activities, and available literature indicate that there are more than 800 plants species showing hypoglycemic activities (**Rajagopal and Sasikala, 2008**). There has been increasing demand for the use of plant products with anti-diabetic activity due to low cost, easy availability and lesser side effects. Epidemiological studies support an inverse relationship between dietary fiber and symptoms associated with type 2 DM and CVD (**Aune et al., 2013**). Importantly, whole grains are more strongly associated with decreased CVD risk than fruit or vegetable-derived fibers. Specifically, whole grain fibers are more effective than fruit or vegetable fibers at reducing blood lipids, and inflammation as well as improving blood glucose in addition of blood pressure regulation (**Satija and Hu, 2012**). Much of this research has focused on the water-soluble fiber, psyllium (*Plantago ovata*), which is contained in the mucilage of the outer layer of the seed known as the seed coat. The mucilage is often referred to as husk, or ground psyllium husk (**Johnson et al., 2017**).

Psyllium (PSY) is classified as a mucilaginous fiber due to its powerful ability to form a gel in water. *Plantago psyllium* is an important medicinal plant which has different compounds such as phenolic compounds (Caffeic acid derivatives), flavonoids, alkaloids, terpenoids, and vitamin C. *Plantago* plants have high levels of phenols and the powerful antioxidant quality of the plant may be due to its phenolic compounds. Phenolic compounds, especially flavonoids have antioxidant qualities, but they are not able to inhibit all mutations induced by mutagenic agents (**Haddadian et al., 2014**). Psyllium contains nutritional antioxidants, flavonoids, polyunsaturated fatty acids (PUFAs), including essential fatty acids (Omega-3 and Omega-6 fatty acids), sulfur containing amino acids, and metabolites with bioactivities, which make it a promising candidate for use in the nutraceutical industry. Several studies suggested that psyllium improved glycemic and lipid control in individuals with diabetes. Psyllium intake has been shown to improve glucose and insulin responses in animal and human studies (**Singh, 2007**). Psyllium have hypolipidemic effect as it lowers serum cholesterol level as a result of the binding of bile acids in the intestinal lumen and reduced risk of coronary heart disease (**Van Rosendaal et al., 2004**).

So, this study was designed to investigate the hypoglycemic and hypolipidemic effects of psyllium seeds on diabetic and hyperlipidemic rats.

## 2. Materials and Methods:

## 2.1- Materials:

Adult male albino rats (Sprague Dawely strain ) weighing  $150 \pm 5$  g were obtained from the National Research Centre,(Giza, Egypt).STZ (**N-Methyl-nitroso carbamoyl- $\alpha$ -D glucosamine**) with molecular formula  $C_8H_{15}N_3O_7$  and molecular weight 265.22,was obtained from El-Gomohria Company for Chemical and Drugs Cairo, Egypt. Cholesterol (**3 $\beta$ -Hydroxy-5-cholestene, 5-Cholesten-3 $\beta$ -ol**) with chemical formula  $C_{27}H_{46}O$ , molecular weight 386.65, was obtained from El-Gomohria Company for Chemicals and Drugs, Cairo, Egypt .Standard balanced diet was used and prepared according to AIN 1993 and adjusted by **Reeves et al. (1993)**. HFHC diet was prepared by modifying diet materials to enhance the elevation of serum total lipid and total cholesterol by adding 1% cholesterol and 4% beef tallow to the standard diet according to **Pengzhan et al. (2003)**. *Plantago psyllium* seeds were obtained from local markets in Cairo. The seeds of *plantago psyllium* were oven dried at 60 °C for 1/2 hr and were ground to make a powder using food processor grinder and added to diets as 0.5 or 1.0% w/w.

## 2.2- Methods:

### 2.2.1-Animal trial:

Eighty adult male albino rats were randomly housed individually in metallic cages with constant controlled environments; temperature  $25 \pm 3^\circ\text{C}$  and 12/12 hr light/dark cycle were held. The experiment was performed at the Animal House of National Cancer Institute. Experimental animals were fed with standard balanced diet and water *ad libitum* for 7 days as acclimation period. After the acclimation period, rats were divided into ten groups (8 rats/each), and hyperlipidemia was induced in six groups (G3,4,7,8,9 and 10) by feeding them the HFHC for 10 other days, while the remaining four groups (G1,2,5 and 6) continued feeding on the standard balanced diet. By the end of the ten days, the blood samples were collected from eye vein to confirm the hyperlipidemic condition through the determination of total cholesterol and triacylglycerols using Biodiagnostic kit according to **Richmond (1973); and Fossati and prencipe(1982)** respectively.

Then, four groups (G1,3,7 and 8) were injected interaperitoneally (i.p.) by saline solution and the remaining groups (G2,4,5,6,9and 10) were rendered diabetic by means of a single intraperitoneal (i.p.) injection of a freshly prepared STZ(50 mg/Kg b.w.) dissolved in 0.1 M sodium citrate buffer pH4.5 and injected within 15 min of preparation to rats **Latha et al. (2014)**. As STZ is capable of inducing fatal hypoglycemia as a result of massive pancreatic insulin release; STZ-treated rats were allowed to drink 5% glucose solution to overcome hypoglycemia after STZ injection. This was followed by monitoring random blood glucose level. The glucose conc. in blood taken from tail vein was determined by enzymatic colorimetric method according to **Trinder (1969)**.Stable blood glucose level  $\geq 200 \pm 5$  mg/dl were considered to indicate diabetes onset .After the confirmation of diabetic and hyperlipidemic conditions of rats, the day on which rats were supplemented with *plantago psyllium* was considered as 1<sup>st</sup> day of experiment.

The experimental groups were classified as follow: (G1) normal rats fed on standard balanced diet(-ve control) [NC], (G2) diabetic rats fed on standard balanced diet (Diabetic control) [DC], (G3) hyperlipidemic rats fed on HFHC diet (Hyperlipidemic control) [HC], (G4)diabetic hyperlipidemic rats fed on HFHC diet (Diabetic-hyperlipidemic control) [DHC], (G5)diabetic rats fed on diet supplemented with 0.5% Psy seeds[D+0.5%Psy], (G6) diabetic rats fed on diet supplemented with 1% Psy seeds [D+1% Psy], (G7) hyperlipidemic rats fed on HFHC diet supplemented with 0.5% Psy seeds [H+0.5%Psy], (G8) hyperlipidemic rats fed on HFHC diet supplemented with 1% Psy seeds [H+1%Psy], (G9) diabetic hyperlipidemic rats

fed on HFHC diet supplemented with 0.5 % Psy seeds [DH+0.5% Psy], finally, (G10) diabetic hyperlipidemic rats fed on HFHC diet supplemented with 1.0% Psyllium seeds [DH+1% Psy] (**Ahmed et al ., 2010**) .

Diet was introduced to the rats in special cups, water was introduced in a well-sealed bottles. All rats had free access to food and water all times for six weeks. Food intake was recorded daily and animals were weighed weekly to monitor the body weight changes and to calculate feed efficiency ratio (FER). At the end of the 6 weeks, and after 12 hrs fasting, all rats were sacrificed under ether anesthesia and the blood samples were collected directly from hepatic portal vein **Guo et al. (2002)**.

Blood samples were taken in two centrifuge tubes. The first tube was heparinized and immediately used for the determination of GPx and G6PD activities. The second tube was used for separation of serum left for 15 minutes at room temperature then centrifuged at 4000 rpm for 20 minutes, then a part of fresh serum samples were used immediately for the determination of glucose level and the others were separated and kept in plastic vials at -20°C until analysis. Liver and Pancreas were separated immediately and washed by saline solution (0.9 % NaCl) then blotted on filter paper and weighed; part of pancreas were preserved in 10% neutral buffered formal saline for electron microscopic examination. Liver samples were stored at -20°C until used for lipids profile determination.

