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Research Article

Evaluation of Some Biochemical and Haematological Parameters in Experimentally Induced Diabetic Rats

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ABSTRACT

Diabetes, defined by high blood sugar levels and glycosuria, is characterized by changes in insulin sensitivity, damage to the pancreas, and alterations in lipid and protein metabolism in advanced stages. In this study, utilized 33 male Wistar Albino rats and established three groups: control, diabetes, and control + citric acid buffer. Blood samples for glucose control were taken from the rat's tail in all groups on day of 0, 3rd, 6th, 9th, 16th, 23rd, 30th and from the heart under anaesthesia after 4 weeks. At the end of the study, hematological and biochemical parameters were measured.. While chloride level decreased in the diabetes group compared to the control group (P<0.05), iron, glucose, urea, ALT, and ALP levels increased in the diabetes group (P<0.05). Compared to the control group, LDH and albumin levels decreased significantly in both the diabetes and citric acid groups (P<0.05). Phosphate levels increased significantly in the citric acid group compared to the control group (P<0.05). Compared to the control group, the increase in GRAN, GRANN % , MON, MONN %, MPV, PDW, and PLCR levels and the decrease in LMM %, PLT, PCT, and PLCC levels were statistically significant (P<0.05) in the diabetes group. In conclusion, it was found that liver histopathology would be useful for assessing changes in liver function caused by streptozotocin, and kidney histopathology would be useful for assessing changes in kidney parameters. In addition to all these, it would be meaningful to evaluate the changes in iron and hepcidin levels to better understand the changes in iron levels better.

Keywords: *Diabetes, rat, biochemical parameter, haematological parameter*

Deneysel Olarak Diyabet Oluşturulan Ratlarda Bazı Biyokimyasal ve Hematolojik Parametrelerin Değerlendirilmesi

ÖZET

Diyabet, insülin direnci ve pankreastaki beta hücrelerinin hasarı sonucu yüksek kan glikoz seviyeleri, glikozüri ile karakterize, ileri aşamalarında lipid ve protein metabolizmasında da değişiklikler görülen bir hastalıktır. Sunulan araştırmada 33 adet Wistar Albino erkek rat kullanıldı ve kontrol, diyabet, kontrol+sitrik asit tamponu olmak üzere 3 grup oluşturuldu. Tüm gruplardan glikoz kontrolü için kan örnekleri 0., 3., 6., 9., 16., 23., ve 30. günlerde kuyruktan, 4 hafta sonra ise aneztezi altında kalpten alındı. Çalışma sonunda hematolojik ve biyokimyasal parametreler ölçüldü. Kontrol grubuna kıyasla diyabet grubunda klorür düzeyi azalırken (P<0,05), demir, glikoz, üre, ALT ve ALP düzeyleri diyabet grubunda artış gösterdi (P<0,05). Kontrol grubuna kıyasla, LDH ve albumin düzeyleri hem diyabet hem de sitrik asit gruplarında önemli ölçüde azaldı (P<0,05). Kontrol grubuna kıyasla sitrik asit grubunda fosfat düzeyleri önemli ölçüde artmıştır (P<0,05). Kontrol grubuna kıyasla, diyabet grubunda GRAN, %GRANN, MON, % MONN, MPV, PDW ve PLCR düzeylerindeki artış ve % LMM, PLT, PCT ve PLCC düzeylerindeki azalma istatistiksel olarak anlamlıdır (P<0,05). Sonuç olarak, streptozotosin kaynaklı karaciğer aktivitesindeki değişiklikler için karaciğer histopatolojisi, böbrek parametrelerindeki değişiklikler için böbrek histopatolojisi yapılmasının faydalı olacağı görüldü. Tüm bunlara ek olarak, demir düzeylerindeki değişiklikleri daha iyi anlamak için demir ve hepsidin düzeylerindeki değişiklikleri değerlendirmek anlamlı olacaktır.

Anahtar Kelimeler: *Diyabet, rat, biyokimyasal parametre, hematolojik parametre*

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Introduction

Diabetes mellitus (DM) is a persistent progressive disease defined by permanent hyperglycaemia that may develop owing to damage to insulin release, inability of insulin to show sufficient activity within the cell, or both (Goyal et al., 2023). It is stated that the incidence of DM, which is considered a global health problem (Kottaisamy et al., 2021), is increasing daily. According to the International Diabetes Federation (IDF), there are approximately 463 million diabetic patients in the world, and most of these patients are reported to be seen in low- and middle-income countries (Alie et al., 2024). Factors such as unhealthy eating habits, lack of exercise, and increased stress have lasting effects on lifestyle aspects of diabetes. These factors, therefore, contribute to the alarming rise in obesity and diabetes worldwide amidst the rapid pace of global urbanization and modernization (Chandrasekaran and Weiskirchen, 2024).

There are two major types of diabetes mellitus, type 1 and type 2: type I diabetes is also referred to as insulin-dependent diabetes mellitus and is characterized by insufficient insulin release from pancreatic beta cells. Insulin is a hormone that allows glucose to enter cells after being transported by the blood. In type II diabetes, target organs are desensitized to insulin. Insulin also positively or negatively regulates many genes, leading to various disruptions in carbohydrate, protein, and lipid metabolism in diabetes mellitus (Ozougwu et al., 2013; Köprülü, 2023; Ali et al., 2024).

Experimental DM models are widely used due to the role of animal models in understanding disease pathogenesis. Although *in vitro* and *in silico* studies have made significant progress in recent years, animal models still play a critical role in uncovering the complex aetiology and multiple systemic interactions of diabetes (Kottaisamy et al., 2021). It is stated that the model created in rats better reflects the naturally developing diabetes in humans, and rats are the first preferred animal species in diabetes research due to their various physiological characteristics (Ghasemi and Jeddi 2023).

Streptozotocin is the most widely used diabetogenic agent in type I and type II diabetes modelling. The glycopyranosyl group in its structure facilitates its uptake by pancreatic beta cells via glucose transporter-2 (GLUT2), while the nitrosourea group destroys pancreatic beta cells (Ghasemi and Jeddi 2023). It was also shown that Streptozotocin not only affects the pancreas but may also cause renal, hepatic, and bone marrow toxicity (Anonymous, 2012).

Experimental animal models are widely used in the research of effective treatment methods against diseases such as diabetes (Kottaisamy et al., 2021). It is seen in the literature data that significant changes occur in various haematological and biochemical parameters in the diabetes model created with Streptozotocin in rats (Yakhchalian et al., 2018). Although the animal, breed, administration dose, duration, and the agent used in the studies varied, in this study, a detailed profile was made in streptozotocin-induced diabetes.

