Effect of Two Novel Thiazole and Thiadiazine Derivatives on Hyperglycemia and Oxidative Stress in Streptozotocin-Induced Diabetic Mice

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Introduction

Diabetes mellitus (DM) is the most common lifestyle metabolic disease and it is a major source of morbidity and mortality in developing countries.

The prevalence of diabetes for all age groups worldwide was estimated to be 415 million in 2015 and it is projected to be 642 million in 2040

This may be due to:

✓population growth

✓Aging

✓Obesity

Over 80% of diabetes deaths occur in low- and middle-income countries.

In Asia young to middle-aged people whose affected with diabetes is comparatively high

Diabetes mellitus occurs due to

✓Defects in insulin secretion

✓Resistance to insulin action

✓Defects in insulin conformation

DM may cause dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels

Hyperglycemia

Oxidative stress

Diabetes mellitus (DM)

Hyperglycemia

An excessive amount of glucose in blood sream circulation. The blood sugar level is higher than 200 mg/dl.

Oxidative stress

Increased oxidant production and/or a decrease in antioxidant capacity in animal cells characterized by the release of free radicals.

It plays a major role in the pathogenesis of both types of diabetes mellitus and can promote the development of its complications.

It occurs due to:

✓Generation of reactive oxygen species

✓ Alterations in metabolic pathways

✓ Increase in intracellular calcium

✓Increase in the activation of endoplasmic reticulum stress

Affects β-cells through

✓Impairing insulin secretion

✓Decreasing insulin gene expression

✓Causing apoptosis

In biomedical research, it is necessary to design new and effective molecules that effectively prevent or reverse ß-cell failure.

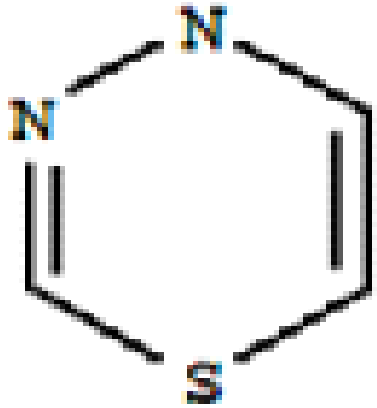
Thiazole and **Thiadizine** derivatives are attractive candidates for drug development because

They are:

✓Efficiently synthesized

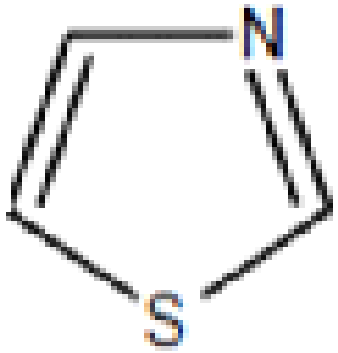
✓Active against a number of diseases and conditions, including diabetes.

Thiadizine derivatives C2H2N2S



Thiadiazin

Thiazole derivatives C3H3NS



Thiazol

Figure (1): Thiazole (T) and Thiadiazine (Z)

Significance: to

✓Improve the drugs efficiency

✓Reduce the drugs toxicity

✓Facilitate dealing with broad cohort of DM patients.

Objective

✓To investigate the effects of Thiazole and Thiadiazine on hyperglycemia and oxidative stress.

✓To determine whether these two novel derivatives have any effect on blood glucose and serum insulin concentration

✓To determine the effects of the Thiazole and Thiadiazine on cholesterol and triglycerides profile.

✓To study the *in vivo* toxicity of the two compunds.

Materials and Methods

Chemicals

The two investigated compounds in this study were synthesized and kindly provided by

Prof. Mahamoud El-Taleb
Prof. Hassan Tashtoush and
Bushra Ababneh
(Department of Chemistry, Faculty of Science,Yarmouk University, Jordan).

The chemical structures and names of these compounds are presented in Fig (3 and 4).

