



Study of antidiabetic activity Cu (II) Schiff base complex on the pancreatic function and tissue in diabetic rat

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Abstract

Background: Considering the high prevalence of diabetes and the importance of a treatment strategy for it, the present study was conducted.

Martials and Methods: For this purpose, a Cu (II) Schiff base complex was synthesized and dissolved in DMSO solvent. Sixty-four rats were selected and randomly classified into eight groups. Four groups were diabetic by intraperitoneal injection of 80 mg/kg bw of Streptozotocin. The non-diabetic groups include control, sham 1 (receive normal saline), sham 2 (receive DMSO), and sham 3 (receive Schiff base). Diabetic groups include sham 4 (without treatment), sham 5 (receive Glibenclamide), and treatment groups (receive 50 and 100 mg/kg bw of Schiff base). After 40 days, the rats were anesthetized, and their blood was taken to evaluate pancreatic functional parameters. Also, their pancreas was removed for stereological study. All the passage steps were performed, and the prepared slides were stained with H&E and aldehyde-fuchsin. The data were analyzed using SPSS(20), ANOVA and Tukey test ($p < 0.05$). **Results:** Weight, the serum level of insulin, HDL, and total protein in diabetic rats decreased compared to the control, and the levels of glucose, triglycerides, total cholesterol, and LDL increased. These parameters were improved using Glibenclamide and Cu (II) Schiff bas. Also, reduction in pancreatic weight, size of Langerhans islets, and β -cells number in the diabetic groups were adjusted using Glibenclamide and Cu Schiff base.

Conclusion: Based on these results, Cu Schiff bas has an antidiabetic effect, and improves the structure and function of diabetic pancreas.

Key words: β -cells, Cu (II) Schiff base, Cholesterol, Triglycerides, Diabetes

دراسة النشاط المضاد لمرض السكر لمركب قاعدة شيف Cu (II) على وظيفة البنكرياس والأنسجة في
الفئران المصابة بمرض السكر
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المخلص

الخلفية: نظرًا لانتشار مرض السكر وأهمية استراتيجية العلاج له، أجريت هذه الدراسة. الأساليب والطرق: لهذا الغرض، تم تصنيع مركب قاعدة شيف Cu (II) وإذابته في مذيب DMSO. تم اختيار أربعة وستين فأرًا وتصنيفهم عشوائيًا إلى ثمانية مجموعات. تم حقن أربع مجموعات بمرض السكر عن طريق الحقن داخل الصفاق بجرعة 80 مجم / كجم من وزن الجسم من ستربتوزوتوسين. تشمل



المجموعات غير المصابة بمرض السكري المجموعة الضابطة، والشام 1 (تتلقى محلول ملحي طبيعي)، والشام 2 (تتلقى ثنائي ميثيل سلفوكسيد)، والشام 3 (تتلقى قاعدة شيف). تشمل المجموعات المصابة بمرض السكري الشام 4 (بدون علاج)، والشام 5 (تتلقى جليبينكلاميد)، ومجموعات العلاج (تتلقى 50 و 100 مجم / كجم من وزن الجسم من قاعدة شيف). بعد 40 يومًا، تم تخدير الفئران، وتم أخذ دم منها لتقييم المعايير الوظيفية للبنكرياس. كما تم إزالة البنكرياس للدراسة المجسمة. تم تنفيذ جميع خطوات المرور، وتم صبغ الشرائح المحضرة باستخدام H&E والألدهيد-فوكسين. تم تحليل البيانات باستخدام SPSS (20) و ANOVA واختبار Tukey ($p < 0.05$). النتائج: انخفض الوزن ومستوى الأنسولين في المصل و HDL والبروتين الكلي في الفئران المصابة بمرض السكري مقارنة بمجموعة التحكم، وارتفعت مستويات الجلوكوز والدهون الثلاثية والكوليسترول الكلي والكوليسترول الضار. وقد تم تحسين هذه المعايير باستخدام جليبينكلاميد وقاعدة شيف النحاسية (II). كما تم تعديل انخفاض وزن البنكرياس وحجم جزر لانغرهانس وعدد خلايا بيتا في المجموعات المصابة بمرض السكري باستخدام جليبينكلاميد وقاعدة شيف النحاسية. الاستنتاج: بناءً على هذه النتائج، فإن قاعدة شيف النحاسية لها تأثير مضاد لمرض السكري، وتحسن بنية ووظيفة البنكرياس السكري.

الكلمات المفتاحية: خلايا بيتا، قاعدة شيف النحاسية (II)، الكوليسترول، الدهون الثلاثية، مرض السكري

Introduction

Diabetes mellitus (DM) is an endocrine metabolic disorder characterized by elevated blood glucose levels brought on by inadequate insulin synthesis or function. This metabolic illness causes chronic malfunction that can impact the cellular structure and function of multiple organs (Aroua et al., 2021). This type of diabetes is caused by the complex interactions between environmental and genetic factors, but it happens when the amount of insulin is not enough, which is due to the functional disorder of beta cells in the pancreas or insulin resistance occurring in the target tissue. Millions of people worldwide are impacted by diabetes, so proposing new solutions in the treatment of this disease has always been of interest. Schiff base is a compound that has a double carbon-nitrogen bond and a single nitrogen atom bound to the alkyl or aryl group. Its general formula is $RHC=N-R'$, with groups R and R' having different alternatives. They are known as imine or azomethine, and they are analogs of a ketone or aldehyde in which the amine replaces the carbonyl group. (Yusuf et al., 2023). Under certain conditions, the oxygen atom of the hydroxyl group may form a bridge between two metal atoms and form tridentate ligands that form stable complexes with many metal ions (Mohamed et al., 2023). The bidentate, tridentate, and tetradentate Schiff base complexes contain nitrogen and oxygen donor atoms, which play an important role in biological systems and can be interesting models for metalloenzymes, which effectively catalyze the reduction of dinitrogen and dioxygen. Many tridentate Schiff bases have N_2O , NO_2 , and NSO donor groups as anionic ligands. They stabilize metals in various oxidation states or are used as catalysts for the synthesis of optical and magnetic materials and catalysts, such as SOD16 catalase (Alshaheri et al., 2017).

