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Effect of Newly Synthesized Thiadiazol Derivatives in Treatment of STZ-induced Diabetes in Albino Rats

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Abstract

Hyperglycemia is linked to long-term organ dysfunction and damage. The purpose of this research is to examine a novel chemical made of thiadiazol derivatives for its possible anti-diabetic properties. Methods: Five groups were created from 60 adult male albino rats. Rats in Group I, the control group, received 1 ml of saline orally each day. Group II (positive control; intraperitoneally, streptozotocin at dose of 50 mg/kg was given. to animals in this group).Group III (control group) consists of diabetic rats given oral metformin at a dose of 100 mg/kg daily for 40 days. Group IV, V & VI rats orally administrated with chemical A, B & C for 40-day at dose of 50 mg/kg to diabetic rats. Blood serum and plasma samples, liver, kidney, and pancreatic tissues were obtained at the conclusion of the study period. The final body weight of diabetic rats significantly decreased, whereas the levels of plasma glucose, serum ALT, AST, ALB, TP, urea, creatinine, cholesterol, and triglycerides all increased. Compared to the control group, there was a significant decline in GST and CAT activities as well. Additionally, liver, kidney, and pancreas mean levels of IL-10 and HSP-70 highly increased as compared to the normal group. All elevated biochemical markers decreased after oral administration of newly synthesised thiadiazol derivatives chemicals, which also increased the activity of antioxidant enzymes. Reduce IL-10 and HSP-70 levels as well as compared to rats with diabetes. Studies on molecular docking demonstrated the presence of hydrogen bonds and hydrophobic interactions as well as energy-based confirmation of chemical binding to the proteins HSP-70 and IL-10. Histopathological analysis of liver, kidney, and pancreatic tissues supported our findings. As a result of this investigation, it is possible that newly synthesised thiadiazol derivative chemicals have antioxidant and antihyperglycemic properties in streptozotocin-induced diabetic rats.

Keywords: Hyperglycemia, thiadiazol derivatives, IL-10, HSP-70

1. Introduction

Diabetes is a collection of metabolic diseases that affect protein, lipid, and glucose metabolism. With a global prevalence of up to 45 million, it is a disease that affects a sizable population. It causes chronic renal disease and is linked to cardiac disease [1]. Polyphagia, polyuria, polydipsia, a rise in heart attacks or strokes, neurological issues, and sexual inability are signs of disease [1].

A [(methylnitrosoamino)carbonyl] deoxy-s aminothe streptozotocin (STZ) molecule, a D-glucopyranose compound exerts harmful effects on cells and induces diabetes in the majority of laboratory animals [2]. Diabetes type II was treated with metformin as a first-stage glucose-lowering medication. Metformin lowers production from the liver, slows down digestion and absorption, and by controlling blood sugar levels, aids in preserving the insulin sensitivity [3].

Numerous substances, such as heterocyclic thiazole derivatives having at least one carbon atom and at least one element other than carbon, have been modified as medications to treat diabetes and other disorders. High structural variety is provided by heterocyclic compounds, which are widely and cheaply effective as medicinal agents. It is widely known that heterocyclic compounds with an azole nucleus hold a significant position in the pharmaceutical business due to the wide range of pharmacological activity they exhibit. The biological activity of thiazole compounds have been discovered to be strong [4].

This study aims to shed additional information on a newly synthesised thiadiazol derivative's anti-diabetes activity.

2. Materials and methods

2.1. Chemicals

Sigma Aldrich Chemical Co. was where the chemicals were purchased. Metformin (Glucophage 500 mg) and streptozotocin were derived from it.

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2.2. Chemistry

According to the described method, novel synthetic thiadiazol derivatives were synthesized [5].

2.3. Animal management

Adult female albino rats weighing 200-280 g were housed in the faculty of Science's experimental animal home for seven days previous to the experiment's start under carefully regulated ambient conditions. All procedures adhered to the guidelines for the care and use of animal subjects outlined in the Guide for the Care and Use of Laboratory Animals, which were approved by the Ethics Committee (ZU-IACUC/F/334/2022).

2.4. Diabetic model

STZ was injected IP at a single dose of 50 mg/kg body weight after a 16-hour fast to cause diabetes. To be utilised immediately for five minutes, STZ was freshly made cold citrate buffer (100 mM, pH= 4.5) [6]. All rats had their blood sugar levels tested 72 hours after receiving STZ, and those with fasting blood glucose levels greater than 250 mg/dl were deemed diabetic and employed in the following investigation.

2.5. Toxicity Study:

The median lethal dose (LD 50) of a novel synthetic thiadiazol derivative was determined. The name of the substance A is [4-[3-(Ethoxycarbonyl)-4,5,6,7-tetrahydrobenzo[b]-thiophen-2-yl]amino-4-oxobutanoic Acid].Substance B: [1,3-dihydro-3-[(5-mercapto-1,3,4-thiadiazol-2-yl)imino]-2H--indol-2-one].Compound C is [(E)-N-((5-(4methoxybenzylideneamino)-1,3,4-thiadiazol-2-yl)methyl]benzamide. in albino rats was calculated using a previous technique [7].

2.6. Experimental design

To reach the study's end goal, 60 adult female albino rats were separated into five groups, each with ten animals, following a 7-day period of acclimatisation on a standard basal diet.

Rats in Group I (the control group) received a single oral dose of 1 cc of saline.

Rats in Group II (Positive Control) given STZ (50 mg/kg b.wt.) intravenously after a 16-hour fast. Rats in Group III (standard therapeutic) were given DM induction. Animals received oral metformin (100 mg/kg) post-treatment for 40 days after receiving DM induction for 1 week [8]. Rats in Group IV (Compound A) had DM induced. Animals were given chemical A after receiving DM induction for one week. at an oral dose of (50 mg/kg) dissolved in distilled water every day for 40 days. Rats in Group V (Compound B) had DM induced. Animals were given chemical B after DM induction for one week.-2H-indol-2-one] given orally every day for 40 days at a dose of (50 mg/kg) in water distilled. Rats in Group VI (Compound C) had DM induced. Animals were given chemical C at a dose of (50 mg/kg) orally once a day for 40 days following DM induction.