This study aims to investigate the effects of the streptozotocin molecule, widely used in experimental diabetes modeling, on biochemical and hematological parameters, and to elucidate the possible mechanisms underlying these changes. It also aims to reveal the potential effects of citrate, a solvent for streptozotocin used in this study, which has not been adequately studied. For this purpose, we investigated the extent to which the effect rate of streptozicin affects the biochemical and hematologic parameters in the body to use it in the evaluation of the mechanism of positive or negative prognosis in new treatment methods or research.

Materials and Methods

This study ethical approval (Approval no: 2024/20, date 26.04.2024) was obtained from Selcuk University Experimental Medicine and Application Center Ethics Committee (SÜDAM).

In the present study, 33 male Wistar Albino rats were used. These animals were obtained from Selçuk University Experimental Medicine Research and Application Centre (SÜDAM) and were maintained and fed in polycarbonate cages in 3 separate groups: diabetes, control, and control + citric acid. The animals were divided into groups based on statistical analysis to ensure there was no weight difference between them. The animals were housed in a room (22±2°C), (55±5%) humidity, and 12 hours light/12 hours dark conditions. Feed and water were provided ad libitum.

In experimental animals, streptozotocin and alloxan, chemical agents that target insulin-secreting pancreatic β cells, show high affinity for GLUT2 as a cytotoxic glucose analogue; furthermore, streptozotocin is finding more use due to its greater stability and less toxicity (Kleinert et al. 2018). In this regard diabetes (D) group rats were subcutaneously administered a 40 mg/kg single dose of Streptozotocin (STZ) solution in citrate buffer (pH 4.5), 2 times (3-day intervals) to develop an experimental diabetes model (Özaydın et al., 2021). Fasting blood glucose levels of the animals were assessed with a glucometer by regularly drawing blood from the tail, and those above 250 mg/dL were considered diabetic (Keskin and Uluışık, 2019). Citric acid, the solvent of STZ used to induce diabetes, was administered subcutaneously to the animals in the citric group 2 times (3 days apart).

Blood samples were taken from the tail on day of 0, 3rd, 6th, 9th, 16th, 23rd, and 30th (Table 3) for glucose control and from the heart under anaesthesia by the intracardiac method 4 weeks later. Hematologic analyses were performed immediately. WBC (White Blood Cells), GRAN (Granulocytes), LM (Lymphocytes), MON (Monocytes), GRANN% (Absolute Granulocytes), LMM% (Absolute Lymphocytes), MONN% (Absolute Monocytes), RBC (Red Blood Cells), HGB (Haemoglobin), HCT (Haematocrit), MCV (Mean Corpuscular Volume), MCH (Mean Corpuscular Haemoglobin), MCHC (Mean Corpuscular Haemoglobin Concentration), RDWCV (Red Cell Distribution Width - Coefficient of Variation), RDWSD (Red Cell Distribution Width - Standard Deviation), PLT

(Platelets), MPV (Mean Platelet Volume), PDW (Platelet Distribution Width), PCT (Plateletcrit), PLCC (Platelet Large Cell Count), PLCR (Platelet Large Cell Ratio) values were measured on Hasvet BC-30 Vet device. Serum samples were stored at -80^{O}C until analysis. ALT, AST, ALP, Triglyceride, Cholesterol, Total protein, Albumin, Creatinine, Urea, Uric Acid, Phosphate, Magnesium, Potassium, Sodium, Chloride, Calcium, total and direct bilirubin, LDH, and iron levels (Alinity c8000) were measured in serum.

Statistical Analysis

The data were subjected to a normality test using the Shapiro-Wilk test. Weight on day 30, glucose values on day of 0, 3rd, 6th, 9th, 16th, 23rd, and 30th biochemical parameters including ALT, ALP, LDH, urea, chloride and iron levels, and haematological parameters including GRAN, GRANN %, LMM%, MONN%, RBC, HGB, HCT, MCHC, PDW, PCT and PLCC were found to be non-normally distributed. Parameters that did not fall within the normal range were evaluated using the Kruskal-Wallis and Mann-Whitney U tests. These values were added to the tables as medians. Parameters that fell within the normal range were evaluated using the One-Way ANOVA statistical test (SPSS Statistics 25.0, Corporation, Armonk, New York, USA). When there was a difference between the groups, the post hoc Tukey multiple comparison test was used to examine the difference, and P<0.05 was accepted as the statistical significance limit. Values are presented as Mean ± SD.

Results

The values measured in serum and blood in the study are presented in Tables 1 and 4.

Compared to the control group, chloride level decreased and were statistically significant (P<0.05), while iron, urea, ALT, and ALP levels increased and were statistically significant (P<0.05) in the diabetic group.

Compared to the control group, LDH and albumin level decreased significantly in both the diabetes and citric acid-treated groups (P<0.05).

When compared to the control group, phosphate and ALP level was found to be statistically significant (P<0.05) in the citric acid-treated group. There was no statistically significant difference (P>0.05) in sodium, potassium, triglyceride, cholesterol, calcium, uric acid, AST, total bilirubin, creatinine, magnesium, and direct bilirubin levels in the diabetes and citric acid group compared to the control group.

The weight changes on days 0, 15, and 30 are given in Table 2. When the weight changes were evaluated, it was observed that there was no statistical difference between the groups on day 0 (P>0.05), but on the 15th and 30th days, the live weights of the animals in the diabetes group were lower than those of the other groups, and this was statistically significant (P<0.05).

In the study, glucose values were measured from tail blood taken on day of 0, 3rd, 6th, 9th, 16th, 23rd and 30th, and these values are shown in Table 3. Accordingly, when compared to the control group, it was detected that there was no statistical difference in glucose values on day of 0 (P>0.05), while on the 3rd, 6th, 9th, 16th, 23rd and 30th days, there was an increase only in the diabetes group and this was statistically significant (P<0.05). In the last measurements, the samples that gave measurements above 600 mg/kg, which is the measurement limit of the device, were taken as HI 600 for statistical analysis.

Compared to the control group, GRAN, GRANN%, MON, MONN%, MPV, PDW, and PLCR levels increased and were statistically significant (P<0.05) in the diabetes group.

Compared to the control group LMM%, PLT, PCT and PLCC levels were decreased and statistically significant (P<0.05) in the diabetes group.

Compared to the control group, statistically significant (P>0.05) changes were observed in the haematological parameters HCT, MCHC, PDW, and PCT in the citric acid group.

