# Biochemical effect of *Ginko biloba* extract on carbohydrate metabolism in (induced type two) diabetic rats

# Efectul biochimic al extractului de *Ginkgo biloba* asupra metabolismului glucidic la șobolanii cu diabet zaharat (de tip 2 indus)

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**Cuvinte cheie:** diabet zaharat tip-2, *Ginko biloba*, metabolism glucidic, șobolani.

## Abstract

**Ginkgo biloba extract (EGb 761) has been used in traditional Chinese medicine for 5000 years that possesses various biological activities and has been shown to be useful in diabetes treatment. This study was carried out on 120, 12-14 weeks old male rats and weighted 150-200 gm. Rats were classified into two main large experiments. Experiment 1: Non-diabetic rats Included 40 of normal male rats were divided into two groups each one comprises 20 rats kept in separate metal cages and classified as follows: Group 1: Non-diabetic rats were administered with 0.2 ml of normal saline only (control group).Group 2:Non-diabetic rats were received (GBE) (120 mg/kg), given orally by stomach tube and daily for 6 weeks. Experiment 2: Diabetic rats "STZ group" Included 80 male diabetic rats were divided into four groups each one comprises 20 rats kept in a separate metal cages and classified as follows: Group 1: Diabetic rats were administered with 0.2 ml of normal saline only (diabetic control group).Group 2: Diabetic rats were received (GBE) (120 mg/kg), given orally by stomach tube and daily for 6 weeks. Group 3: Diabetic rats were received glimepiride (20mg/kg), given orally by stomach tube and daily for 6 weeks. Group 4: Diabetic rats received glimepiride in combination with (GBE), given orally by stomach tube and daily (1:1) for 6 weeks. Blood samples were collected from all animals groups after 3 and 6 weeks from treatment. Serum were separated and processed directly for (glucose, Lactate, total cholesterol, triacylglycerol, Minerals ($Na^+$, $K^+$, $Ca^{++}$), L-MDA) concentration-(insulin, Glucagon, Testosterone) levels- (AST and ALT) activities were the parameters of biochemical interest investigated. The obtained results revealed that, a significant increase in serum glucose, total cholesterol, triacylglycerol, ALT, AST, L-MDA concentration. On contrary, a significant decrease in serum lactate, insulin, glucagon, testosterone, $Na^+$, $K^+$, $Ca^{++}$ levels were observed in streptozotocin-induced diabetic rats allover the periods of the experiments when compared with normal control group. The results of this study indicated that (GBE) has potential benefits in diabetes treatment.**

## Rezumat

**Extractul de ginkgo biloba (EGb 761) este folosit în medicina tradițională chineză de peste 5000 de ani, având diverse activități biologice si fiind util în tratamentul diabetului zaharat. Acest studiu a fost efectuat pe 120 de șobolani masculi, de 12-14 săptămâni cu o greutate cuprinsă între 150-200 g. Șobolanii au fost împărțiți pentru 2 expermente. Experimentul 1: șobolani non-diabetici. A inclus 40 de șobolani masculi sănătoși care au fost împărțiți în două grupe fiecare cuprinzând câte 20 șobolani ținuti în cuști metalice separate și clasificați după cum urmează: Grupul 1: șobolani non-diabetici cărora li s-au administrat 0,2 ml soluție salină normală (grup control). Grupul 2: sobolani non-diabetici cărora li s-au administrat extract de ginkgo biloba (GBE) (120 mg / kgc), pe cale orala prin tub gastric, zilnic, timp de 6 saptamani. Experimentul 2: Șobolanii diabetici "grupul STZ" (streptozotocină). A inclus 80 de șobolani masculi diabetici împărțiți în patru grupe, fiecare grupă cuprinzând 20 de șobolani ținuți separat în cuști metalice și clasificați după cum urmează: grupul 1: șobolani diabetici cărora li s-au administrat 0,2 ml de soluție salină normală (grup control). Grupul 2: sobolani diabetici carora li s-au administrat extract de ginkgo biloba (GBE) (120 mg / kgc), pe cale orală prin tub gastric, zilnic timp de 6 săptămâni. Grupul 3: șobolanii diabetici care au primit glimepridă (20mg / kgc), administrată pe cale orala prin tub gastric, zilnic, timp de 6 săptămâni. Grupul 4: șobolani diabetici cărora li s-au administrat glimepridă în combinație cu (GBE), pe cale orala (1:1), prin tub gastric, zilnic timp de 6 săptămâni. Probele de sânge au fost colectate de la toate grupele de animale după 3 și 6 săptămâni de la debutul tratamentului. Serul a fost separat și prelucrat direct pentru determinaea concentrației în glucoză, lactat, colesterol total, triacilgliceroli, minerale ($Na^+$, $K^+$, $Ca^{++}$), L-MDA , nivelurile insulinei, glucagonului, testosteronului și activitatea AST și ALT. Rezultatele**

