

RESEARCH ARTICLE

The influence of *Ginkgo Biloba* on hepatic gene expression of (*PGC1- α* , *PPAR- α* and *GLUT-2*), liver, kidney functions, hematological and lipid profile in type I diabetic rats

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Abstract

Ginkgo biloba is one of a well-known medicinal plant worldwide, where is prescribed in working on various diseases, such as diabetes mellitus type I and II, peripheral vascular abnormalities, and neurodegenerative illnesses like Alzheimer's disease. The purpose of this study was to know how oral *Ginkgo biloba* administration affected the liver, kidneys, hematological parameters, lipid profile, and hepatic gene expression in type I diabetic rats. Seventy-five male adult Sprague Dawley rats were allocated into five equal groups 15 rats each, 1st group; control group, 2nd group; diabetic group, 3rd group; *Ginkgo biloba* group, 4th group; Diabetic treated group received single oral dose of *Ginkgo biloba* after diabetic induction as a treatment and 5th group; rats were administered daily single oral dose of *Ginkgo biloba* as a protective dose from the 1st day of the study prior to diabetes induction and continued after the diabetes induction till the end of the work. The results of study revealed that *Ginkgo biloba* actions in modulating of hepatic key genes GLUT-2 (glucose transporter-2), PPAR- α (Peroxisome proliferator-activated receptor alpha), and PGC1- α (The peroxisome proliferator-activated receptor gamma coactivator-1). Also, *Ginkgo biloba* possesses antihyperlipidemic activities, supports liver and kidney functions and improves glucose metabolism, storage and utilization in liver by enhancing its key genes. based on the outcomes of current study *Ginkgo biloba* is an effective food supplement or a supportive treatment for type I diabetes mellitus.

Keywords Hepatic key genes, Diabetes mellitus, *Ginkgo biloba*, Gene expression.

Introduction

In recent ages, significant public health diseases existed that threatening human life. One of these basic diseases is diabetes mellitus [1]. Diabetes mellitus is considered set of metabolic changes known as "chronic metabolic syndrome," which is associated with an elevated rate of morbidity and mortality. This disease is caused by limited insulin secretion from pancreatic β -cells as a consequence to β -cell damage, as well as a malfunction in insulin performance leading to disorders in the metabolism of carbohydrate, protein, fat [2] and hyperglycemia with glucosuria, polydipsia, and polyuria [3].

The cause of primary idiopathic diabetes may be hereditary or environmental. Diabetes mellitus can be juvenile-onset or mature-onset. The former is insulin-dependent, as it is linked to the pancreas' ability to release insulin being diminished or nonexistent. The non-insulin dependent is characterized by relatively inefficient insulin in spite of normal excretion. [4].

The popular name *Ginkgo* is a Japanese word for the tree; however, the species name *biloba* alludes to the two different lobes that are characteristic of the tree's leaves. It is a matchless plant due to its respective classification in the plant kingdom, and it is considered a living fossil as one of the oldest known seed plants [5].

The active antioxidant constituents in *G. biloba* leaf extract contain 20-27 percent flavonoids (the majority are isorhamnetin, quercetin, kaempferol, and proanthocyanidins), 5-7 % terpenoids (the majority are ginkgolides A, B, C, M, J, and bilobalide) and 5-10% organic acids [6]. *G. biloba* has direct antioxidant properties by scavenging reactive oxygen radicals and chelating transition metals [7]. *G. biloba* treatment, on the other hand, can modulate fatty acid metabolism and enhance non-saturated fatty acid levels in the blood [8].

The basic hepatic liver transporter, glucose transporter 2 (*GLUT-2*), is a high-capacity transporter found on hepatocyte sinusoidal membranes, the basolateral membrane of intestinal epithelial cells, renal proximal tubule cells, and pancreatic beta-cells. Under insulin control, the hepatic glucose transporter *GLUT2* plays a key function in promoting bidirectional glucose transport across the plasma membrane of hepatocytes [9].

The key receptor peroxisome proliferator-activated receptor Alpha (*PPAR- α*) has emerged as an effective insulin sensitizer. There are three *PPAR* isotypes: α , δ and γ , all of which have a role in controlling the expression of genes involved in lipid storage, glucose metabolism, morphogenesis, and the inflammatory reaction [10].

A transcription factor *PGC-1 α* (peroxisome proliferator-activated receptor-gamma coactivator-1 alpha), is a specific gene that influences lipid metabolism and long-chain fatty acid oxidation by upregulating the expression of numerous genes in the tricarboxylic acid cycle and mitochondrial fatty acid oxidation pathway [11].

This study aimed to estimate the *ginkgo biloba* antihyperlipidemic activities and its supportive role in glucose metabolism, utilization, and storage in liver by enhancing its key genes.

Materials and Methods

Plant and chemicals

Ginkgo Biloba was obtained from coated tablets manufactured by MARCYRL Pharmaceutical Industries. Each tablet was adjusted to contain 21.6-26.4% ginkgo flavonoid glycosides and 5.4-6.6% terpene lactones (ginkgolides, bilobalide). Streptozotocin (STZ) was obtained from (Sigma Chemical Co. St. Louis, Mo, USA).