Schiff bases compounds are produced easily with high purity and strong effect. So in recent years, their use has received much attention in biological and medical



sciences, including anti-cancer (Zehra et al., 2023), anti-viral and anti-bacterial (Yusuf et al., 2023), anti-fungal and anti-parasitic, anti-inflammatory (Alam et al., 2023), and anti-diabetic properties (Sankar and Sharmila, 2023). Antidiabetic Schiff base metal complexes, such as Mn (II), Cu (II), and Zn (II) are α -amylase inhibitors, α -glucosidase inhibitors, or both of them. Therefore, in relation to these compounds, many studies have been done in the fields of medicinal chemistry and biological research (Waziri et al., 2023). Despite the properties mentioned in many studies, there are not many reports of using them as clinical medications.

In the Schiff base complex formation, the type of ligands that attach to metal ions, such as copper, determines the characteristics of complex. The ligands have the ability to modify the biological activity of the metal complexes, altering properties such as lipophilicity, solubility, stability, and metabolism in biological systems (Svahn et al., 2018). Copper have catalytic activity and it is a vital metalloelement which is very important in synthesis or function of cellular enzymes (Umar et al., 2023). The activity of Schiff base ligands is usually increased by complexation with this metal ion (Kumari et al., 2023).

According to increasing prevalence of diabetes in human societies, proposing new solutions for the treatment of this disease has always been of interest. Considering the many biological uses reported for Schiff bases, in this research, the effect of the Schiff base Cu (II) complex, which is a synthetic Schiff base, was studied in diabetic rats.

Martials and Methods

1. The synthesis of copper (II) Schiff base complexe

In the first step, a ligand (α, α' -Me₂-salen) was synthesized. So 2 ml of 2 and 2'-hydroxyacetophenone were poured into Erlenn, 10 ml of methanol, and 0.55 ml of ethylenediamine were added to it. The magnet was placed in an Erlenmeyer flask and refluxed for 30 minutes. After the reaction between these two substances, a yellow precipitate of 1, 2 ethylenebis (α methylsalicylideneimine) was obtained, passed through filter paper, and dried (Hariharan, 1969). In the second step, 1 gram of the obtained ligand

was dissolved in methanol and refluxed with 0.66 grams of copper acetate for 2 hours. The resulting purple precipitate was filtered and recrystallized with absolute ethanol to get the Schiff base Cu (II) complex (Kargar et al., 2021). In this regard, the synthetic ligand, α, α' -Me₂-salen, a base ligand, was described using spectroscopic methods, including proton nuclear magnetic resonance spectroscopy (HNMR) by the Bruker Avance DPX 250 MHz NMR Spectrometer (Fig. 1 and Table. 1), and elemental analysis was performed by the CHN ThermoFinnigan Flash EA1112 (Table 2). The solvents used in NMR spectroscopy are CDCl₃ (deuterated chloroform) and DMSO (dimethyl sulfoxide).



Fig 1:

Proton nuclear magnetic resonance Spectroscopy of α, α' -Me ₂ -salen ligand	Ligand	C	H	N
	α, α' -Me ₂ -salen	72.81(72.95)	7.01(6.80)	9.85(9.45)

Table 1: Proton nuclear magnetic resonance Spectroscopy of α, α' -Me₂-salen ligand

Table 2. Elemental analysis of α, α' -Me₂-salen ligand

2. Preparation of treatment solution

DMSO (dimethyl sulfoxide) was used as the Schiff base solvent. The lethal dose (LD) of DMSO solvent for rats is 20–28 gr/ kg bw orally (Lin et al., 2019). According to the mean weight of rats in this research (200–220 gr), LD is up to about 5.6 gr. In this way, 50 and 100 mg/kg bw of Cu (II) Schiff base were dissolved separately in 1 cc of diluted DMSO and normal saline.

3-Grouping and treatment of rats

Sixty-four rats were randomly divided into eight equal groups. Four groups of them became diabetic by intraperitoneal injection of a single dose of 80 mg/kg bw of streptozotocin in citrate buffer at pH = 4.5. The rats were checked daily (for 10 days), and the fasting blood sugar level was more than 250 mg/dL, which confirmed that they were diabetic. The rats were divided into 8 groups as follows:

CH ₃	C(CH ₃)=N	C-H	CH ₂	Ar-H	OH	Ligand
	2.3		3.9	6.7-7.6	16.0	α, α' -Me ₂ -salen

The control group (healthy rats without any treatment), sham 1 (healthy rats receive 0.2 cc normal saline), sham 2 (healthy rats receive 0.2 cc DMSO solvent and normal saline), sham 3 (healthy rats receive 100 mg/kg bw of Schiff base solution), sham 4 (diabetic rats without any treatment), sham 5 (diabetic rats receive 5 mg/kg bw glibenclamide), treatment 1 and 2 (diabetic rats which receive respectively 50 and 100 mg/kg bw of copper (II) Schiff base solution). This process was done daily by gavage for 40 days.

4- Evaluation of function and tissue structure of pancreas



The rats were dissected immediately, and their pancreas was removed, cleaned, and its volume measured using Scherle's immersion method (Pirmoradi et al., 2016) in this way: After weighing the pancreas, it is immersed in a certain volume of water, and the difference in water volume is considered the initial volume of the pancreas. It was fixed in a 7%

formalin solution. All the passage steps were performed using the Tissue Processor (Autotechnicon), and 4 micron sections were obtained (Pousti et al., 2019). Two circular pieces (2 mm in diameter) were punched, and two causal slabs were obtained. All the slabs and the circular pieces were embedded in a paraffin block.

$$N_v = \frac{\sum q}{\sum p \times h \times a(\text{frame})}$$

The prepared slides were stained with hematoxylin and eosin stain and Gomori's aldehyde-fuchsin (for β -cell staining).

To get the final pancreatic volume, the initial volume must be multiplied by the amount of shrinkage. The shrinkage is determined according to the following formula:

Shrinkage = $1 - r$ (after staining) $2 / r$ (befor staining)³

Actual Volume = Wrinkling $\times$ Primery volume

r: the areas of each pieces of the pancreas

The disector technique was used to count β -cells (Noorafshan et al., 2012). In this method, two sections were selected, and the components between those two sections were counted. An unbiased counting frame was used in this method. This frame has two sides Rejection Lines and Acceptance Line, and only components that are completely inside the counting Frame or on the Acceptance line were counted.