Discussion

Streptozotocin acts selectively as a cytotoxic agent for β-cells in pancreatic islets, and single high-dose applications are reported to cause necrosis of all β-cells within 48 hours, leading to the development of diabetes. Multiple low-dose STZ injections, on the other hand, are reported to cause only limited damage to pancreatic islets and the loss of activity in β cells, with the triggering of the inflammatory process leading to insulin insufficiency and hyperglycaemia. It is among the information that blood glucose levels increased to 250-600 mg/dl with the development of severe diabetes in most of the rats within 3 weeks following STZ injection (Furman, 2021). In the present study, significant increases in glucose levels were found in male Wistar albino rats from the 3rd day following subcutaneous 40 mg/kg streptozotocin administration twice with 3-day intervals compared to the control group. Hyperglycemia in STZ-induced DM is thought to occur due to oxidative stress and rapid and irreversible necrosis of pancreatic β-cell islets.

Although the mechanism underlying STZ-induced liver damage has not been fully explained, it has been reported that STZ leads to degenerative necrosis in hepatocytes and vacuolization in hepatic lobules (Ali et al., 2017; Arabloei Sani et al., 2022). It is also revealed that such pathological changes observed in the liver may develop due to changing enzyme levels (Zafar et al., 2009).

Yakhchalian et al. (2018) reported that significant increases were observed in ALT and AST levels following one dose of 60 mg/kg STZ administration to rats. Fernandes et al. (2009) reported that in their study with the same dose of STZ, although increases in serum ALT and AST levels were revealed, significant decreases were observed in liver tissue ALT-AST levels compared to the control group, and there were also decreases in cardiac AST levels. Mohamed et al. (2019) reported that a single dose of 45 mg/kg intraperitoneal administration of Streptozotocin used as a diabetogenic agent did not affect ALT and AST levels, but pathological changes were found

Table 1. Biochemical parameter results

Biochemical parameter	Control group (n=10)	Diabetes group (n=11)	Citric group (n=12)	P
Triglyceride (mg/dL)	93.20±7.18 [a]	102.18±9.82 [a]	100.50±7.19 [a]	P=0.727
AST (U/L)	107.40±4.58 [a]	161.64±29.02 [a]	110.17±10.98 [a]	P=0.078
ALT (U/L) (Median)	45.10±2.79 [b] (41.50)	108.64±14.97 [a] (92.00)	50.25±5.88 [b] (45.00)	P=0.001
ALP (U/L) (Median)	188.30±12.85 [b] (190.50)	709.18±140.52 [a] (510.00)	150.58±12.21 [c] (143.00)	P=0.001
Total Bilirubin (mg/dL)	0.10±0.00 [a]	0.11±0.009 [a]	0.10±0.00 [a]	P=0.380
Direct bilirubin (mg/dL)	0.17±0.01 [a]	0.19±0.01 [a]	0.19±0.01 [a]	P=0.312
Cholesterol (mg/dL)	61.20±2.85 [a]	71.00±2.69 [a]	70.75±3.76 [a]	P=0.072
Albumin (g/dL)	2.88±0.03 [a]	2.55±0.04 [b]	2.62±0.02 [b]	P=0.001
Creatinine (mg/dL)	0.42±0.01 [ab]	0.46±0.01 [a]	0.39±0.01 [b]	P=0.001
Blood Urea Nitrogen (mg/dL) (Median)	17.00±0.52 [b] (17.00)	22.64±1.07 [a] (22.00)	15.17±0.32 [b] (15.00)	P=0.001
Uric acid (mg/dL)	0.79±0.02 [a]	1.94±0.59 [a]	0.78±0.07 [a]	P=0.038
Na (mmol/L)	140.10±0.58 [a]	138.45±1.11 [a]	139.91±0.34 [a]	P=0.250
K (mmol/L)	4.41±0.11 [a]	4.84±0.38 [a]	4.45±0.11 [a]	P=0.386
Cl (mmol/L) (Median)	100.70±0.71 [a] (101.00)	96.54±0.95 [b] (96.00)	101.25±0.37 [a] (101.00)	P=0.001
Magnesium (mg/dL)	2.7±0.08 [a]	2.7±0.19 [a]	2.3±0.07 [a]	P=0.102
Calcium (mg/dL)	9.31±0.05 [ab]	9.57±0.11 [a]	9.27±0.06 [b]	P=0.031
Phosphate (mg/dL)	6.45±0.38 [b]	6.84±0.32 [ab]	7.58±0.24 [a]	P=0.044
Fe (ug/dL) (Median)	188.20±3.68 [b] (190.50)	246.09±10.68 [a] (236.00)	200.45±7.09 [b] (194.00)	P=0.001
LDH (U/L) (Median)	1140.40±132.81 [a] (1228.00)	483.18±113.98 [b] (441.00)	644.83±113.63 [b] (600.00)	P=0.002

[a,b] Different letters in the same row indicate statistical significance (P<0.05). Values are presented as Mean ± SE.

Table 2. Results of weight change in animals

Day	Control group	Diabetes group	Citric group	P
Day of 0	316.60±4.35 [a]	317.82±3.75 [a]	317.33±3.23 [a]	P=0.975
Day of 15	400.80±9.37 [a]	328.36±6.27 [b]	394.17±6.10 [a]	P=0.001
Day of 30 (Median)	421.60±7.91 [b] (412.00)	326.00±7.01 [c] (330.00)	421.50±5.75 [a] (417.00)	P=0.001

[a,b] Different letters in the same row indicate statistical significance (P<0.05) between groups. Values are presented as Mean ± SE.

in the liver tissue as a result of histological analysis. Tella et al. (2019) reported that STZ administered at a dosage of 40 mg/kg did not cause any abnormality in AST levels. In the present study, compared to the control group, it was determined that the ALT level in the diabetes group increased and was statistically significant (P<0.05), while the AST level did not change (P>0.05). Oche et al. (2014) reported an increase in serum ALP concentrations after STZ injection in rats. In this study, it was determined that there was an increase in ALP enzyme activity in the diabetes group compared to the control group, and this difference was statistically significant (P<0.05). As a result, it is thought that the increase in serum levels of liver enzymes (AST, ALT, and ALP) is an indicator of liver damage. In addition, the differences between the studies may be related to the route, dose, and duration of administration.