Experimental animals

Present study was carried out on 75 male adult Sprague Dawely rats (150-200) body weight. Animals were kept under hygienic conditions in metal cages with hard wood shavings as bedding and maintained on light/darkness cycle 12/12 hours and given feed and water ad-libitum throughout the experimental period. This study was accepted and completed by the approval of the Zagzaig University Committee (Animal Care and Welfare Committee). The approval Number is **ZU-IACUC/2/F/83/2021**.

Experimental Design

The study lasted 60 days and consisted of five groups Each group was occupied by 15 rats.

1st Group (CG): The group was represented as a negative control or non-diabetic one ,and were given a standard diet.

2nd Group (DG): The rats of this group were considered as diabetic control or positive control by once I/P injection of STZ (Sigma, USA) at the dose of 60mg/kg at 30th day of the study [12].

3rd Group (GB): This group involved rats that given *ginkgo biloba* (MARCYRL Pharmaceutical Industries) at the dose of 200mg/kg BW once daily by oral from the 1st day till the end of study for 60 days.

4th Group (D+GB): As a treatment group, rats of this group were diabetic at 30th day of the study with once I/P injection of STZ at the dose of 60mg/kg BW then applied by *ginkgo biloba* at the dose of 200mg/kg b.wt once daily by oral till the end of study [13].

5th Group (GB+D+GB): As a protective group, rats of this group were given *ginkgo*

biloba at the dose of 200mg/kg b.wt once daily by oral from the 1st day of study ,then at 30th day of the study diabetes was induced by STZ 60mg/kg BW with once I/P injection of STZ 60mg/kg BW then *Ginkgo biloba* were applied 200mg/kg b.wt once daily till the end of study [14].

The study lasted 60 days. On the 30th day , the induction of diabetes was applied to groups (DG), (D+GB) and (GB+D+GB) by once intra- peritoneally injection of STZ (Sigma, USA) at the dose of 60mg/kg. Samples of fasting blood were obtained from tip of tail of rats after 3 days of STZ injection overnight and glucose levels was measured (ACCU check, Germany). Rats which had fasting blood glucose levels more than 250 mg/dl were included in the work as diabetic rats. Treatment with *Ginkgo biloba* [21.6-26.4% ginkgo flavonoid glycosides and 5.4-6.6% terpene lactones (ginkgolides, bilobalide)] started at dose of 200mg/kg BW once daily by oral and the blood samples were measured weekly by (ACCU check, Germany) till the end of study.

Samples

Blood sampling, Hematological and biochemical analysis

Five ml fasting state samples of blood were obtained aseptically via cardiac puncture of all rats at the end of the 60th days in a sterile vacuoner tube containing Na₂EDTA as an anticoagulant for Haematological examination (RBCs, WBCs, Platlets and HB). In other sterile tube without anticoagulant, blood sample was obtained for separation of serum for biochemical analysis

(FSG, AST, ALT, Urea, creatinine, albumin, globulin, total protein, triglyceride, HDL-C, LDL-C and VLDL-C) [15].

Tissue samples and hepatic genes mRNA expressions

Hepatic tissues were collected freshly and stored at -80 °C using Trizol. RNA extraction process occurred at (Laboratory of biotechnology, Faculty of Veterinary Medicine, Zagazig University) using Trizol (Invitrogen; Thermo Fisher Scientific, Inc.), according to the manufacturer's instructions. Quantification of total RNA was measured at 260 nm. . The A260/A280 ratio was analyzed using the NanoDrop® ND-1000 Spectrophotometer (NanoDrop Technologies; Wilmington, Delaware, United States) for 1.5 µl of the RNA. Total (1 µg) RNA was transformed to cDNA through the process of revers transcription using a High-Capacity cDNA Reverse Transcription Kit cDNA Kit; (Applied Biosystems™, USA) in a 20 µl reaction volume. Quantitative PCR was performed using TOPreal™ qPCR 2X PreMIX (SYBR Green with low ROX) (Cat. # P725 or P750) (Enzynomics, Korea). Primers were prepared as the manufacturer instructions and kept at -20°C until used for subsequent PCR analysis .Primers Sequence as listed in (Table 1) was selected by the primer3 website. By using GADPH, the mRNA levels were normalized as a housekeeping gene and by using the $\Delta\Delta CT$ method, relative quantification was performed.

Table 1:

Primers' sequences and expected product sizes used in the work.

Gene	Primer sequence (5'→3')		Expected product size (bp)	accession No.
<i>GAPDH</i>	<i>GAPDH Forward</i>	CAACTCCCTCAAGATTGTCAGCAA	118 bp	NM_017008
	<i>GAPDH Reverse</i>	GGCATGGACTGTGGTCATGA		
<i>PGC1-α</i>	<i>PGC1-α Forward</i>	TTCAGGAGCTGGATGGCTTG	70 bp	NM_031347.1
	<i>PGC1-α Reverse</i>	GGCAGCACACTCTATGTCA		
<i>PPAR-α</i>	<i>PPAR-α Forward</i>	GTCCTCTGGTTGTCCCCTTG	176 bp	NM_013196.2
	<i>PPAR-α Reverse</i>	GTCAGTTCACAGGGAAGGCA		
<i>Glut-2</i>	<i>Glut-2 Forward</i>	GGTGTTCCTCTGGATGACCG	183 bp	NM_012879.2
	<i>Glut-2 Reverse</i>	CATTCCGCCTACTGCAAAGC		

GAPDH: Glyceraldehyde-3- phosphate dehydrogenase, *PGC1-α*: The peroxisome proliferator-activated receptor gamma coactivator-1 alpha, *PPAR-α*: Peroxisome proliferator-activated receptor alpha, *Glut-2*: glucose transporter-2.

