Antidiabetic Effect of Flaxseed (*Linum usitatissimum* L.) on Hepatic Lipid Metabolism of Alloxan-Induced Diabetic Rats

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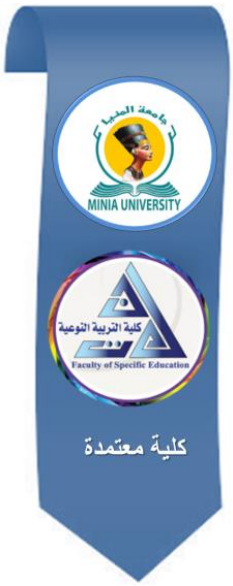

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Abstract

Medicinal plants and their constituents have long been regarded as a safe treatment for a variety of diseases, particularly diabetic complications. Flaxseed (*Linum usitatissimum L.*) was used to investigate the hyperglycemic and hyperlipidemic effects based on its antioxidant content because of its Herbacetin, a dietary flavonoid with many pharmacological activities. Thirty-five male albino rats weighing 180 ±5 g were used and divided into 5 groups, each of 7 rats for 30 days. The first group fed on a basal diet, served as a normal control group. Twenty- eight rats were injected with alloxan with a single intravenously (40 mg/kg b.w) to induce diabetes and randomly classified in to four groups, diabetic (untreated), the other three groups treated with oral administration of flaxseed extract (FE) at a dose of 150 ml/kg BW and (10% and 20%) flaxseed powder (FP), for a period of 30 days, flavonoids, total phenols and Scavenging activity were detected. Also, changes in body weight, feed efficiency ratio (FER), blood glucose, insulin, lipid peroxidation and the antioxidant defense system and lipid-regulating enzymes were evaluated.FE followed by FP groups showed significant improvement in diet consumption parameters compared to diabetic control, flaxseed administration caused a significant reduction in plasma glucose and plasma insulin. Furthermore, significant amelioration in tissue liver lipid peroxidation (MDA) was conducted in treated-diabetic rats however, SOD, GPx and GSH antioxidant enzymes increased significantly compared to the negative control group. High flavonoid contents with total phenols tend to make significantly mended the hepatic lipid-regulating enzymes such as glucose 6-phosphate dehydrogenase (G6PD), β-oxidation activity and fatty acid synthase (FAS) near- normal levels especially PE group followed by FP 20% then FP 10% compared to non-treated

diabetic control.In conclusion, Oxidative damage associated with diabetes was ameliorated with treatment with flaxseed extract and powder. The attenuate effects are mainly attributed to antioxidant properties and the presence of bioactive and nutraceutical compounds especially flavonoid contents in high amounts.

Key Words: Glucose 6-phosphate dehydrogenase, Antioxidant enzymes, Insulin, Glucose and Fatty acids.

Introduction

Flaxseed or linseed (*Linum usitatissimum L.*) comes from the flax plant, an annual herb. The major importance of flaxseed is in the human nutrition sector because it is developing as an important functional food element thanks to the content of active compounds, pointed to provide health benefits. There are several ways to eat flaxseed: milled, in the form of oil or add to a bakery product **(Bernacchia *et al.*, 2014).**

The one of the primogenial cultivated crops (flaxseed), continues to be commonly grown for oil, fiber, and food **(Oomah, 2001)**. Flaxseed has been emerging as one of the key sources of bioactive components **(Kaur et al., 2018**), which has been certain that it's strengthened fibre, omega-3 fatty acids and lignan secoisolariciresinol diglucoside **(Parikh *et al.*, 2019).** For thousands of years, flaxseed has been intended for oil crops or fibre resources. The major lignan compounds in flaxseed are secoisolariciresinol (SECO) and its diglucoside (SDG). Flax lignan was also a source of beneficial biologically active components origin in plant foods, such as phytochemicals, and it was considered as a functional crop **(Toure & Xu, 2010**).