### **2.2.2- Biochemical analysis:**

Glucose in serum was performed by enzymatic colorimetric method using Vitro kits according to **Trinder (1969)**. Serum insulin was determined using (Coat –A-Count) radioimmunoassay insulin kit (PITKIN-4) as described by **Spin et al. (1998)**. The calculation of insulin resistance was performed according to the method of homeostasis model assessment of insulin resistance (HOMA) as described by **Matthews et al. (1985)**. HOMA- $\beta$  scores were calculated using fasting serum insulin and fasting blood glucose concentrations at the end of the experimental period according to **Wilson and Islam (2012)**. Determination of serum TL was performed by colorimetric method using Spin react kit according to **Kaplan (1984)**. Serum PL were determined by colorimetric method using Spectrum kit according to **Tietz (1990)**. Determination of serum TAGs was performed by enzymatic colorimetric method using Spectrum kit according to **Fossati and prencipe (1982)**. Serum TC level was determined by enzymatic colorimetric method using Spectrum kit according to **Richmond (1973)**. Serum HDL-C level was determined by enzymatic colorimetric method using spectrum kit according to **Lopez-Virella et al. (1977)**. LDL-C level has been calculated indirectly by means of the Friedewald equation (**Fridewald et al.,1972**). Serum VLDL-C was calculated according to **Fridewald et al. (1972)**. Atherogenic index was calculated according to **Lecumberri et al. (2007)**. The risk ratio of LDL-C /HDL-C was calculated as described by **Notarnicola et al. (2005)**. The risk ratio of TC/HDL-C was calculated according to **Garg et al. (2014)**. The risk ratio of TAGs/HDL-C was calculated according to (**Brehm et al., 2004**). Determination of serum TAC was performed by colorimetric method using Biodiagnostic kit according to **Koracevic et al. (2001)**. Serum MDA was determined according to **Ohkawa et al. (1979)** by thiobarbituric acid (TBA) method. The MDA/TAC ratio is proposed as oxidative stress index as reported by **Suresh et al. (2010)**. Determination of GPx activity was carried according to **Paglia and Valentina (1967)**. Determination of blood G6PD activity was performed by enzymatic colorimetric method using Biodiagnostic kit according to **Dror et al. (1970)**. While, liver was homogenized with chloroform and methanol in a blender and then extracted by the method of **Folch et al. (1957)** for TC and TAGs level measurements.

### 2.2.3-Microscopic Examination:

Pancreatic specimens from all animals were dissected immediately, and fixed in 10% neutral-buffered formal saline for at least 72 hrs. All pancreatic specimens were washed in tap water for half an hr and then dehydrated in ascending grades of alcohol, cleared in xylene and embedded in paraffin. Serial sections of 6  $\mu\text{m}$  thick were cut and stained with haematoxylin and eosin for investigation according to **Drury and Wallington (1980)**.

### 2.3 Statistical Analysis:

Data were statistically analyzed by Statistical Package for Social Science (SPSS) version 16.0 statistical packages. Values were presented as mean  $\pm$ SD. Statistical differences between groups were performed using one way ANOVA, the mean difference was significant at the level ( $P \leq 0.05$ ) level according to **Levesque (2007)**.

## 3. Results

### 3.1- Biological measurements:

Data in **table (1)** of nutritional evaluation showed that +ve control groups showed marked elevation in food intake as compared to -ve control group. On the other hand, diabetic and hyperlipidemic groups fed on psyllium seeds supplemented diets showed marked reduction ( $P \leq 0.05$ ) in food intake as compared to +ve control groups. Generally, the reduction in food intake was dose dependent. While, diabetic hyperlipidemic groups fed on psyllium seeds supplemented diet showed significant increase ( $P < 0.05$ ) in food intake as compared to its corresponding control group. Concerning the results of body weight change, there was a significant reduction ( $p \leq 0.05$ ) in body weight in diabetic control rats and diabetic-hyperlipidemic rats as compared to healthy group. While, there were remarkable increases ( $p \leq 0.05$ ) in body weight in hyperlipidemic group as compared to healthy group.

From the present results, supplementation with *Plantago psyllium* seeds with the tested doses caused a significant increase ( $p \leq 0.05$ ) in body weight in diabetic groups when compared to their corresponding +ve control. While, the rate of weight gain in hyperlipidemic and diabetic hyperlipidemic groups supplemented with *plantago psyllium* seeds were lower than that in their corresponding positive control. With respect to the calculated FER which affected for far by the changes in body weight and food intake, data showed that there was a significant reduction ( $p < 0.05$ ) in FER in +ve control groups except hyperlipidemic group as compared to -ve control group. Our findings also demonstrated that dietary supplementation with (0.5% and 1 %) *plantago psyllium* seeds significantly improved ( $p < 0.05$ ) FER in diabetic treated groups. while, there were non significant change in FER in hyperlipidemic and diabetic hyperlipidemic treated groups as compared to their corresponding control.

Furthermore, data in **table (1)** showed that there was a significant increase ( $p < 0.05$ ) in relative liver weight in +ve control groups when compared to -ve control. The present results showed that addition of *plantago psyllium* seeds with two different doses caused a significant reduction ( $p < 0.05$ ) in relative liver weight in all treated groups. Considering the relative weight of pancreas, it's clear that there were a significant decrease ( $p < 0.05$ ) in relative pancreatic weight in diabetic and diabetic hyperlipidemic groups as compared to healthy group. However, there was no significant difference in relative pancreatic weight between hyperlipidemic and healthy groups. The results demonstrated that there were a significant improvement ( $p < 0.05$ ) in relative pancreatic weight in diabetic and diabetic hyperlipidemic rats after dietary supplementation with two tested doses of *plantago psyllium* seeds.

**Table (1): Food intake, body weight change, feed efficiency ratio and relative organs weight (liver and pancreas) in experimental groups (mean±SD)**

Group no	Parameters Groups	Food intake	Body weight change (g)	Feed efficiency ratio (FER)	Relative liver weight (g%)	Relative pancreatic weight (g%)
G1	NC	362.14±3.07 <sup>a</sup>	90.71±8.30 <sup>a</sup>	0.24±0.02 <sup>a</sup>	2.72±0.02 <sup>f</sup>	2.34±0.05 <sup>a</sup>
G2	DC	412.28±6.29 <sup>b</sup>	-43.14±4.25 <sup>cd</sup>	-0.10±0.01 <sup>e</sup>	3.92±0.02 <sup>b</sup>	1.42±0.07 <sup>e</sup>
G3	HC	402.71±5.02 <sup>c</sup>	98 ±4.60 <sup>c</sup>	0.24±0.01 <sup>a</sup>	4.28±0.10 <sup>a</sup>	2.30±0.00 <sup>a</sup>
G4	DHC	367.42±4.79 <sup>d</sup>	48.42±2.07 <sup>c</sup>	0.13±0.01 <sup>c</sup>	4.28±0.07 <sup>a</sup>	1.67±0.04 <sup>d</sup>
G5	D+0.5 %psy	382.57±1.98 <sup>ef</sup>	43.14±4.45 <sup>cd</sup>	0.11±0.01 <sup>d</sup>	3.0±0.07 <sup>e</sup>	2.00±0.05 <sup>bc</sup>
G6	D+1% psy	379.00±3.16 <sup>e</sup>	60.28±5.05 <sup>b</sup>	0.15±0.01 <sup>b</sup>	2.7±0.01 <sup>f</sup>	2.28±0.08 <sup>a</sup>
G7	H+0.5 % psy	384.71±3.14 <sup>f</sup>	31.71±3.86 <sup>e</sup>	0.08±0.00 <sup>g</sup>	3.44±0.08 <sup>d</sup>	2.04±0.53 <sup>b</sup>
G8	H+1% psy	379.28±1.79 <sup>e</sup>	21.85±1.46 <sup>f</sup>	0.06±0.00 <sup>g</sup>	3.0±0.01 <sup>e</sup>	2.12±0.16 <sup>b</sup>
G9	DH+0.5%psy	389.00±2.16 <sup>g</sup>	31.42±4.31 <sup>e</sup>	0.04±0.00 <sup>h</sup>	3.61±0.07 <sup>c</sup>	2.04±0.53 <sup>b</sup>
G10	DH+1% psy	383.00±2.70 <sup>e</sup>	16.85±2.96 <sup>g</sup>	0.08±0.01 <sup>f</sup>	3.10±0.69 <sup>d</sup>	2.31±0.08 <sup>a</sup>
LSD		3.90	4.80	0.0	0.07	0.08

P≤0.05, there are no significant difference between means have the same letters in the same column

### 3.2. Biochemical measurements:

Mean values of the statistical analysis present in **table (2)** showed that there were a significant increase ( $P \leq 0.5$ ) in serum glucose and a significant decrease in serum insulin ( $P \leq 0.5$ ) levels in diabetic and diabetic hyperlipidemic control groups comparing to normal control .While, there were a significant increase ( $P \leq 0.5$ ) in serum insulin level in hyperlipidemic control rats with non-significant change in glucose level indicating increase risk of insulin resistance. Supplementation with psyllium seeds (0.5 & 1.0 %) improved serum glucose and insulin levels in STZ-diabetic rats in a dose dependent manner .Moreover, hyperlipidemic rats that fed on psyllium supplemented diets showed marked reduction ( $P < 0.05$ ) in serum insulin level when compared with hyperlipidemic control group which indicating that psyllium seeds increase insulin sensitivity and decrease insulin resistance, the improvement in insulin level was dose dependent. There were a significant improvement in insulin resistance and sensitivity which illustrated by a significant decrease ( $P \leq 0.5$ ) in homeostasis model assessment of insulin resistance (HOMA-IR) and significant elevation in pancreatic  $\beta$  cell function (HOMA-  $\beta$ ) score in diabetic treated groups.