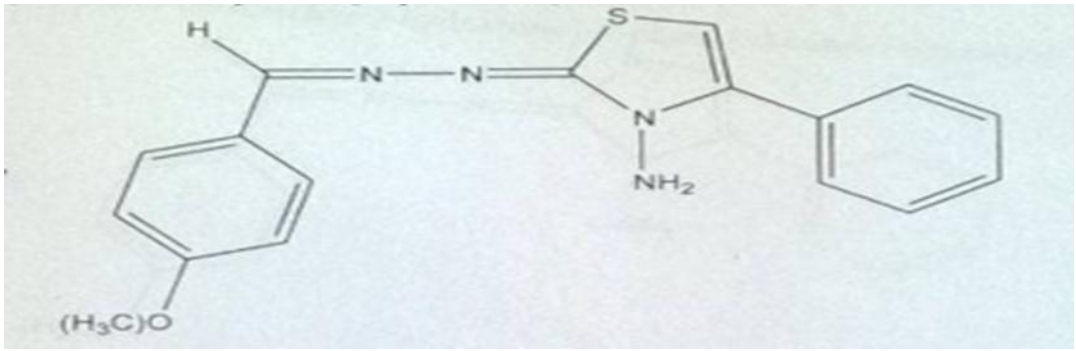


Fig 2: 2-[(4-methoxy-benzylidene)-hydrazono]-4-phenyl-thiazol-3-ylamine

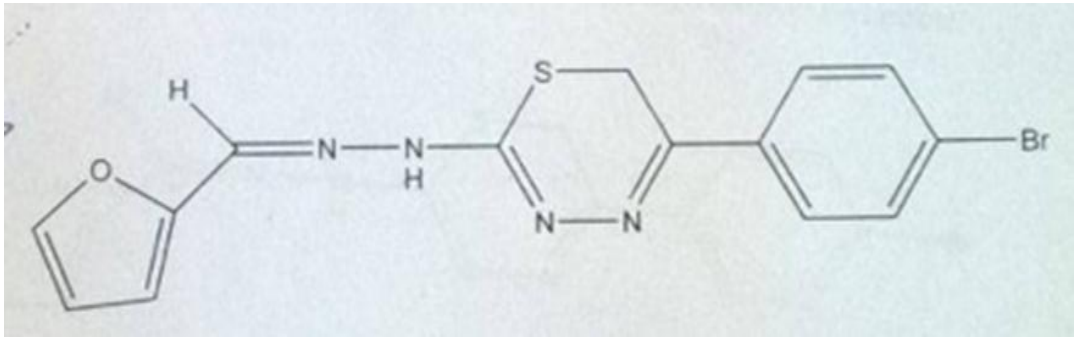


Fig 3: N-[5-(4-Bromo-phenyl)--6H-[1,3,4]tiadiazin-2-yi]-N'-furan-2-ylmethylene-hydrazine

Animals

110 male adult Balbc mice

Old: 55-60 days.

Average Weight: 30g.

Housed in the animal house in the Yarmouk University .

Environment at 21°C-23°C on an illumination schedule of 12h of light and 12h of darkness.

Standard pellet food and water.

DMSO toxicity test and Thiazole and Thiadiazine acute toxicity were examined.

Mice were divided into eight groups:

✓Negative control non diabetic injected with D.W (C)

✓Positive control diabetic untreated injected with DMSO 100% (A)

✓Thiazole (T) derivatives treated diabetic groups (20 (T1)), (10 (T2)), and (5 (T3)) mg/kg

✓Thiadizine (Z) derivatives treated diabetic groups (20 (Z1)), (10 (Z2)), and (5 (Z3)) mg/kg.

✓ Single dose of (0.05) ml intraperitoneally for 18 days).

Diabetes induced in 100 mice by (iP) injection of STZ (50 mg/kg; dissolved in normal saline).

- Single dose of 0.2 ml intraperitoneally for 5 days.

At the end of the experiment:

Weight was determined.

Blood was collected.

Pancreas were taken and homogenized.

Serum glucose levels were determined by (GOX).

-Serum insulin levels were determined by ELISA.

-The activities of the (SOD) enzymes , was measured.

-The lipid profile (TC), (TG) were determined.