**obținute au arătat o creștere semnificativă a glicemiei, colesterolului total, triacilglicerolilor, ALT, AST, L-MDA. Din contră, s-a înregistrat o scădere semnificativă a nivelurilor lactatului seric, insulinei, glucagonului, testosteronului, $Na^+$, $K^+$, $Ca^{++}$ la șobolanii cu diabet induse prin streptozotocină pe toată durata experimentelor în comparație cu rezultatele grupului de control. Rezultatele acestui studiu au indicat că (GBE) are beneficii potențiale în tratamentul diabetului zaharat.**

## Introduction

Diabetes mellitus is a group of diseases characterized by chronic hyperglycemia and other metabolic abnormalities resulting from the deficient action of insulin *James et al., (2003).*

Diabetic patients are at increased risk for cardiovascular disease, blindness, nerve and kidney damage and limb amputations. Diabetics are also at greater risk for developing different cancers due to the immunological disturbances induced by aberrant metabolism *Zimmet et al., (2003).*

*Wang et al.,* (2006) provided evidence that *Ginko biloba* increases aerobic glycolysis through enhancing the activities of citrate synthetase, malate dehydrogenase and succinate dehydrogenase, cytochrome oxidase (fourrate-limiting enzymes in aerobic glycolysis).

Ginkgo biloba was significantly decrease the levels of free radicals and this protective effect of ginkgo biloba attributed to its free radical scavenging activity, induction of detoxification enzymes and provides protection against degenerative diseases *Glasiella et al., (2011).*

*Chung et al.,* (2001) reported that 50mg/kg Ginko biloba administered for 40 days decreased the activity of the rate-limiting gluconeogenic enzyme glucose-6-phosphatase in liver preparations in diabetic mice by 46 and 20%.

Accordingly, the purpose of this experiments to investigate the possible protective effect of treatment *Ginko biloba* extract in experimentally induced diabetes in male rats.

## Material and Methods

A total number of 120 male albino rats of 12-14 weeks old age and weighting 150-200 gm were used in the experimental investigation of these study. Rats were obtained from the Research Institutes of Ophthalmology, Giza, Egypt.

Animals were housed in separate metal cages, fresh and clean drinking water was supplied ad-libtium through specific nipple.

Rats were kept at a constant environmental and nutritional condition throughout the period of the experiment.

Induction of diabetes with the streptozotocin results in loss of β-cell mass often accompanied by infiltration of the islets by activated immune cells.

Rats were fasted for 18 hour and allowed free access of water. The experimental induction of diabetes in male rats was induced by a single intraperitoneal (i.p.) injected dose of 50 mg /kg b.w. of Streptozotocin (STZ) (Sigma Chemical Co., USA) freshly dissolved in citrate buffer, PH 4.5. Control rats were received an equivalent amount of buffer alone.

A week later, STZ-treated rats were fasted for 12 hour, and blood samples were collected from the orbital venous sinus for glucose determination. Only those rats in diabetic group (group II) with blood glucose levels higher than 250 mg/dl were considered diabetic *(Ramanathan et al., 1999).*

### Experimental design

The experimental work was classified into two main large experiments as follow:

**Experiment A:** Non-diabetic rats "Normal control group"

Included 40 of normal male rats were divided into two groups each one comprises 20 rats kept in separate metal cages and classified as follows:

**Group 1:** Non-diabetic rats were administered with 0.2 ml of normal saline only (control group).

**Group 2:** Non-diabetic rats were received Ginko biloba extract (120 mg/kg), given orally by stomach tube and daily for 6 weeks.

**Experiment B:** Diabetic rats "STZ group"

A total number of 80 male diabetic rats were divided into four groups each one comprises 20 rats kept in a separate metal cages and classified as follows:

**Group 1:** Diabetic rats were administered with 0.2 ml of normal saline only (diabetic control group).

**Group 2:** Diabetic rats were received Ginko biloba extract (120 mg/kg), given orally by stomach tube and daily for 6 weeks.

**Group 3:** Diabetic rats were received glimepiride (20 mg / kg.bw), given orally by stomach tube and daily for 6 weeks.

**Group 4:** Diabetic rats received glimepride in combination with *Ginkgo biloba* extract, given orally by stomach tube and daily (1:1) for 6 weeks.

Blood samples were collected in the morning after over night fasting from all rats by decapitation every 3 and 6 weeks from the onset of treatment, then obtained in dry and clean tubes and serum was separated by centrifugation at 3000 r.p.m for 15 minutes.

The clear serum were aspirated by Pasteur pipette and received in dry sterile sample tube, processed directly for enzymes determination, then kept in a deep freeze at -20 ℃ until used for subsequent biochemical analysis.