2.7. Collection and sampling of blood

After the study was finished and the last dose was administered, rats were starved for 12 hours. Blood samples were then obtained from the retro-orbital venous plexus while the rats were under light ether anaesthesia. where three separate tubes—one containing sodium fluoride to measure blood sugar and the other empty so that serum could be recovered by centrifuging it for 20 minutes at 4000 rpm—were used to collect blood samples. Until various biochemical data were examined, transferred serum and plasma were stored frozen at -20 ^{o}C.

2.8. Tissue sample

Animals were killed via cervical dissection after blood was drawn, and numerous organs (the liver, kidney, and pancreas) were removed. Animals tissue was then rinsed in ice-cold phosphate-buffered saline (pH 7.4) to remove any remaining blood.

To generate a 10% (w/v) tissue, the first portion of various tissue samples was homogenised in ice-cold phosphate-buffered saline (pH 7.4). For the second portion of the histopathological research, various tissue samples were employed.

2.9. Physiological parameters

Body weight of all the animals was recorded both before and after the study.

2.10. Biochemical analysis

2.10.1. Plasma glucose level

Glucose oxidase peroxidase activity was used to measure plasma glucose using a commercial kit made by Elitech clinical systems, France [9].

2.10.2. Liver Function Tests

Amodified bromcresol green binding test (BCG) by which, the concentration of serum albumin was measured [10]. Total protein was measured using the Biodiagnostic kit technique [11].A colorimetric assay kit used to measure the serum ALT and AST activity [12] & [13]. Bilirubin is measured photometrically [14].

2.10.3. Kidney Function Tests

The Berthelot enzymatic colorimetric method was used to determine the serum urea concentration [15]. Also, creatinine was measured using a commercial kit [16].

2.10.4. Lipid profile:

Using a commercial kit, the CHOD-POD colorimetric method was used to assess the serum cholesterol concentration [17]. Also, the content of serum triglycerides was determined using the GPO-PAP enzymatic colorimetric method [18].

2.10.5. Estimation of antioxidant parameters

Using kits acquired from Biodiagnostic Company (Biodiagnostic, Egypt), the tissue activities of GST [19] and catalase [20] were assessed.

2.10.6. Estimation of Interleukin 10 (IL-10) & Heat shock protein 70 (HSP-70):

Rat IL-10 was identified using ELISA technique based on the double-antibody approach (catalogue no. 201-11-0109, SunRed Biotechnology Company).

ELISA was used to evaluate the presence of heat shock protein 70 (HSP-70) in rat samples obtained from SunRed Biotechnology Company (Catalogue No. 201-11-0523) using the double-antibody sandwich technique.

2.11. Histopathological examination

Following that, various tissues were submerged in molten paraffin wax, imbedded, and blocked out. Hematoxylin and eosin was used to stain paraffin sections (4-5 um), which were then viewed using a light electric microscope. [21]

Statistical Analysis

Using SPSS software (SPSS, ver.14.00, USA), all results were examined. The data was presented as mean SEM. The ANOVA test was used to compare the mean values of the researched variables across various groups. Significant was defined as P0.05 [22].

3. **Results**

3.1. Toxicity studies

Results showed that new synthesized thiadiazol derivatives (compounds A, B & C) were safe till 2000 mg/kg; as the selective dose was 50 mg/kg.

3.2. Effect of different chemical compounds on body weight

Results in Table 1 showed that compound A showed statistically significant decrease in final body weigh in compared to control group (P< 0.01). While compound B and compound C showed statistically non-significant decrease in body weight.

Table 1: Effect of different chemical compounds on body weight of all studied groups

Groups	**Initial Body weight (g)**	**Final body weight (g)**
Control Mean ± SEM	216.5± 8.5	320±12.3 ^{C}
Positive (STZ-induced) Mean ± SEM % change	224.4± 18.9 3.6%	102±3.8*** -68.1%
Metformin Mean ± SEM % change	208± 12.7 -3.9%	256±16.6 ^{b} -20%
Compound A Mean ± SEM % change	229.4± 13.2 5.9%	166±12.5** -48.1%
Compound B Mean ± SEM % change	208.6± 7.2 -3.6%	272.6±36.2 -14.8%
Compound C Mean ± SEM % change	212.7± 25.9 -1.7%	252.3±42.8 -21.1%
P value	**P > 0.05**	**P< 0.001**

* P< 0.05, ** P< 0.01, *** P< 0.001 compared to control group. ^{a}P< 0.05, ^{b}P< 0.01, ^{c}P< 0.001 compared to positive control group. % change = Percent of change compared to control group.

3.3. Plasma glucose level in different studied groups.

Results in Table 2 declared high increase final level of glucose in Positive (STZ-induced, compound A and compound B (P< 0.001), Metformin and compound C showed slight significant increase final level of glucose in compared to control group (P< 0.01).

Table 2: Effect of different chemical compounds on plasma glucose concentration of all studied groups

Groups	Glucose (Initial) (mg/dl)	Glucose (final) (mg/dl)
Control Mean ± SEM	88.7±2.05	103.2±4.5^{c}
Positive (STZ-induced) Mean ± SEM % change	367.2±11.3*** 313.9%	471.2±32.2*** 356.5%
Metformin Mean ± SEM % change	374.4±12.18*** 322%	206.8±9.6**^{c} 100.3%
Compound A Mean ± SEM % change	403.6±31.7*** 355%	382.8±55.8***^{a} 270.9%
Compound B Mean ± SEM % change	366±29.1*** 312.6%	380.3±30.8*** 268.5%
Compound C Mean ± SEM % change	373.5±10.9*** 321%	247.1±21.1**^{c} 139.4%
P value	**P< 0.001**	**P< 0.001**

* P< 0.05, ** P< 0.01, *** P< 0.001 compared to control group. ^{a}P< 0.05, ^{b}P< 0.01, ^{c}P< 0.001 compared to positive control group. % change = Percent of change compared to control group**.**

3.4. Effect of different chemical compound on Mean values of ALT, AST, ALB and total protein in all studied groups.

Table 3 declared high increase in values of ALT & AST in Positive (STZ-induced), compounds A,B,C (P< 0.001). There was high decrease in values of ALB Positive (STZ-induced), compounds A, B. Also, There was high decrease in values total protein Positive(STZ-induced) ,compounds A,B ,C in compared to control group (P< 0.001).