Linum usitatissimum L., also known as flaxseed, is an herb in the Linaceae family. Its anti-inflammatory and antioxidant properties are believed to assist in wound healing **(Draganescu *et al.*, 2015 & Rafiee *et al.*, 2017).** Many educations discuss biologically active compounds in flaxseed that participate in the wound healing process such as omega 3 fatty acids (**Jurić et al., 2020)** and flaxseed carbohydrates **(Trabelsi *et al.*, 2020)**. In addition, the phenolic compound is also one of the numerous components found in flaxseed,

for example caffeic acid, pcoumaric acid, and ferulic acid, together with the presence of secoisolariciresinol diglucoside (SDG) impedes to antioxidant possessions for wound remedial process **(Wang *et al.*, 2017).** Reactive oxygen species (ROS) such as superoxide anions prevent or slow down the wound healing process by mischievous the cellular structure. Antioxidant molecules present in flaxseed can protect the healthy cell by sequestering the ROS hence preventing oxidative stress **(Draganescu et al., 2015 & Rafiee et al., 2017).** During adenosine triphosphate (ATP) production, the premature leak of electrons to oxygen was one of the issues for free radical production. As a result, superoxide anions were formed from the premature leak of electrons in the electron carriage chain during aerobic respiration and slow down the healing method of a wound as they will damage the cell's DNA **(Atkin *et al.*, 2019).**

Diabetes mellitus (DM) is a metabolic disturbance, which is characterized by a persistent rise in blood glucose level (BGL) as a consequence of the change in macromolecules such as carbohydrate, fat, and protein metabolism **(Shyam & Kadalmani, 2014)**. The two main pathophysiologies of DM are impairment of insulin action and secretion **(Akter, *et al.*, 2013*).*** Type 1 DM and type 2 DM are the two most common forms of DM **(Patel *et al.*, 2012).** Currently DM is becoming a leading public health problem globally. The World Health Organization (WHO) records nine percent (9%) of adults living in both developing and developed countries stick from DM **(Hosseini et al., 2015)**.

The insulin hormone has the major function of regulating blood glucose levels. The absence of insulin or inadequate activity of the hormone due to cut-price sensitivity of the insulin sense can cause an abnormality in blood glucose homeostasis **(Al-Qudah et al., 2016)**. Exposure to the diabetogenic substance of alloxan decreases disrupts blood glucose homeostasis and the level of insulin. Alloxan is a diabetogenic substance that is cytotoxic to the pancreatic islets **(Diab et al., 2015)**. The current oral medicines for DM are in the sulfonylurea, biguanide, and acarbose groups **(Lopamudra & Choudhury, 2016).**

The occurrence of DM, a chronic metabolic disorder characterized by persistent hyperglycemia, has been consistently

cumulative over the past few decades, and becoming a global epidemic in modern society **(Infante-Garcia & Garcia-Alloza, 2019)**. The progression of diabetes reasons numerous complications, such as renal disorder, hypertension, hyperlipidemia, hyperglycemia, vascular diseases, and neurodegeneration **(Forbes & Cooper , 2013)**. Therefore, this study was conducted to estimate the ameliorative effects of defatted (*Linum usitatissimum L.*) - enriched flavonoids on hepatic lipid metabolizing and lipid-regulating enzymes of alloxan-induced diabetic rats.

Materials and methods

Materials:

Cellulose, Casein, vitamin mixture, minerals, and the kits which were used for biochemical analysis were purchased from El-Gomhoria Company for Trading Drugs, Chemicals and Medical Requirements. Flaxseed was obtained from the Agricultural Research Centre, Giza, Egypt.

Thirty-five albino rats of Sprague-Dawley strain weighing approximately 180 ± 5 g were purchased from Helwan Farm for Experimental Animals, Cairo, Egypt.

Methods:

Plant material:

The flaxseed powder (FP) and extract (FE) was made following the descriptions of **Mechchate et al., (2021)** with minor modifications. Flaxseeds were washed with tap water, sun- dried, then ground into a fine powder using an electrical grinder to fine particles to obtain flaxseed powder (FP). Moreover, the portion of the powder was defatted (because it's high - fat content) using 10 g of FP was washed with hexane (30 mL) until the hexane is clear, then, extraction was performed with the ultrasound assisted extraction apparatus applied for 40-45 min extraction, the defatted powder was mixed with 70% methanol. The extract was filtered through Whatman filter paper (No. 5) and concentrated to dryness then mixed with distilled water (DW), then the extract was concentrated under vacuum and dried in desiccators. The dried extract was used for further assessment.

Experimental animal design

Preparation of basal diet

The basal diet was prepared according to **Reeves et al., 1993**. It consists of 20 % protein, 10 % sucrose, 4.7% corn oil, 2% choline chloride, 3.5 % salt mixture, 1% vitamin mixture, and 5% fibers.