**Table (2): Serum glucose, insulin levels and insulin resistance and  $\beta$ - cell function indices in experimental groups (mean  $\pm$ SD)**

Group No.	Parameters Group	Glucose (mg/dl)	Insulin ( $\mu$ U/ml)	Insulin resistance (HOMA-IR)	$\beta$ -cell function index (HOMA- $\beta$ )
G1	NC	152 $\pm$ 1.63 <sup>g</sup>	10.14 $\pm$ 0.14 <sup>d</sup>	3.8 $\pm$ 0.05 <sup>g</sup>	41 $\pm$ 1.13 <sup>d</sup>
G2	DC	391.85 $\pm$ 1.95 <sup>b</sup>	5.64 $\pm$ 0.26 <sup>l</sup>	5.4 $\pm$ 0.27 <sup>d</sup>	6.1 $\pm$ 0.29 <sup>h</sup>
G3	HC	154.14 $\pm$ 1.86 <sup>g</sup>	19.37 $\pm$ 0.25 <sup>a</sup>	7.3 $\pm$ 0.12 <sup>a</sup>	76.54 $\pm$ 1.83 <sup>a</sup>
G4	DHC	434 $\pm$ 2.0 <sup>a</sup>	6.58 $\pm$ 0.19 <sup>h</sup>	7.0 $\pm$ 0.21 <sup>b</sup>	6.38 $\pm$ 0.19 <sup>h</sup>
G5	D+0.5 %psy	285.42 $\pm$ 2.76 <sup>d</sup>	7.3 $\pm$ 0.22 <sup>g</sup>	5.12 $\pm$ 0.09 <sup>e</sup>	11.88 $\pm$ 0.48 <sup>g</sup>
G6	D+1.0 % psy	184.14 $\pm$ 4.67 <sup>f</sup>	9.5 $\pm$ 0.17 <sup>e</sup>	4.28 $\pm$ 0.12 <sup>f</sup>	28.38 $\pm$ 1.0 <sup>e</sup>
G7	H+0.5 % psy	153.57 $\pm$ 1.13 <sup>g</sup>	13.8 $\pm$ 0.20 <sup>b</sup>	5.42 $\pm$ 0.09 <sup>d</sup>	55.0 $\pm$ 1.33 <sup>b</sup>
G8	H+1.0 % psy	151.71 $\pm$ 1.97 <sup>g</sup>	10.97 $\pm$ 0.19 <sup>c</sup>	4.1 $\pm$ 0.08 <sup>f</sup>	44.54 $\pm$ 1.44 <sup>c</sup>
G9	DH+0.5% psy	317.85 $\pm$ 4.22 <sup>c</sup>	8.0 $\pm$ 0.08 <sup>f</sup>	6.25 $\pm$ 0.34 <sup>c</sup>	11.42 $\pm$ 0.18 <sup>g</sup>
G10	DH+1.0 % psy	228.57 $\pm$ 2.63 <sup>e</sup>	9.1 $\pm$ 0.11 <sup>e</sup>	5.1 $\pm$ 0.10 <sup>e</sup>	19.79 $\pm$ 0.44 <sup>f</sup>
LSD (P $\leq$ 0.05)		2.89	0.65	0.19	1.07

P $\leq$ 0.05, there are no significant difference between means have the same letters in the column

Results represented in **table (3and 4)** showed serum lipids profile and concluded that STZ-induced diabetes and HFHC diet caused marked elevation (p $<$ 0.05) in serum TL, PL , TC, TAGs , LDL-C, and VLDL-C levels and significant reduction (p $<$ 0.05) in serum HDL-C level as compared to healthy rats. The statistical analysis also indicated that supplementation of rat's diets with psyllium seeds by levels (0.5 & 1.0%) caused significant decrease (p $<$ 0.05) in serum TL, PL, TC, TAGs, LDL-C, and VLDL-C levels and significant increase (p $<$ 0.05) in serum HDL-C level as compared to +ve control groups. The hypolipidemic effect of psyllium seeds was dose dependent.

**Table (3): Serum total lipids (TL) ,phospholipids (PL) and triacylglycerols (TAGs) levels in experimental groups (mean  $\pm$  SD).**

Group No.	Parameters Groups	TL (mg/dl)	PL (mg/dl)	TAGs (mg/dl)
G1	NC	813.00 $\pm$ 6.65 <sup>l</sup>	207.71 $\pm$ 3.59 <sup>j</sup>	136.00 $\pm$ 4.04 <sup>h</sup>
G2	DC	1113.14 $\pm$ 6.74 <sup>f</sup>	385.57 $\pm$ 3.20 <sup>g</sup>	203.28 $\pm$ 3.77 <sup>d</sup>
G3	HC	1656.57 $\pm$ 4.39 <sup>c</sup>	594.57 $\pm$ 3.45 <sup>d</sup>	254.85 $\pm$ 4.56 <sup>b</sup>
G4	DHC	2192.85 $\pm$ 4.70 <sup>a</sup>	857.85 $\pm$ 4.14 <sup>a</sup>	291.00 $\pm$ 3.41 <sup>a</sup>
G5	D+0.5 %psy	994.57 $\pm$ 3.73 <sup>g</sup>	356.71 $\pm$ 5.46 <sup>h</sup>	165.42 $\pm$ 3.73 <sup>f</sup>
G6	D+1.0 % psy	856.28 $\pm$ 4.23 <sup>h</sup>	294.28 $\pm$ 3.59 <sup>l</sup>	144.14 $\pm$ 3.41 <sup>g</sup>
G7	H+0.5 % psy	1566.28 $\pm$ 5.28 <sup>d</sup>	548.57 $\pm$ 3.99 <sup>e</sup>	200.42 $\pm$ 6.13 <sup>d</sup>
G8	H+1.0 % psy	1365.57 $\pm$ 4.23 <sup>e</sup>	486.71 $\pm$ 5.31 <sup>f</sup>	183.85 $\pm$ 2.79 <sup>e</sup>
G9	DH+0.5% psy	1811.28 $\pm$ 6.96 <sup>b</sup>	799.71 $\pm$ 3.63 <sup>b</sup>	239.42 $\pm$ 3.30 <sup>c</sup>
G10	DH+1.0 % psy	1653.14 $\pm$ 8.57 <sup>c</sup>	737.57 $\pm$ 5.15 <sup>c</sup>	199.85 $\pm$ 3.48 <sup>d</sup>
LSD (P $\leq$ 0.05)		6.15	4.52	4.2

P $\leq$ 0.05, there are no significant difference between means have the same letters in the same column

**Table (4): Serum total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), very low density lipoprotein cholesterol (VLDL-C) and high density lipoproteins cholesterol (HDL-C) levels in experimental groups (mean±SD).**

Group NO.	parameters Groups	TC (mg/dl)	LDL-C (mg/d)	VLDL-C (mg/dl)	HDL-C (mg/dl)
G1	NC	120.28±3.45 <sup>l</sup>	49.22±4.36 <sup>h</sup>	27.20±0.80 <sup>g</sup>	43.88 ±3.25 <sup>a</sup>
G2	DC	164.28±3.68 <sup>f</sup>	103.60±5.11 <sup>e</sup>	37.11 ±0.83 <sup>d</sup>	23.00 ±2.16 <sup>e</sup>
G3	HC	256.28±5.12 <sup>c</sup>	188.82±5.63 <sup>c</sup>	47.28 ±0.74 <sup>b</sup>	20.17±1.91 <sup>f</sup>
G4	DHC	328.00±4.93 <sup>a</sup>	253.30±5.01 <sup>a</sup>	58.20 ±0.68 <sup>a</sup>	16.50 ±1.12 <sup>g</sup>
G5	D+0.5 %psy	144.00±3.55 <sup>g</sup>	80.77±3.67 <sup>f</sup>	33.08 ±0.71 <sup>e</sup>	30.14 ±2.41 <sup>c</sup>
G6	D+1.0 % psy	127.14±4.59 <sup>h</sup>	57.02±3.89 <sup>g</sup>	28.82±0.68 <sup>f</sup>	41.28 ±4.23 <sup>a</sup>
G7	H+0.5 % psy	206.57±4.31 <sup>d</sup>	138.07±7.02 <sup>d</sup>	39.66 ±0.77 <sup>c</sup>	28.14 ±1.86 <sup>c</sup>
G8	H+1.0 % psy	185.14 ± 3.48 <sup>e</sup>	107.15±2.74 <sup>e</sup>	36.77±0.55 <sup>d</sup>	35.00 ± 3.05 <sup>b</sup>
G9	DH+0.5% psy	269.14±3.62 <sup>b</sup>	194.25±5.23 <sup>b</sup>	47.88±0.66 <sup>b</sup>	27.00 ±2.16 <sup>cd</sup>
G10	DH+1.0 % psy	208.57 ± 4.85 <sup>d</sup>	135.40±5.82 <sup>d</sup>	39.97±0.69 <sup>c</sup>	33.20±2.00 <sup>b</sup>
LSD (P ≤0.05)		4.49	5.30	0.77	2.73

P≤0.05 there are no significant difference between means have the same letters in the same column

Moreover, the data presented in **table (5)** showed heart disease risks. It was clear from results that there were a significant increase in several atherogenic indices TC/HDL-C, TAGs/HDL-C, LDL-C/HDL-C ratios and AI in all +ve control groups as increase risk of coronary heart disease (CHD). Then after supplementation of psyllium (two doses) there were a significant reduction (P<0.05) in TC/HDL-C, TAGs/HDL-C, LDL-C/HDL-C and AI which indicated that psyllium fiber may provide cardio-protective benefits.