Table 3: Mean values of ALT, AST, ALB and total protein in all studied group

Groups	ALT (U/L)	AST (U/L)	ALB (g/dl)	T. protein (g/dl)
Control Mean ± SEM	29±2.6C	126.3±6.1 C	3.24±0.08 C	5.73±0.13 C
Positive (STZ-induced) Mean ± SEM % change	54.3±1.07*** 87.2%	200.3±4.4*** 58.5%	2.28±0.04*** -29.6%	4.1±0.29*** -28.4%
Metformin Mean ± SEM % change	31.4±1.3 C 8.2%	126.5±1.8 C 0.15%	3.21±0.23 C -0.92%	5.71±0.06 C -0.34%
Compound A Mean ± SEM % change	50.8±0.67*** 75.1%	198.2±21.2*** 56.9%	2.54±0.11*** -21.6%	4.69±0.18***a -18.15%
Compound B Mean ± SEM % change	51.6±1.2*** 77.9%	149.7±9.1 b 18.5%	2.69±0.14** -16.9%	4.99±0.03*** b -12.9%
Compound C Mean ± SEM % change	43.3±1.06*** C 49.3%	151.5±0.9 b 19.9%	3.26±0.13 C 0.61%	4.8±0.04***b -16.2%
P value	**0.001**	**P< 0.001**	**P< 0.001**	**P< 0.001**

* P< 0.05, ** P< 0.01, *** P< 0.001 compared to control group. ^{a}P< 0.05, ^{b}P< 0.01, ^{c}P< 0.001 compared to positive control group. % change = Percent of change compared to control group**.**

3.5. Effect of different chemical compound on mean level of urea, creatinine, cholesterol, Triglyceride in all studied groups.

Table 4 found that compounds A, B and C showed slight increase in mean level of urea. Also it was found that mean level of creatinine, cholesterol, and triglyceride showed significant increase in Compound A & B. Results of Compound C showed slight non-significant increase in mean level of creatinine, cholesterol and high increase in triglyceride in compared to control group.

Table 4: Effect of different treatments on urea, creatinine, cholesterol, triglyceride in all studied groups

Groups	Urea (mg/dl)	Creatinine (mg/dl)	Cholesterol (mg/dl)	Triglyceride (mg/dl)
Control Mean ± SEM	11.7±0.28[b]	0.47±0.02[c]	70.9±2.6[c]	81.2±3.9[c]
Positive (STZ-nduced) Mean ± SEM % change	17.6±0.6** 50.4%	0.60±0.007*** 27.6%	103.7±6.2*** 46.2%	148.4±8.9*** 82.7%
Metformin Mean ± SEM % change	13.4±0.89[b] 14.5%	0.50±0.016[c] 6.38%	76.9±3.7[c] 8.46%	93.8±3.8**[c] 15.5%
Compound A Mean ± SEM % change	14.4±1.7[a] 23.07%	0.55±0.01**[a] 17.02%	94.1±1.7*** 32.7%	134.4±9.6*** 65.5%
Compound B Mean ± SEM % change	13.3±1.15[a] 13.6%	0.53±0.01*[a] 12.76%	83.6±0.66*[b] 17.9%	114.5±4.5**[b] 41%
Compound C Mean ± SEM % change	13.7±1.2[b] 21.7%	0.48±0.02[c] 2.12%	79.0±2.3[c] 11.42%	111.4±6.8**[b] 37.19%
P value	**P< 0.01**	**P< 0.001**	**P< 0.001**	**P= 0.001**

* P< 0.05, ** P< 0.01, *** P< 0.001 compared to control group. [a]P< 0.05, [b]P< 0.01, [c]P< 0.001 compared to positive control group.
% change = Percent of change compared to control group**.**

3.6. Effect of different chemical compounds on GST and catalase activity in different tissues of all studied groups.

Results in Table 5 demonstrated that as compared to the control group, catalase and GST activity in the liver somewhat decreased, with a statistically non-significant decrease in compound B & C and a substantial decrease in compound A. According to our results in Table 6, the kidney's catalase antioxidant activity somewhat decreased when compared to the control group, with compound A statistically significantly decreasing when compared to compound B, C, and D. In contrast, compound A, B, and C showed a statistically significant decrease in GST activity.

Table 5: Effect of different chemical compounds on hepatic GST and catalase activity of all studied groups

Liver tissue		
Groups	**GST (U/g)**	**Catalase (U/g)**
Control Mean ± SEM	94.1±5.0[c]	34.1±0.7[b]
Positive (STZ-induced) Mean ± SEM % change	55.3±1.2*** -41.2%	27.5±2.2** -19.3%
Metformin Mean ± SEM % change	59.3±0.54[c] 7.23%	32.1±0.32 16.7%
Compound A Mean ± SEM % change	64.7±1.5*[c] 16.9%	33.5±0.69* 21.8%
Compound B Mean ± SEM % change	59.5±1.2[c] 7.5%	29.9±0.23 8.7%
Compound C Mean ± SEM % change	61.2±3.5c 10.6%	29.7±2.2[a] 8%
P value	P< 0.001	P< 0.05

* P< 0.05, ** P< 0.01, *** P< 0.001 compared to control group. [a]P< 0.05, [b]P< 0.01, [c]P< 0.001 compared to positive control group.
% change = Percent of change compared to control group**.**

Table 6: Effect of different chemical compounds on kidney GST and catalase activity of all studied groups