Results

DMSO toxicity test

- Group injected by (0.2) ml pure 100% DMSO: All mice died after two days

- Group injected by (0.1) ml pure DMSO + (0.1) ml D.W: Three mice died during14 days

- last group injected by (0.05) ml pure DMSO + (0.15) ml D.W: Did not record any death during the 14 days.

Thiazole and Thiadiazine acute toxicity test

The (i.p.) injection of mice with our compounds in 5, 10, 20, 70, 100, 150, 300 mg/kg dose couldn't reach the (LD_{50}).

Mice weight

After 18 days, all groups showed a decrease in the body weight as compared with the control group.

Table (1): Mean body weight before and after treatment

GROUP	BEFOR	AFTER
C	22±0.29	21±0.49
A	28±0.58	25±0.38
T1	25±0.23	24±0.31
T2	24±0.25	22±0.36
T3	24±0.41	20±0.52
Z1	24±0.34	21±0.41
Z2	24±0.35	21±0.21
Z3	25±0.29	22±0.40

Blood glucose levels

✓Blood glucose was significantly higher in the diabetic mice than in the control mice .

✓Treatment with different doses of both compounds significantly reduced blood glucose levels in diabetic mice as compared to the diabetic control.

✓The dose of both compounds, which has induced a significant inhibitory effect on blood glucose level was 20mg/kg.