**Table (5) : Serum TC/HDL-C , TAGs/HDL-C , LDL-C/ HDL-C ratios and AI in experimental groups (mean±SD).**

Group NO.	Parameters Groups	TC / HDL-C Ratio	TAGs/HDL-C ratio	LDL/HDL-C ratio	AI
G1	NC	2.75±0.21 <sup>g</sup>	3.11±0.23 <sup>f</sup>	1.13±0.16 <sup>g</sup>	1.75±0.21 <sup>l</sup>
G2	DC	7.20±0.80 <sup>d</sup>	8.91±0.91 <sup>c</sup>	4.55±0.60 <sup>d</sup>	6.20±0.80 <sup>d</sup>
G3	HC	12.80±1.30 <sup>b</sup>	12.73±1.24 <sup>b</sup>	9.44±1.07 <sup>b</sup>	11.80±1.30 <sup>b</sup>
G4	DHC	19.95±1.28 <sup>a</sup>	17.70±1.14 <sup>a</sup>	15.41±1.07 <sup>a</sup>	18.95±1.28 <sup>a</sup>
G5	D+0.5 %psy	4.80±0.36 <sup>f</sup>	5.52±0.54 <sup>e</sup>	2.69±0.26 <sup>f</sup>	3.80±0.36 <sup>g</sup>
G8	D+1.0 % psy	3.10±0.26 <sup>g</sup>	3.51±0.31 <sup>f</sup>	1.39±0.20 <sup>g</sup>	2.01±0.26 <sup>h</sup>
G6	H+0.5 % psy	7.36±0.51 <sup>d</sup>	7.14±0.50 <sup>d</sup>	4.92±0.48 <sup>d</sup>	6.36±0.51 <sup>d</sup>
G9	H+1.0 % psy	5.32±0.44 <sup>f</sup>	5.29± 0.51 <sup>e</sup>	3.08±0.29 <sup>f</sup>	4.32±0.44 <sup>f</sup>
G7	DH+0.5% psy	10.02±0.88 <sup>c</sup>	8.91±0.70 <sup>c</sup>	7.24±0.74 <sup>c</sup>	9.02±0.88 <sup>c</sup>
G10	DH+1.0 %psy	6.30±0.42 <sup>e</sup>	6.04± 0.42 <sup>e</sup>	4.09±0.35 <sup>de</sup>	5.30±0.42 <sup>e</sup>
LSD(P≤0.05)		0.8	0.78	0.6	0.8

P≤0.05, there are no significant difference between means have the same letters in the same column

Furthermore, results in **table (6 and 7)** indicated that diabetes mellitus and hyperlipidemia increased lipid peroxidation that was manifested by marked elevation (p<0.05) in serum MDA level in +ve control groups as compared to -ve control groups. Moreover, there was a disturbance in antioxidants status that was showed in the significant reduction of total antioxidants capacity (TAC) level, GPx and G6PD activities as compared to

-ve control group. Also, there was a significant elevation ( $P<0.05$ ) in MDA/TAC ratio. On the other hand, supplementation of experimental diets with psyllium seeds (0.5 & 1.0 %) improved lipid peroxidation and antioxidants status that was showed by marked reduction ( $p<0.05$ ) in serum MDA level and MDA/TAC ratio and significant elevation ( $P<0.05$ ) of serum TAC level and GPx and G6PD activities in all treated groups as compared to their corresponding +ve control groups. Generally, this improvement was dose dependent.

**Table (6): Serum malondialdehyde (MDA) and total antioxidant capacity (TAC) levels and oxidative stress index in experimental groups (means  $\pm$ SD).**

Group NO.	Parameters Groups	MDA (nmol/ml)	TAC (mM/L)	MDA/TAC (OSI)
G1	NC	133.14 $\pm$ 1.95 <sup>f</sup>	1.02 $\pm$ 0.01 <sup>a</sup>	130.14 $\pm$ 1.57 <sup>f</sup>
G2	DC	241.71 $\pm$ 1.49 <sup>d</sup>	0.41 $\pm$ 0.01 <sup>g</sup>	581.42 $\pm$ 4.72 <sup>c</sup>
G3	HC	253.40 $\pm$ 3.0 <sup>c</sup>	0.51 $\pm$ 0.01 <sup>f</sup>	498.28 $\pm$ 5.8 <sup>d</sup>
G4	DHC	311.42 $\pm$ 7.20 <sup>a</sup>	0.31 $\pm$ 0.01 <sup>h</sup>	1004 $\pm$ 4.6 <sup>a</sup>
G5	D+0.5 % psy	197.57 $\pm$ 2.07 <sup>c</sup>	0.64 $\pm$ 0.02 <sup>e</sup>	308.28 $\pm$ 6.26 <sup>e</sup>
G6	D+1.0 % psy	164.00 $\pm$ 2.30 <sup>g</sup>	0.87 $\pm$ 0.01 <sup>b</sup>	188.57 $\pm$ 2.76 <sup>g</sup>
G7	H+0.5 % psy	190.42 $\pm$ 1.71 <sup>f</sup>	0.71 $\pm$ 0.01 <sup>d</sup>	268.71 $\pm$ 3.25 <sup>f</sup>
G8	H+1.0 % psy	158.00 $\pm$ 2.16 <sup>h</sup>	0.91 $\pm$ 0.01 <sup>b</sup>	174.28 $\pm$ 3.14 <sup>h</sup>
G9	DH+0.5% psy	282.85 $\pm$ 3.53 <sup>b</sup>	0.51 $\pm$ 0.01 <sup>f</sup>	559.42 $\pm$ 1.81 <sup>b</sup>
G10	DH+1.0 % psy	243.14 $\pm$ 2.04 <sup>d</sup>	0.79 $\pm$ 0.01 <sup>c</sup>	306.85 $\pm$ 3.48 <sup>e</sup>
LSD(P $\leq$ 0.05)		3.4	0.05	4.32

P $\leq$ 0.05, there are no significant difference between means have the same letters in the same column

**Table (7): Blood glutathione peroxidase (GPx) and Glucose 6 phosphate dehydrogenase (G6PD) activities in the experimental groups (mean  $\pm$  SD).**

Group No.	Parameters Groups	GPx activity (mU/ml)	G6PD activity (U/g Hb)
G1	NC	470.42 $\pm$ 1.71 <sup>a</sup>	14.18 $\pm$ 0.56 <sup>a</sup>
G2	DC	362.14 $\pm$ 1.57 <sup>d</sup>	8.04 $\pm$ 0.26 <sup>g</sup>
G3	HC	361.57 $\pm$ 4.11 <sup>d</sup>	10.07 $\pm$ 0.42 <sup>e</sup>
G4	DHC	302.57 $\pm$ 5.41 <sup>f</sup>	6.04 $\pm$ 0.29 <sup>h</sup>
G5	D+0.5 % psy	400.57 $\pm$ 5.09 <sup>b</sup>	9.40 $\pm$ 0.22 <sup>f</sup>
G6	D+1.0 % psy	467.14 $\pm$ 1.67 <sup>a</sup>	12.07 $\pm$ 0.36 <sup>c</sup>
G7	H+0.5 % psy	400.71 $\pm$ 1.79 <sup>b</sup>	11.48 $\pm$ 0.32 <sup>d</sup>
G8	H+1.0 % psy	468.42 $\pm$ 1.90 <sup>a</sup>	13.08 $\pm$ 0.30 <sup>b</sup>
G9	DH+0.5% psy	345.00 $\pm$ 4.08 <sup>e</sup>	7.98 $\pm$ 0.33 <sup>g</sup>
G10	DH+1.0 % psy	394.28 $\pm$ 3.68 <sup>c</sup>	9.44 $\pm$ 0.25 <sup>f</sup>
LSD (P $\leq$ 0.05)		3.66	0.365

P $\leq$ 0.05, there are no significant difference between means have the same letters in the same column

The results presented in **Table (8)**, showed the hepatic TC and hepatic TAGs levels. The results indicated that there were a significant elevation in TC and TAGs in liver tissue in all +ve control groups as compared to negative control .While psyllium supplementation resulted in a significant reduction in hepatic lipids in all treated groups as compared to their corresponding controls.