Kidney tissue		
Groups	**GST (U/g)**	**Catalase (U/g)**
Control Mean ± SEM	99±4.4 [c]	20.8±1.9[a]
Positive (STZ-induced) Mean ± SEM % change	47.2±0.87 *** -52.5%	31.0±0.33 * 49.0%
Metformin Mean ± SEM % change	50.5±1.0 [c] 6.99%	21.2±2.7 [a] 1.92%
Compound A Mean ± SEM % change	94.1±3.9** 99.3%	27.2±1.9 30.7%
Compound B Mean ± SEM % change	82.3±1.6** 74.3%	27.1±0.7 30.2%
Compound C Mean ± SEM % change	79.7±0.68** 68.8%	24.2±2.1 16.34%
P value	P< 0.001	P< 0.01

* P< 0.05, ** P< 0.01, *** P< 0.001 compared to control group. [a]P< 0.05, [b]P< 0.01, [c]P< 0.001 compared to positive control group.
% change = Percent of change compared to control group**.**

Table 7: Effect of different chemical compounds on pancreatic GST and catalase activity of all studied groups

Pancreatic tissue		
Groups	**GST (U/g)**	**Catalase (U/g)**
Control Mean ± SEM	77.8±5.2[a]	129.2.7±9.3[c]
Positive (STZ-induced) Mean ± SEM % change	43.1±1.2 ** -44.6%	67.9±13.4 *** -47.4%
Metformin Mean ± SEM % change	43.8±0.66 [a] 1.62%	70.6±6.2 [c] 3.97%
Compound A Mean ± SEM % change	50.1±1.7 [a] 16.2%	116.6±6.4** 71.7%
Compound B Mean ± SEM % change	49.2±3.1[a] 14.15%	112.5±3.7** 65.68%
Compound C Mean ± SEM % change	49.3±0.67 [a] 14.38%	104.5±5.3** [a] 53.90%
P value	P< 0.001	P< 0.001

* P< 0.05, ** P< 0.01, *** P< 0.001 compared to control group. [a]P< 0.05, [b]P< 0.01, [c]P< 0.001 compared to positive control group.
% change = Percent of change compared to control group.

3.7. Levels of heat shock protein-70 (ng/ml) in different organs of all studied groups.

Results presented in Table 8 showed that Levels of heat shock protein-70 were increased significantly in positive group in compared to control group. While in groups of compounds A, B and C showed slight increase which was significantly non-significant in compared to control group.

Table 8: Levels of heat shock protein-70 (ng/ml) in different organs of all studied groups

Groups	Hsp-70 (ng/ml)		
	liver	**kidney**	**Pancreas**
Control Mean ± SEM	46.8±2.4[b]	53.7±6.6 [b]	30.6±1.8[c]
Positive (STZ-induced) Mean ± SEM % change	111.4±7.9** 138.03%	111±7.7** 106.7%	95.7±9.8*** 212.7%
Metformin Mean ± SEM % change	53.5±13.5[b] 14.3%	56.3±5.1 [b] 4.84%	37.0±2.1[c] 20.9%
Compound A Mean ± SEM % change	65.5±14.5[a] 39.95%	67.2±2.6 [a] 25.13%	46.5±7.5[c] 51.96%
Compound B Mean ± SEM % change	59.2±3.3[b] 26.49%	60.3±6.6 [a] 12.2%	41.6±1.2[c] 35.9%
Compound C Mean ± SEM % change	56.6±2.0[b] 20.94%	54.2±2.6 [b] 0.93%	36.3±4.1[c] 18.62%
P value	**P< 0.001**	**P< 0.001**	**P< 0.001**

* P< 0.05, ** P< 0.01, *** P< 0.001 compared to control group. [a]P< 0.05, [b]P< 0.01, [c]P< 0.001 compared to positive control group. % change = Percent of change compared to control group.

3.8. Levels of interleukin-10 in different organs of all studied groups.

Table 9 declared that Levels of IL-10 were increased significantly in positive group. While in groups of compounds A, B and C showed slight increase which was significantly non-significant in compared to control group.

Table 9: Levels of interleukin-10 in different organs of all studied groups

Groups	IL-10 (pg/ml)		
	liver	**kidney**	**pancreas**
Control Mean ± SEM	133±1.0[c]	94.4±10.6	97.6±0.88 [b]
Positive (STZ-induced) Mean ± SEM % change	226.4±17.6*** 70.22%	126.4±9.7 33.8%	124.2±6.8** 27.2%
Metformin Mean ± SEM % change	148±8.6[b] 11.27%	102.4±7.4 8.47%	95.6±4.3 [b] -2.04%
Compound A Mean ± SEM % change	178.8±10.2[a] 34.4%	115.3±6.9 22.13%	105.6±7.7 8.19%
Compound B Mean ± SEM % change	165±4.3[b] 24.06%	112.2±6.8 18.85%	99.2±5.7 [b] 1.63%
Compound C Mean ± SEM % change	146.0±2.0[b] 9.77%	104.7±5.8 10.91%	96.0±9.0 [b] -1.6%
P value	**P< 0.01**	**P> 0.05**	**P< 0.05**

* P< 0.05, ** P< 0.01, *** P< 0.001 compared to control group. [a]P< 0.05, [b]P< 0.01, [c]P< 0.001 compared to positive control group. % change = Percent of change compared to control group.

Compounds A, B, and C's pancreatic sections displayed healthy parenchyma, typical acini, and normal islets (Figure 2). Compounds A, B, and C's kidney sections all displayed normal glomeruli and renal tubules and healthy renal parenchyma (Figure 3).

3.9. Histopathological examination

The histological examination revealed groups A, B, and C of chemicals to have normal hepatocytes, blood sinusoids, and healthy liver parenchyma (Figure 1).