Thirty - five male albino rats weighing 180 ±5 g were used and divided into 5 groups, each of 7 rats for 30 days. The first group fed on a basal diet, served as a normal control group. Twenty - eight rats were injected by alloxan with a single intravenously (40 mg/kg b.w) to induce diabetes and randomly classified in to four groups, diabetic (untreated), the other three groups treated with oral administration of flaxseed extract (FE) at a dose of 150 ml/kg BW and (10% and 20%) flaxseed powder (FP), for a period of 30 days.

After injection of rats with alloxan, animals were divided into 4 subgroups as follows:

Subgroup (1) Diabetic rats were fed on basel diet as positive control group.

Subgroup (2) Diabetic rats were fed on basel diet supplemented with 10% flaxseed powder.

Subgroup (3) Diabetic rats were fed on basel diet supplemented with 20% flaxseed powder.

Subgroup (4) Diabetic rats were treated with oral administration of flaxseed extract (FE) at a dose of 150 ml/kg BW

At the end of the experiment (4weeks) all rats fasted overnight, lightly anesthetized under ether. Blood was withdrawn into clean dry centrifuge plastic tubes. Blood samples were centrifuged and serum was obtained then stored at -20º C in a clean well stopped vial until analysis.

Feeding and Growth Parameters:

Feed intake (FI) was determined, feed efficiency ratio (FER), body weight gain (BWG%) and organs relative weight were calculated according to **(Chapman et al., 1959).**

Biochemical analysis

Serum glucose and insulin were determined according to the method described by **(Astoor and King, 1954)** and **(Temple et al., 1992)**, respectively. The liver enzyme alanine aminotransferase (ALT), Aspartate aminotransferase (AST) were determined according to **Sherwin, 1984, (Young, 1990)** respectively. Serum urea nitrogen, and creatinine concentration were determined by the method of **Fossati et al., (1980),** and **Henry, (1974)** respectively. The estimation of Glutathione GSH activity was determined by the procedure of **Carlberg and Mannervik, (1985) .**Serum MDA was determined according to **Draper and Hadly, (1990).** Serum activity, and serum SOD were measured according to **Aebi, (1984),** and **Nishikimi et al., (1972)**, respectively. Fatty acid synthase (FAS) and fatty acid β-oxidation activity (β-oxidation) were evaluated using the methods illustrated by **Nepokroeff et al., (1975) and Lazarow, (1981)**. Glucose 6-phosphate dehydrogenase (G6PD) activities were evaluated by the spectrophotometrical method described by **Pitkanen et al., (1997).**

Scavenging Effect on DPPH Radicals:

The antioxidant activity of Ribes rubrum oil was measured using the DPPH assay **(Malencic et al., 2007).**

Analysis of total phenols and flavonoids:

The total phenolics of the extracts were determined using the Folin and Ciocalteu reagent, following the method described by **(Chandra et al., 2014)** with slight modifications. Sample and standard readings were made using a spectrophotometer (Cary 50 Bio UV-Vis Spectrophotometer, Varian) at 765 nm against the reagent blank. On the other hands, the aluminum chloride colorimetric method illustrated by **(Marinova., et al 2005)** with slight modifications total flavonoid determination, quercetin was used to make the standard calibration

curve, that was used for the determination of the total flavonoid content of the sample.

Statistical analysis

The statistical analysis was carried out by using SPSS, PC statistical software (Version 18.0 SPSS Inc., Chieago, USA) using the Dunk 'test multiple range post-hoc test. Data were analyzed by one-way analysis variance (ANOVA). The values were considered significantly different at P <0.05 **(Snedecor and Cochran, 1980)**.

Results and Discussion

Determination of active compounds content in flaxseed

The total phenolic content of defatted flaxseed is presented in Table (1).

Table (1): Contents of active compounds of defatted flaxseed.

Flavonoids % (mg QE/g dry wt.)	**Total phenols %** (mg GAE/g dry wt)
51.15 ±3.6	**28.42±2.7**

Table (2): Antioxidant activity of *Linum usitatissi-mum L.*

Antioxidant activity is expressed as percent DPPH radical scavenging activity with higher values indicating greater antioxidant activity. The antioxidant activity of FP 10% and FP 20 % were 62.2±2.4 % and 78.7±2.2%, respectively. However, FE 150 ml/kg has antioxidant activity with a mean value of 93.2±1.7.