Statistical Analysis

One-way analysis of variance (ANOVA) was used to examine the values of all groups in the expression analysis. Results were expressed as means ± SE (standard error) of the mean and $P \leq 0.05$ were considered a significant in all tests, unless stated otherwise. Differences were considered to be significant at the level of ($P \leq 0.05$).

Results

Blood and fasting serum glucose concentration

The results of the fasting blood glucose levels, were measured weekly after induction of diabetes by STZ from week 5 to week 8, revealed that type1 diabetes induced a significant ($P < 0.001$) increase in the mean values compared to control group. The results of 5th week and 8th week in DG were (412±16.52 mg/dl), (454.62±13.9 mg/dl)

respectively compared to the control group (104.67±3.71 mg/dl), (114.67±3.71 mg/dl) respectively. However, orally administration of *G.biloba* either diabetic or non-diabetic groups (GB), (D+GB) and (GB+D+GB) significantly $P < 0.01$ reverted the mentioned parameters towards the normal average of physiological level. The results of the 5th and 8th weeks, GB group were 117.67±7.97 mg/dl, and 112±5.13 mg/dl respectively. The D+GB group revealed 263.67±4.91 mg/dl, and 201.67±31.36 mg/dl correspondingly, moreover the GB+D+GB group had (265±3.46 mg/dl, and 239.67±1.77 mg/dl levels respectively. Besides, the results of fasting serum glucose concentration in the DG at the end of study is significant ($P < 0.00001$) higher (271.33±3.75 mg/dl) than CG (109.33±2.60 mg/dl). However, *G.biloba* groups either diabetic or non-diabetic groups (GB), (D+BG) and (GB+D+GB) showed significant decrease ($P < 0.00001$) in FSG concentration (119.33±2.03 mg/dl), (235.33±3.75 mg/dl),

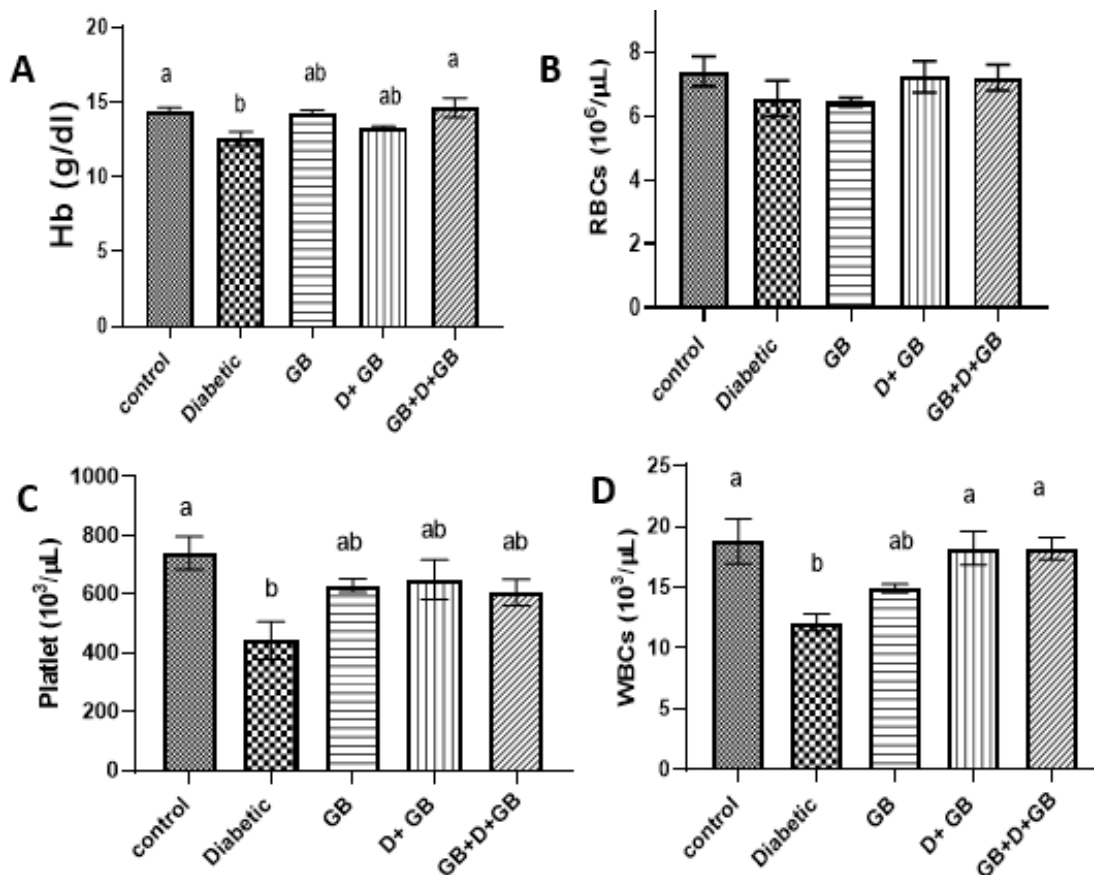
(208.67±7.69 mg/dl) respectively compared to diabetic one (DG).