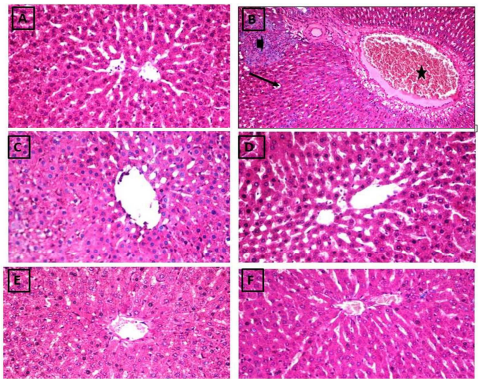

Figure 1: Histopathological examination of liver tissue. A (negative control) displayed normal hepatic parenchyma; note the normal hepatocytes, blood sinusoids, and portal area (H&E X 200); B (STZ-induced) displayed vacuolated hepatocytes (arrow), a congested hepatoportal blood vessel (star), and mononuclear cell infiltrations in the portal tract (arrow head); and C (Metformin), compound B. C & D displayed normal hepatic parenchyma, With normal hepatocytes, blood sinusoids, and portal area.

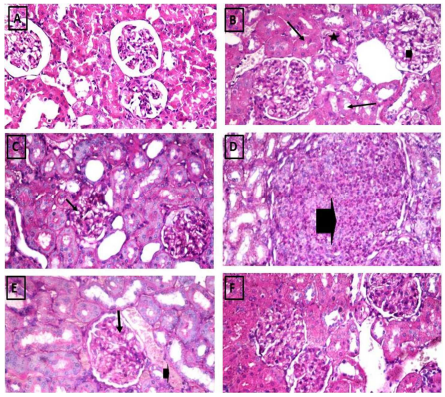

Figure 2: Histopathological examination of kidney tissue. Normal renal glomeruli and tubules were visible in Figures A (negative control) and B (STZ-induced), respectively, while Figures C (Metformin) revealed renal tubules that appeared to be in good health with a small amount of vacuolation in the renal glomeruli (arrow), respectively. D (compound A) showed a significant focal area of mononuclear cell infiltrations in the renal cortex (arrow head), H&E X 400; E (compound B) showed renal tubules that appeared to be in good health, albeit with a small amount of vacuolation in the renal glomeruli (arrow) and dilated interstitial blood vessels (arrow head); and F (compound C) displayed renal glomeruli and tubules that appeared.

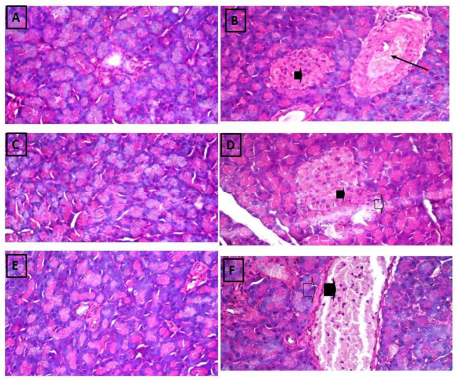

Figure 3: Histopathological examination of pancreatic tissue. A (negative control) displayed normal pancreatic acini, islets, and ducts (H&E X 400), B (STZ-induced) displayed dilated and congested blood vessels (arrows), and C (Metformin) displayed normal pancreatic acini, islets, and ducts (H&E X 400), F (compound C) showed normal pancreatic acini with dilatation and congestion in the interstitial blood vessel (arrow head), (H&E X 40), D (compound A) showed normal pancreatic acini with hyperplasia of pancreatic islets (arrow head), (H&E X 400), E (compound B) normal pancreatic acini, islets, and duct, (H&

4. Discussion

One of the persistent metabolic diseases with an elevated blood sugar level is diabetes mellitus [23]. According to studies, DM progressed quickly because of a variety of problems that appeared in the early stages of the disease, including heart, kidney, nerve, and retinal damage [24]. Due to T2D's heterogeneity, finding new biomarkers for the disease and its consequences is still difficult. The heterogeneity is not just related to treatment response or glycemic control [25].

Our findings showed that the diabetic-induced group's final body weight decreased significantly ($p>0.001$). The end body weight of the metformin and synthetic thiadiazol derivatives chemical groups improved significantly compared to the control group.

The outcomes are consistent with those who claimed that a fall in weekly body weight was another sign of diabetes. Increased muscular atrophy and the loss of various tissue proteins are the main contributors to the decrease in body weight [26]. Additionally, the findings indicated that hyperglycemia and STZ-induced body weight reduction [27].

Metformin is given as a type 2 diabetic medication. It made diabetics react to insulin normally. It causes metabolic abnormalities of glucose, lipids, and protein tissue loss, like the majority of diabetic medications [28].

Administration of synthetic thiadiazol derivative chemicals increased body weight in diabetic rats, possibly as a result of effective hyperglycemic state control.

The findings demonstrated that STZ indicated a critical plasma glucose elevation. These are consistent with earlier research [29]. In comparison to the control group, the metformin and therapeutically treated groups showed a drop in plasma glucose. Metformin reduces liver production, delays stomach and small intestine digestion and absorption, and protects the body's sensitivity to insulin by regulating blood sugar levels. [30].

By altering the heterocyclic ring, scientists who are interested in heterocyclic compounds and their derivatives can create a novel chemical with strong biological activity. The 1, 3, and 4 thiadiazole substituted heterocyclic compounds were discovered to be the most significant in many biological functions among many other heterocyclic compounds. It has been discovered that 1,3,4 thiadiazole is a significant heterocyclic nuclei with a wide range of biological action, including anticancer, anti-inflammatory, antibacterial, antihypertensive, antifungal, and antidiabetic properties. Thiadiazole ring modification and substitution improves efficacy while minimising toxicity [31].

Long-term consumption of a high-fat diet leads to the buildup of fat in tissues other than the adipose tissue. Hepatic fat accumulation results from decreased -oxidation in the liver and increased circulatory fatty acid absorption. The liver's condition is frequently harmed by diabetes,. AST and ALT are regarded as biomarkers of liver health.

According to our findings, diabetic rats had significantly higher serum enzyme values than healthy control rats in terms of liver function indices.

Liver enzymes, which are indicators of cellular leakage and a loss of the functional integrity of the hepatic cell membrane, indicate hepatocellular damage [32].