Linum usitatissimum L. Doses	**Scavenging activity of DPPH radicals (%)**
FP 10 %	62.2±2.4
FP 20 %	78.7±2.2
FE 150 ml/kg	93.2±1.7

The effect of flaxseed on FI, BWG and FER on experimental rats.

The effect of flaxseed powder and flaxseed extract on feed intake (FI), body weight gain (BWG) and feed efficiency ratio (FER) of diabetic rats are recorded in Table (3).

Results indicated that the mean value of feed intake (FI) of the negative control rats recorded 18.33±1.27 g/day. However, when rats were become diabetic (positive control group), their food intake was decreased significantly with a mean value of 12.64±1.16 g / day.

Data revealed that, rats fed on flaxseed with 10% FP, 20% FP, and FE (150 ml /kg BW) had reduced feed intake significantly with a mean value of (15.45±1.65 g/day, 17.33±1.44 g/day and 17.45±1.43, respectively) compared to the positive control group.

Regarding body weight gain (BWG), it was significantly lowered ($P< 0.05$) for the positive control group when compared with the negative control group (36.22±0.32 g, and 63.31±0.41 g, respectively). When rats were intake flaxseed at level 10% FP, 20% FP, and FE (150 ml /kg BW) had increased BWG significantly with a mean value of (43.21±0.23 g/day, 49.24±0.22 g/day and 52.31±0.14, respectively) compared to positive control group.

Data of feed efficiency ratio (FER) were shown in table (1). Results revealed that the positive control group decreased significantly ($P< 0.05$) when compared with the negative control group with a mean value of (0.040 ± 0.02 and 0.128 ± 0.04, respectively). Diet supplemented with L-glutamine (2%, and 3%) were increased significantly FER with a mean value of (0.146 ± 0.04, and 0.109 ± 0.02, respectively) when compared with the positive control group (0.04 ± 0.02). However, a diet supplemented with L-glutamine (1%) was increased non-significantly with a mean value (0.087 ± 0.03) when compared with the positive control group (0.04 ± 0.02).

Individuals who consume flaxseed have additional benefits on the adiposity and a greater tendency to lose weight (**Wu et al., 2010)**. Abdominal obesity is asserted as a potential risk factor of multiple sclerosis (MS) **(Robinsonand Graham, 2004).** Thus, the reversion of

this fat accumulation is an important preventive measure against this disease onset. The mechanism by which flaxseed works in the reversal of abdominal obesity remains unclear, although evidence suggests that the abundance of polyunsaturated fatty acids in the diet can serve as a modulator for body fat deposition **(Wu *et al.*, 2010)** .

Results of body weight gain in this study were in the same line with those reported by **(Zanoni et al., 2011),** who found that the diabetic animals had lower body weight than the normal glycemic animals.

Khalesi *et al.*, (2011) concluded that although food consumption was slightly lower in groups with a higher percentage of flaxseed, no significant difference was observed between the average food intake between any treatment group and the control group ($p > 0.05$). Also within groups analysis of food intake showed no significant difference.

Table (3): The effect of flaxseed on FI, BWG and FER on experimental rats.

Values are expressed as mean ± S.D. Means with the different superscript letters in the same column were significantly different at $P \leq 0.05$.

Parameters / Groups	BWG %	Feed intake(g/d)	FER
Normal Control (NC)	63.31 ± 0.41^{a}	18.33 ± 1.27^{a}	0.099 ± 0.002^{a}
Diabetic Control (DC)	36.22 ± 0.32^{c}	12.64 ± 1.16^{b}	$0.050\pm.005^{c}$
DC +FP (10 % diet)	43.21 ± 0.23^{b}	15.45 ± 1.65^{a}	0.081 ± 0.003^{b}
DC + FP (20 % diet)	49.24 ± 0.22^{b}	17.33 ± 1.44^{a}	0.088 ± 0.002^{b}
DC + FE (150ml/kg BW)	52.31 ± 0.14^{ab}	17.45 ± 1.43^{a}	0.094 ± 0.004^{ab}

Efficient role of *Linum usitatissimum L.* on plasma glucose and insulin levels of the experimental rats.