Hematological measurements

As in Figure 1, results showed in diabetic gp. DG that there was a significant decrease ($p < 0.05$) in Hb concentration, platelets and WBCs (12.53 ± 0.49 g/dl), ($444.33 \pm 63.50 \times 10^3/\mu\text{l}$) and ($12.09 \pm 0.71 \times 10^3/\mu\text{l}$) respectively compared with the control group CG (14.4 ± 0.23 g/dl), ($741 \pm 56.0 \times 10^3/\mu\text{l}$) and ($18.8 \pm 1.84 \times 10^3/\mu\text{l}$) respectively, showing features of anemia and leukopenia. Meanwhile, *ginkgo biloba*

treated groups either diabetic or non-diabetic in GB, D+BG and GB+D+GB showed significant increase ($P < 0.05$) in HB (14.25 ± 0.20 g/dl), (13.27 ± 0.12 g/dl), (14.63 ± 0.64 g/dl) respectively, platelets ($630 \pm 22.52 \times 10^3/\mu\text{l}$), ($651 \pm 66.84 \times 10^3/\mu\text{l}$), ($606.67 \pm 44.38 \times 10^3/\mu\text{l}$) respectively and WBCs levels ($14.89 \pm 0.36 \times 10^3/\mu\text{l}$), ($18.22 \pm 1.39 \times 10^3/\mu\text{l}$), ($18.17 \pm 0.92 \times 10^3/\mu\text{l}$) respectively compared to diabetic one. Otherwise, RBCs count, the results showed that there were no significant differences among groups, $P = 0.448$ ($P > 0.05$).

Figure 1: Effect of oral administration of *ginkgo biloba* (21.6-26.4% ginkgo flavonoid glycosides and 5.4-6.6% terpene lactones) 200 mg/kg BW at 60 days pre and post diabetic induction on the mean value of ; **A.** Hemoglobin (HB gm/dL), **B.** Red blood cells (RBCs $10^6/\mu\text{L}$), **C.** Platelets ($10^3/\mu\text{L}$) and **D.** White blood cells (WBCs $10^3/\mu\text{L}$), in type (I) STZ-induced diabetic rats. All values are mean \pm S.E.M; n=8. Control: control group; diabetic: diabetic group; GB: *Ginkgo biloba* group; D+GB: Diabetic+ *Ginkgo biloba* group; GB+D+GB: *Ginkgo biloba*+ Diabetic+ *Ginkgo biloba* group.



Biochemical parameters of the serum

Serum concentrations of AST, ALT, creatinine and urea in different groups were measured. In the diabetic group (DG), serum *ginkgo biloba* in groups (GB), (D+GB) and (GB+D+GB) showed significant decrease ($p \leq 0.001$) in AST and ALT compared to diabetic one. Concerning to urea and creatinine, there were significant increase ($p < 0.00001$) and ($p < 0.05$) respectively in DG compared to CG.

AST and ALT were significantly increased ($p \leq 0.001$) compared to control group. However, rats were administered orally with

Meanwhile *ginkgo biloba* treated groups either diabetic or non-diabetic (GB), (D+GB) and (GB+D+GB) showed significant decrease in urea and creatinine ($p < 0.00001$) and ($p < 0.05$) respectively compared to (DG) (Table 2).

Table 2: The effect of *Ginkgo biloba* on biochemical parameters (ALT, AST, Creatinine and Urea) and Lipid profile (Total cholesterol, Triglycerides, HDL-C, LDL-C and VLDL-C) for 60 days in type (I) STZ-induced diabetic rats.

	ALT (μ /L)	AST (μ /L)	Creatinine mg/dL	Urea mg/dL	Cholesterol mg/dL	TG mg/dL	HDL-C mg/dL	LDL-C mg/dL	VLDL-C mg/dL
Control	53.00 ^b ± 1.732	183.5 ^{bc} ± 3.175	0.733 ^b ± 0.049	23.5 ^b ± 2.02073	104.66 ^{bc} ± 6.009	86.00 ^b ± 6.658	52.00 ^a ± 1.154	70.5 ^{abc} ± 4.330	16.566 ^b ± 1.69
Diabetic	108.0 ^a ± 10.50	238.00 ^a ± 9.237	1.536 ^a ± 0.248	58.667 ^a ± 4.09	136.00 ^a ± 0.577	139.5 ^a ± 10.037	37.33 ^b ± 4.33	84.00 ^a ± 0.577	27.233 ^a ± 1.714
GB	56.00 ^b ± 3.464	175.00 ^{bc} ± 13.279	0.7300 ^b ± 0.017	23.00 ^b ± 577	94.00 ^c ± 3.511	79.00 ^b ± 6.429	44.00 ^{ab} ± 2.309	53.33 ^{bc} ± 3.756	17.133 ^b ± 1.702
D+GB	68.00 ^b ± 4.358	162.33 ^c ± 7.623	0.7233 ^b ± 0.003	26.5 ^b ± 866	95.00 ^c ± 8.082	65.5 ^b ± 0.288	45.5 ^{ab} ± 2.020	49.5 ^c ± 6.062	13.4 ^b ± 0.115
GB+D+G B	73.00 ^b ± 5.033	206.33 ^{ab} ± 2.603	0.7400 ^b ± 0.051	31.00 ^b ± 1.154	124.00 ^{ab} ± 1.154	69.333 ^b ± 5.811	49.5 ^a ± 0.866	74.5 ^{ab} ± 6.062	18.00 ^b ± 0.346
P-value	0.0004	0.001	0.002	0.000002	0.0003	0.00009	0.015	0.002	0.0003