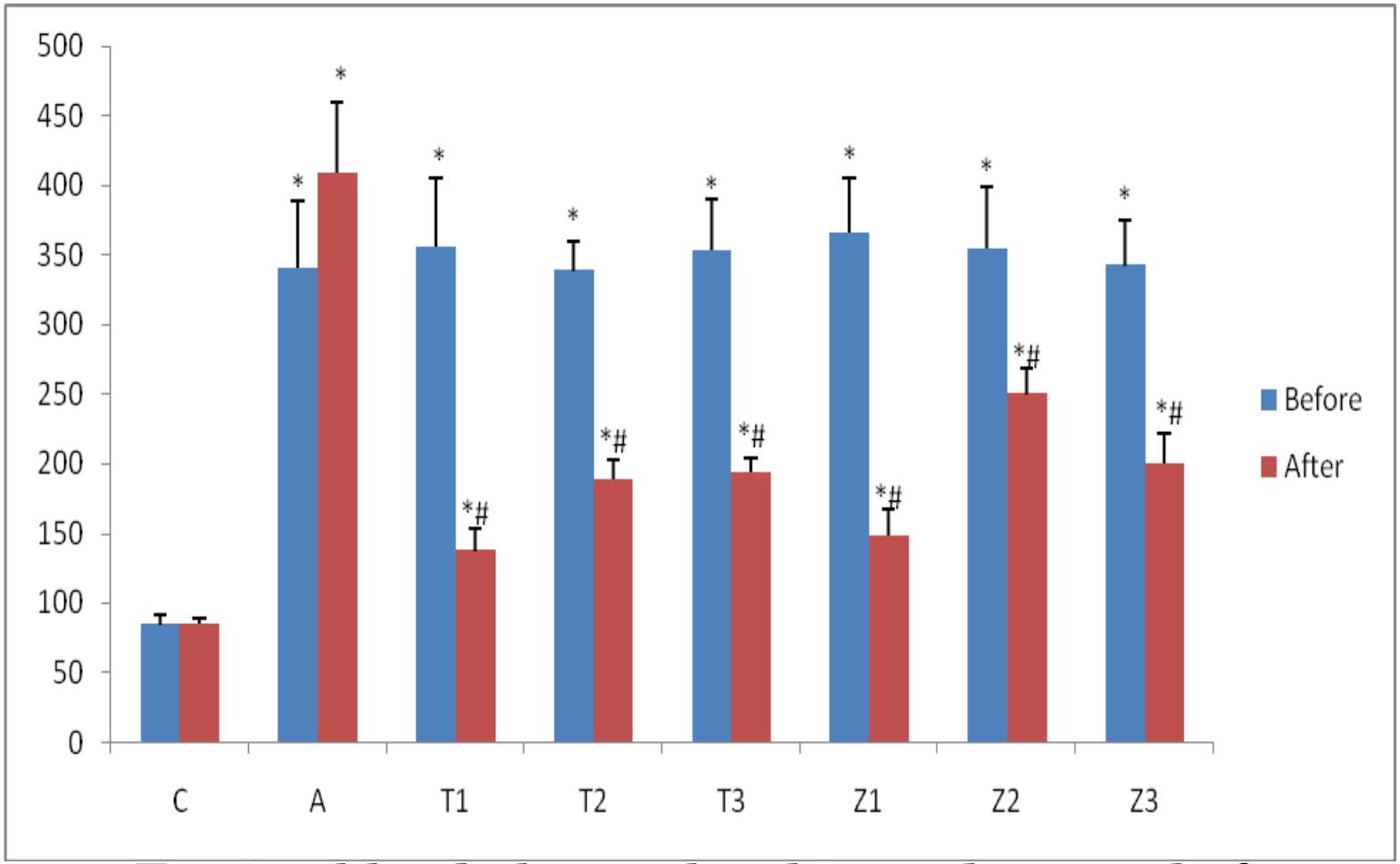


Figure 4: Fasting blood glucose level in each group before and after treatment. Data represent the mean ± SEM. $^{*}P < 0.05$ vs control group; $^{\#}P < 0.05$ vs diabetic group**. Abbreviations**: **C**: control, **A**: Diabetic, **T1**: Diabetic + 20mg Thiazole , **T2**: Diabetic + 10mg Thiazole , **T3**: Diabetic + 5mg Thiazole , **Z1**: Diabetic + 20mg Thiadizine , **Z2**: Diabetic + 10mg Thiadizine, **Z3**: Diabetic + 5mg Thiadizine .

Serum insulin level

Insulin levels were significantly lower in diabetic control group as compared to the normal control group ($P < 0.05$).

The groups treated with different doses of the two compounds showed significant increase in the serum insulin level on day 18 after administration.