**Table (8): Total cholesterol (TC) and triacylglycerols (TAGs) levels in liver tissue of experimental groups (means  $\pm$  SD).**

Group No.	Parameters Groups	TC (mg/g tissue)	TAGs (mg/g tissue)
G1	NC	2.9 $\pm$ 0.17 <sup>h</sup>	3.1 $\pm$ 0.18 <sup>h</sup>
G2	DC	4.6 $\pm$ 0.30 <sup>e</sup>	4.45 $\pm$ 0.17 <sup>e</sup>
G3	HC	6.4 $\pm$ 0.21 <sup>b</sup>	5.4 $\pm$ 0.34 <sup>c</sup>
G4	DHC	7.3 $\pm$ 0.21 <sup>a</sup>	6.7 $\pm$ 0.17 <sup>a</sup>
G5	D+0.5% psy	3.9 $\pm$ 0.17 <sup>g</sup>	3.9 $\pm$ 0.13 <sup>f</sup>
G6	D+1% psy	3.0 $\pm$ 0.19 <sup>h</sup>	3.5 $\pm$ 0.31 <sup>g</sup>
G7	H+0.5% psy	5.2 $\pm$ 0.23 <sup>d</sup>	4.68 $\pm$ 0.24 <sup>c</sup>
G8	H+ 1% psy	4.2 $\pm$ 0.24 <sup>f</sup>	3.6 $\pm$ 0.20 <sup>g</sup>
G9	DH+0.5% psy	6.7 $\pm$ 0.17 <sup>c</sup>	5.9 $\pm$ 0.17 <sup>b</sup>
G10	DH+1% psy	5.4 $\pm$ 0.39 <sup>d</sup>	5.0 $\pm$ 0.21 <sup>d</sup>
LSD		0.25	0.24

P $\leq$ 0.05, there are no significant difference between means have the same letters in the same column

### 3.3- Microscopic examination:

It was clear from the microscopic examination of pancreas that in **Fig (1)**, normal control group revealed no histopathological changes. It showed the normal structure of the tissue, the pancreatic endocrine island with normal cellular architecture with their normal secretory activity, normal exocrine architecture with normal acina. Also, the blood vessel with normal thickness without any deposited material. as well as the exocrine acini which appear normal. On the other hand, **Fig (2)** showed section of pancreas from diabetic control rats characterized by reduced cellularity of pancreatic island which replaced by hyaline deposition. The blood vessels wall thickened due to the hyaline deposition. These findings explain the reduction in insulin secretion and hyperglycemia which occurs as a consequence of STZ induction.

Our results provided that, a section of the pancreatic tissue of hyperlipidemic rat showed vacuolation of the exocrine pancreatic tissue due to fatty acid deposition, on the other hand, the pancreatic island without any damage noticed as illustrated in **Fig (3)**. a section of the pancreatic tissue of diabetic hyperlipidemic rats showed decreased cellularity of pancreatic island which replaced by hyaline deposition with vacuolation of the exocrine pancreatic tissue due to fatty acid deposition as illustrated in **Fig (4)**.

**Fig (5)** showed pancreas from diabetic rats treated with 0.5% psyllium seeds that's characterized by the pancreatic islands which still destructed and minimal hyaline deposition and also the blood vessels retain its thickness with minimal hyaline deposition. While, **Fig (6)** a section of the pancreatic tissue of the diabetic rat with 1% psyllium seeds showing that the pancreatic island get improved and retain its cellularity, also the secretory activity of the cells get improved.

**Fig (7)** showed a section of the pancreatic tissue of hyperlipidemic rat with 0.5% psyllium seeds showing the pancreatic endocrine island with more normal cellularity and good secretory activity, on the other hand the exocrine pancreatic tissue noticed to be normal without the fatty deposits. While **Fig (8)** showed a section of the pancreatic tissue of the hyperlipidemic rat with 1% psyllium seeds showing that the pancreatic island get improved and retain its cellularity, also the secretory activity of the cells get improved.

**Fig (9)** showed a section of the pancreatic tissue of diabetic hyperlipidemic rat with 0.5% psyllium seeds indicate a normal pancreatic endocrine island but still with minimal cellularity and hyaline deposition on the blood vessel wall, on the other hand there is no appearance to the fatty deposition in the exocrine pancreatic tissue. On the other hand **Fig**

(10) showed a section of the pancreatic tissue of the diabetic hyperlipidemic rat 1% psyllium seeds indicated that the pancreatic island get improved without fatty acids depositions in the exocrine pancreatic tissue , also in the left side showed that the blood vessels with normal thickness without hyaline deposition in its wall.

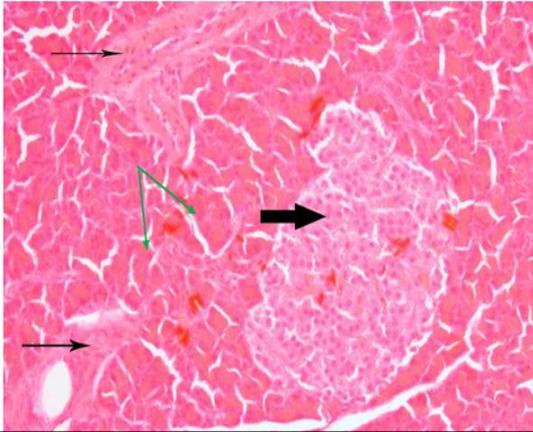


Figure (1) A photomicrograph of a section of pancreas in healthy rats showed normal histological structure of islet cells. (Hx& E. X 200)

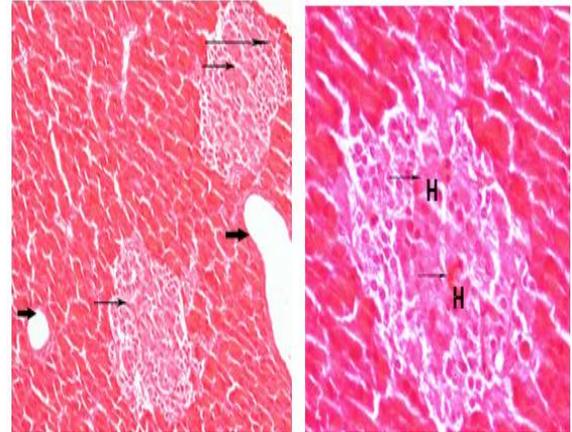


Figure (2) A photomicrograph of a section of the pancreatic tissue of a diabetic rat showing in the right side the pancreatic island with reduced cellularity which replaced by hyaline deposition (**H**) also the blood vessels wall thickened due to the hyaline deposition (thick arrow), The left side showing the hyaline deposition in the pancreatic tissue (thin arrow)(Hx& E. X 200, 400)

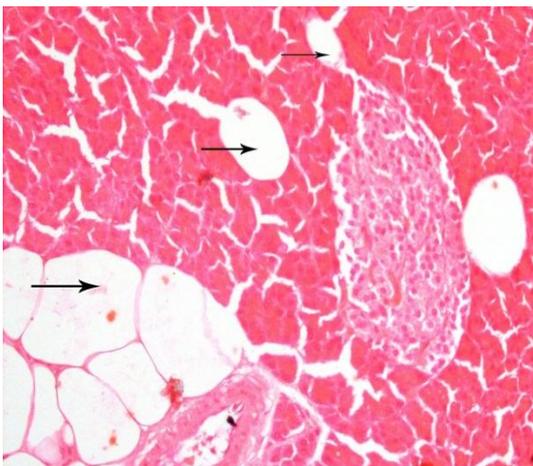


Figure (3) A photomicrograph of a section of pancreas in hyperlipidemic rats with vacuolation in the exocrine pancreatic tissue without any damage noticed (Hx& E.X 200)

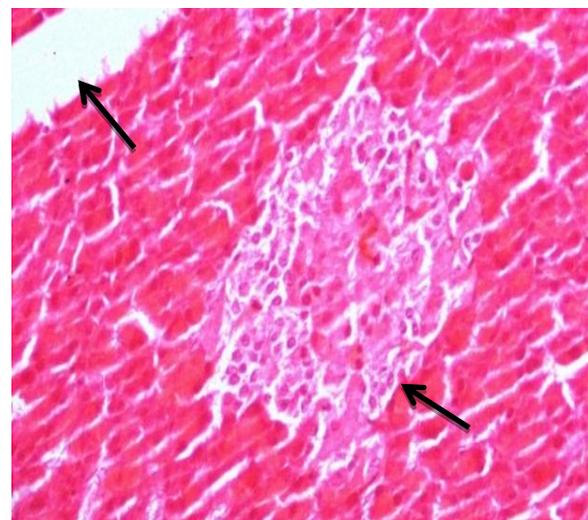


Figure (4) A photomicrograph of a section of pancreas in diabetic hyperlipidemic rats showed the pancreatic island with reduced cellularity, thickened blood vessels and vacuolation in the exocrine pancreatic tissue (Hx & E. X 200 ).