Serum (glucose, Lactate, total cholesterol, triacylglycerol, ($Na^+$, $K^+$, $Ca^{++}$), L-malondialdehyde) concentration - (insulin, Glucagon, Testosterone) levels and (AST and ALT) activities were analyzed calorimetrically according to the methods described by (*Trinder., 1969), (Burtis et al., 1999), (Richmond., 1973), (Schettler and Nussel., 1975), (Sunderman., 1958), (Gindler and King., 1972), (Placer et al., 1966), (Baba et al.., 1979), (Dudley et al., 1985) and (Reitman and Frankel., 1957)* respectively.

**Statistical analysis** of the obtained results were carried out using student's F-test according to *Snedecor and Cochran (1969).*

## Results and Discussion

### Streptozotocin (STZ)

The results revealed that, I.P. injection of STZ to male albino rats induced pathophysiological symptoms as occur in experimental diabetic rats.

Our results showed a significant increase in serum (glucose, total cholesterol, triacylglycerol, ALT, AST, L-MDA) concentration were observed in streptozotocin-induced diabetic rats all over the periods of the experiments. These results are nearly similar to those reported by *(Yilmaz et al., 2004)* reported that glucose concentration in the blood plasma of streptozotocin-treated rats was significantly higher than in the normal control group.

Hypercholesterolemia is common in diabetes, contributing to the high prevalence of coronary heart disease *Gentile et al., (2000)*.

The pronounced increase in Plasma cholesterol levels in diabetic rats is in agreement with results reported previously by *(Black et al., 1993)* observed that, glucose, triglyceride, and cholesterol concentrations were significantly elevated in streptozocin (STZ)-induced (55 mg/kg intravenously) diabetic male Wistar rats.

*Ahmed et al., (2001)* who showed that, there was a significant increase in plasma non-esterified cholesterol, triglycerides and phospholipids in STZ- induced diabetic rats, accompanied by a decrease in high density lipoprotein (HDL)-cholesterol.

*Sundaram et al., (1996)* who demonstrated that, plasma MDA showed 80 % increase in the early stages of diabetes, and more progressive increase later which explained as the factors favoring the formation of reactive oxygen species may catalyze lipid peroxidation in the plasma and other tissues and in poorly controlled diabetic, glucose oxidation through the pentose phosphate pathway initiates excessive formation of NADPH, this in turn can promote lipid

peroxidation in the presence of cytochrome P-450 system.

*Mohammad et al.,(2006)* who showed that, the aminotransferases (AST and ALT) levels were significantly increased in the liver of STZ-treated animals. The increase in aminotransferases levels may be due to the cellular damage in the liver caused by STZ-induced diabetes. Moreover, *Voss et al., (1988)* proposed that STZ in hyperglycemic animals caused a time dependent rise in AST, ALT, and ALP levels.

Our results showed a significant decrease in serum (lactate, insulin, glucagon, testosterone, $Na^+$, $K^+$, $Ca^{++}$) levels were observed in streptozotocin-induced diabetic rats all over the periods of the experiments. These results are nearly similar to those reported by *(Ismail et al., 2002)* who observed that plasma lactate levels in rabbits with diabetes mellitus were significantly lower when compared with the controls.

Furthermore, *Tanaka et al., (1988)* and *Margiavichene et al., (1986)* did not observe any increases in lactate level between diabetes and controls in rats.

These results agree with the results reported by *Krukoff and Patel., (1990)* who found that, two weeks after a single injection of STZ (65 mg/kg.bw I.P.) plasma $Na^+$ level was depressed. Also, *Brooks et al., (1989)* noticed the same results after injecting (50 or 75 mg / kg.bw I.V.) in male Sprague-Dawley rats.

Many workers explained the observed reduction of serum $Ca^{+2}$ level in diabetics to be due to reduction in duodenal $Ca^{+2}$ transport *(Schneider and Schedl.,1972)* or impaired renal reabsorption of $Ca^{+2}$ *Cheug., (1980).*

*Krukoff and Patel, (1990)* who stated that, a significant decrease in serum $k^+$ level was observed in Streptozotocin diabetic rats.

*Robertson. (2004)* who reported that, diabetes mellitus comprises a group of chronic diseases characterized by hyperglycemia or diminished insulin secretion or both and profound effects on lipid metabolism.

In the contrary, *(Nishida et al., 2002)* observed that, the untreated diabetic rats had the increased plasma levels of triglycerides, cholesterol, insulin and leptin at 35 wk, as compared with the healthy control rat.

*Noguchi et al., (1990)* who noticed that, the plasma testosterone levels of STZ-diabetic mice were lower than those of normal mice.

## Ginko Biloba extract

The results of this study showed that oral administration of *Ginko biloba* extract was significantly reduced elevated serum glucose level in streptozotocin (STZ)-induced diabetic rats allover the periods of the experiments.

These results are nearly similar to those recorded by *Lai et al., (2006)* who showed that, (GbE) make a significant decrease in glucose level in diabetic rats after oral administration by three possible mechanisms that could potentially account for the modulation in blood glucose levels:

(1) modulation of glucose uptake;
(2) modulation of glucose disposal;
(3) modulation of insulin secretion.