Serum protein profile

Data revealed as in Figure 2 that diabetic gp. (DG) revealed a significant decrease ($p < 0.05$) in albumin (4.253 ± 0.578 gm/dl) compared to control group (CG) (4.563 ± 0.108 gm/dl). Meanwhile, rats administered orally with *ginkgo biloba* in groups (GB), (D+GB) and (GB+D+GB) had a significant increase ($p < 0.05$) in the level of albumin (4.553 ± 0.060 gm/dl), (4.326 ± 0.037 gm/dl) and (4.63 ± 0.040 gm/dl) respectively compared to (DG) with no significant changes between groups in total protein, globulin and A/G ratio, $P = 0.129$, 0.076 and 0.251 ($P > 0.05$) respectively.

Serum lipid profile

The results showed a significance increase in serum cholesterol ($p < 0.001$), triglyceride ($p < 0.0001$), LDL-C ($p < 0.05$) and VLDL-C ($p < 0.001$) in STZ-diabetic rats (DG) and a significant decrease ($p < 0.05$) in HDL-C level compared with control group (CG). However, rats administered orally with *ginkgo biloba* in groups (GB), (D+GB) and (GB+D+GB) showed a significant decrease in triglyceride ($p < 0.0001$), cholesterol ($p < 0.001$), LDL-C ($p < 0.05$), VLDL-C ($p < 0.001$) and a significant increase ($p < 0.05$) in HDL-C level compared to (DG) (Table 2).

mRNA Expression of Hepatic genes

The study illustrated the hepatic key genes mRNA expression of *PGC1- α* (The peroxisome proliferator-activated receptor alpha coactivator-1), *PPAR- α* (Peroxisome proliferator-activated receptor alpha) and *Glut-2* (glucose transporter-2).

The results of this current work showed a significant downregulation ($p < 0.0001$) in *Glut-2*, *PPAR- α* and *PGC1- α* mRNA expression in diabetic group (DG) (0.33 ± 0.01), (0.19 ± 0.05) and (0.28 ± 0.04) respectively compared with control group

(CG) (1 ± 0.05), (1.01 ± 0.08) and (1 ± 0.01) respectively. However, *Ginkgo biloba* treated groups either diabetic or non-diabetic (GB), (D+GB) and (GB+D+GB) showed a significant upregulation ($P < 0.0001$) in mRNA expression of *Glut-2* (1.5 ± 0.01), (4.19 ± 0.55) and (1.42 ± 0.14) respectively, *PPAR- α* (1.65 ± 0.16), (5.11 ± 0.35) and (1.39 ± 0.07) respectively and *PGC1- α* (1.1 ± 0.04), (3.83 ± 0.09) and (1.48 ± 0.17) respectively, compared with diabetic one Figure 3.

Figure 2: Effect of oral administration of *ginkgo biloba* (21.6-26.4% ginkgo flavonoid glycosides and 5.4-6.6% terpene lactones) 200 mg/kg BW at 60 days pre and post diabetic induction on the mean value of ; A. Total protein (g/dL), B. Albumin (g/dL), C. Globulin (g/dL) and D. Albumin/ Globulin ratio (A/G) in type (I) STZ-induced diabetic rats. All values are mean \pm S.E.M; n=8. control: control group; diabetic: diabetic group; GB: *Ginkgo biloba* group; D+GB: Diabetic+ *Ginkgo biloba* group; GB+D+GB: *Ginkgo biloba*+ Diabetic+ *Ginkgo biloba* group.