Total cells = $N_v \times V$

N_v : Cell number in per unit volume $\sum Q$: Total number of cells $\sum p$: Fram numbers
a (frame) :area (100 μm) h: height of the disector

The volume of islets of Langerhans was determined as follow:

The islets of Langerhans in selected slabs were counted by point -counting method, and the volume of them was determined using below formula:

$V_v = P(\text{islet}) / P(\text{reference})$ $V(\text{islets}) = V_v \times V(\text{primary}) \times (1 - d)$

V_v : volume density of islet P: numbers of the points hitting the islet and the reference space. V (primary): primary volume of pancreas

The number of cell were measured as followed:

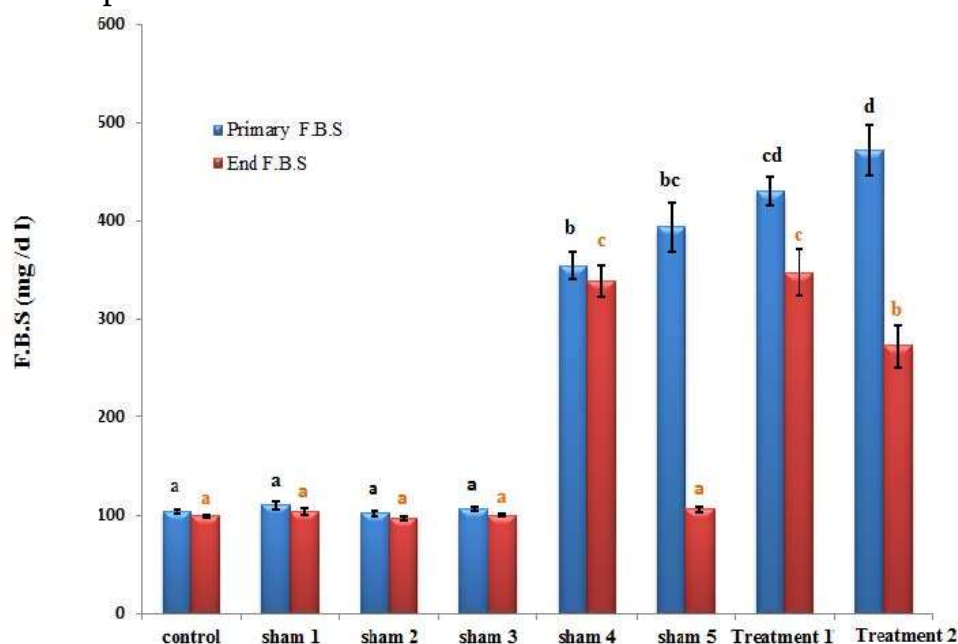
Thirty stained slides with Aldehyde Fuchsin were observed with an optical microscope at x40 and x100 and photographed. The number of beta cells (purple in color) was determined using the disector technique, image analysis, and Grids-sterio



lite software. In each slide, 5 frames were selected, each having an area of $250 \times 250 \mu\text{m}^2$, and all the cells observed in these frames were counted. The ratio of the average number of cells at the selected level was considered the average density (Pirmoradi et al., 2016).

5-Analysis of obtained data

The obtained data were analyzed using SPSS (20) software, one-way analysis of variance (ANOVA) test, and the groups were compared by Tukey tests at significant level $p < 0.5$.



Results

The obtained findings indicated the effect of Cu (II) Schiff base in improving function and adverse tissue changes caused by the induction of diabetes in the pancreas. The groups in the figures have been defined as follows: control (healthy rats), sham 1 (healthy rats receive 0.2 cc normal saline), sham 2 (healthy rats receive 0.2 cc DMSO solvent and normal saline), sham 3 (healthy rats receive 100 mg/kg bw of Schiff base solution), sham 4 (diabetic rats without any treatment), sham 5 (diabetic rats receive 5 mg/kg bw glibenclamide), treatment 1 and 2 (diabetic rats which receive respectively 50 and 100 mg/kg bw of copper (II) Schiff base solution).