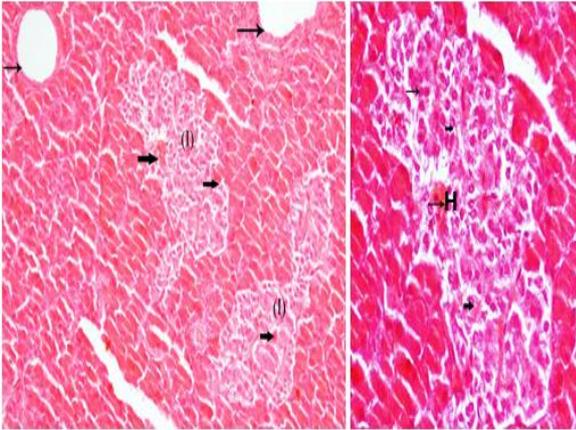


Figure (5) A photomicrograph of a section of pancreas of D+0.5 %Psy seeds group which still destroyed and minimal hyaline deposition (H) and also the blood vessels retain its thickness (Hx&E. X 200, 400)

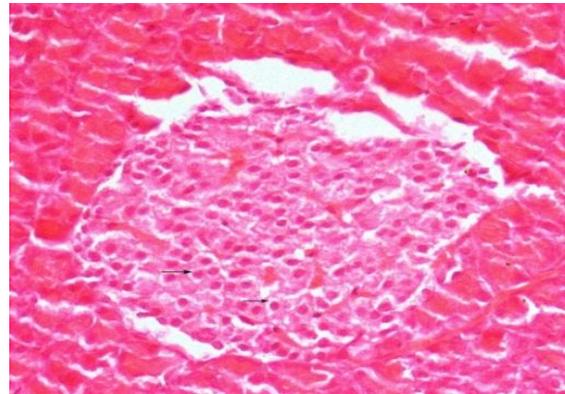


Figure (6) A photomicrograph of section of pancreatic tissue of the D+1.0%Psy seeds group showing that the pancreatic island get improved and retain its cellularity, also the secretory activity of the cells get improved (arrows). (H<sub>x</sub>&E. X200)

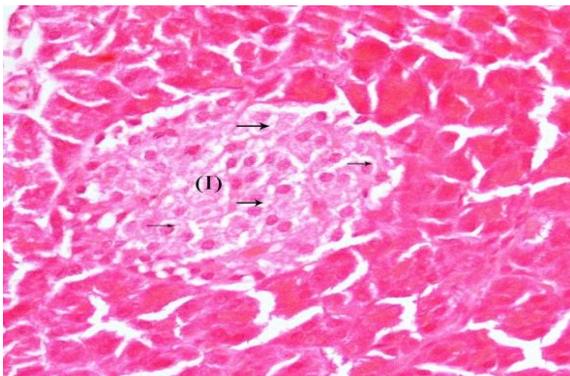


Figure (7) A photomicrograph of a section of the pancreatic tissue of H+ 0.5% Psy seeds group with normal cellularity without fatty acid deposition (Hx&E. X 200 )

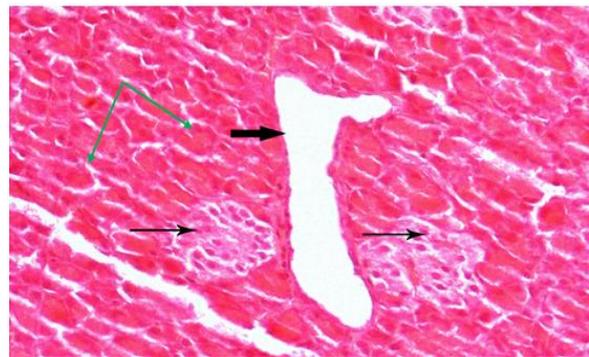


Figure (8) A photomicrograph of a section of the pancreatic tissue of H+ 1.0%Psy seeds group showing normal pancreatic island (thin arrows) with normal exocrine part as normal looking acini (green arrows) also blood vessels look like normal.(H<sub>x</sub>&E. X200)

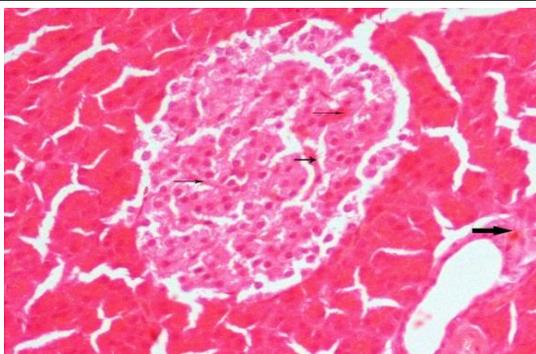


Figure (9) A photomicrograph of a section of the pancreatic tissue of DH+0.5% Psy seeds group showing normal pancreatic endocrine island but still with minimal cellularity (thin arrows) and hyaline deposition on the blood vessel wall (thick arrows) (Hx&E. X 200 )

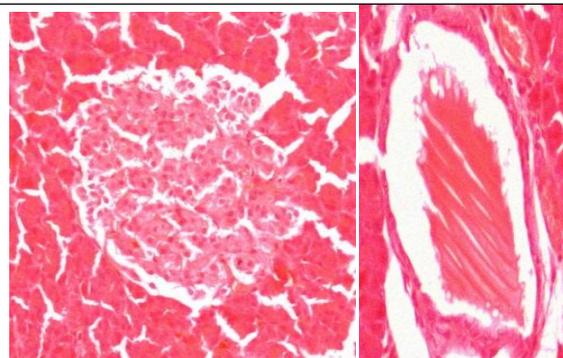


Figure (10) A photomicrograph of a section of the pancreatic tissue of the DH rat with 1% Psy seeds group showing in the right side that the pancreatic island get improved without fatty acids depositions in the exocrine pancreatic tissue ,also in the left side showing the blood vessels with normal thickness without hyaline deposition in its wall (Hx&E. X 200, 400 )

## 4. Discussion:

### 4- Discussion :

The goal of the present study was designed to investigate the anti-diabetic and/ or the hypolipidemic effects of *plantago psyllium* seeds added to diet in two tested doses at (0.5 and 1 % w/w) in experimental groups which were fed on balanced diet or HFHC diet by measuring changes in the biological and biochemical parameters.

The results of the present study showed that injection with STZ produced hyperglycemia and hypoinsulinemia in rats .On the other hand, psyllium seeds reversed STZ-induced change in glucose and insulin levels.STZ enter  $\beta$  cells via a glucose transporter (GLUT2) using a variety of intracellular toxic mechanisms such as production of oxygen free radicals that causes degeneration of pancreatic  $\beta$ -cells leading to hypoinsulinemia and subsequent hyperglycemia (**Bhateja and Singh, (2016);and Guang-Kai et al.,(2017).**

Moreover, induction of hyperlipidemia caused insulin resistance which indicated by compensatory hyperinsulinaemia and marked increase in HOMA-IR. In agreement with our study **Ribeiro et al. (2012 )** found that experimental model fed on a HFHC diet led to obesity and insulin resistance which reflected by hyperinsulinemia . Similarly, **Haroun et al. (2011)** investigated that both HFHC and high fructose diets intake caused insulin resistance with hyperglycemia, hyperinsulinemia, hyperlipidemia and hypertension in rats.