Our results showed that, oral administration of *Ginkgo biloba* Extract was significantly increased serum lactate concentration observed all over the periods of the experiments as compared to diabetic rats.

These results are nearly similar to those recorded by *Oliver et al., (1993)* who recorded that *Ginkgo biloba* extract helps lower blood sugars and helps our liver and kidneys metabolize blood sugars more efficiently, as it may further affect blood sugars levels by decreasing the activity of an enzymes that are involved in releasing stored from the liver into the blood.

Our results showed that, oral administration of *Ginko biloba* extract Were significantly decreased serum total cholesterol, triacylglycerol and L-MDA concentration observed all over the periods of the experiments as compared to diabetic rats.

These results are nearly similar to those recorded by *Anstey et al., (2008)* who found that, gink biloba can be regulated at the protein level of ABCA1 expression level of gene and protein can increase the expression of ACAT1, indicating that gink biloba cells can effectively promote the transformation and cholesterol reverse transport, which can reduce the

cholesterol content of the purpose of their role in lowering cellular cholesterol and cholesterol intake has little to do.

*Horsch and Walther., (2004)* who observed that, the oral administration of (GBE) caused a significant reduction in serum and liver cholesterol, triglycerides, free fatty acids, phospholipids, (VLDL) and (LDL) cholesterol levels and increased (HDL) cholesterol levels.

*Park et al., (2003)* who reported that, Ginkgo biloba extract (EGb 761) treatment decreased serum malondialdehyde levels and increased catalase activities compared with the placebo group ($P < 0.05$ for both).

Our results showed that, oral administration of *Ginko biloba* extract was significantly increased serum potassium concentration while a non significant decrease in serum sodium concentration and anon significant changes in serum calcium concentration were observed all over the periods of the experiments as compared to diabetic rats.

These results are nearly similar to those recorded by *(Anstey et al., 2008)* who carried out a research project on the effect of Ginko biloba extract on serum electrolytes levels of normal subjects. They found that Ginko biloba non significantly changed both $K^+$ and $Ca^{+2}$ levels and slightly decreased Na+ level but still within the normal range.

*Lai et al.,* (2006) reported that daily administration of insulin to STZ-diabetic rats usually correct their trace elements concentration. This may be an explanation for the improvement which follows *Ginko biloba* treatment which correct the condition of polyuria and excessive loss of electrolyte in urine.

Our results also showed that, oral administration of *Ginko biloba* extract were significantly increased serum insulin, glucagon and testosterone levels all over the periods of the experiments as compared to STZ-diabetic rats.

These results are in agreement with the findings of *Lai et al., (2006)* who stated that, GbE make a significant increase in insulin level in diabetic rats after oral administration by activating the Langerhans beta cells in pancreas.

*Randle (1998)* recorded that, *Ginko biloba* contains substances that helps to control blood sugar levels and increases glucagon production. Therefore, the level of glucagon affected by herbs, which stimulate insulin release and this, decrease the level of blood glucose leading to increase of glucagon to make glycogen lysis to reserve the balance of glucose level.

*Ferrandini et al., (1993)* stated that, treating adult male rats with *Ginko biloba* extract for 60 days increased their blood testosterone level and reduced the prostate weight in the treated animals as compared to control animals.

## Glimepiride

Second generation of oral hypoglycemic agent, such as glipizide and Glimepiride are often the treatment of choice in non insulin dependent diabetes mellitus.

Glimepiride induced significant reduction in serum glucose level of STZ-diabetic male albino rats, this was accompanied by significant increase in serum insulin level. This hypoglycemic and hyperinsulinaemic effect are in parallel with that observed by *Simpson et al., (1990).*

*Johnson and Dobmeier (1990)* reported that Glimepiride (10 mg b.i.d) produced hypoglycemic action in diabetic patients.

Our results also showed that, oral administration of glimepiride was significantly increased in serum insulin level observed all over the periods of the experiments as compared to STZ-diabetic rats.

*Jackson and Bressler (1981)* explained that sulfonylureas stimulate insulin release through elevation of cAMP in the pancreatic β-cells, either by stimulation of adenylcyclase activity *(Kuo et al., 1973)* or inhibition of phosphodiesterase *Gohil and Packer (2002).*

Our results showed that, oral administration of Glimepiride was significantly increased in serum testosterone level observed all over the periods of the experiments as compared to STZ-diabetic rats.

*Noguchi et al., (1990)* reported that testosterone level decreases in STZ-diabetic mice. He found that those diabetic animals showed significant deficiency in epidermal growth factor, which is important in maintaining spermatogenesis and sperm count.

Administration of insulin to diabetic mice restored epidermal growth factor concentration and sperm count to normal levels. The restorative effects of insulin on sperm production appeared to be mediated, partially, by epidermal growth factor, because its effect was significantly reduced by the concomitant administration of epidermal growth factor antiserum.