Fig 2. The level of blood glucose in the studied groups

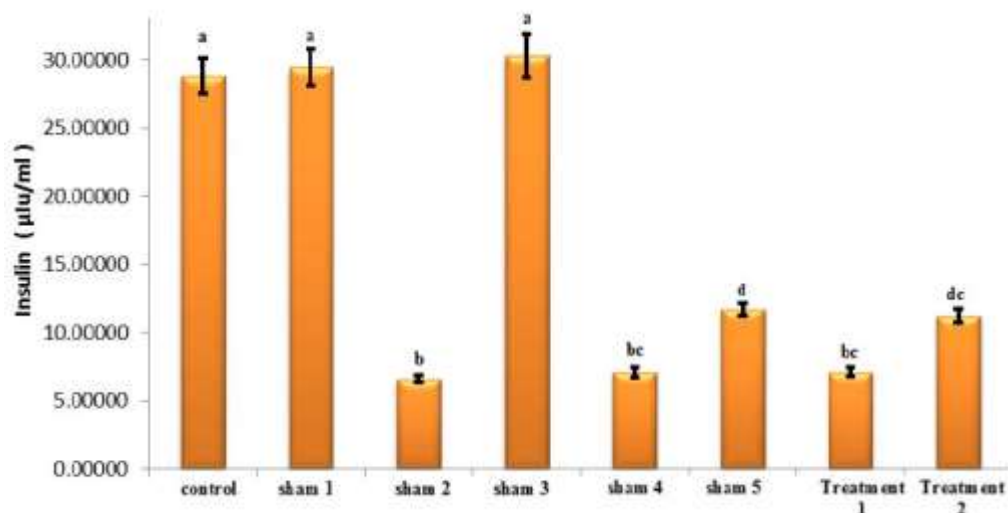


Fig 3. The level of Insulin in the studied groups

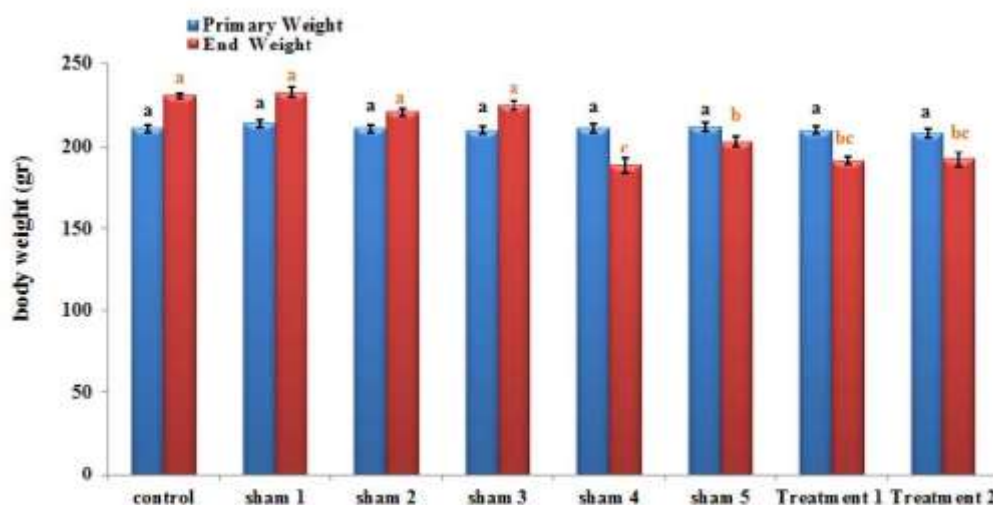


Fig 4. The weight change during the research in the studied groups

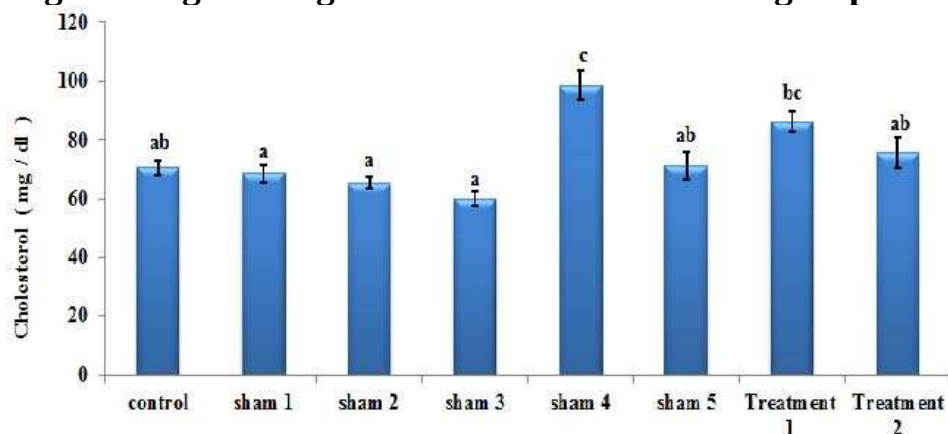




Fig 5. The level of cholesterol in the studied groups

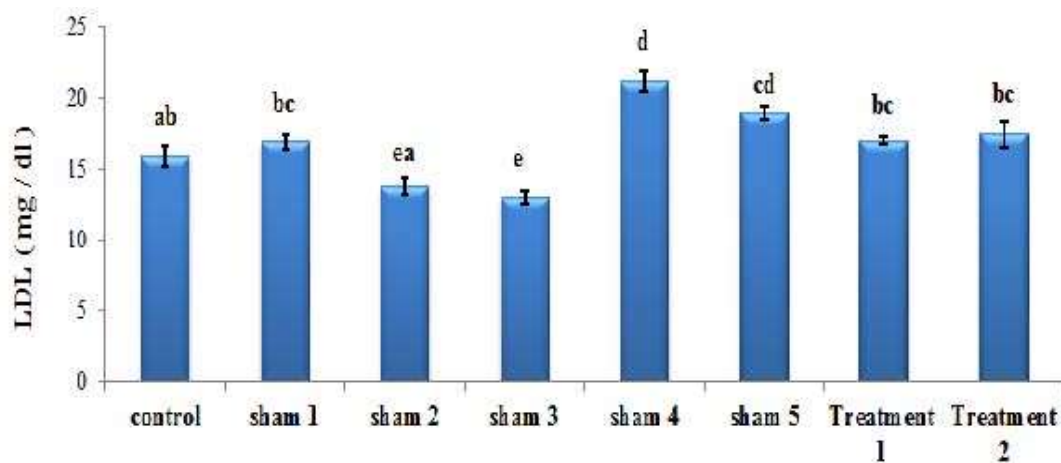


Fig 6. The level of LDL in the studied groups

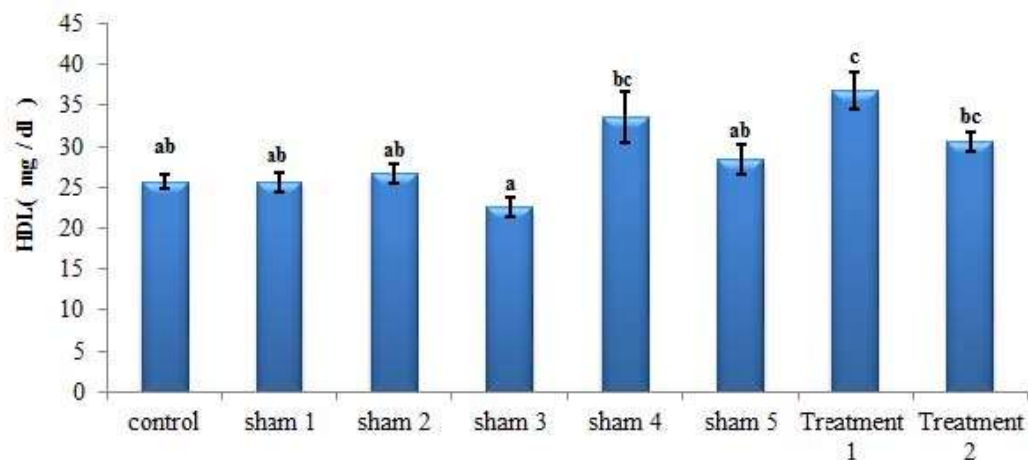
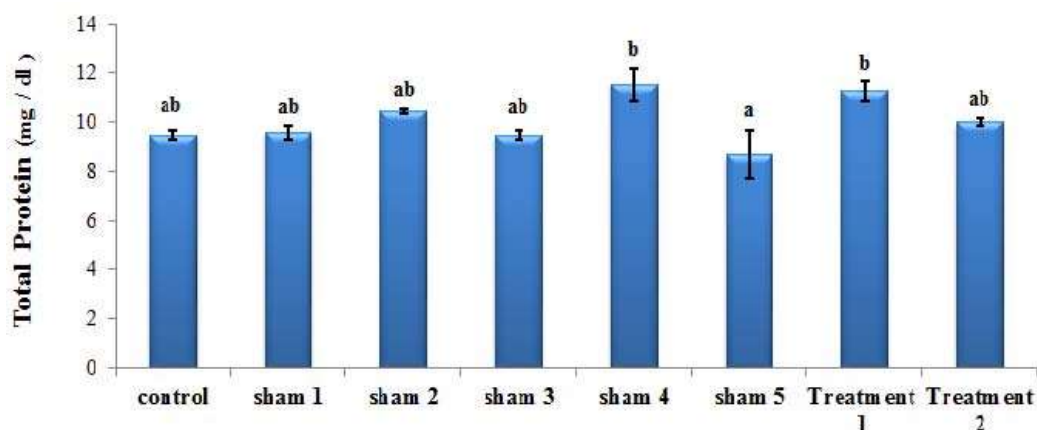
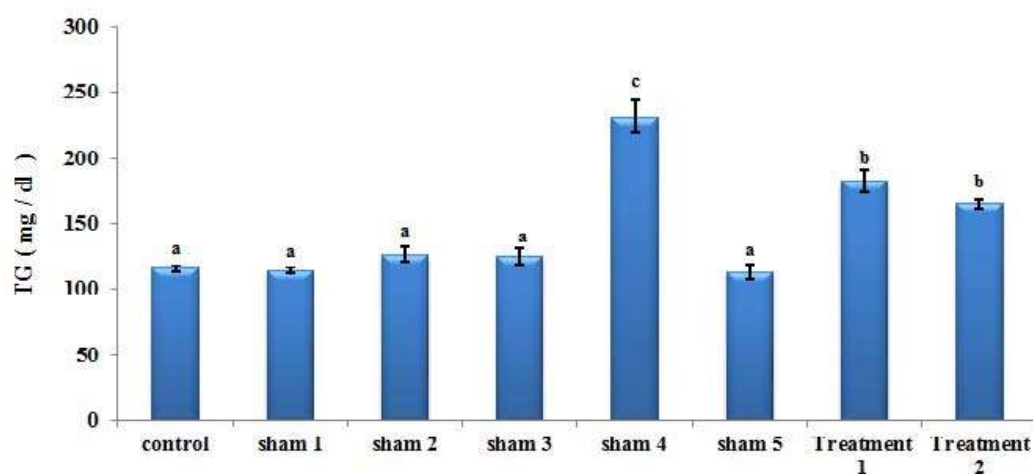




Fig 7. The level of HDL in the studied groups

Fig 8. The level of Triglyceride in the studied groups

Fig 9. The level of Total protein in the studied groups





The stereological study of the pancreas indicates the improvement of complications caused by diabetes in the groups, which were treated with Glibenclamide and Cu (II) Schiff base complex. The effect of the synthesized Schiff base was less than that of Glibenclamide (an anti-diabetic drug), and the higher dose of it (80 mg/kg bw) comparing to lower dose (50 mg/kg bw) showed a greater effect in reducing the complications of diabetes (Figs. 10–12). These results confirm the changes observed in the resulting micrographs (Fig. 13).