It is reported that lactate dehydrogenase (LDH) is used in monitoring heart and liver damage in diabetic rats (Sharkawi et al., 2020; Mutavdzin Krneta et al., 2024). Wardani et al. (2022a) reported that LDH levels were significantly higher in rats given Streptozotocin compared to the control group. As a result of another study

Table 3. Glucose values of animals on different days

Glucose exchange	Control group (n=10)	Diabetes group (n=11)	Citric group (n=12)	P
Day of 0	128.40±3.55[a]	127.91±3.28[a]	117.42±3.26[a]	P=0.042
Day of 3 (Median)	103.50±2.72[c] (103.00)	277.36±27.42[a] (249.00)	115.92±3.92[b] (112.00)	P=0.001
Day of 6 (Median)	118.20±3.06[b] (120.50)	479.36±24.20[a] (448.00)	111.42±2.43[b] (110.00)	P=0.001
Day of 9 (Median)	121.80±4.95[b] (124.00)	548.27±14.91[a] (539.00)	115.33±2.88[b] (114.00)	P=0.001
Day of 16 (Median)	119.30±6.07[b] (117.50)	557.27±18.91[a] (600.00)	142.58±19.09[b] (119.50)	P=0.001
Day of 23 (Median)	117.80±2.78[b] (117.00)	593.64±4.40[a] (600.00)	118.25±4.96[b] (113.50)	P=0.001
Day of 30 (Median)	107.00±3.66[b] (104.00)	584.09±9.54[a] (600.00)	113.17±7.36[b] (104.50)	P=0.001

[a,b] Different letters in the same row indicate statistical significance (P<0.05) between groups. Values are presented as Mean ± SE

Table 4. Hematologic Parameters [1]

Hematologic Parameters	Control group (n=10)	Diabetes group (n=11)	Citric group (n=12)	P
WBC 10^9/L	8.19±1.12[a]	11.24±1.69[a]	11.89±1.63[a]	P=0.222
GRAN 10^9/L (Median)	1.97±0.15[b] (1.81)	3.32±0.34[a] (3.57)	2.83±0.41[ab] (2.39)	P=0.032
LM 10^9/L	5.83±0.90[a]	7.25±1.35[a]	8.44±1.19[a]	P=0.311
MON 10^9/L	0.39±0.07[b]	0.67±0.06[a]	0.61±0.06[ab]	P=0.019
GRANN % (Median)	0.26±0.02[b] (0.23)	0.31±0.02[a] (0.32)	0.23±0.01[b] (0.22)	P=0.006
LMM % (Median)	0.69±0.02[a] (0.72)	0.62±0.02[b] (0.61)	0.71±0.01[a] (0.72)	P=0.002
MONN % (Median)	0.05±0.002[b] (0.04)	0.07±0.008[a] (0.07)	0.05±0.002[ab] (0.05)	P=0.029
RBC 10^{12}/L (Median)	7.35±0.09[ab] (7.35)	7.73±0.38[a] (7.47)	6.38±0.47[b] (6.85)	P=0.039
HGB g/dL (Median)	16.32±0.20[ab] (16.20)	17.26±0.45[a] (17.00)	14.73±1.00[b] (15.55)	P=0.041
HCT % (Median)	43.48±0.34[a] (43.20)	46.04±2.04[a] (46.60)	37.60±2.74[b] (39.85)	P=0.020
MCV fL	59.22±0.55[a]	59.76±0.45[a]	58.92±0.62[a]	P=0.542
MCH pg	22.21±0.28[a]	22.73±0.88[a]	23.60±0.75[a]	P=0.382
MCHC g/L (Median)	375.20±3.34[b] (377.50)	379.91±13.26[ab] (359.00)	401.50±13.97[a] (394.00)	P=0.251
RDWCV (Coefficient of Variation)	0.15±0.004[a]	0.16±0.002[a]	0.18±0.020[a]	P=0.415
RDWSD (Standard Deviation) fL	34.42±0.94[a]	37.04±0.81[a]	40.27±5.31[a]	P=0.489
PLT 10^9/L	1140.30±59.99[a]	682.18±53.54[b]	879.50±106.06[ab]	P=0.002
MPV fL	6.69±0.07[b]	7.53±0.09[a]	6.96±0.08[b]	P=0.001
PDW (Median)	15.05±0.04[c] (15.10)	15.79±0.09[a] (15.80)	15.47±0.19[b] (15.20)	P=0.002
PCT mL/L (Median)	7.61±0.36[a] (7.57)	5.11±0.40[c] (5.18)	6.14±0.74[b] (6.90)	P=0.014
PLCC mL/L (Median)	525.20±23.32[a] (512.50)	369.09±30.20[b] (369.00)	437.33±52.60[ab] (490.50)	P=0.036
PLCR	0.46±0.007[b]	0.54±0.008[a]	0.49±0.011[b]	P=0.001

[a,b] Different letters in the same row indicate statistical significance (P<0.05). Values are presented as Mean ± SE.

[1]WBC; White Blood Cells, GRAN; Granulocytes, LM; Lymphocytes, MON; Monocytes, GRANN; Absolute Granulocytes, LMM; Absolute Lymphocytes, MONN; Absolute Monocytes, RBC; Red Blood Cells, HGB; Haemoglobin, HCT; Haematocrit, MCV; Mean Corpuscular Volume, MCH; Mean Corpuscular Haemoglobin, MCHC; Mean Corpuscular Haemoglobin Concentration, RDWCV; Red Cell Distribution Width Coefficient of Variation, RDWSD; Red Cell Distribution Width Standard Deviation, PLT; Platelets, MPV; Mean Platelet Volume, PDW; Platelet Distribution Width, PCT; Plateletcrite, PLCC; Platelet Large Cell Count, PLCR; Platelet Large Cell Ratio.

conducted in the same direction, significant increases in LDH levels were detected following STZ administration to rats at a dose of 50 mg/kg (Sharkawi et al., 2020). In a recent study, LDH isoform levels were investigated in rats given STZ, and it was reported that LDH1-LDH3-LDH4 levels were higher than in the control group (Mutavdzin Krneta et al., 2024). Streptozotocin has been shown to cause increases in LDH levels measured in kidney and liver tissues, and these levels have been found to reflect increased oxidative stress in the relevant tissues (Sukanya et al. 2024) In contrast, Adowele et al. (2006) reported a decrease in LDH levels after the injection of STZ into Wistar rats, stating that these levels may reflect the destruction occurring in pancreatic beta cells. Similarly, in the presented study, decreases in LDH levels were detected, and it was hypothesized that this situation may be due to the enzyme's inability to reach sufficient activity, which is known to be necessary for the function of pancreatic beta cells. It was also emphasized that the fact that LDH is a glycolytic enzyme may reflect the disrupted glucose homeostasis. In addition in this study, it was revealed that a statistically significant decrease ($P<0.05$) occurred in the diabetes group compared to the control group in LDH levels, but this decrease was also observed in the citric acid group, suggesting that this may be due to the STZ solvent citric acid.