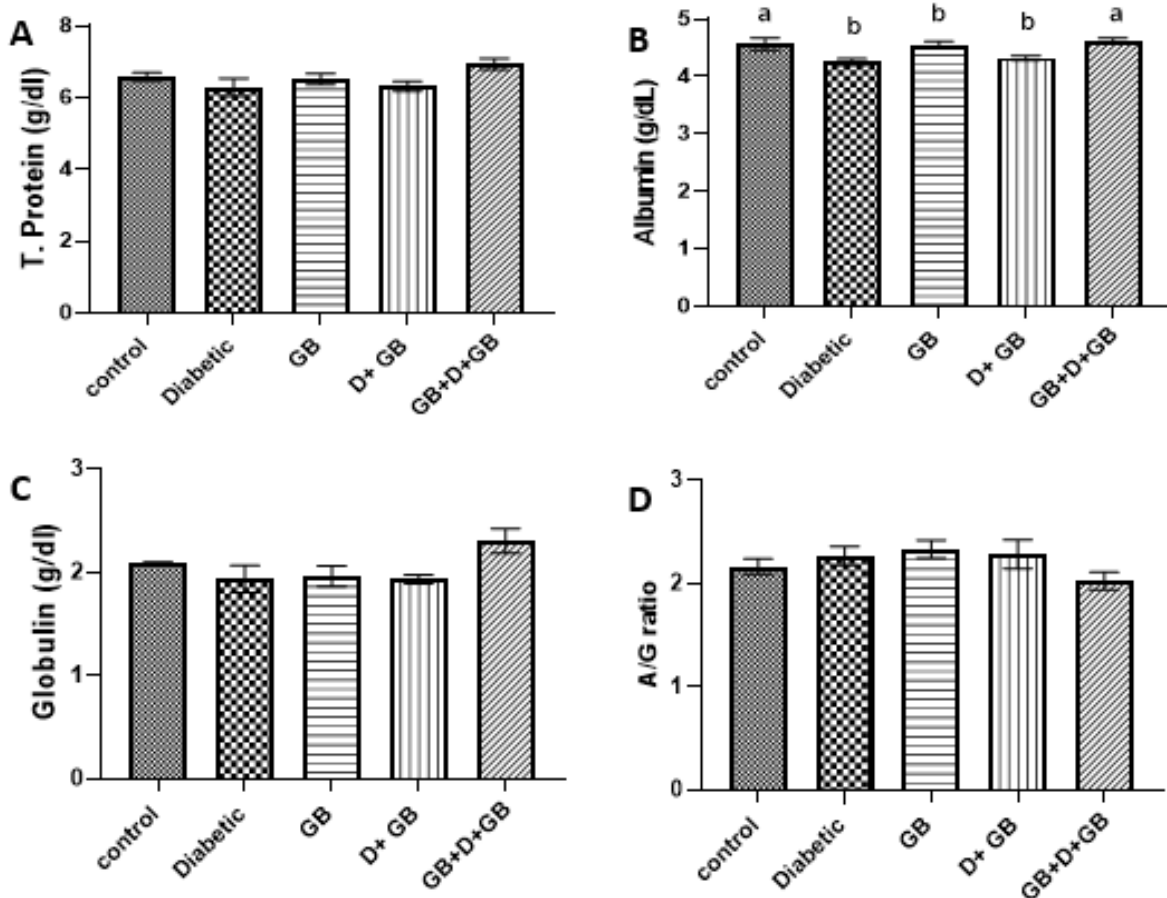
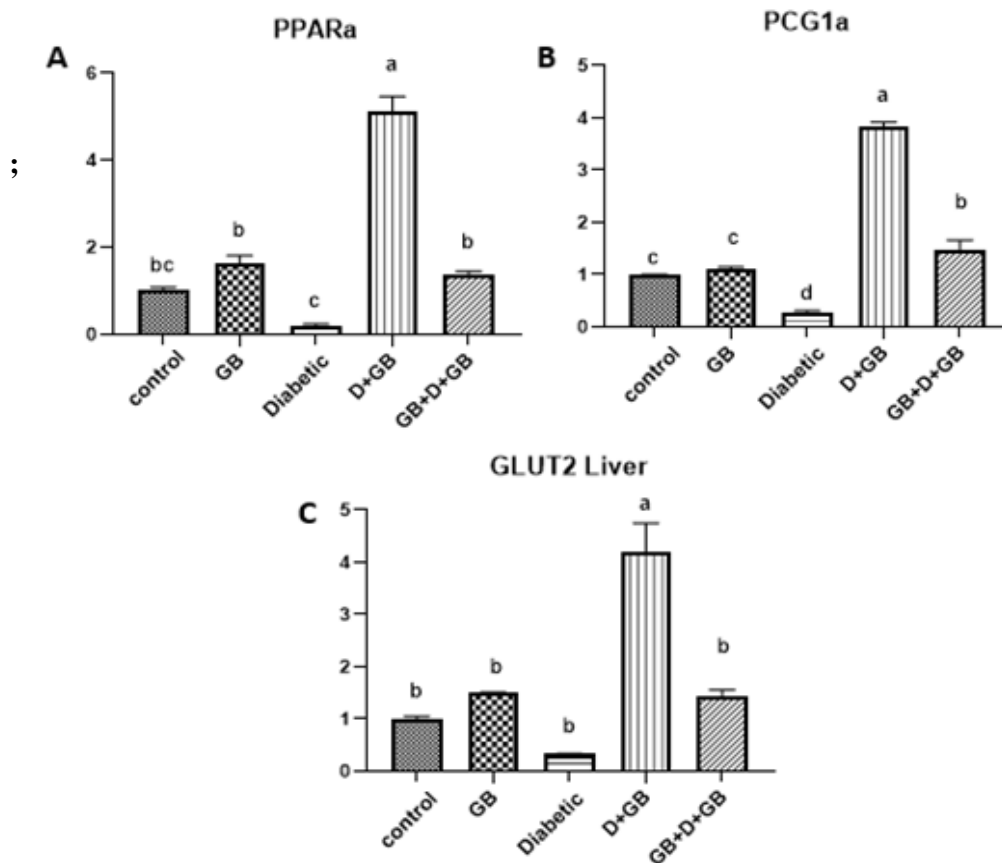