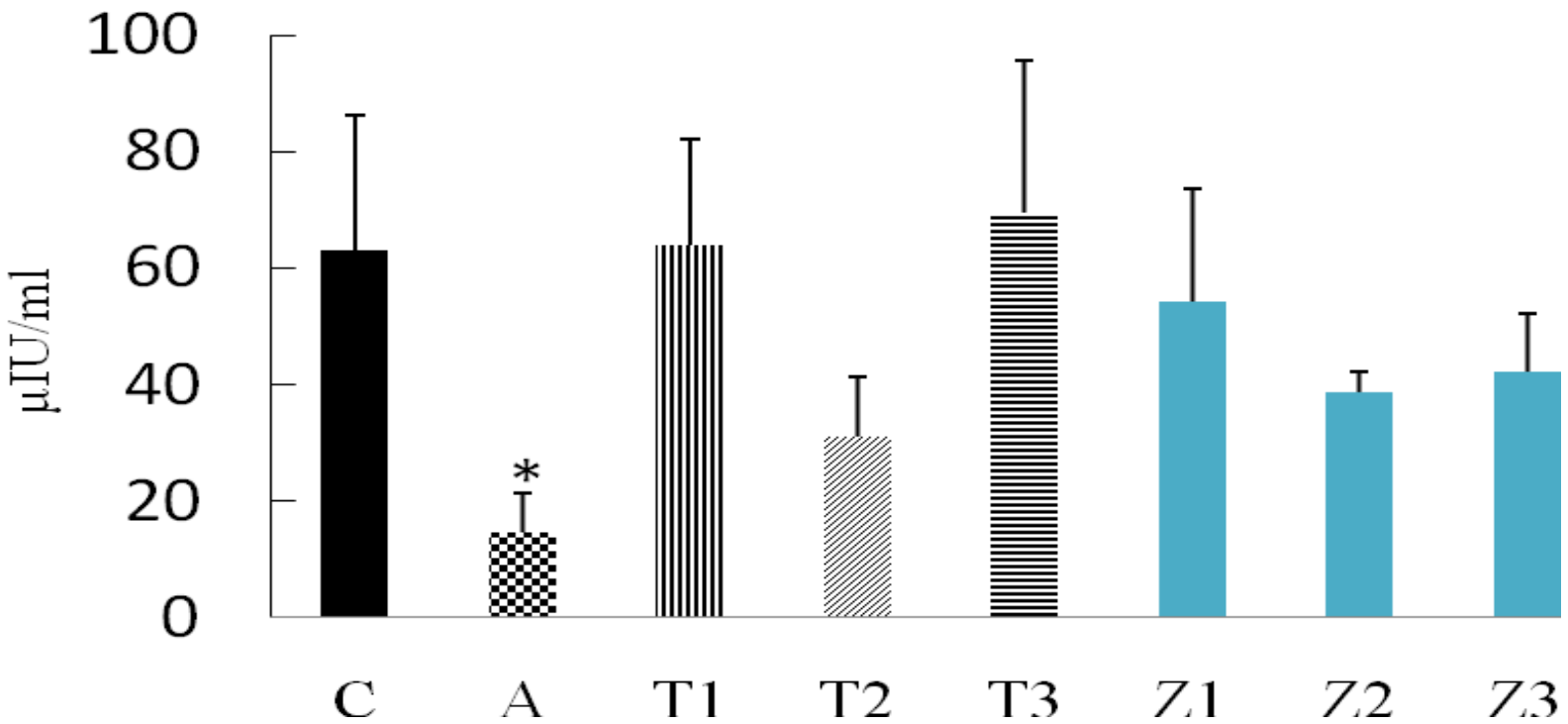


Figure (5): Serum insulin level in each group. Data represent the mean ± SEM. $^{*}P < 0.05$ vs control group**. Abbreviations**: **C**: control, **A**: Dibetic, **T1**: Diabetic + 20mg Thiazole , **T2**: Diabetic + 10mg Thiazole , **T3**: Diabetic + 5mg Thiazole , **Z1**: Diabetic + 20mg Thiadizine , **Z2**: Diabetic + 10mg Thiadizine, **Z3**: Diabetic + 5mg Thiadizine .

Serum lipid profile levels

Our results showed that there were no significant differences in the total cholesterol levels among the groups