Streptozotocin is reported to cause an increase in markers of renal function (Dey et al., 2022). In addition, it is stated that the administration may lead to various disorders such as oxidative stress formation, inflammation, and histopathological changes in kidney tissue (Zhou et al., 2014). Wardani et al. (2022b) found significant increases in BUN and creatinine levels as a result of modelling with a single dose of Streptozotocin in male Wistar rats. In another study by Guo et al. (2021), although creatinine levels were reported to be lower than those of the control group as a result of modelling in rats, the development of nephropathy could be confirmed by histopathological method. It was reported that Streptozotocin administered at 60 mg/kg in male Wistar rats did not cause any increase in serum creatinine levels within a 2-month period, which is consistent with our study (Azarkish et al., 2017). In this study, it was observed that the increase in urea level was statistically significant ($P<0.05$), while creatinine levels increased but did not show statistical significance ($P>0.05$). Although elevated serum levels of urea and creatinine may result from diabetic hyperglycaemia–induced renal dysfunction, histopathologic examination of renal tissue clearly remains valuable in such studies. It has been reported that increased iron concentrations contribute to the formation of oxidative stress through increased ROS and NOS (Puntarulo 2005). Saravanan et al. (2013) reported an increase in serum iron levels following single dose streptozotocin administration. Wang et al. (2014) found significant increases in serum-liver iron levels following modelling compared to the control group. The data obtained in the present study are in line with the mentioned studies. On the other hand, Zou et al. (2017) stated that an iron chelator given for therapeutic purposes had a curative effect on diabetic nephropathy, although they reported that no change occurred in serum iron levels in their modelling. Aigner et al. (2013) stated that glucose may function as a regulator of serum iron concentrations by triggering hepsidin release from β cells. It is thought that the elevation in iron levels may be related to hepsidin expression and elevated oxidative stress.

Numerous studies have revealed that electrolyte levels may vary in experimental diabetes modeling on rats (Owu et al., 2016; Birudu et al., 2020). Birudu et al. (2020) reported that serum sodium, potassium, and chloride levels were higher in rats with the alloxan diabetes model compared to the control group. In another alloxan-induced study, it was observed that chloride levels were lower than in the control group (Akah et al., 2009). In another study using Streptozotocin, Owu et al. (2016) revealed that potassium and chloride levels did not change, although serum sodium levels increased. In the present study, no change was observed in potassium, magnesium, and sodium levels, but chloride levels were lower than in the control group. It suggests that the decrease in chloride levels observed in the study may have been observed as a result of osmotic diuresis.

It has been reported that STZ remains stable only in the pH range of 4.2-4.5 and becomes unstable in unbuffered aqueous solutions. For these reasons, saline solution is rarely used for this purpose, while citrate buffer solution is widely used (Ghasemi et al. 2023). Despite all this, it is stated that citrate can cause peritoneal irritation even at low concentrations and can cause significant changes in acid-base balance (Gvazava et al. 2020). In this context, the study presented here has shown that there were increases in phosphate levels, which play important roles in the acid-base buffer system, in the sham group.

It is stated that streptozotocin administration causes various changes in hematologic parameters in rats. It is also stated that hematologic index changes in prediabetic rats are an important marker for glycemic control (Yakhchalian et al., 2018; Krisnamurti et al., 2022).

It has been reported that streptozotocin-induced hyperglycaemia causes a decrease in red blood cells by causing non-enzymatic glycosylation in erythrocyte membrane proteins (Hajam et al., 2020; Krisnamurti et al., 2022). Rehman et al. (2023) reported that no change occurred in the erythrocyte and haemoglobin panel of red blood cell parameters following STZ injection in Wistar rats. In addition, as a result of the modelling created by Mahmouidi et al. (2021) with alloxan, no difference was detected in RBC and RBC-related variables compared to the control group. This study is consistent with the fact that no change was detected in RBC levels and related parameters. In contrast, it was observed that HCT levels decreased in the citrate group. Accordingly, Oladipo et al. (2011) reported that sodium citrate can cause various changes in red blood cells in Wistar rats.

In this study, although statistically insignificant increases in lymphocyte and WBC levels were determined, like the study conducted by Eze et al. (2019), no statistical difference was detected compared to the control group,

whereas significant increases in monocyte levels were revealed. However, Oyedemi et al. (2011) reported that MON levels decreased significantly (P<0.05) in the diabetes group compared to the control group in their study with STZ administered by a single dose of 50 mg/kg intraperitoneally. It is thought that the difference between the studies may be related to the route and dose of administration.

Rehman et al. (2023) reported that PLT levels increased significantly (P<0.001) in the diabetic group compared to the control group in their study of diabetes induced with 65 mg/kg (IP/single dose). In another study, it was reported that saline (IP) was administered to the control group, and 60 mg/kg (6 mg/100 g) STZ (IP) diluted in normal saline was administered to the STZ groups. It was stated that blood samples were taken from the control group, and the 1st group administered STZ on the 5th day, while blood samples were taken from the 2nd group, who administered STZ on the 15th day. It was reported that PLT levels increased statistically significantly on the 5th day and decreased statistically significantly on the 15th day in STZ groups compared to the control group (Ali et al., 2019). Keskin et al. (2016) reported that PLT levels were statistically significantly (P<0.05) lower in the diabetes group (60 mg/kg IP STZ) compared to the control group. In another study on PLT levels measured in STZ-induced (35 mg/kg IP) rats, it was stated that PLT levels were statistically significantly lower in the diabetes group compared to the control group (Gayathri and Kannabiran, 2009). In another study on PLT levels, it was reported that diabetes was induced with 50 mg/kg (IP) STZ, and PLT levels decreased significantly (p<0.05) in the diabetes group compared to the control group, as in our study (Oyedemi et al., 2011). In the present study, significant decreases in PLT levels in the streptozotocin group compared to the control group were revealed. It is thought that this decrease may be due to the change in glucose concentration after streptozotocin administration, changes in hematologic parameters, especially platelets, and suppression of hemopoiesis due to insulin deficiency or insufficiency. Scridon et al., (2019) wistar rats showed decreases in PCT levels and increases in MPV values following a single dose of 60 mg/kg STZ injection, consistent with our study findings. However, no significant correlation was found between glucose levels and various platelet indices in this study. It was noted that elevated levels of *in vitro* aggregation did not occur due to the long duration of the study. Although increases were also observed in PDW and PLCR levels, these values were found to be statistically insignificant. In our study, however, significant increases were recorded in both parameters. A study conducted by Oudeh et al. (2023) on Wistar rats revealed no significant difference between sexes in terms of platelet indices following the induced type I diabetes model. Furthermore, it was determined that PCT and MPV parameters showed strong negative and positive correlations with glucose, respectively, more prominent in female rats. In contrast, no correlation was found between PDW levels and this parameter.