Our results showed that, oral administration of glimepiride was significantly decreased in serum total cholesterol concentration observed all over the periods of the experiments as compared to STZ-diabetic rats.

The hypocholesterolemic action is in parallel with that observed by *(Simpson et al., 1990)* who noticed that cholesterol fell in all type 2-diabetic patients on glimepiride for eight weeks of treatment.

*Annamala and Augusti.,(1980)* reported that sulphonylureas e.g. Glimepiride, significantly improved the diabetic state and result in reduction of serum and liver lipids in diabetic rabbits when administrated in constant dose for several days. This is similar to the results on experimental diabetic male rats of this work.

Our results showed that, oral administration of glimepiride was significantly increased in serum sodium concentration while non significant changes in serum potassium and calcium concentration were observed all over the periods of the experiments as compared to diabetic rats.

These changes resulted from Glimepiride treatment on serum electrolytes levels may be due to its ability to stimulate insulin release from the pancreatic β-cells *Simpson et al., (1990).*

Consequently, the released insulin inhibits the urinary excretion of Ca+2 and Zn+2 and increasing their serum levels *Victery et al., (1981).*

### Ginko biloba - glimepiride combination:

The results of this study showed that combination of *Ginko biloba* extract with glimepiride resulted in significantly reduced elevated plasma glucose level in streptozotocin (STZ)-induced diabetic rats allover the periods of the experiments. It has been found that combination of *Ginko biloba* extract with Glimepiride resulted in significant increase in serum insulin level of diabetic rats through the whole experimental period.

*Bodmer et al.,(2008)* who stated that, combination of (GbE) with sulphonylureas as glimepiride (oral hypoglycemic) make a synergistic decrease in glucose level, this combination allow diabetic patient to overcome side effects of sulphonylureas.

**Table 1.**

Mean ± S.E. of serum (Glucose, Insulin, Testosterone, T Cholesterol, Triacylglycerol, AST, ALT) in relation to treatment and weeks of sampling:

| Parameter | Weeks | Control | GBE | STZ | STZ+ GBE | STZ+ GLI | STZ+ GBE +GLI |
|---|---|---|---|---|---|---|---|
| **Glucose (mg/dl)** | 3 | 94.90 ± 3.91 | 81.34 ±2.46 | 285.39 ±3.05 | 234.46 ±3.07 | 115.44 ±2.55 | **103.34 ±1.62** |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | 6 | 101.29 ±1.44 | 100.77 ±3.42 | 291.79 ±4.14 | 208.10 ±2.09 | 193.14 ±1.45 | **140.40 ±2.07** |
| **Insulin (µlU/ml)** | 3 | 26.44 ±0.74 | 28.44 ±0.40 | 09.46 ±0.35 | 16.56 0.28 | 19.50 ±0.51 | **21.53 0.69** |
| | 6 | 29.07 ±0.76 | 30.14 ±0.59 | 11.63 ±0.20 | 18.54 0.21 | 18.27 0.40 | **26.03 0.59** |
| **Testos-erone (ng/ml)** | 3 | 2.79 ±0.09 | 2.89 ±0.08 | 1.76 ±0.06 | 2.24 ±0.08 | 2.59 ±0.08 | **1.94 ±0.06** |
| | 6 | 2.41 +0.06 | 2.51 ±0.05 | 1.87 ±0.06 | 2.51 ±0.08 | 2.29 ±0.11 | **2.17 ±0.09** |
| **T. Cho-esterol (mg/dl)** | 3 | 110.36 ±2.07 | 114.87 ±2.40 | 165.76 ±1.99 | 137.37 ±1.81 | 142.44 ±1.20 | **141.09 ±1.57** |
| | 6 | 120.90 1.95 | 92.71 ±1.93 | 176.64 ±2.03 | 120.19 ±1.18 | 121.60 ±1.66 | **117.71 ±1.32** |
| **Triacyl-glycerol (mg/dl)** | 3 | 80.81 ±2.15 | 73.50 ±1.70 | 149.21 ±1.87 | 118.63 ±2.62 | 118.03 ±2.33 | **120.54 ±2.61** |
| | 6 | 92.26 ±2.19 | 63.99 ±1.80 | 141.94 ±2.23 | 106.69 ±2.84 | 118.31 ±2.41 | **119.87 ±1.69** |
| **AST (U/ml)** | 3 | 28.34 ±0.98 | 29.73 ±1.54 | 55.40 ±1.73 | 38.21 ±1.43 | 49.31 ±1.01 | **54.49 ±1.71** |
| | 3 | 26.44 ±0.74 | 24.37 ±1.78 | 58.60 ±1.54 | 55.21 ±1.72 | 54.74 ±1.72 | **49.00 ±1.04** |
| **ALT (U/ml)** | 3 | 29.74 ±1.54 | 30.20 ±0.60 | 48.73 ±1.07 | 32.00 ±1.25 | 49.17 ±1.01 | **51.31 ±1.71** |
| | **6** | **28.34 ±0.40** | **25.19 ±0.89** | **49.71 ±2.46** | **34.10 ±1.30** | **51.57 ±1.73** | **44.21 ±2.05** |