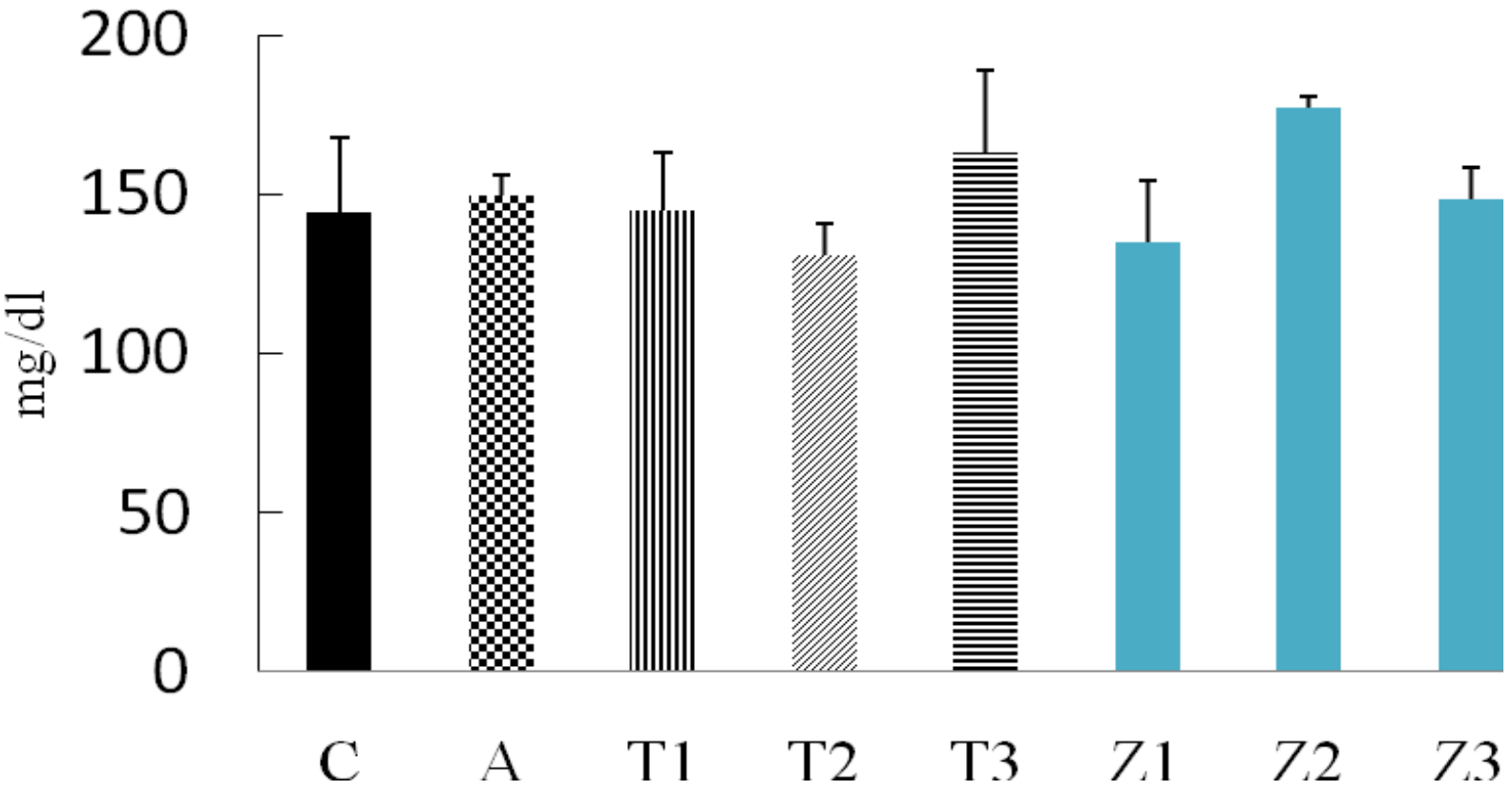


Figure (6): Serum cholesterol level in each group. Data represent the mean ± SEM.. **Abbreviations**: **C**: control, **A**: Dibetic, **T1**: Diabetic + 20mg Thiazole , **T2**: Diabetic + 10mg Thiazole , **T3**: Diabetic + 5mg Thiazole , **Z1**: Diabetic + 20mg Thiadizine , **Z2**: Diabetic + 10mg Thiadizine, **Z3**:Diabetic + 5mg Thiadizine .

Serum triglyceride levels were significantly increased in diabetic control group as compared to the normal mice after 18 days of diabetes. Treatment of diabetic mice with both compounds significantly decreased serum triglyceride levels when compared to the diabetic control group and the normal control group ($P < 0.05$).