Results in Table (4) showed the effect of flaxseed extract and flaxseed powder on the plasma glucose of the experimental rats. Results showed that plasma glucose was increased significantly in rats suffering from diabetes with a mean value of 292.12 ± 4.56 mg/dl compared with the normal control group with a mean value of 85.11 ± 2.61 mg/dl. Results revealed that all treated rats showed a reduction in plasma glucose compared diabetic rats.

Results in Table (4) showed the effect of flaxseed extract and flaxseed powder on insulin levels of the experimental rats. Data indicated that insulin level was decreased significantly in rats suffering diabetes with a mean value of 6.31 ± 0.44 µU/ml compared with the normal control group with a mean value of 15.77 ± 1.02 µU/ml Results revealed that all treated rats showed an increase in insulin levels compared to diabetic rats. The best results were seen in rats fed on flaxseed extract (150ml/kg BW).

The increased levels of fasting blood glucose in diabetic rats were lowered by the administration of *Linum usitatissimum* (FPE and FHE) in a dose and time - dependent manner. The reduced glucose levels might be suggested by the insulin - like effect on peripheral tissues by either promoting glucose uptake metabolism by inhibiting hepatic gluconeogenesis, or by absorption of glucose into the muscle and adipose tissues, through the stimulation of a regeneration process and revitalization of the remaining beta cells. Moreover, oral administration of FPE and FHE effectively reversed body weight loss by reversing muscle wasting and protein loss and also significantly attenuated hyperglycemia as compared to DN rats **(Kaur *et al.*, 2016)**.

Trans fatty acids present in flaxseed oil offer an effective dietary strategy for the prevention of atherosclerotic cardiovascular disease **(Bassett et al., 2011)** and decrease postprandial glucose responses. Flaxseeds are the richest source of plant lignans. The lignan Secoisolariciresinol diglycoside (SDG) is present in greater quantity in the seed coat. In humans, ingested SDG is converted by bacteria in the colon to biologically active lignans enterodiol and enterolactone **(Hano**

***et al.*, 2006**). These SDG metabolites possess antioxidant activity and have been shown to effectively inhibit the development of type 1 and 2 diabetes **(Prasad, 2000)**. The effect of FHE on the amelioration of DN can thus be attributed to the presence of SDG in the extract.

Table (4): Efficient role of *Linum usitatissimum L.* on plasma glucose and insulin levels of the experimental rats.

Groups Parameters Parameters	Glucose (mg/dL)	Insulin (µU/mL)
Normal Control (NC)	85.11 ± 2.61^{f}	15.77 ± 1.02^{a}
Diabetic Control (DC)	292.12 ± 4.56^{a}	6.31 ± 0.44^{f}
DC +FP (10 % diet)	173.22 ± 1.23^{b}	9.62 ± 1.09^{cd}
DC + FP (20 % diet)	136.3 ± 7.24^{c}	11.89 ± 1.12^{c}
DC + FE (150ml/kg BW)	117.18 ± 1.32^{cd}	13.48 ± 1.04^{b}

Values are expressed as mean ± S.D. Means with the different superscript letters in the same column were significantly different at $P \leq 0.05$.

Efficient role of *Linum usitatissimum L.* on tissue liver lipid peroxidation and antioxidant enzymes of experimental rats.

Results in Table (5) illustrate the effect of Linum usitatissimum L. on tissue liver lipid peroxidation and antioxidant enzymes of experimental rats.

Results of superoxide dismutase (SOD) concentration; as a marker of oxidative stress; diabetic control group showed a significant decrease in SOD concentration compared with the normal control group with a mean value of (117.34±7.24 u/ml and 188.19±6.97 u/ml) respectively. Furthermore, feeding Diabetic rats on oral administration

of FE at a dose of 150 ml/kg BW and FP (10% and 20%) resulted in a marked decrease in SOD concentrations compared with the diabetic control group.

Concerning glutathione peroxidase (GPx), concentration; results showed that there was a decrease in GPx concentration of diabetic control group with a mean value of (32.54±2.66 µ /mg) compared with the normal control group (77.46±4.27µ /mg). All treated groups showed a significant increase in GPx concentration compared with the diabetic control group.

The data in the same table clarified that Glutathione (GSH) level was a decrease in the diabetic control group with a mean value of (1.06±0.02 µ /mg) compared with the normal control group (3.21±0.03µ /mg). However, all treated groups showed a significant increase in GSH levels compared with the diabetic control group.