Our findings are consistent with those who previously showed that high ALT activity in rats suggested liver cell injury brought on by glucotoxicity and fatty acid absorption (chronic hyperglycemia) [33].

It is abundantly obvious that these chemicals play a protective role in maintaining healthy liver function because newly synthesised thiadiazol derivatives reduced the increased blood ALT & AST values.

One of the most severe and well-known complications of diabetes is renal disease [34].

According to our results, the STZ- group exhibited a significant rise in serum urea, creatinine, cholesterol, and triglycerides in compared to the control group. Previous studies reported that higher levels of blood urea nitrogen, serum creatinine, and uric acid were largely present in diabetic rats [35].

These findings were consistent with earlier research that shown that an increase in circulating free fatty acids caused increases of hepatic TG synthesis. High TG levels are linked to the development of atherogenic dyslipidaemia, which is characterised by elevated levels of high TG, low HDL cholesterol, and elevated levels of LDL or apo lipoprotein-B [36].

In STZ-induced diabetic rats, there was a high significant increase in serum lipid profile tests, accompanied by a decrease in high density lipoprotein, according to prior research [35] &[37].

DM is associated with oxidative stress, which develops as a result of increased production of free radicals [38].

Diabetes causes systemic tissue and organ damage that is exacerbated by oxidative stress because hyperglycemia and metabolic imbalances often change the antioxidant status. Diabetic rats in our study displayed changes in antioxidant markers, such as decreased CAT and GST activity, which is unmistakably a sign of increased oxidative stress brought on by chronic hyperglycemia. These changes were in contrast to the healthy control rats. Previous studies revealed that the antioxidant GPX was significantly lower in diabetics [33] [39].

Our studies have demonstrated how metformin medication can lessen variations in lipid, antioxidant, liver, kidney, blood sugar, body weight, and other indicators. The stimulation of insulin release, regeneration of b-pancreatic cells, and improved insulin sensitivity of target tissues are some of the hypothesised mechanisms that account for these benefits. Metformin enhances metabolism by reducing intracellular energy load and activating AMP-activated protein kinase (AMPK), a crucial regulator of energy metabolism. Metformin predominantly affects the liver through gluconeogenesis (de novo glucose synthesis) reduction, lipid synthesis inhibition, and fatty acid oxidation enhancement (hepatic steatosis enhancement) [40].

According to our findings, synthesised targeted compounds decreased the parameters of blood glucose, liver enzyme activity, kidney, and lipid profile. This effect was minimal with compound A, moderate with compound B, and pleasant with compound C. This highlights how important these compounds are as potential therapy options for type II diabetes (DM).

Because they are made with thiadiazole & thiazolidinone nuclei, which have a tendency to lessen type 2 diabetes, our named compounds are in agreement with those who discovered that synthetic thiadiazole & thiazolidinone targeted compounds generated a considerable decrease in blood glucose levels. All of the synthetically produced derivatives have a sizable hypoglycemic impact. The ring with fast aromatic activity is caused by a compound that neither has electron withdrawing nor electron donating groups. Thiadiazole works by making the Glucokinase enzyme more active [41].

Rosiglitazone, pioglitazone, troglitazone, and other thiazole compounds target the PPAR. These were found to target other enzymes and receptors involved in the aetiology of diabetes [41].

Glycation is the non-enzymatic reaction between reducing sugars and large molecules like proteins, lipids, or nucleic acids. Increased protein glycation and the buildup of AGEs in human tissues are two conditions that are strongly correlated with elevated blood glucose. This sharply raises the inflammatory level and has long been linked to the emergence of cancer [42].

According to our findings, the levels of IL-10 in various tissues were considerably higher in the STZ- group compared to the control group. When compared to the control group, the compound groups A, B, and C showed a modest rise that was statistically non-significant.

These are consistent with data showing that patients with diabetes had increased serum levels of IL-10 and INF- [43].

Today, low-grade chronic inflammation is acknowledged as a key component of T2DM. Proinflammatory cytokines, contribute to the development of insulin resistance and beta-cell dysfunction, which come before the onset of type 2 diabetes (T2DM). It was widely believed that reducing inflammation would increase insulin sensitivity, beta-cell function, and glucose metabolism. In addition to controlling the expression of TNF- and IL-1, IL-6 also reduced the expression of IL-10 and INF- [44].

Our findings demonstrated that levels of HSP-70 in several tissues were significantly higher in the STZ- group compared to the control group. When compared to the control group, the compound groups A, B, and C showed a modest rise that was statistically non-significant.

The heat shock proteins (HSPs), mediate the cellular stress response, a self-protective mechanism that counteracts external pressures. The HSPs were initially identified as chaperones because they control the structure and operation of numerous cellular proteins to shield the organism from stress [45].

Previous research has shown how HSP70 contributes to the development of insulin-deficient diabetes and the generation of -cell directed immunity. In isolated rat islets and human -cells, HSP70 expression is elevated in response to cellular stress, providing effective protection against mediators that damage -cells [46].

Our results suggested that IL-10 and HSP-70 may be beneficial markers in the diagnosis of patients with DM.

According to the results of the histological analysis, the STZ group had severely altered liver, kidney, and pancreatic tissues. Furthermore, rats with STZ diabetes showed less histological change when exposed to groups of synthetic chemicals A, B, and C. The findings are consistent with those who claimed that the pancreatic tissues of diabetic control rats displayed a reduction in Langerhans islet size as well as numerous degradation and lesions. Additionally, there was a decrease in the number of -cells and some necrosis and destruction were seen [48] &[49]. The hyperglycemia that STZ produces in rats is also linked to the production of reactive oxygen species (ROS), which lead to oxidative damage to organs like the liver, heart, kidney, eyes, nerves, and small and big blood vessels.

In general, the current results support the notion that compounds A, B, and C's effects are due to their antidiabetic qualities.

5. Conclusion

A newly created thiadiazol derivative appears to mitigate the physiological and histological abnormalities brought on by STZ in the experimental animals, according to the results of the current study.

6. Conflicts of interest

The authors have no conflicts of interest to disclose.