Figure 3: Effect of oral administration of *ginkgo biloba* (21.6-26.4% Ginkgo flavone glycosides and 5.4-6.6% terpene lactones) 200mg/kg BW at 60 days pre and post diabetic induction on the mean fold change ; **A.** Hepatic peroxisome proliferator-activated receptor alpha (*PPAR- α*) relative *mRNA/Gapdh* (%control), **B.** Hepatic peroxisome proliferator-activated receptor gamma coactivator-1 alpha (*PGC1- α*) relative *mRNA/Gapdh* (% control) and **C.** Hepatic glucose transporter-2 (*GLUT-2*) relative *mRNA/Gapdh* (% control) in type (I) STZ-induced diabetic rats. All values are mean \pm S.E.M ; n=8. Control: control group; GB: *Ginkgo biloba* group; diabetic: diabetic group; D+GB: Diabetic+ *Ginkgo biloba* group; GB+D+GB: *Ginkgo biloba*+ Diabetic+ *Ginkgo biloba* group.



Discussion

Diabetes is a global disease that will become increasingly frequent in the future decades, and it is a major global health issue [16]. This is a pathological disorder with oxidative stress as one of the primary causes [17]. *Ginkgo biloba* is a medicinal herb that contains flavonoids, antioxidants, and terpenes that suppress platelet activation factor [18]. Because of its neuroprotective, immunomodulatory, and anti-inflammatory properties, *G. biloba* leaf extract is also

utilized to treat neurological and cardiovascular problems [19]. So, for *G. biloba* benefits and values, many authors reported a daily single dose of 120 mg of ginkgo leaf extracts in the clinical trials [20].

Concerning to Erythrogram and Hemoglobin, our results recorded significant reduction in platelets and Hb values in STZ-diabetic rats. (DG) compared with the control one. However, *Ginkgo biloba* administered groups. (GB), (D+GB) and (GB+D+GB) revealed a significant increase of HB

compared with diabetic one. The observed anemia may be due to oxidative stress on bone marrow and polyuria resulted in excessive excretion of water-soluble vitamins [21]. These results agreed with [13] **with** using GBE 200mg/kg body weight orally once a day for a period 30 days. Also, [22] found that (EGb 761) helped in elevation of HB, erythrocyte count and made changes in hematological parameters and erythrocyte osmotic fragility.

Concerning Leukogram, decrease in the count of TLC (total leukocytic count) was obtained in STZ- diabetic rats in gp (DG) compared with control group (CG) showing features of leukopenia. Meanwhile *ginkgo biloba* treated groups either diabetic or non-diabetic (GB), (D+GB) and (GB+D+GB) showed significant increase close to control group (CG). Such results may be due to oxidative stress caused by STZ that caused bone marrow hypoperfusion and improper hematopoiesis due to oxidative stress on bone marrow caused by STZ and the results partially agreed with [23]. Also, the obtained results agreed with [24] who used *ginkgo biloba* extract treated at 50 mg/kg, 100mg/kg, and 200 mg/kg body weight for 15 days and showed a great improvement in leukogram picture due to its antioxidant and immunostimulant capacity.

Lipid metabolism is substantially influenced by uncontrolled hyperglycemia [25]. STZ-diabetic rats (DG) had higher blood cholesterol, triglycerides, and LDL-C levels than the control group (CG), but lower HDL-C levels. This could be due to changes in triglyceride-rich lipoprotein metabolism and insulin resistance, that both contribute to the development of diabetic dyslipidemia [26], or it could be due to an increase in hepatic lipase as a result of reduced lipogenesis and enhanced lipolysis in the hepatic tissue, which is the result of glucose underutilization [27]. However diabetic rats administered orally with *Ginkgo biloba* showed a significant decrease in serum cholesterol, triglycerides and LDL-C and a significant increase in HDL-C. These results agreed with [28] who revealed that The *G.*

biloba regulates fatty acid profile by lowering the levels of LDL and TG and increasing the levels of HDL in blood.

Concerning Liver function enzymes , an elevation in serum ALT , AST were obtained in STZ- induced diabetic rats (DG) while decrease in albumin levels were existed, that might be due to the toxic impacts of STZ on liver by oxidative hepatic cell damage which led to increase liver enzymes in blood and decrease albumin synthesis [29]. Meanwhile, diabetic rats were administered orally with *Ginkgo biloba*, showed significant decrease in liver enzymes activities indicating to partial restoration of body enzymes activities .The results agreed with [30] who explained the effect of 90-day GKB extract (120mg / capsule) on 80 diabetic patients and the results illustrated partial restoration of serum liver enzymes activities ALT, AST, Albumin, and total protein to normal levels compared to no treated diabetic patients.