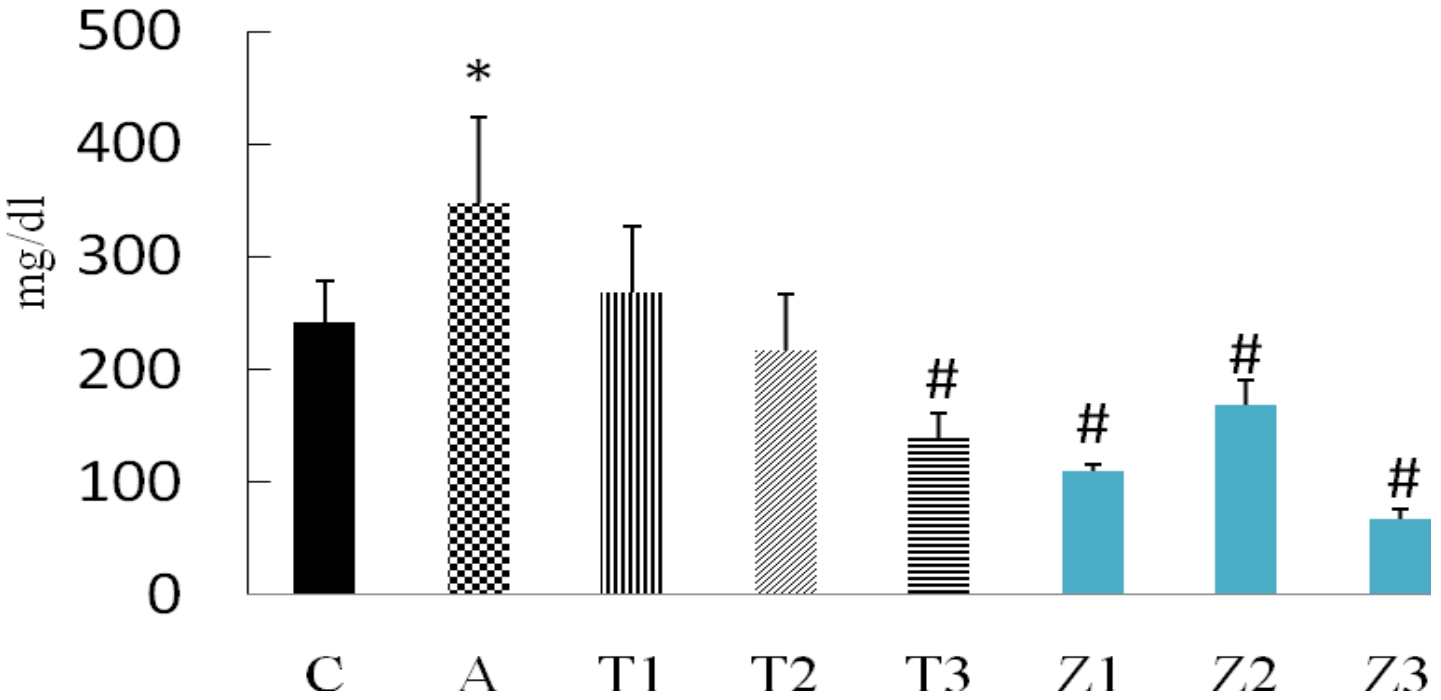
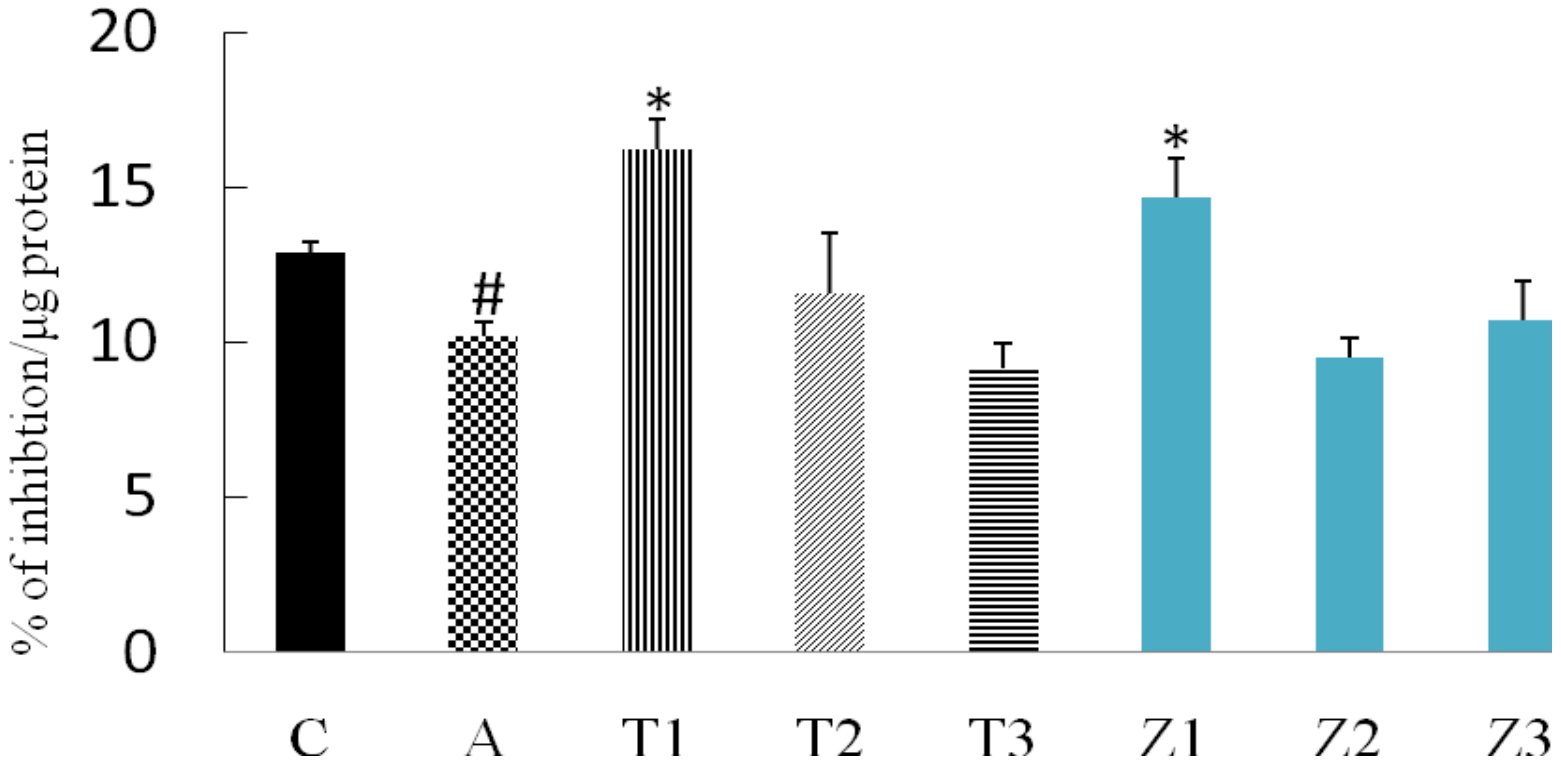