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8. Authors' contributions

The authors confirm that the data supporting the findings of this study are available within the article.

9. References

[1] Charytan D.M., Solomon S.D., Ivanovich P., Remuzzi G., Cooper ME, McGill J.B., et al. (2019): Metformin use and cardiovascular events in patients with type 2 diabetes and chronic kidney disease. *Diabet Obes and Metabolism,* 21: 1199–208..

[2] Doux, S.P. (1986): Mechanism of nitrosourea induced β cell damage: Alteration in DNA Diabetes. 35:866-72.

[3] Jaiganesh C. and Subramanian S. (2017): Metformin-3-hydroxyflavone, A New Schiff Base Complex Modulates the Activities of Carbohydrate Regulatory Enzymes in High Fat Diet Fed-Low Dose Streptozotocin Induced Type 2 Diabetes in Experimental Rats Journal of Chemical and Pharmaceutical Research, 9(6):90100.

[4] Reddy, G. M. et al. (2016): Synthesis, antimicrobial activity and advances in structure-activity relationships (SARs) of novel tri-substituted thiazole derivatives. Eur. J. Med. Chem. 123, 508–513.

[5] Faten Zahran Mohammed, Youstina William Rizzk, Ibrahim Mohey El-Deen, Emad M. Gad, Mohammed El Behery, and Ahmed R. E. ahdy. (2022): Discovery of 2-Amino-4H-1, 3, 4-thiadiazine-5(6H)-one Derivatives and Their In Vitro Antitumor Investigation .Medicinal Chemistry & Drug Discovery. 7(7): e202104333

[6] Masiello, P., Broca, C., Gross, R., Roye, M., Manteghetti, M., Hillaire-Buys, D., Ribes, G. (1998). Experimental NIDDM: development of a new model in adult rats administered streptozotocin and nicotinamide. Diabetes, 47(2), 224-229.

[7] Meier, J., and Theakston, R.D.G. (1986): Approximate LD50 determination of snake venuoms using eight to ten experimental animals. Toxicon, 24 (4), 395-401.
[8] Kiliari, E.K., Mullapudi, B., Moka, P.V., Silakabattini, K. and Nelli, G. (2014):inhibition of DPP-IV Activity and Enhancement Of GLP-1Expression By Aqueous Peel Extract Of *Punicagranatumin* Albino Wistar rats. Journal of Globale Trends in Pharmaceutical Science ; (5)2: 1528-1541.
[9] pruden E.L. Mc Pherson R.A. and Fuhrman S.A., (1995): Clinical guide to laboratory Test-Ed. Tiet N.W./ Saunders W.B. Company .3th ed. Section 1: general clinical test: 268-273.
[10] Doumas et al., 1971/ Doumas, B.T., Watson, W.A. and Biggs, H.C. (1971): Albumin standard and the management of serum albumin with bromocresol green. Chin. Chim.Acta., 31:87-96.
[11] Doumas, B. T., Bayse, D. D., Carter, R. J., Peters Jr, T., & Schaffer, R. (1981). A candidate reference method for determination of total protein in serum. I. Development and validation. Clinical chemistry, 27(10), 1642-1650.
[12] Reitman, S. and Frankle, S. (1957): Colorimetric method for the determination of SGOT and SGPT. Amer L Clin Path., 28:504-509.
[13] Reitman, S. and Frankle, S. (1957): Colorimetric method for the determination of SGOT and SGPT. Amer L Clin Path., 28:504-509.
[14] P,Trinder, January 1, (1969) : Colorimetric method for the determination of total bilirubin , Rapid Communication https://doi.org/10.1177/000456326900600108.
[15] Robert S. Kaplan the Accounting Review, Vol. 59, No. 3. (Jul., 1984), pp. 390-418. Stable
[15] Young DS. (1995): Effects of drugs on Clin Lab. Tests, 4th ed AACC Press, 1995.
[17] Young DS. (2001), Effects of disease on Clinical Lab. Tests, 4th ed AACC 2001.
[18] Stein E.A. (1987): Lipids, lipoproteins. InTietz NW, ed. Fundamentals of clinical Chemistry. 3rd ed. Philadelphia: WB Saunders; 448-481.
[19] Habig, W. H., Pabst, M. J., and Jakoby, W. B. (1974): Glutathione *S*-transferases: The first enzymatic step in mercapturic acid formation. J. Biol. Chem., 249: 7130–7139.
[20] Aebi, H., (1984): Methods Enzymol., 105, 121-126.
[21] Bancroft J, Gamble M. (2008). Theory and Practice of Histological Technique 4th Ed., Churchill Livingston, New York, London, San Francisco, and Tokyo 2008.
[22] Statistical package for social science (SPSS) (2008): computer software, Ver. 16. London, UK: SPSS Company.
[23] Yimer, E.M., Zewdie, K.A. and Hishe, H.Z. (2018): Netrin as a Novel Biomarker and Its Therapeutic Implications in Diabetes Mellitus and Diabetes-Associated Complications.
[24] Keskin, M., Çulha, C., Gülçelik, N.E., Ademoğlu, E., Keskin, A. and Aral, Y. (2017): Fetuin-A levels determine cardiovascular risk in young diabetic patients. Biomedical Research.28 (15): 6767-6772.
[25] Ahluwalia, T.S., Kilpeläinen, T.O., Singh, S.P. and Rossing, P. (2019): Editorial: Novel Biomarkers for Type 2 Diabetes 10: 649.
[26] Zhou B, Li Q, Wang J, Chen P, Jiang S. (2019): Ellagic acid attenuates streptozocin induced diabetic nephropathy via the regulation of oxidative stress and inflammatory signaling. Food Chem Toxicol.,123: 16–27.
[27] Kumari, S., Kamboj, A., Wanjari, M., Sharma, A.K. (2021): Nephroprotective effect of Vanillic acid in STZ-induced diabetic rats. Journal of Diabetes & Metabolic Disorders. https://doi.org/10.1007/s40200-021-00782-7.
[28] Guex, C.G., Reginato, F.Z., Jesus, P.R-D.,Brondani, G.C. (2019): Antidiabetic effects of Olea europaea L. leaves in diabetic rats induced by high-fat diet and low-dose streptozotocin.
[29] Guex, C.G., Reginato, F.Z., de Jesus, P.R., Brondani, J.C., Lopes, G.H.H. and Bauermann, L.F. (2019): Antidiabetic effects of Olea europaea L. leaves in diabetic rats induced by high-fat diet and low-dose streptozotocin. J Ethnopharmacol. 10(235):1-7.
[30] Gunaydin G. et al.(2019): Diabetes drug has unexpected, broad implications for healthy aging, Turkish Journal of Biochemistry, 4..
[31] Vaishnav, Y., Jha, A.K., , Verma, S., , Kashyap, P., Kaur, S.D. (2017): A Review on Antidiabetic Activity of Substituted 1, 3, 4 –Thiadiazole Derivatives. Research J. Pharm. and Tech. 10 (12).
[32] George J. Dugbartey , Stephen Atule , Karl K. Alornyo , Ismaila Adams. (2024): Hepatoprotective potential of alpha-lipoic acid against gliclazide induced liver injury in high-glucose-exposed human liver cells and experimental type 2 diabetic rats. Biochemical Pharmacology. 277: 116447
[33] Alwan, I.A. (2023): Association between Type 2 Diabetesand Elevaton of Liver Enzymes. International Journal of Pharmaceutical and Bio-Medical Science. 3(5): 201-204.
[34] Jia, Q., Yang, R., Liu, X-F., Ma, S-F. and Wang, L. (2019): Genistein attenuates renal fibrosis in streptozotocin-induced diabetic rats. Molecular Medicine Reports. 19: 423-431.
[35] Al-Shimaa M. Abas, Faten Z. Mohamed, Ahmed R. Bayomi, Emad .M.Gad (2022): Biochemical Studies on Benzimidazole Compounds as Anti- diabetic Agents. Biochemistry Letters, 18(1) 2022, pages 33-55.
[36] Vergès, B. (2015): Pathophysiology of diabetic dyslipidaemia: Where are we? Diabetologia.58: 886–899.
[37] El-Bidawy, M.H., Hussain, A.O., Al-Ghamd, S., Aldossari, K.K., Haidara, M. A. and Al-Ani, B. (2021): Resveratrol ameliorates type 2 diabetes mellitus-induced alterations to the knee joint articular cartilage ultrastructure in rats. Ultrastructural Pathology. https://doi.org/10.1080/01913123.2021.1882629.
[38] Martín-Gallán P, Carrascosa A, Gussinyé M and Domínguez C: Biomarkers of diabetes-associated oxidative stress and antioxidant status in young diabetic patients with or without subclinical complications. Free Radic Biol Med 34: 1563-1574, 2003.
[39] He, L-Y., Li, .Y, Niu, S-Q., Bai, J., Liu, S-J. and Guo, J-L. (2023): Polysaccharides from natural resource: ameliorate type 2 diabetes mellitus via regulation of oxidative stress network. Front. Pharmacology. 14:1184572.