Diabetic nephropathy (DN), the most prevalent diabetic complication, is the most common cause of end-stage renal disease [31]. The obtained data suggested that diabetic gp. (DG) had higher serum creatinine and urea levels than the control group. However, diabetic rats administered *ginkgo biloba* orally in groups (GB), (D+GB), and (GB+D+GB) showed a significant reduction in renal cell activity, indicating that *Ginkgo biloba* can restore renal cell function. The results agreed with [32] when GB therapy was utilized for 4 weeks in STZ-induced diabetic rats, the results showed that creatinine and urea were significantly higher in the diabetic group than in the control group. Urea, creatinine, and glucose levels were considerably reduced in all ratstreatedwithGB.

In terms of GLUT-2 mRNA expression in the liver, the results showed a significant downregulation in GLUT-2 mRNA expression in the diabetic group, but a significant upregulation in GLUT-2 mRNA

expression in the *ginkgo biloba* treated groups, both diabetic and non-diabetic, reflecting the effect of *ginkgo biloba* in improving glucose transportation and metabolism. The findings were consistent with those of [33], who looked at the effects of Lupinus Albus (LA) seed extract (7mg/100g BW) on streptozotocin (STZ)-induced diabetic rats and found a slight increase in expression of biomarkers genes for pancreatic beta cells (β -cells) function, liver GLUT-2, and glucokinase when compared to STZ diabetic rats.

Regards to *PPAR- α* expression, the results showed marked downregulation in *PPAR- α* mRNA expression in 2nd diabetic group. However, the treated groups with *ginkgo biloba* showed upregulation in *PPAR- α* mRNA expression compared with diabetic one that indicated to the role of *ginkgo biloba* improvement of the glycogen content in the liver. The results agreed with [34] who illustrated in his study by using flavonoids 100mg/kg b.w. made upregulation in flavonoids treated rats compared to diabetic one.

Results of this current investigation revealed a downregulation in mRNA expression of *PGC-1 α* in diabetic group compared with control negative gp. Meanwhile, *ginkgo biloba* treated groups either diabetic or non-diabetic showed upregulation in *PGC-1 α* mRNA expression compared with diabetic one indicated to the ability of *ginkgo biloba* to regulate metabolic hemostasis in liver. The results agreed to [35] that implied that in the diabetic rats, decreased *PGC-1 α* expression was associated with increased mitochondrial ROS generation in the renal cortex, increased proteinuria, glomerular hypertrophy, and higher glomerular 8-OHdG (a biomarker for oxidative stress).

Conclusion

This study concluded that *ginkgo biloba* extracts might be a good therapeutic option for treating type-I diabetes mellitus and its complications because of its strong

antihyperglycemic and antilipidemic effects, besides it controls serum liver enzymes, urea, and creatinine levels. Besides, it improves glucose metabolism in liver by modulating and enhancing the hepatic key genes.

Conflict of interest

The authors have no conflict of interest to declare.

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تأثير الجينكو بيلوبا على التعبير الجيني الكبدى لـ (PGC1- α و PPAR- α و GLUT-2) ووظائف الكبد والكلية وأمراض الدم والشحوم في الفئران المصابة بداء السكري من النوع الأول

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أصبحت أوراق الجينكو بيلوبا نباتاً طبيياً معروفاً في جميع أنحاء العالم، حيث يتم وصفه في علاج مرض مختلف مثل مرض السكري واضطرابات الأوعية الدموية الطرفية والاضطرابات العصبية مثل مرض الزهايمر.. تم تصميم هذه الدراسة لمعرفة تأثير تناول الجينكو بيلوبا عن طريق الفم على وظائف الكبد والكلية والمعايير الدموية والدهون وتعبير الجينات الكبدية في البالغة في Sprague Dawely الفئران المصابة بداء السكري من النوع الأول. تم تخصيص خمسة وسبعين ذكوراً من جردان خمس مجموعات متساوية 15 جرداً لكل مجموعة، المجموعة الأولى؛ المجموعة الضابطة، المجموعة الثانية؛ مجموعة مرضى السكري، المجموعة الثالثة. مجموعة الجينكو بيلوبا، المجموعة الرابعة؛ تلقت المجموعة التي عولجت من مرض السكري جرعة فموية واحدة من الجينكو بيلوبا بعد تحريض مرضى السكري كعلاج والمجموعة الخامسة؛ تم إعطاء الجرذان جرعة فموية واحدة يومياً من الجينكو بيلوبا كجرعة وقائية من اليوم الأول للدراسة قبل تحريض مرض السكري واستمرت بعد GLUT-2 تحريض مرض السكري حتى نهاية العمل. أظهرت نتائج الدراسة إجراءات الجينكو في تعديل جينات المفاتيح الكبدية (مُنشَط جَامَا المُنشَط لمستقبلات PGC1- α (مستقبل ألفا المنشط بالبيروكسيسوم)، و PPAR- α (ناقل الجلوكوز-2)، 2 بيروكسيسوم المنشط-1). أيضاً، تمتلك الجينكو أنشطة مضادة لفرط شحميات الدم، وتدعم وظائف الكبد والكلية، وتحسن استقلاب الجلوكوز وتخزينه واستخدامه في الكبد من خلال تعزيز جيناته الرئيسية. خلصت هذه الدراسة إلى أن التوصية باستخدام الجينكو بيلوبا كمكمل غذائي أو علاج داعم لمرض السكري من النوع الأول.