This study demonstrates that STZ injection can cause significant changes in platelet-related parameters. Furthermore, this variation in platelet indices is thought to be related to increased glucose levels. Additionally, the duration of the study in animals undergoing diabetes research may also influence these parameters, which is another point that needs to be considered.

In the presented study, possible damage developing in various tissues and organs could not be confirmed by histopathology. Furthermore, the relatively short period covered by the study may explain why the damage developing in organs such as the liver and kidneys was not sufficiently reflected in the relevant parameters. For these reasons, the possible effects of streptozotocin need to be evaluated over a longer duration. In addition, the examination of only biochemical and hematological parameters was not considered sufficient to explain the effects of STZ at the molecular level, and it was concluded that further studies are needed regarding the effects of STZ.

Conclusion

Considering the results obtained in this study, it was observed that LDH levels decreased in both the diabetes and citric acid-treated groups, and albumin levels increased in both groups compared to the control group. Therefore, it is thought that the changes in LDH and albumin levels may be due to citric acid. In addition, it was observed that only the phosphate level increased in the citric acid-treated group compared to the control group. The effect of citric acid should be kept in mind in future studies. Although the changes in hepatic activity caused by Streptozotocin seem to be seen in ALT enzyme activity, it is thought that liver histopathology and kidney histopathology should also be performed due to changes in renal function markers. In addition to all these, it was concluded that the change in iron levels was important, and it is important to look at it together with hepcidin levels in future studies.

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Author contribution statement

Concept and design: B.S.A, A.M.A., F.A., Z.B; Data collection or processing: B.S.A, Z.B.; Analysis or interpretation: B.S.A, Z.B.; Literature search: B.S.A, A.M.A., F.A., Z.B; Writing: B.S.A, A.M.A., F.A., Z.B.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

Adewole, S. O., Caxton-Martins, E. A., & Ojewole, J. A. (2006). Histochemical and Biochemical Effects of Melatonin on Pancreatic β-cells on Streptozocin–treated Diabetic Rats. *Pharmacology-online*, *2*, 1-21

Aigner, E., Felder, T.K., Oberkofler, H., Hahne, P., Auer, S., Soyal, S., Stadlmayr, A., Schwenoha, K., Pirich, C., Hengster, P., Datz, C., & Patsch, W. (2013). Glucose acts as a regulator of

serum iron by increasing serum hepcidin concentrations. *The Journal of nutritional biochemistry*, 24(1), 112-117. https://doi.org/10.1016/j.jnutbio.2012.02.017

Akah, P.A., Alemji, J.A., Salawu, O.A., Okoye, T.C., & Offiah, N.V. (2009). Effects of Vernonia amygdalina on biochemical and hematological parameters in diabetic rats. *Asian Journal of Medical Sciences*, 1(3), 108-113

Ali, M.Y., Paul, S., Tanvir, E.M., Hossen, M.S., Rumpa, N.E.N., Saha, M., Bhoumik, N.C., Aminul, I.M., Hossain, M.S., Alam, N., Gan, S.H., & Khalil, M.I. (2017). Antihyperglycemic, antidiabetic, and antioxidant effects of Garcinia pedunculata in rats. *Evidence-Based Complementary and Alternative Medicine*, 2017(1), 2979760. https://doi.org/10.1155/2017/2979760

Ali, A., Shaheen, S., Memon, Z., Agha, F., Shahid, M.A., & Zahid, N. (2019). Effects of diabetogenic agent streptozotocin on hematological parameters of Wistar albino rats an experimental study. *Journal of Advances in Medicine and Medical Research,* 30(5), 1-8. https://doi.org/10.9734/JAMMR/2019/v30i530194

Ali, M.S., Ahmed, S., Islam, M.R., Ahamed, M.S., Rahaman, M.A., Khatun, M., & Alam, M.A. (2024). Diabetes mellitus control including fruits in diet: Exhaustive review and meta-analysis. *Asian Journal of Food Research and Nutrition*, 3(1), 43-59

Alie, M.S., Girma, D., Adugna, A., & Negesse, Y. (2024). Diabetes mellitus service preparedness and availability: a systematic review and meta-analysis. *Frontiers in Endocrinology*, *15*, 1427175. https://doi.org/10.3389/fendo.2024.1427175

Anonymous. (2012). Liver Tox: Clinical and Research Information on Drug-Induced Liver Injury. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases. https://www.ncbi.nlm.nih.gov/books/NBK547852 [accessed 15 April 2025]

Arabloei Sani, M., Yaghmaei, P., Hajebrahimi, Z., & Hayati Roodbari, N. (2022). Therapeutic effect of p-cymene on lipid profile, liver enzyme, and akt/mtor pathway in streptozotocin-ınduced diabetes mellitus in wistar rats. *Journal of Obesity*, 2022(1), 1015669. https://doi.org/10.1155/2022/1015669

Azarkish, F., Hashemi, K., Talebi, A., Kamalinejad, M., Soltani, N., & Pouladian, N. (2017). Effect of the administration of Solanum nigrum fruit on prevention of diabetic nephropathy in streptozotocin-induced diabetic rats. *Pharmacognosy Research*, 9(4), 325-332. https://doi.org/10.4103/pr.pr_47_17

Birudu, R.B., Pamulapati, P., & Kumar, M.S. (2020). Effects of aegle marmelos (l.) methanolic leaf extracts on cardiovascular parameters in diabetic rats. *Journal of Diseases and Medicinal Plants*, 6(4), 77-81. https://doi.org/10.11648/j.jdmp.20200604.11

Chandrasekaran, P., & Weiskirchen, R. (2024). The role of obesity in type 2 diabetes mellitus-An overview. *International Journal of Molecular Sciences*, 25(3), 1882. https://doi.org/10.3390/ijms25031882