Concerning the first studied marker of oxidative stress; malondialdehyde (MDA) concentration; results showed that there was an increase in MDA concentration of diabetic control group with a mean value of (14.434±1.09nmol/ml) compared with the Normal control group (6.52±0.33nmol/ml). All treated groups showed a significant decrease in MDA concentration compared with the Diabetic control group.

Rapid lipid peroxidation could have been caused by highly reactive by-products of ethanol metabolism. In a rat model, an ethanol-induced increase in lipid peroxidation was also reported by **(Macdonald *et al.*, 2010).** The diet containing FP was effective in preventing lipid peroxidation by significantly lowering the levels of MDA in the liver homogenate of EtOH-AIN-FPC in comparison to the EtOH-AIN group. Lower levels of MDA in the liver homogenate of the EtOH-CP-FS group implicate the role of flaxseed in preventing ethanol-induced lipid peroxidation. The CHF also produced marked protection against lipid peroxidation.

Antioxidant enzymes such as SOD, glutathione reductase, and catalase work together against toxic reactive oxygen species. In response to the increased production of reactive oxygen species resulting from alcohol metabolism, the antioxidant enzyme activities

may have been elevated as a defense mechanism. **(Das &Vasudevan , 2005)** also made a similar observation in liver homogenates of rats subjected to chronic ethanol exposure and noted elevated SOD activity. These findings suggest that alcohol administration can result in increased oxidative stress leading to the stimulation of antioxidant enzymes activities to cope with the free radicals. Flaxseed and its protein significantly ameliorated ethanol-induced alteration in the antioxidant enzyme activities in the liver homogenate. Flaxseed protein exhibited antioxidant property by quenching the free radicals produced by ethanol metabolism. Similarly, other oilseed protein such as soy protein isolate was also reported to possess an antioxidant properties by efficiently reducing paraquat-induced oxidative stress in a rat model **(Takenaka et al., 2003).** Thus, flaxseed protein can also be explored as a potential source of natural antioxidants. Flaxseed also markedly attenuated alteration in antioxidant enzymes activity caused by ethanol. The antioxidant properties of phenolics and lignan components of flaxseed potentially scavenged the free radical produced by alcohol metabolism.

Hyperglycemia is responsible for the diminution of antioxidant enzymes such as SOD and GSH. LPO is another process that involves a source of secondary free radical; thus, it acts as a second messenger or can directly react with other biomolecules, further enhancing the biochemical lesions. Moreover, administration of different doses of FPE and FHE ameliorated the oxidative stress via the increasing levels of antioxidant enzymes **(Kaur et al., 2017).**

Hypercholesterolemia induces oxidative stress by causing a reduction in the tissue defense antioxidant enzymes, leading to acceleration of lipid peroxidation, cellular injury, atherosclerosis, and heart disease **(Green et al., 2011)**. Antioxidant enzymes such as CAT, SOD, GPx, GR, and GST activity were reduced in diabetic rats compared to normal rats **(Prabha et al., 2013)**. Addition of flaxseeds on rats diet improved all the antioxidant enzymes CAT, SOD, GPx, GR, and GST and modestly reduced the levels of TBARS. It might be due to the antioxidant action of flaxseeds **(Zanwar et al., 2013)**.

Table (5): Efficient role of Linum usitatissimum L. on tissue liver lipid peroxidation and antioxidant enzymes of experimental rats.

Parameters / Groups	SOD (µ/ mg)	GPX (µ /mg)	GSH (µ /mg)	MDA (µmol /g)
Normal Control (NC)	188.19±6.97 [a]	77.46±4.27 [a]	3.21±0.03 [a]	6.52±0.33 [d]
Diabetic Control (DC)	117.34±7.24 [d]	32.54±2.66 [c]	1.06±0.02 [d]	14.434±1.09 [a]
DC +FP (10 % diet)	141.21±5.64 [c]	39.61±3.66 [bc]	1.35±0.01 [c]	11.17±1.17 [b]
DC + FP (20 % diet)	154.26±5.81 [b]	48.34±5.11 [ab]	1.82±0.02 [c]	9.89±1.21 [c]
DC + FE (150ml/kg BW)	163.23±5.76 [b]	56.42±4.71 [ab]	2.47±0.01 [b]	8.48±0.26 [dc]

Values are expressed as mean ± S.D. Means with the different superscript letters in the same column were significantly different at $P \leq 0.05$.