Figure (7): Serum triglycerides level in each group. Data represent the mean ± SEM. $^{*}P < 0.05$ vs control group; $^{\#}P < 0.05$ vs control and diabetic group**. Abbreviations**: **C**: control, **A**: Dibetic, **T1**: Diabetic + 20mg Thiazole , **T2**: Diabetic + 10mg Thiazole , **T3**: Diabetic + 5mg Thiazole , **Z1**: Diabetic + 20mg Thiadizine , **Z2**: Diabetic + 10mg Thiadizine, **Z3**:Diabetic + 5mg Thiadizine .

Antioxidant enzyme

pancreatic SOD activity decreased in the diabetic group ($P < 0.1$). Treatment the diabetic mice with 20mg/kg Thiazole or with 20mg/kg Thiadizine compounds had significantly increased the pancreatic SOD activity.



Figure(8): Effect of treatments on the SOD activity in the pancreas. Data represent the mean ± SEM. $^{*}P < 0.05$ vs diabetic group; $^{\#}P < 0.1$ vs control group. One unit of SOD activity was defined as the amount of enzyme which inhibited the color formation by 50%. **Abbreviations**: **C**: control, **A**: Dibetic, **T1**: Diabetic + 20mg Thiazole , **T2**: Diabetic + 10mg Thiazole , **T3**: Diabetic + 5mg Thiazole , **Z1**: Diabetic + 20mg Thiadizine ,**Z2**: Diabetic + 10mg Thiadizine, **Z3**:Diabetic + 5mg Thiadizine

Conclusions

✓The Thiazole and Thiadiazine compounds seems to have low toxicity values.

✓Thiazole and the Thiadiazine derivatives have the potential to reduce hyperglycemia and to restore pancreatic insulin secretion.

✓ The two compounds have decreased the serum triglycerides level and increased the pancreatic SOD activity in the treated diabetic mice.


Thank you!