Dey, P., Kundu, A., Lee, H.E., Kar, B., Vishal, V., Dash, S., Kim, I.S., Bhakta, T., & Kim, H.S. (2022). Molineria recurvata ameliorates streptozotocin-induced diabetic nephropathy through antioxidant and anti-inflammatory pathways. *Molecules*, 27(15), 4985. https://doi.org/10.3390/molecules27154985

Eze, E.D., Afodun, A.M., Kasolo, J., & Kasozi, K.I. (2019). Lycopene improves on basic hematological and immunological parameters in diabetes mellitus. *BMC Research Notes*, 12(1), 805. https://doi.org/10.1186/s13104-019-4841-8

Fernandes, A.A.H., Novelli, E.L.B., Fernandes Junior, A., & Galhardi, C.M. (2009). Effect of naringerin on biochemical parameters in the streptozotocin-induced diabetic rats. *Brazilian archives of biology and technology*, 52, 51-59

Furman, B.L. (2021). Streptozotocin-induced diabetic models in mice and rats. *Current protocols*, 1(4), e78. https://doi.org/10.1002/0471141755.ph0547s70

Gayathri, M., & Kannabiran, K. (2009). The Effects of oral administration of an aqueous extract of Ficus bengalensis stem bark on some hematological and biochemical parameters in rats with streptozotocin-induced diabetes. *Turkish Journal of Biology*, *33*(1), 9-13. https://doi.org/10.3906/biy-0805-12

Ghasemi, A., & Jeddi, S. (2023). Streptozotocin as a tool for induction of rat models of diabetes: a practical guide. *EXCLI journal*, *22*, 274-294. https://doi.org/10.17179/excli2022-5720

Goyal R, Singhal M, Jialal I. Type 2 Diabetes. [Updated 2023 Jun 23]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK513253/ [accessed 2 April 2025]

Guo, L., Jiang, B., Li, D., & Xiao, X. (2021). Nephroprotective effect of adropinin against streptozotocin-induced diabetic nephropathy in rats: inflammatory mechanism and YAP/TAZ factor. *Drug Design, Development and Therapy*, 15, 589-600. https://doi.org/10.2147/DDDT.S294009

Gvazava, I. G., Kosykh, A. V., Rogovaya, O. S., Popova, O. P., Sobyanin, K. A., Khrushchev, A. K., Timofeev, A.V., & Vorotelyak, E. A. (2020). A simplified streptozotocin-induced diabetes model in nude mice. *Acta Naturae*, *12*(4), 98-104

Hajam, Y.A., Rai, S., Ghosh, H., & Basheer, M. (2020). Combined administration of exogenous melatonin and insulin ameliorates streptozotocin induced toxic alteration on hematological parameters in diabetic male Wistar rats. *Toxicology Reports*, *7*, 353-359. https://doi.org/10.1016/j.toxrep.2020.01.020

Keskin, E., Dönmez, N., Kılıçarslan, G., & Kandır, S. (2016). Beneficial effect of quercetin on some haematological parameters in streptozotocin-induced diabetic rats. *Bulletin of Environment, Pharmacology and Life Sciences*, *5*(6), 65-8. ISSN 2277-1808

Keskin, E., & Uluışık, D. (2019). The effect of melatonin on some coagulation parameters in streptozotocin-induced diabetic rats. *Kocatepe Veterinary Journal*, 12(2), 130-134. https://doi.org/10.30607/kvj.511340

Kleinert, M., Clemmensen, C., Hofmann, S. M., Moore, M. C., Renner, S., Woods, S. C., Huypens, P., Beckers, J., de Angelis, M.H., Schürmann, A., Bakhti, M., Klingenspor, M., Heiman, M., Cherrington, A.D., Ristow, M., Lickert, H., Wolf, E., Havel, P.J., Müller, T.D., & Tschöp, M. H. (2018). Animal models of obesity and diabetes mellitus. *Nature Reviews Endocrinology*, *14*(3), 140-162

Kottaisamy, C.P.D., Raj, D.S., Prasanth Kumar, V., & Sankaran, U. (2021). Experimental animal models for diabetes and its related complications-a review. *Laboratory Animal Research*, 37(1), 23. https://doi.org/10.1186/s42826-021-00101-4

Köprülü, R.E.P. (2023). How to create an experimental diabetes mellitus model?. *Pharmacia*, 70, 105-111. https://doi.org/10.3897/pharmacia.70.e96028

Krisnamurti, D.G.B., Purwaningsih, E.H., Tarigan, T.J.E., Soetikno, V., & Louisa, M. (2022). Hematological indices and their correlation with glucose control parameters in a prediabetic rat model. *Veterinary World*, 15(3), 672. https://doi.org/10.14202/vetworld.2022.672-678

Mahmoudi, F., Mahmoudi, F., Gollo, K.H., & Amini, M.M. (2021). Biosynthesis of novel silver nanoparticles using Eryngium thyrsoideum Boiss extract and comparison of their antidiabetic activity with chemical synthesized silver nanoparticles in diabetic rats. *Biological Trace Element Research*, 199(5), 1967-1978. https://doi.org/10.1007/s12011-020-02315-4

Mohamed, R.S., Marrez, D.A., Salem, S.H., Zaghloul, A.H., Ashoush, I.S., Farrag, A.R.H., & Abdel-Salam, A.M. (2019). Hypoglycemic, hypolipidemic and antioxidant effects of green sprouts juice and functional dairy micronutrients against streptozotocin-induced oxidative stress and diabetes in rats. *Heliyon*, 5(2), e01197. https://doi.org/10.1016/j.heliyon.2019.e01197

Mutavdzin Krneta, S., Gopcevic, K., Stankovic, S., Jakovljevic Uzelac, J., Todorovic, D., Labudovic Borovic, M., Rakocevic, J., & Djuric, D. (2024). Insights into the cardioprotective effects of pyridoxine treatment in diabetic rats: A study on cardiac oxidative stress, cardiometabolic status, and cardiovascular biomarkers. *Diagnostics*, *14*(14), 1507. https://doi.org/10.3390/diagnostics14141507

Oche, O., Sani, I., Chiaka, N.G., Samuel, N.U., & Samuel, A. (2014). Pancreatic islet regeneration and some liver biochemical parameters of leaf extracts of Vitex doniana in normal and streptozotocin–induced diabetic albino rats. *Asian Pacific journal of tropical biomedicine*, *4*(2), 124-130. https://doi.org/10.1016/S2221-1691 (14)60220-3

Oladipo, G.S., Okoh, P.D., Osaat, R.S., & Leko, B.J. (2011). Effect of sodium citrate on red blood cell count in wistar rat. *Scientia Africana, 10*(2)