Efficient role of *Linum usitatissimum L.* on activities of hepatic lipid-regulating enzymes of experimental rats.

Table (6) showed the effect of FP and FE on the activities of hepatic lipid-regulating enzymes of experimental rats. Results showed that there was a significant decrease of glucose-6-phosphate dehydrogenase (G6PD) in the diabetic control group with a mean value of 50.07 ± 1.13 nmol/min/mg protein when compared with the normal control group (31.02 ± 1.12 nmol/min/mg protein) . All treated groups showed a significant decrease in G6PD levels compared with the diabetic control group. Moreover, the best value of G6PD levels was noted in the group which treated with flaxseed extract (FE) at a dose of 150 ml/kg.

Regarding β-Oxidation, the diabetic control group showed significantly higher β-Oxidation than that of the normal control group fed a normal diet with mean values of (6.38 ± 0.28 nmol/min/mg protein & 2.45 ± 0.24nmol/min/mg protein) respectively. All treatments groups significantly decreased in β-Oxidation than the diabetic control group.

Fatty acid synthase (FAS) level was significantly increased in diabetic rats (positive control group) with a mean value of (48.52 ± 1.50 nmol/min/mg protein) compared with that of normal control group (34.46 ± 1.24 nmol/min/mg protein). fatty acid synthase (FAS) near - normal levels especially flaxseed extract group followed by flaxseed powder 20% then flaxseed powder 10% compared to non-treated diabetic control.

Flaxseeds are grouped as "functional food and/or endocrine active food" by virtue of the presence of physiologically active food components that may provide health benefits beyond basic nutrition **(Hasler *et al.*, 2000)**. Trans fatty acids present in flaxseed oil offer an effective dietary strategy for the prevention of atherosclerotic cardiovascular disease and decrease postprandial glucose responses **(Bassett *et al.*, 2011)**.

Glucose-6-Phosphate dehydrogenase is known as a useful biomarker for the antioxidant system and its activity is increased in oxidative stress **(Salvemini et al., 1999; Gul et al., 2004).** The soluble fibers of flaxseed also allow intestinal glucose uptake to be delayed, which can attenuate the need for insulin production and, as a consequence, diminish its synthesis. Another mechanism involved in the normalization of the glycemic profile is related to the fact that lignan suppresses the gene expression of phosphoenolpyruvate carboxykinase (PEPCK), which is related to the production of glucose, through gluconeogenesis, helping in glycemic control. The effects of regularization of the glycemic profile have also been attributed to PUFAs found in brown flaxseed (**Mohammadi et al., 2018).**

Table (6):Efficient role of *Linum usitatissimum L.* on activities of hepatic lipid-regulating enzymes of experimental rats.

Parameters / Groups	G6PD (nmol/min/mg protein)	β-Oxidation (nmol/min/mg protein)	FAS (nmol/min/mg protein)
Normal Control (NC)	31.02 ± 1.12^{d}	2.45 ± 0.24^{d}	34.46 ± 1.24^{c}
Diabetic Control (DC)	50.07 ± 1.13^{a}	6.38 ± 0.28^{a}	48.52 ± 1.50^{a}
DC +FP (10 % diet)	43.03 ± 1.16^{b}	4.96 ± 0.19^{ab}	42.33 ± 1.50^{ab}
DC + FP (20 % diet)	39.08 ± 1.16^{bc}	4.19 ± 0.18^{b}	39.54 ± 1.45^{b}
DC + FE (150ml/kg BW)	35.03 ± 1.14^{cd}	3.64 ± 0.21^{c}	38.21 ± 1.34^{b}

Values are expressed as mean ± S.D. Means with the different superscript letters in the same column were significantly different at $P \leq 0.05$.
G6PD: glucose-6-phsophate dehydrogenase; β-Oxidation: fatty acid β-oxidation; FAS: fatty acid synthase;

The results of the study concluded that the increased levels of fasting blood glucose in diabetic rats were lowered by the administration of Linum usitatissimum in a dose and time - dependent manner. The diet containing flaxseed was effective in preventing lipid peroxidation by significantly decrease in SOD and MDA, significant increase in GPx and GSH levels compared with the diabetic control group. All treated groups showed a significant decrease in G6PD levels compared with the diabetic control group. Defatted (Linum usitatissimum L.) - enriched flavonoids possesses a property of ameliorative effects on hepatic lipid metabolizing and lipid-regulating enzymes of alloxan-induced diabetic rats.