**Legend:** ++: P<0.01, NS: Non-Significant, Values with different small/capital letters within the same column/raw, respectively differed significantly at least at P<0.05

**Table 2**

Mean ± S.E. of serum (Sodium, Potassium , Calcium, Glucagon, Lactate, L-malondialdehyde) in relation to treatment and weeks of sampling:

| Parameter | Weeks | Control | GBE | STZ | STZ+ GBE | STZ+ GLI | STZ+ GBE +GLI |
|---|---|---|---|---|---|---|---|
| **Sodium (µg/ml)** | 3 | 110.93 ±2.31 | 125.76 ±2.01 | 81.34 ±2.20 | 79.77 ±1.50 | 78.84 ±1.50 | **73.66 ±1.70** |
| | 6 | 104.61 ±1.45 | 101.06 ±2.45 | 77.54 ±2.80 | 72.79 ±1.57 | 100.94 ±2.13 | **65.30 ±1.69** |
| **Potassium (µg/ml)** | 3 | 12.39 ±0.45 | 11.66 ±0.21 | 6.50 ±0.20 | 6.99 ±0.26 | 5.70 ±0.16 | **9.46 ±0.35** |
| | 6 | 11.62 ±0.20 | 9.43 ±0.34 | 6.54 ±0.29 | 9.34 ±0.32 | 6.87 ±0.26 | **9.04 ±0.32** |
| **Calcium (µg/ml)** | 3 | 3.57 ±0.13 | 3.10 0.15 | 1.49 ±0.08 | 1.50 ±0.08 | 1.60 ±0.11 | **1.11 ±0.05** |
| | 6 | 4.21 ±0.13 | 4.67 ±0.14 | 1.74 ±0.06 | 1.94 ±0.19 | 1.93 ±0.06 | **1.37 ±0.07** |
| **Glucagon (µlU/ml)** | 3 | 120.31 ±1.17 | 128.56 ±2.74 | 75.91 ±1.83 | 85.47 ±1.37 | 99.23 ±2.02 | **102.31 ±2.01** |
| | 6 | 109.23 ±2.91 | 105.14 ±1.89 | 80.63 ±1.87 | 86.34 ±1.36 | 97.63 ±1.66 | **103.37 ±1.75** |
| **Lactate (mg/dl)** | 3Weeks | 42.17 ±2.68 | 45.44 ±2.15 | 29.67 ±1.54 | 34.60 ±1.02 | 34.06 ±1.30 | **30.26 ±0.62** |
| | 6 | 42.11 ±1.01 | 48.80 ±1.08 | 31.89 ±1.61 | 37.19 ±1.23 | 34.71 ±1.05 | **37.51 ±1.02** |
| **L-malondialdehyde (nmol/ml)** | 3 | 9.69 ±0.23 | 9.80 ±0.25 | 12.84 ±0.54 | 11.87 ±0.36 | 11.53 ±0.30 | **10.34 ±0.19** |
| | **6** | **9.74 ±0.23** | **9.81 ±0.19** | **13.50 ±0.41** | **11.64 ±0.31** | **10.54 ±0.38** | **9.67 ±0.19** |

**Legend:** ++ : P < 0.01, NS : Non-Significant, Values with different small/capital letters within the same column/raw, respectively differed significantly at least at P < 0.05

## Conclusions

Initial treatment in cases of type II diabetes is diet and weight loss, especially in cases of obesity, with the use of the right property to maintain the level of glucose in the blood. The use of extract of *Ginkgo biloba* had an effective influence to reduce the level of glucose and fat in the blood of rat that developed by the diabetes, this extract had no side effects as evidenced by the study of its effect on both normal and diseased rat with diabetes.

The use of extract *Ginkgo biloba* and glimepiride together has led to the strengthening of each other in reducing the levels of glucose and fats in the blood of rat with diabetes, allowing patients to reduce the dose of glimepiride and so reduce side effects in addition to the advantages of Ginkgo biloba in the treatment of such cases.