Also, in agreement with our results **Karhunen et al. (2010)** found that psyllium fiber enriched meals improve glucose and insulin level significantly than non- fiber enriched meals. The glucose-reducing action of psyllium is proposed due to the formation of a viscous gel in aqueous solution. This gel may hinder the access of glucose to the absorptive epithelium of the small intestine, thereby blunting postprandial glucose peaks. In addition, soluble fiber may delay gastric emptying, thus slowing carbohydrate uptake. Another mechanism that may contribute to the postprandial effect of psyllium is the sequestration of carbohydrates ingested with the meal, thus retarding their access to digestive enzymes (**Pal et al., 2014**). Also, the hypoglycemic activity of psyllium seeds may be due to the inhibition of liver gluconeogenesis. Furthermore, the increased level of serum insulin by increase insulin secretion from the remnant of  $\beta$ -cells and enhancement of peripheral metabolism of glucose. Hypoglycemic activity of psyllium seeds may be due to modulating effects on insulin sensitization and/or insulin secretion and a regulating action on digestion and intestinal absorption.

One of the possible mechanism by which psyllium seeds produce hypoglycemic activity is that, Caffeic acid which present at high level in *planatago psylum* seeds reduce blood glucose level by virtue of their ability to inhibit glucose-6-phosphatase activity, with the related effects on hepatic glucose production and enhancing the glucose kinase (GK) activity in the liver . Hepatic GK has a major effect on glucose homeostasis and is a potential target for pharmacological treatment of Type 2 diabetes. The increase of hepatic GK can cause an increased utilization of the blood glucose for energy production or glycogen storage in the liver (**Kalaiarasi and Pugalendi, (2009); and Mohammed et al., 2015**).

Moreover, STZ-induced diabetes seems to cause impairment in lipid and lipoprotein metabolism. Also, insulin deficiency is associated with hypercholesterolemia and hypertriglyceridemia due to metabolic abnormalities. In normal conditions, insulin increases the receptor-mediated removal of LDL-C, and decreased activity of insulin during diabetes causes hypercholesterolemia. The increased concentration of TC could result in a relative

molecular ordering of the residual PL, resulting in a decrease in membrane fluidity (**Murali et al., 2002**). A good explanation for the increment of TAGs in diabetes is that lipoprotein lipase (LPL), which hydrolyses TAGs into monoglycerides and fatty acids, is inhibited by apolipoprotein CIII and is activated by apolipoprotein CII and insulin. Reduced insulin action may thus increase plasma TAGs by lowering their clearance rate. Enhanced hepatic production of TAGs rich VLDL-C also contributes to the increase in TAGs. Briefly, the transfer of cholesterol ester from HDL-C and LDL-C to triacylglycerols rich lipoprotein (VLDL-C and chylomicrons), and the transfer of TAGs in the opposite direction is mediated by cholesterol ester transfer protein (CETP), the activity of which is increased in type 2 diabetes. TAGs in the LDL-C particle is hydrolyzed by hepatic lipase, making it smaller and denser. In response to elevated concentrations of plasma triacylglycerols-rich lipoproteins, as is typically the case in patients with type 2 diabetes, the rate of transfer is increased. Hyperglycemia is associated with enhanced glycation of LDL-C and an increase in free radical production (**Scheffer et al., 2003**).

Furthermore, other possible mechanism for hyperlipidemia in DM is explained by **Smith and Lall, (2008)** that in diabetes, many factors may affect blood lipid levels and this is because carbohydrates and lipid metabolism are interrelated to each other. If there is any disorder in carbohydrate metabolism it also leads to disorder in lipid metabolism. So, there is high concentration of cholesterol, TAGs and due to this there is a reduction in HDL-C levels. Also, insulin deficiency causes excessive metabolism of free fatty acids, this may lead to a disorder in lipid metabolism. Moreover, free fatty acids (FFA) elevation is often associated with hyperlipidemia, which is a risk factor of insulin resistance. Hyperlipidemia includes an increase in TC, FFA, and TAGs levels. These lipid indicators are normally down regulated by insulin. When insulin resistance happens, one or more of these parameters will increase in the blood. Insulin stimulates uptake of FFA by liver and adipose tissue, and conversion of FFA into TAGs. Insulin also induce uptake of TAGs in lipid protein by adipocytes. When adipose tissue lost response to insulin, the levels of FFA and TAGs will increase in the blood.

On the other hand, One of the mechanism of action of psyllium for increasing lipid oxidation and reducing fat may be due to activation of the transient receptor potential vanilloid receptor (TRPV1) channel. It promotes calcium entry that is necessary to prevent preadipocyte-to-adipocyte differentiation. TRPV1 activation may ultimately reduce the number and size of fat cells, and therefore reduce the propensity for obesity to be developed.

Also, another mechanism by which psyllium promotes weight loss may be due to increase the energy expenditure in adipose tissue by stimulating lipolysis and thermogenesis by stimulation of adrenaline secretion from adrenal gland. This increase in serum adrenaline leads to activation of hormone-sensitive lipase (HSL), the key enzyme in the regulation of lipid stores. Moreover, HDL-C protects against or reverse atherosclerosis by their ability to serve as acceptor particles for macrophage cholesterol efflux, prevention of endothelial dysfunction, and maintenance of endothelial integrity (**Linsel-Nitschke and Tall, 2005**). A decrease in the HDL-C was observed in the present study on diabetic rats, which will increase the chances of atherosclerosis. Treatment with psyllium seeds showed marked elevation in the HDL-C level as compared to that in the controls. The increase in HDL-C is associated with a decrease in coronary risk (**Singh et al., 2007**).

Moreover, three major hypotheses have frequently been postulated to explain the cholesterol-lowering action of soluble dietary fiber, including psyllium (**Anderson et al., 2000; Cornfine et al., 2010; and Anderson et al., 1999**). First, the digestion of macronutrients is delayed by viscous soluble fiber, which slows gastric emptying, thus decreasing the transport and mixing of digestive enzymes, and increasing the resistance of the unstirred water layer lining the mucosa to intestinal absorption (**Lairon, 2007**). This can lead

to a reduced glycemic response due to a reduction in glucose absorption (**Bourdon et al., 1999**), and a subsequent decrease in postprandial glucose levels, which is accompanied by a reduction in insulin levels. Decreased insulin levels can then result in the inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase) and a subsequent reduction in hepatic cholesterol synthesis (**Lundin et al., 2004**). Second, the presence of soluble fiber in the small intestine may physically prevent bile salt reabsorption into the enterohepatic circulation, resulting in increased fecal bile salt excretion. This may deplete bile salt in the liver, causing cholesterol to be rapidly catabolized in hepatocytes to replenish the bile salt pool via activation of cholesterol 7- $\alpha$ -monooxygenase. In addition, there is increased production of LDL-C surface membrane receptors, thus enhancing LDL-C uptake from the bloodstream and consequently lowering cholesterol levels (**Marlett et al., 2002; Ellegard and Andersson, 2007**). Third, fiber reduces hepatic cholesterol synthesis that is modulated by fermentation products, such as propionate, leading to decreased cholesterol absorption and bile acid reabsorption by physically disrupting the intraluminal formation of micelles (**Anderson et al., 2000**). It is well known that soluble dietary fibers are not digested or absorbed in the small intestine, but instead undergo anaerobic bacteria fermentation in the cecum and colon to produce short-chain fatty acids (Short-chain fatty acids, particularly propionate, seem to deplete plasma cholesterol by inhibiting hepatic cholesterol metabolism via mechanisms that include reducing HMG-CoA receptor activity and inhibiting of acetyl-CoA reductase, which catalyzes the synthesis of acetyl-CoA from acetate. The hypolipidemic effect of psyllium seeds doesn't seem to be due to only one component, but rather to the synergetic action of its different constituents, including soluble fiber, phenolic compound, flavonoids, oleic, linoleic, linolenic, caffeic acids and chlorogenic acid. Flavonoids may act by making liver cells more efficient to remove LDL-C from blood by increasing LDL-C receptor densities in liver and by binding to apo-lipoprotein B (**Gunness et al., 2010**)).

Moreover, elevated blood sugar in diabetes can trigger direct protein glycation and glucose auto-oxidation which results in molecular and functional changes in proteins and production of free radicals that contribute to development of oxidative stress in STZ-diabetic rats (**Ghosh et al., 2015; and Koroglu et al., 2015**). Furthermore, increased level of serum glucose, as a reducing agent, can reduce molecular oxygen ( $O_2$ ) under physiological conditions, yielding acetaldehydes, hydrogen peroxide ( $H_2O_2$ ) and free radical intermediates. Free radical scavenging enzymes such as GPx and G6PD are the first line of defense against injury, and are involved in the disposal of superoxide anions and hydrogen peroxide. The present work has observed decreased activities of GPx and G6PD in diabetic rats and rats fed on HFHC diet, which may be an important factor in limiting the antioxidant capacity because of increased MDA level. Administration of the psyllium seeds along with a HFHC diet caused a significant increase in the activities of these enzymes indicating that the compounds present in the seeds such as flavonoids protect the tissues from lipid peroxidation by their antioxidant ability and consequent reduction in lipid peroxidation. Also, psyllium seeds reversed TAC and MDA changes induced by STZ and HFHC diet. TAC represents a suitable biochemical parameter for evaluating the overall antioxidant status resulting from antioxidant intake or production and their consumption by the increasing level of oxidative stress (**Kusan and Ferrari, 2008**)).