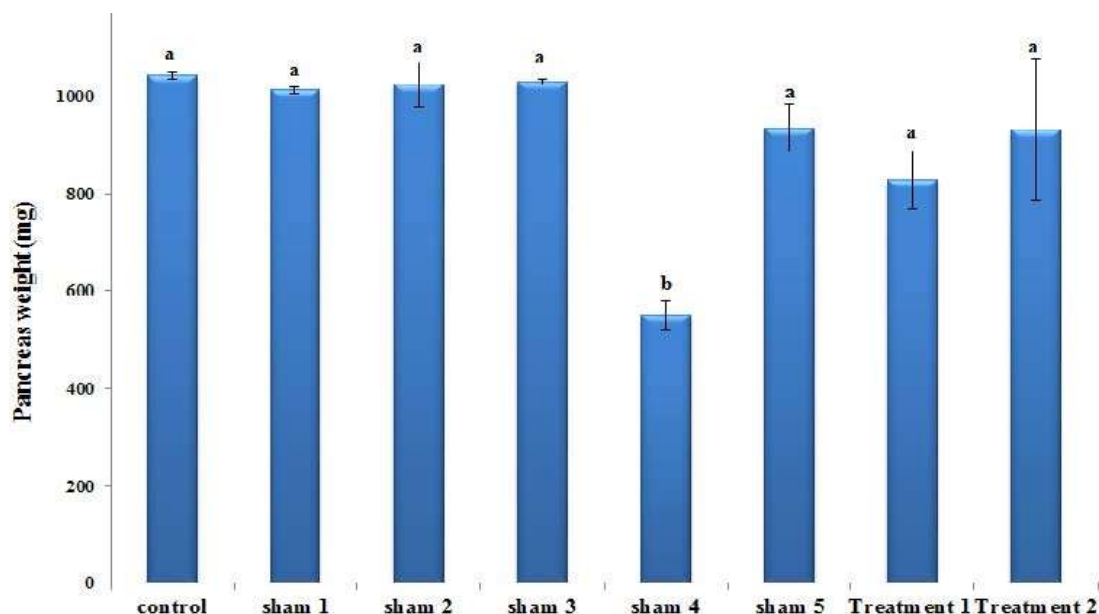


Fig 10. The weight of pancreas in the studied groups



Fig 11. The pancreatic islets volume in the studied groups

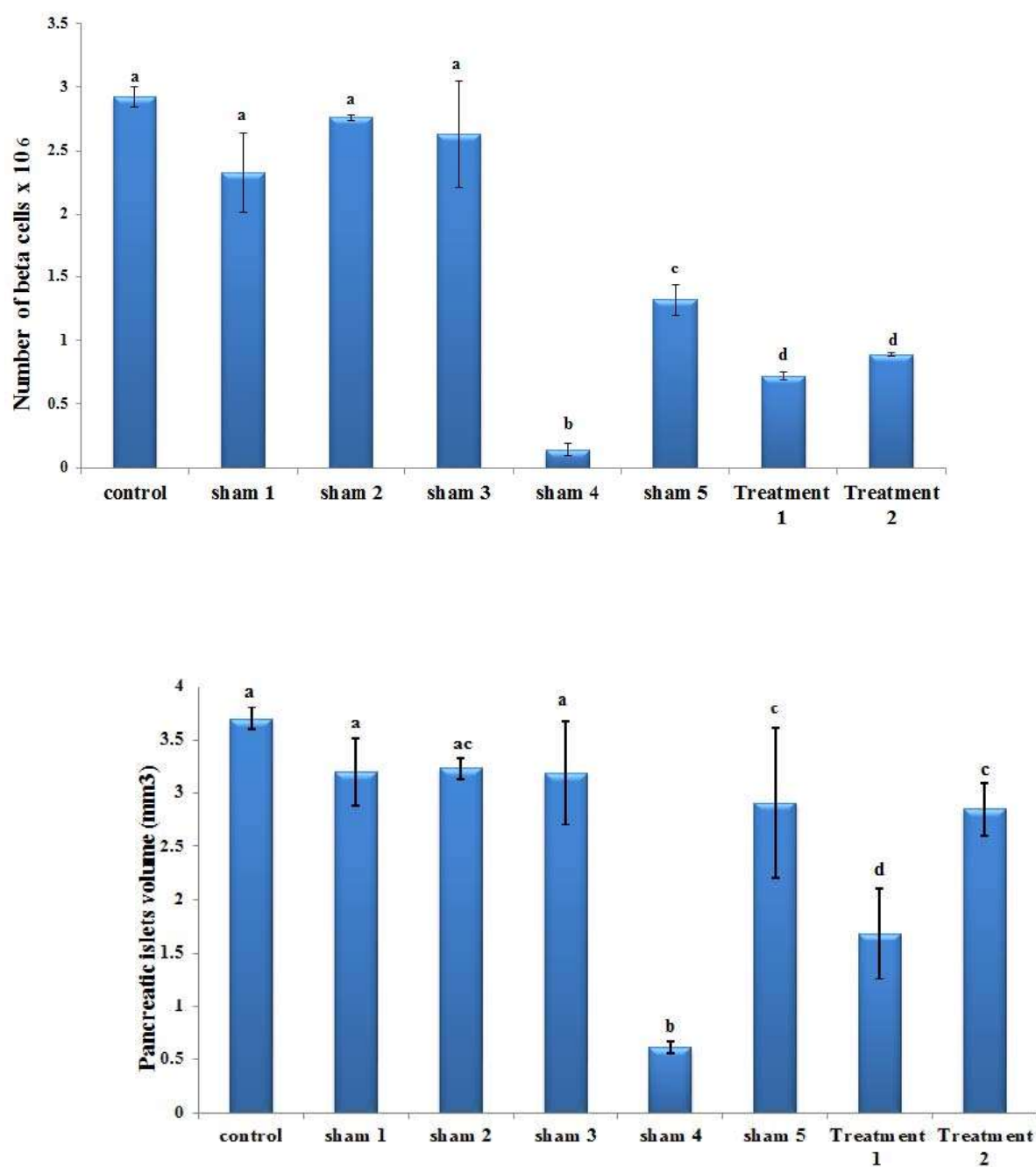


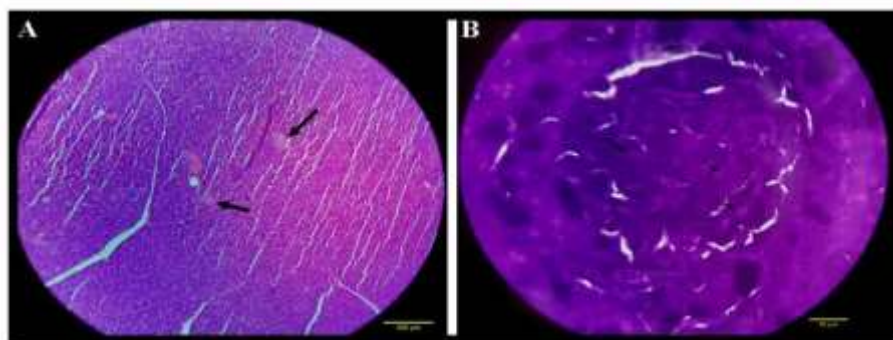


Fig 12. The number of β - cells in the studied groups

C: The control group (healthy rats)

The control group showed a normal architecture of pancreas (Fig. 13C).
D: The sham group 1 (healthy rats +normal saline) group
E: The sham group 2 (healthy rats + DMSO and normal saline) the
F: The sham group 3 (healthy rats + cu(II) schiff base) 13C).

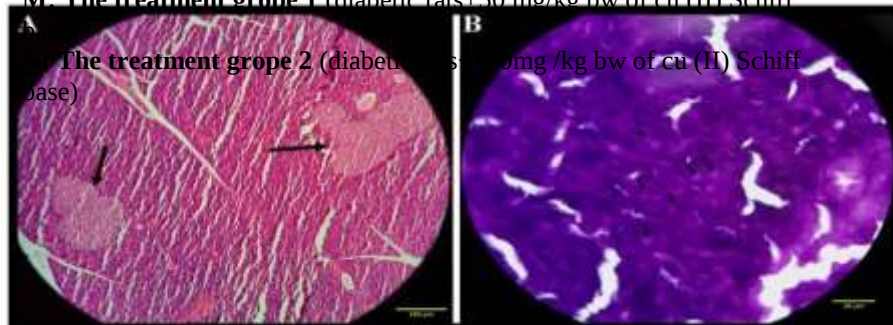
No pathological changes were seen in groups sham 1-3 (Fig 13D-F), but atrophy, wrinkling (irregular shape), a decrease in the size of the islets of Langerhans, and a decrease in the number of β cells were observed in the diabetic group or sham 4 (Fig 13G). The group treated with 100 mg/kg bw of Cu (II) Schiff base, similar to the group that received Glibenclamide (Sham 5), showed improved changes in the weight of pancreas, size of the islets of Langerhans, and the density of beta cells compared to the diabetic group. and the treated group with 100 mg/kg bw of cu (II) Schiff base showed a stronger effect in improving these changes, but none of the treated groups reached the control level.