## References

1. **Ahmed I., Lakhani M.S., Gillett M.; John A., Raza H. (2001)** - Hypotriglyceridemic and hypocholestrolemic effects of anti-diabetic Momordica charantia (karela) fruit extract in streptozotocin- induced diabetic rats. *Diabetes Res. Clin. Pract*. 51(3): 155-161.
2. **Annamala P.T, Augusti K.T. (1980)** - Experimental (BASEL), 36(4): 283. Cited by H.E.Mohamed, Biochemical studies on the effect of selected antidiabetic drugs in normal animals and experimental diabetes mellitus, Ph.D thesis, Biochemistery, Faculty of Pharmacy, University of Zagazig, (1987).
3. **Anstey K.J., Lipnicki D,M., Low L.F. (2008)** - Cholesterol as a risk factor for dementia and cognitive decline: a systematic review of prospective studies with meta analysis (J). *Am J Geriatr Psychiatry*; 16 (5): 343 54.
4. **Baba S. (1979)** - Metabolism of insulin and proinsulin. Excerpta Med. I.C.S., 468:270.
5. **Black S.C., Katz S., Neill J.H. (1993)** - Influence of omega-3 fatty acid treatment on cardiac phospholipid composition and coronary flow of streptozocin-diabetic rats. *Metabolism.* 42(3): 320-326.
6. **Bodmer M., Meier C., Krahenbuhl S., Jick S.S, Meier C.R. (2008)** - Metformin, sulfonylureas, or other antidiabetes drugs and the risk of lactic acidosis or hypoglycemia: a nested case-control analysis. *Diabetes Care*; 31: 2086-2091.
7. **Brooks D.P., Nutting D.F., Crofton J.T., Leonard A. (1989)** - Vasopressin in rats with genetic and streptozotocin-induced diabetes. Diabetes. Vol. 38, P.54.
8. **Burtis A.; Achwoo, E.R., Youngchim C. (1999)** - Tietz Texbook of Clinical Chemistry, 3 rd Ed.
9. **Cheung W.Y. (1980)** - Science, 207:19. Cited by H.E. Mohamed, Biochemical studies on the effect of selected antidiabetic drugs in normal animals and experimentally diabetes mellitus, Ph.D thesis, Biochemistery, Faculty of Pharmacy, University of Zagazig (1987).
10. **Chung S.H., Choi C.G., Park S.H. (2001)** - Comparisons between white Ginseng radix and Ginko biloba for antidiabetic activity and mechanism in KKAy mice. *Arch Pharm Res* 24: 214-218.
11. **Dudley R.A; Schmitt A.B., Altschuler R.L. (1985)** - Guidelines for immunoassay data reduction.Clin.Chem.,31:1264-71.
12. **Ferrandini C, Droy-Lefaix M.T., Christen Y.** Eds (1993): Ginkgo biloba Extract (EGb 761) as a Free Radical Scavenger. Elsevier, Paris, France.
13. **Gentile S.; Turco S.; Guarino G. (2000)** - Comparative efficacy study of ator-vastatin vs. simvaslatin, provastatin, lovastnlin and placebo in type 2 diabetic patients with hypercholcslerolemia. *Diabetes*, 2: 355-362.
14. **Gindler,E.M., King J.D. (1972)** - Rapid colirimetric determination of calcium in biologic fluids with methylthymol blue. *Am J Clin Path.,* 58: 376-382.
15. **Gonzalez Perez Da Silva G., Zanoni J.N., Buttow N.C.** (2011): Neuroprotective action of Ginkgo biloba on the enteric nervous system of diabetic rats. *World J Gastroenterol.*; 17(7): 898-905
16. **Gohil K., Packer L. (2002)** - Bioflavonoid-rich botanical extracts show antioxidant and gene regulatory activity. *Ann N Y Acad Sci.;* 957: 70-77.
17. **Horsch S., Walther C. (2004)** - Ginkgo biloba special extract EGb 761 in the treatment of peripheral arterial occlusive disease (PAOD) - a review based on randomized, controlled studies. *Int J Clin Pharmacol Ther.*, 42(2):63-72.
18. **Jackson J.E. And Bressler R. (1981)** - Clinical pharmacology of sulfonylurea hypoglycemic agents. *Drugs* 22: 211.
19. **James R.; Alberti M.D., Mayer B. (2003)** - Report of the Expert Committee on the diagnosis and classification of Diabetes Mellitus. *Diabetes Care*, 26(1): S5 -S11.
20. **Johnson J.F., Dobmeier M.E. (1990)** - Symptomatic of hypoglycemia secondary to

glipizide-trimethoprim sulfamethoxazole drug interaction. *DICP*, 24(3): 250-251.