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التأثير المضاد لبذور الكتان على التمثيل الغذائي للدهون الكبدية في الفئران المصابة بمرض السكرالمستحث بـالألوكسان

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الملخص العربى

تعتبر النباتات الطبية ومكوناتها علاجًا آمنًا لمجموعة متنوعة من الأمراض ، لا سيما مضاعفات مرض السكري. لذلك تهدف هذه الدراسه الى معرفة تأثيرات استخدام بذور الكتان لفحص تأثيرات ارتفاع السكر في الدم ودهون الدم بناءً على محتواها من مضادات الأكسدة وخصوصا محتواها من الهيرباستين ، وهو فلافونويد غذائي له العديد من الأنشطة الدوائية .تم استخدام خمسة وثلاثين فأرا من ذكور فئران الالبينو البالغة وزن (180 ± 5 جم) وتم تقسيمهم إلى 5 مجموعات (كل مجموعة = 7فئران) وكانت مدة التجربة 30 يومًا. المجموعة الاولى تغذت على الغذاء الاساسى (المجموعة الضابطة). بينما تم حقن 28 فأرا بمادة الألوكسان بجرعة واحدة عن طريق الوريد (40 ملجم / كجم من وزن الجسم) لاحداث الاصابة بمرض السكري وتم توزيعهم عشوائيًا إلى أربع مجموعات ، المجموعة الثانية المصابة بالسكري (غير معالجة) ، والمجموعات الثلاث الأخرى حيث المجموعه الثالثة و الرابعة تم تغذية الفئران على مسحوق بذور الكتان بنسبتى (10٪ و 20٪) بينما المجموعه الخامسة تم تغذيتهم عن طريق الفم بمستخلص بذور الكتان بجرعة 150 مل / كجم من وزن الجسم لمدة 30 يومًا ، وقد تم تقدير مركبات الفلافونويد والفينولات الكلية . كما تم تقييم التغيرات في وزن الجسم ، ونسبة كفاءة التغذية ، وجلوكوز الدم ، والأنسولين ، وبيروكسيد الدهون ونظام الدفاع المضاد للأكسدة والإنزيمات المنظمة للدهون .وقد أظهركلا من مستخلص الكتان و مسحوق الكتان تحسنًا معنويًا في معايير استهلاك النظام الغذائي مقارنةً بالتحكم في مرض السكري ، وأظهر تناول بذور الكتان في انخفاض معنوي في جلوكوز البلازما وأنسولين البلازما. علاوة على ذلك ، تم إجراء تحسين كبير في بيروكسيد دهون الكبد (MDA) في الفئران المصابة بداء السكري ، والعكس بالنسبة للإنزيمات المضادة للأكسدة SOD و GPx و GSH تحسنت مع تناول مستخلص الكتان و مسحوق الكتان عن المجموعة الضابطة الموجبة .تميل محتويات الفلافونويد العالية مع الفينولات الإجمالية إلى إصلاح الإنزيمات المنظمة للدهون الكبدية بشكل كبير مثل الجلوكوز 6-فوسفات ديهيدروجينيز (G6PD) ونشاط الأكسدة بيتا- سينسيزو الأحماض الدهنية بالقرب من المستويات الطبيعية خاصة فى المجموعة التى تم تغذيتها على مستخلص الكتان تليها المجموعة التى تغذت على بذور الكتان بنسبة 20% ، ثم المجموعة التى تغذت على بذور الكتان بنسبة 10% مقارنة بالمجموعة المصابة بالسكرى الغير معالجة. وفى نهاية الدراسة لوحظ انخفاض الضرر التأكسدي المصاحب لمرض السكري عن طريق العلاج بخلاصة بذور الكتان ومسحوقها. وتعزى التأثيرات المخففة بشكل أساسي إلى الخصائص المضادة للأكسدة ووجود المركبات النشطة بيولوجيًا والمغذيات خاصة محتويات الفلافونويد بكميات كبيرة.

الكلمات المفتاحية: جلوكوز6 فوسفات ديهيدروجينيز، انزيمات مضادات الأكسدة، الانسولين ، جلوكوز و الأحماض الدهنية