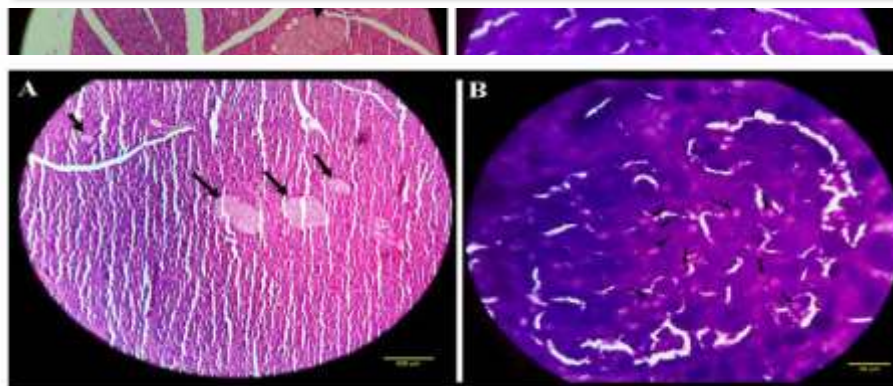
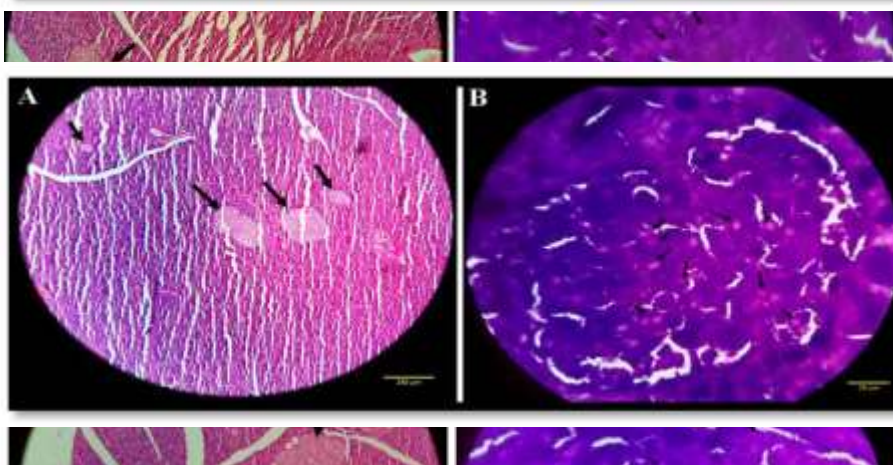
G: The sham group 4 (diabetic rats without treatment)

H: The sham group 5 (diabetic rats + Glibenclamide)

M: The treatment grope 1 (diabetic rats+50 mg/kg bw of cu (II) Schiff base)



The treatment grope 2 (diabetic rats + 100mg /kg bw of cu (II) Schiff base)





The photomicrograph of the pancreas in the studied groups Fig 13.



In each group: A: H&E staining/ magnification = 10×
B: Gomori's aldehyde-fuchsin staining/ magnification = 100×

Discussion

The results of this study indicate an increase in glucose and a decrease in insulin in the untreated diabetic group (sham 4) compared to the control group, and it was adjusted in the group taking glibenclamide (sham 5) and the groups treated with synthetic Schiff base (treatment 2). Using streptozotocin (STZ) for diabetes induction in an animal model causes the production of free radicals, reactive oxygen, and nitrogen species in β cells, and destroys them. It enters the β cells through the glucose transporter (GLUT2) and causes DNA alkylation and activation of the repair process of polyADP-ribosylation reactions (Kim et al., 2018). This is due to the inflammation and apoptosis in the β cells (Gohari et al., 2018). Since STZ is known as a donor of free radical NO, it is obvious that oxidative stress occurs, especially in pancreatic tissue (Kim et al., 2018). Furthermore glucotoxicity can be associated with excessive nitric oxide (NO) production and oxidative stress. Of course, the damage caused by STZ on the DNA is well repaired after its effect is removed. Chandra Shill et al. (2024) consistent with the results of this research, reported in murine models of diabetes, a change in the transmembrane potential of the mitochondria and an increase in the absorption of calcium ions (Ca^{2+}) were observed as a result of diabetes induction by STZ, and this causes pancreatic dysfunction. When beta cells are destroyed, insulin secretion is reduced, and blood glucose increases. The reduction of β cell number, pancreatic volume and Langerhans islets, which is in accordance with the results of our histological study, is due to the collision of toxic intermediates that are secreted from those cells, such as pro-inflammatory cytokines and free radicals such as nitric oxide (Pirmoradi et al., 2016).

The amount of insulin in the group receiving DMSO solvent (sham 2) had a significant decrease compared to the control group, which was unexpected. This solvent effect depends on its concentration, and at this dose, it indirectly acts on glucose transporters and decreases blood glucose. The use of organic solvents such as DMSO, to maintain the function of enzymes compared to aqueous environments has the advantages of preventing side reactions dependent on water, and increasing stability (Carmean et al., 2021). For these reason, there was no significant difference between the solvent (DMSO) receiving group, and the control group in the evaluation of the studied parameters except insulin level. Carmean et al. (2021) suggested that DMSO regulates the secretion of insulin depend on glucose concentration.

Based on this study, the improvement of the parameters and approaching the level of the control group in the group using Glibenclamide were fully expected. Glibenclamide belongs to Sulfonylureas family which, by blocking potassium



receptors in the Beta cells of the Langedoc Islands, stimulates and releases more insulin from beta cells of the islets of Langerhans, and controls blood glucose. Also, it increases insulin sensitivity in some tissues, such as the liver and muscle, reduces hepatic glycogenolysis and gluconeogenesis, and increases peripheral glucose consumption (Chandra Shil et al., 2024).