Oudeh, S., Javahery Vayghan, A., & Ahmadi-hamedani, M. (2023). Duration of the diabetic state altered platelet indices from baseline values in a streptozotocin-induced rat model for type 1 diabetes mellitus. *Veterinary Clinical Pathology*, 52(2), 236-242. https://doi.org/10.1111/vcp.13229

Owu, D.U., Nwokocha, C.R., Ikpi, D.E., & Ogar, E.I. (2016). Effect of vitamin C supplementation on platelet aggregation and serum electrolytes levels in streptozotocin-induced diabetes mellitus in rats. *Nigerian Journal of Physiological Sciences*, 31(1), 55-61

Oyedemi, S.O., Adewusi, E.A., Aiyegoro, O.A., & Akinpelu, D.A. (2011). Antidiabetic and haematological effect of aqueous extract of stem bark of Afzelia africana (Smith) on streptozotocin–induced diabetic Wistar rats. *Asian Pacific Journal of Tropical Biomedicine*, 1(5), 353-358. https://doi.org/10.1016/S2221-1691(11)60079-8

Ozougwu, J.C., Obimba, K.C., Belonwu, C.D., & Unakalamba, C.B. (2013). The pathogenesis and pathophysiology of type 1 and type 2 diabetes mellitus. *Journal of Physiology and Pathophysiology*, 4(4), 46-57. https://doi.org/10.5897/JPAP2013.0001

Özaydın, T., Öznurlu, Y., & Sur, E. (2021). Streptozotosin ile diyabet oluşturulan ratlarda Koenzim Q 10›un testis dokusu üzerine etkileri. *Eurasian Journal of Veterinary Sciences*, 37(4), 235-242. https://doi.org/10.15312/EurasianJVetSci.2021.348

Puntarulo, S. (2005). Iron, oxidative stress and human health. *Molecular Aspects of Medicine*, *26*(4-5), 299-312. https://doi.org/10.1016/j.mam.2005.07.001

Rehman, H.U., Ullah, K., Rasool, A., Manzoor, R., Yuan, Y., Tareen, A.M., Kaleem, I., Riaz, N., Hameed, S., & Bashir, S. (2023). Comparative impact of streptozotocin on altering normal glucose homeostasis in diabetic rats compared to normoglycemic rats. *Scientific Reports*, *13*(1), 7921. https://doi.org/10.1038/s41598-023-29445-8

Saravanan, G., Ponmurugan, P., & Begum, M.S. (2013). Effect of S-allylcysteine, a sulphur containing amino acid on iron metabolism in streptozotocin induced diabetic rats. *Journal of Trace Elements in Medicine and Biology*, *27*(2), 143-147. https://doi.org/10.1016/j.jtemb.2012.07.009

Scridon, A., Perian, M., Mărginean, A., Vântu, A., Gherţescu, D., Fişcă, C., Halatiu, V., Grigoras, T., & Şerban, R. C. (2019). Streptozotocin-induced diabetes mellitus–a paradox of high intrinsic platelet reactivity and low in vitro platelet aggregation. *Acta Endocrinologica (Bucharest)*, *15*(1), 46. https://doi.org/10.4183/aeb.2019.46

Sharkawi, S.M., El-Shoura, E.A., Abo-Youssef, A.M., & Hemeida, R.A. (2020). The potential hepatoprotective effects of lovastatin combined with oral hypoglycemic agents in streptozotocin-induced diabetes in rats. *Immunopharmacology and Immunotoxicology*, *42*(2), 165-173. https://doi.org/10.1080/08923973.2020.1733013

Sukanya, T., Madhusudhan, C., & Salikineedy, K. (2024). The Role Of Metformin, Magnesium, And Vitamin D In Modulating Redox Enzymes In Streptozotocin-Induced Diabetes: An Albino Rat Model Study. *Journal of Advanced Zoology*, *45*(2)

Tella, T., Masola, B., & Mukaratirwa, S. (2019). The effect of Psidium guajava aqueous leaf extract on liver glycogen enzymes, hormone sensitive lipase and serum lipid profile in diabetic rats. *Biomedicine And Pharmacotherapy*, *109*, 2441-2446. https://doi.org/10.1016/j.biopha.2018.11.137

Wang, H., Li, H., Jiang, X., Shi, W., Shen, Z., & Li, M. (2014). Hepcidin is directly regulated by insulin and plays an important role in iron overload in streptozotocin-induced diabetic rats. *Diabetes*, 63(5), 1506-1518. https://doi.org/10.2337/db13-1195

Wardani, G., Nugraha, J., Mustafa, M.R., Kurnijasanti, R., & Sudjarwo, S.A. (2022a). Antioxidative stress and antiapoptosis effect of Chitosan nanoparticles to protect cardiac cell damage on streptozotocin-induced diabetic rat. *Oxidative Medicine and Cellular Longevity*, 3081397. https://doi.org/10.1155/2022/3081397

Wardani, G., Nugraha, J., Mustafa, M.R., & Sudjarwo, S.A. (2022b). Antioxidative stress and anti-inflammatory activity of fucoidan nanoparticles against nephropathy of streptozotocin-induced diabetes in rats. *Evidence-Based Complementary and Alternative Medicine*, 2022(1), 3405871. https://doi.org/10.1155/2022/3405871

Yakhchalian, N., Mohammadian, N., Hatami, K., Nosrati, H., & Yousofvand, N. (2018). Hematological and serum biochemical analysis of streptozotocin-induced insulin dependent diabetes mellitus in male adult wistar rats. *BioRxiv*, 359844. https://doi.org/10.1101/359844

Zafar, M., Naqvi, S.N.U.H., Ahmed, M., & Kaimkhani, Z.A. (2009). Altered liver morphology and enzymes in streptozotocin ınduced diabetic rats. *International Journal of Morphology*, 27(3), 719-725

Zhou, X., Feng, Y., Zhan, Z., & Chen, J. (2014). Hydrogen sulfide alleviates diabetic nephropathy in a streptozotocin-induced diabetic rat model. *Journal of Biological Chemistry*, *289*(42), 28827-28834. https://doi.org/10.1074/jbc.M114.596593

Zou, C., Liu, X., Liu, R., Wang, M., Sui, M., Mu, S., Li, L., Ji, L., & Xie, R (2017). Effect of the oral iron chelator deferiprone in diabetic nephropathy rats. *Journal of Diabetes,* 9(4), 332-340. https://doi.org/10.1111/1753-0407.12420