Moreover, the antioxidant activities of psyllium seeds may be due to caffeic acid which present in high levels in psyllium seeds are based on carbonyl group separated from the aromatic ring. The antioxidant mechanism of action is assumed to be through its radical-scavenging activity that is linked to their hydrogen- or electron-donating ability and to the stability of the resulting phenoxyl radicals. It has been documented that caffeic acid possess non-enzymatic antioxidant activity such as scavenging free radicals, and enzymatic

antioxidant activity such as increasing protein level of antioxidant enzymes (**Kalaiarasi and Pugalendi, 2011**). In the present study decreasing lipid peroxidation by administration of psyllium seeds may be attributed to psyllium ability to modulate lipid parameters, protein glycation, glucose-oxidation, thus leading to decrease production of lipid peroxidation products and may be attributed to its antioxidant activity, because psyllium have many phenolic compounds, which have inhibitory effects on lipid peroxidation and preserve the antioxidant compounds

On the other hand, psyllium seeds are rich source of natural antioxidants, PUFAs ( $\omega$ -3 and  $\omega$ -6 fatty acids) and essential and sulfur-rich amino acids, as recommended by the FAO for human health. Psyllium contains phenolics and flavonoids that possess reducing capacity and reactive oxygen species (ROS) scavenging activities. Also, Psyllium contains different metabolites most of the metabolites are natural antioxidants, phenolics, flavonoids, alkaloids and can be used as nutrient supplements. *Plantago* species are considered to be a natural reservoir of diverse biologically active secondary metabolites, such as lipids, flavonoids, alkaloids, and terpenoids (**Patel et al., 2016**).

The present work indicates significant increase in hepatic total cholesterol and triacylglycerols in diabetic and hyperlipidemic groups. **Ravi et al. (2005)** reported that there were a significant increase in the total lipids of liver in STZ-induced diabetic rats and this may indicates an increased synthesis of lipids and storage capacity, which caused an increase in serum triacylglycerols and phospholipids. Authors reported that variety of derangement in metabolic and regulatory mechanisms due to insulin deficiency is responsible for the observed accumulation of lipids. The increase in lipids observed in diabetic rats was due to the impairment of insulin secretion, which resulted in enhanced mobilization of lipid from the adipose tissue to the plasma. Also, **Guo et al. (2014)** showed that fiber which present in psyllium seeds decreased the concentrations of plasma and liver cholesterol in rats fed with a hypercholesterolemic diet by increasing daily excretions of fecal bile acids.

On the other hand, the histopathological results indicate significant morphological changes in diabetic rats which indicated by decreasing the cellularity of pancreatic  $\beta$ -cells by replacing it with hyaline deposition. Also, the thickened and hyalinized blood vessels causing not enough oxygen reach the tissue which resulted in degenerative changes. In agreement with our results **Erukainure et al. (2013)** who showed shrinkage and atrophy of  $\beta$ -cells of islets of Langerhans in the diabetic animals compared to normal islets in control group. Then treatment with fiber –enriched cake increased the number of islets as compared to diabetic untreated animals.

Our results indicated the role of psyllium in mediating mechanisms in protecting the pancreatic tissue from diabetes induced disorders. The reduction of hyperglycemia may be a cause of such protection. Our study provides valuable information that supports the possibility of preventing or at least attenuating pancreatic island damage in diabetes by diet supplementation with psyllium which contain high amount of antioxidants.

## **5. Conclusion:**

The results of the present study showed that diet supplemented with psyllium seeds showed hypoglycemic hypolipidemic effects in addition of having significant antioxidant prosperities. Therefore, it was concluded that *plantago psyllium* seeds may be considered helpful to lower glucose and lipid levels in treatment of hyperglycemia and hyperlipidemia as well as protect against cardiovascular diseases risk.

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## المستخلص العربي

"تأثير تناول بذور السيليوم علي خفض سكر ودهون الدم في الجرذان المصابة بالسكري وارتفاع دهون الدم " صممت هذه الدراسة لمعرفة تأثير إضافة بذور السيليوم بجرعتين (0.5% و 1%) الى الوجبات المستخدمة في تجربته ودورها في تحسين مستوي السكر والدهون بالدم في مجموعات الجرذان المصابة بمرض السكري والمجموعات المصابة بارتفاع دهون الدم. حيث اجريت تجربته علي 80 من ذكور الجرذان البالغين ووزعت علي عشر مجموعات تحتوي كل مجموعة علي 8 من الجرذان كالاتي: المجموعة (1) : الضابطة، المجموعة (2) : المصابة بالسكري، المجموعة (3) : المصابة بارتفاع دهون الدم، المجموعة (4) : المصابة بالسكري وارتفاع دهون الدم، المجموعتين (5 و 6) : المصابتان بالسكري وتناولتا الوجبات مدعمة بمستوي (0.5% و 1% السيليوم) علي التوالي، المجموعتين (7 و 8) : المصابتان بارتفاع دهون الدم و تناولتا الوجبات المدعمة بمستوي (0.5% و 1%) من بذور السيليوم علي التوالي، و اخيرا، المجموعتين (9 و 10) : المصابتان بالسكري و ارتفاع دهون الدم و تناولتا الوجبات المدعمة بمستوي (0.5% و 1% السيليوم).

واستمرت التجربة لمدة 6 اسابيع ثم تم ذبح الجرذان بعد صوم 12 ساعه وتم تجميع عينات الدم والاعضاء (الكبد والبنكرياس) اللازمة للتقديرات البيوكيميائية. حيث تم تقدير مستوي الجلوكوز ومستوي الانسولين ومعامل مقاومه الانسولين ومؤشر كفاءة خلايا البنكرياس بالدم (بيتا). وكذلك تم قياس دهون الدم وتشمل (الدهون الكامله , الفوسفوليبيدات , الكوليستيرول الكلي , الدهون الثلاثيه , الكوليستيرول منخفض الكثافه , الكوليستيرول عالي الكثافه) وايضا تم تقدير المؤشرات الخاصه بمخاطر امراض القلب والشرابين. بالاضافه الي ذلك تم تقييم حاله الاكسده عن طريق تقدير القدره الكليه لمضادات الاكسده , و نشاط كل من انزيمي الجلوتاثيون بيروكسيداز , و الجلوكوز 6 فوسفات ديهيدروجينيز, وتركيز المألون داي الدهيد , وكذلك مؤشر الاكسده. كما تم تدعيم النتائج بالفحص الميكروسكوبي لخلايا البنكرياس. واطهرت النتائج ان تناول الجرذان للوجبات المدعمة ببذور السيليوم (0.5, 1%) لمدته 6 اسابيع قد أدى الى تحسن مستوي الجلوكوز في الجرذان المصابة بالسكري وذلك عن طريق خفض مستوي السكر وزيادة كفاءه خلايا البيتا وزيادة افراز الانسولين، كما اوضحت الدراسة ايضا ان بذور السيليوم ادت الي انخفاض معامل مقاومه الانسولين وانخفاض مستوي الانسولين في المجموعات المصابة بارتفاع دهون الدم، كما تحسنت ايضا حاله الدهون العامه حيث تم انخفاض (الدهون الكامله , الفوسفوليبيدات , الكوليستيرول , الدهون الثلاثيه , الكوليستيرول منخفض الكثافه ) , وزيادة معدل الكوليستيرول عالي الكثافه. كما أثبتت الدراسة الدور الهام لبذور السيليوم في حمايه القلب من أمراض تصلب الشرايين. كما اكدت الدراسة علي دور السيليوم في حمايه الانسجه من التلف المحدث بواسطه الضغط التأكسدي كما اظهر الفحص الميكروسكوبي لخلايا البنكرياس وذلك عن طريق تحسن شكل خلايا البنكرياس . كما اظهرت النتائج تأثير بذور السيليوم كمضاد للاكسده حيث انخفض معدل المألون داي الدهيد ومؤشر الاكسده في الدم وزيادة القدره الكليه لمضادات الاكسده وزيادة نشاط انزيم الجلوتاثيون بيروكسيداز , وانزيم الجلوكوز 6 فوسفات ديهيدروجينيز. ويرجع هذا الدور الوقائي للسيليوم و تأثيره كعامل مضاد للاكسده لان هذه البذور غنيه بالالياف والفلونويدات و الأحماض الدهنية غير المشبعة التي بدورها تحمي الخلايا من الشقوق الحره.

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