[40] Foretz M, Viollet B. (2009): Mecanisme d'action hepatique de la metformine dans le diabete de type 2. Med des Mal Metab;3(1):48e54.

[41] Harika, M.S., Sudha, B.N. and Raghavendra, H.G. (2014): Synergistic Activity of Thiadiazole And Thiazolidinone Derivatives Against Alloxan Induced Diabetes In Rats. Sch. Acad. J. Pharm., 3(3): 301-305.

[42] Schr○ter, D.; H○hn, A. (2018): Role of Advanced Glycation End Products in Carcinogenesis and their Therapeutic Implications. Curr. Pharm. Des. 2018, 24, 5245–5251.

[43] Mona H. Hafez, Samar M. Ez Elarab, Hossam G. Tohamy & Ali H. El-Far . (2024): Thymoquinone attenuates diabetes-induced hepatic damage in rat via regulation of oxidative/nitrosative stress, apoptosis, and inflammatory cascade with molecular docking approach. Scientific Reports 14: 13016.

[44] Akbari M., Hassan-Zadeh V. (2018): IL-6 signalling pathways and the development of type 2 diabetes. *Inflammopharmacology*. 26(3):685–698. doi: 10.1007/s10787-018-0458-0.

[45] Feder, M.E. Hofmann, G.E. (1999): Heat-shock proteins, molecular chaperones, and the stress response: evolutionary and ecological physiology. Annu Rev Physiol. 61:243–82.

[46] Gerazova-Efremova K, Dinevska-Kjovkarovska S, Miova B. (2019): Heat-Shock Protein 70-Mediated Heat Preconditioning Attenuates Hepatic Carbohydrate and Oxidative Disturbances in Rats With Type 1 Diabetes. Can J Diabetes. 43(5):345–53. 10.1016/j.jcjd.2019.01.002.

[47] Almalki D.A., Alghamdi S.A. and Al-Attar A.M. (2019): Comparative Study on the Influence of Some Medicinal Plants on Diabetes Induced by Streptozotocin in Male Rats. BioMed Research International. Article ID 3596287, 1-11.

[48] Osama M. Ahmed, Asmaa A. Abdel Fattah, Manal Abdul-Hamid, Ayman M. Abdel-Aziz, Hader I. Sakr, Ahmed A. Damanhory, Samraa H. Abdel-Kawi, Nehmat Ghaboura and Moaaz M. Y. Awad. (2023): Antidiabetic and Liver Histological and Ultrastructural Effects of Cynara scolymus Leaf and Flower Head Hydroethanolic Extracts in Nicotinamide/Streptozotocin-Induced Diabetic Rats. Evidence-Based Complementary and Alternative Medicine. Volume 2023, Article ID 4223026, 13 pages..

[49] Jia Q., Yang R., Liu X-F., Ma S-F. and Wang L. (2019): Genistein attenuates renal fibrosis in streptozotocin-induced diabetic rats. Molecular Medicine Reports. 19: 423-431.