21. **Krukoff T.L., Patel K.P. (1990)** - Alterations in brain hexokinase activity associated with streptozotocin-induced diabetes mellitus in the rat. *Brain Res*., 522(1):157.
22. **Lai D.M., Tu Y.K., Liu I.M. (2006)** - Mediation of beta-endorphin by ginsenoside Rh2 to lower plasma glucose in streptozotocin-induced diabetic rats. *Planta Med* 72: 9-13.
23. **Margiavichene L.E., Gribausckas P.S., Norkus A.V., Gribauskene R.A., Masalskene V.V., (1986)** - Lipid metabolism and the activity of cardiospecific enzymes in diabetes mellitus. *Probl Endokrinol.,* 32(5): 28-32.
24. **Mohammed S., Hossen N., Ahmed M., Amran, S. (2006)** - Green tea in health care: a natural medicine, a natural drink. *J Appl Sci Res.,* 2(6): 306-309.
25. **Nishida S., Segawa T., Murai I., Nakagawa S.** (2002) - Long- term melatonin administration reduces hyperinsulinrmia and improves the altered fatty acid compositions in type 2 diabetes. *J Pineal Res*., 32(1): 26 - 33.
26. **Noguchi S., Ohba Y., Oka T.** (1990) - Involvement of epidermal growth factor deficiency in pathogenesis of oligozoospermia in streptozotocin- induced diabetic mice. *Endocrinology* 127(5): 2136.
27. **Oliver, R.C., Tervonen, T., Flynn, D.G., Keenan, K.M. (1993)** - Enzyme activity in crevicular fluid in relation to metabolic control of diabetes and other periodontal risk factors. *J Periodontal.,* 91(5): 423-6.
28. **Park E.K., Choo M.K., Kim E.J., Han M.J., Kim D.H. (2003**) - Antiallergic activity of ginko biloba. *Biol Pharm Bull.,* 26: 1581–1584
29. **Placer B.S., Bolla K.I., Stewort W., Ford D.F., Angew J., Frumkin H. (1966):** Technican symposium 5-16 May. Paris, Conference 6: 12-15.
30. **Ramanathan M., Jaiswal A.K., Bhattacharya S.K. (1999)** - Superoxide dismutase,catalase jand glutahiones peroxidase activities in he brain of streptozotocin induced diabetic rats. *Indian J Exp Biol*., 37: 182-183.
31. **Randle P.J. (1998)** - Regulatory interactions between lipids and carbohydrates: the glucose fatty acid cycle after 35 years. *Diabetes Metab Rev* 14: 263-283, 1998
32. **Reitman A., Frankel S. (1957)** – Reitman - Frankel colorimetric method of GOT/AST and GPT/ALT Transaminases. *Amer J Clin Path.,* 28 : 56-63
33. **Richmond W. (1973)** - Preparation and properties of acholestrol oxidase from nocardia sp. And its application to the enzymatic assay of total cholesterol in serum. *Clin. Chem.* 19, 1350-1356.
34. **Robertson R.P. (2004)** - Chronic oxidative stress: a central mechanism for glucose toxicity in pancreatic islet beta cell in diabetes. *J Biol Chem.,* 279: 4235-2354.
35. **Schettler G., Nussel E. (1975)** – Colorimetric method for determination of triglycerides. *Arb Med Sozial Med Prav Med.* 10, 25
36. **Schneider L.E., Schedl H.P. (1972)** - Diabetes and intestinal Co-absorption in the rats. *Am J Physiol*., 223: 1319.
37. **Simpson H.C., Sturley R., Stirling C.A., Reckless J.P. (1990)** -- Combination of insulin with glipizide increases peripheral glucose disposal in secondary failure type 2 diabetic patients. *Diabetic Med.,* 7(2): 143.
38. **Snedecor J., Cochran R.** (1969): Statistical methode 6th Ed. The Iowa State Univ., Press, Iowa, USA.
39. **Sundaram R.K., Bhaskar A., Vijayalingam S., Viswa-Nathan M., Mohan R, Shanmugasundaram K.R. (1996)** - Antioxidant status and lipid peroxidation in type I diabetes mellitus with and without complications. Clin. Sci. (Land.), 90, 255-260.
40. **Tanaka T., Nanbara S., Tanaka T. Koide H., Hayashi T.** (1988) - Aminotransferase activity in liver of diabetic mice. *Diabetes Res. Clin. Pract*., 19: 71-75.
41. **Trinder P.** (1969) *Ann Clin Biochem.,* 6: 24 .
42. **Victory W., Levenson R., Vander A.J. (1981)** - Effect of glucagon on zinc excretion in anesthetized dogs. *Am J Physiol.,* 240 *(Renal) Fluid Electrolyte Physiol.* 9: 299.
43. **Voss C**., **Brachmann, K., Hartmann, K. (1988)** - Effect of Streptozotocin on transaminases, creatinine and urea in serum of rats. *Exp Clin Endocrinol.,* 92(1): 37-42.
44. **Wang J.Y., Li X.G., Yang X.W. (2006)** - Ginsenine, a new alkaloid from the berry of ginko biloba *J Asian Nat Prod Res.,* 8: 605-608.
45. **Yimaz H.R., Uz E., Yucel N., Altuntas I., Ozcelik N. (2004)** - Protective effect of caffeic acid phenethyl ester (CAPE) on lipid peroxidation and antioxidant enzymes in diabetic rat liver. *J Biochem Mol Toxicol.,* 18: 234-8.
46. **Zimmet P.Z., Mccarty D.J., DeCouten M.P. (2003)** - The global epidemiology of non insulin dependent diabetes mellitus and the metabolic syndrome. *J Diabetes Complications*, 11(2):60-68.