In this study, we synthesize 1,2 bis (α methylsalicylideneamino) 22, α,α' -Me₂-salen ligand, and Cu (II) Schiff base complexes, which used for treatment. Cu (II) complexes support Schiff base ligands, and they make compounds with strong antioxidant properties (Singh et al., 2021). It seems the use of synthetic Cu (II) Schiff base complex reduces the adverse effects of diabetes to some extent. The ability of this compound is related to its molecular structure. The C-N double bond is considered an important factor in improving the effect of this compound. This complex is a tridentate O,N,O'-donor Schiff base (Lakshmi et al., 2016). These donor groups increase the lipophilicity of the complexes, and reduce their polarity. Therefore, their transport through the cell membrane is facilitated and can exert its effect on the cell (Kargar et al., 2021). This compound reduced the blood sugar, due to the increased amount of blood insulin. On the other hand, its consumption in treated diabetic rats, causes an increase in the number of beta cells. Obviously, by increasing these cells, the secretion of insulin will increase, and regulate the amount of glucose. The similar effect of this synthetic compound to Glibenclamide, which is an approved antidiabetic, suggests a hypoglycemic effect for it. The observation of hypoglycemic effect only in dose 80mg/kg/ bw of the Cu (II) Schiff base complex suggests that its effect is dose-dependent.

The role of copper in the physiological process in the body, its participation in the synthesis of natural antioxidants, its ability to restrain cell proliferation, and its lower toxicity were reported in previous studies. The addition of copper to the Schiff base ligand increases its effect (Kumari et al., 2023). Therefore, these results are expected. Moreover, the ability of copper Schiff base to induce apoptosis, which was shown by Gültekin et al. (2024), and the participation of copper ions in the inhibition of ROS production (Xia et al., 2019), may play a role in the effect of this compound. It improves complications caused by glucose toxicity, lipid toxicity, chronic inflammation, and oxidative stress in the diabetic groups.

It seems that all the changes that were seen in the levels of fats profile including LDL, HDL and cholesterols are related to the induction of diabetes with streptozotocin. Beta cells exposed to streptozotocin show changes similar to the action of NO. According to Ryzhova et al. (2018), STZ raises the activity of guanylyl cyclase, which catalyzes the cyclic guanosine monophosphate (cGMP). This enzyme is required for many biological action, and its lack causes cell damage.

Previous studies have shown that some Schiff base metal complexes, similar to insulin, exhibit α -amylase and α -glucosidase enzymes (Uddin et al., 2020; Shamim et al., 2021). Copper ions, block the action of the insulin hormone by blocking the enzymes α -amylase and α -glycosidase, which are involved in the metabolism of carbohydrates. Our synthetic ligand may inhibit the α -glucosidase enzyme due to the addition of copper to it. As a result, Schiff base prevents the accumulation of glucose in the blood and improves diabetes (Yusuf et al., 2023).



The pancreas secretes α -amylase, while the intestines contain the enzyme α -glucosidase. Disaccharides are converted to monosaccharides by these enzymes. Inhibiting these enzymes delays the digestion and absorption of carbohydrates, which results in the suppression of both postprandial hyperglycemia and excessive insulin. Our findings are in accordance with the results of Sankar and Sharmila (2023), who showed that the Cu (II) complex has modulated all functional parameters of the pancreas, and this ability is probably related to inhibition of the α -amylase enzyme.

This compound acts similar to ascarbose, a standard antidiabetic drug. The presence of a phenyl ring with sulfonamide promotes the binding of these complexes to the α -amylase enzyme and inhibits its activity. Furthermore, heterocyclic rings in this complex structure facilitate



hydrophobic interactions with the active sites of the enzyme and create a strong binding affinity (Sankar and Sharmila, 2023). Additionally, the Cu (II) complex, due to its presence of hydrogen bonds and hydrophobic interaction, is able to bind with α -glucosidase and inhibit its activity, thus preventing the breakdown of disaccharides and the accumulation of glucose in the blood (Deswal et al., 2022). It also has an amine charged with a hydrogen donor, indicating that these compounds have great potential for their biological activities (Netz et al., 2023).

Some ions, such as iron, zinc, and copper in complex Schiff bases, play an important role in the active center of α -glucosidase. Probably Cu (II) ion is inhibited by a synergic effect from the combination of this ion and the synthetic ligand. Lakshmi et al. (2016) evaluated the ability of these synthesized compounds to inhibit α -amylase and showed that they encountered drug. He reported the stronger effect of copper Schiff base in inhibiting the activity of alpha-amylase and alpha-glycosidase, and preventing the breakdown of disaccharides compared to the anti-diabetic drug Acarbose. Therefore, the structures of our synthetic complex might result in synergistic action between the Cu ion and the ligand in producing a α -glucosidase effect, reducing blood glucose (Aispuro-Pérez et al., 2020). Obviously, NO radicals are generated in STZ-induced diabetes, as was shown in our study. NO content increase in response to the action of liposaccharides and cytokines. Although inflammation was not investigated in this study, the observed changes in serum parameters, especially the lipid profile, may be due to the effect of oxidative stress and inflammation caused by it. The improvement of these parameters and approaching the control level as a result of the treatment with Cu (II) Schiff base show that this substance has compensated for this lesion with its antioxidant, and anti-inflammatory (Alam et al., 2023) properties. Based on the research, the metal ion polarity will be reduced, and the lipophilicity of the complexes will increase due to the partial sharing of positive charges with donor groups.

Conclusion

The results of this research and the similarity of the effect of the synthesized compound, Cu (II) Schiff base complex, especially in high dose (80 g/kg bw), with the well-known anti-diabetic drug, Glibenclamide, show the improving effect of this compound in the treatment of diabetes. Although Cu (II) Schiff base could not completely repair the undesirable changes, and its effect is dose-dependent. Considering the stronger effect of this substance on improving the parameters measured in the pancreatic tissue compared to the serum parameters, it seems that it regulates blood glucose by releasing insulin. The cooperation of ligand and copper metal in this complex has been effective in increasing its positive effect. It is suggested to carry out more research, especially to study the effect of this substance on the beta cell line, in order to obtain information about the action mechanism of



this complex.

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Competing

interests

All authors declare that they have no conflicts of interest related to this research.



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