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Streptozotosinle Oluşturulan Diyabetik Rat Modelinde Egzersiz ve Alıç Sirkesi: Glukoz Metabolizması, Lipid Profili ve Karaciğerle İlişkili Serum Biyokimyasal Parametreleri

Exercise and Hawthorn Vinegar in a Streptozotocin-Induced Diabetic Rat Model: Glucose Metabolism, Lipid Profile, and Liver-Related Serum Biochemical Parameters

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ÖZET

Amaç: Bu çalışmada, streptozotosin (STZ) ile oluşturulan diyabetik rat modelinde koşu bandı egzersizi, alıç sirkesi ve bu iki uygulamanın kombinasyonunun vücut ağırlığı, glukoz metabolizması, lipid profili ve karaciğerle ilişkili serum biyokimyasal göstergeleri üzerindeki etkilerinin değerlendirilmesi amaçlanmıştır.
Materyal ve Metot: Çalışmada 42 adet Wistar albino cinsi erkek rat kullanılmıştır. Ratlar; sağlıklı kontrol (SK, n=6), diyabet kontrol (DK, n=9), diyabet+egzersiz (DE, n=9), diyabet+alıç sirkesi (DA, n=9) ve diyabet+egzersiz+alıç sirkesi (DEA, n=9) gruplarına ayrılmıştır. Diyabet, tek doz 50 mg/kg intraperitoneal STZ uygulanarak oluşturulmuştur. Egzersiz sekiz hafta boyunca haftada beş gün ve günde 30 dakika uygulanmış; alıç sirkesi aynı süre boyunca 1 mL/kg dozunda oral gavajla verilmiştir. Vücut ağırlığı ve açlık kan glukozu tekrarlı ölçümlerle izlenmiş; terminal serum göstergeleri uygun çoklu karşılaştırma düzeltmeleri kullanılarak değerlendirilmiştir.
Bulgular: Vücut ağırlığı ve seri açlık kan glukozu için grup, zaman ve grup×zaman etkileri anlamlı bulunmuştur. Bununla birlikte sekizinci haftada hiçbir müdahale grubu DK grubundan anlamlı olarak farklılaşmamıştır. Yanlış keşif oranı düzeltmesinden sonra terminal glukoz, insülin, AST, ALT ve albümin düzeyleri bakımından genel grup farklılıkları anlamlılığını korumuştur. Anlamlı ikili karşılaştırmaların tamamı SK grubunu içermiş; hiçbir müdahale grubu DK grubundan farklı bulunmamıştır. Lipid göstergelerinde anlamlı grup farklılığı saptanmamıştır.
Tartışma ve Sonuç: Müdahale gruplarında bazı parametrelerde sayısal değişimler gözlenmesine karşın, bu değişimler DK grubuna göre istatistiksel olarak anlamlı bulunmamıştır. Bulgular, mevcut doz, süre ve deneysel model koşullarında egzersiz, alıç sirkesi ve kombine uygulamanın glisemik kontrol, lipid profili ve karaciğerle ilişkili serum göstergelerinde mevcut protokole göre diyabet kontrolünde üstünlük sağlamadığını göstermektedir.

Anahtar Kelimeler: Alıç Sirkesi, Diyabet, Egzersiz, Lipid Profili, Streptozotosin

ABSTRACT

Objective: The aim of the present study was to examine the effects of treadmill exercise, hawthorn vinegar, and their combination on body weight, glucose metabolism, lipid profile, and liver-related serum biochemical markers in streptozotocin (STZ)-induced diabetic rats.
Material and Methods: Forty-two male Wistar albino rats were allocated to healthy control (SK, n=6), diabetic control (DK, n=9), diabetes+exercise (DE, n=9), diabetes+hawthorn vinegar (DA, n=9), and diabetes+exercise+hawthorn vinegar (DEA, n=9) groups. Diabetes was induced with a single intraperitoneal dose of STZ (50 mg/kg). Exercise was performed for 30 minutes/day, five days/week for eight weeks, and hawthorn vinegar was administered by oral gavage at 1 mL/kg for the same period. Body weight and fasting blood glucose were monitored repeatedly; terminal serum markers were evaluated with multiple-comparison corrections.
Results: Significant group, time, and group×time effects were observed for body weight and serial fasting blood glucose. However, no intervention group differed significantly from the DK group at week 8. After false discovery rate correction, overall group differences remained significant for terminal glucose, insulin, AST, ALT, and albumin. All significant pairwise comparisons involved the SK group, and no intervention group differed from the DK group. Lipid markers showed no significant group differences.
Discussion and Conclusion: Although some numerical changes occurred in the intervention groups, none was statistically significant relative to the DK group. Under the present dose, duration, and model conditions, exercise, hawthorn vinegar, and their combination showed no superiority over diabetic control in glycemic, lipid, or liver-related serum outcomes.

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Keywords: Diabetes, Exercise, Hawthorn Vinegar, Lipid Profile, Streptozotocin

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INTRODUCTION

Diabetes mellitus refers to a group of chronic and systemic metabolic diseases characterized by deficient insulin secretion, impaired insulin action, or both (1, 2). The International Diabetes Federation 2025 projects that in 2024, there were 589 million adults aged 20-79 years (11.1%, one in nine adults) living with diabetes, which is projected to increase to 853 million by 2050 (3). Diabetes is not just high blood sugar, it is a systemic disorder that affects the metabolism of carbohydrates, lipids and proteins. The impaired antilipolytic effect of insulin in adipose tissue results in increased flux of free fatty acids which in turn promotes hepatic triglyceride synthesis and very-low-density lipoprotein production. This process may be involved in the development of diabetic dyslipidemia (4, 5). Mutually reinforcing effects of prolonged hyperglycemia, dyslipidemia, oxidative stress, and inflammation may predispose to multiorgan involvement(2,5).

In experimental diabetes research, STZ is one of the most widely used diabetogenic agents because of its toxic effects on pancreatic beta cells. The phenotype induced by STZ varies according to factors such as dose, route of administration, animal age and strain, and the accompanying diet. A single high dose of STZ may produce a phenotype characterized by marked beta-cell damage and predominant insulin deficiency (6-8). Although no animal model fully reproduces all features of human diabetes, STZ models enable the concurrent investigation of glycemic status, lipid profile, and organ-related biochemical markers under controlled experimental conditions.

In the fed state the liver plays a central role in the regulation of glucose and lipid homeostasis, storing glucose as glycogen, and during fasting it releases glucose into the circulation by glycogenolysis and gluconeogenesis (9). The liver is also involved in the metabolism of lipoproteins and the synthesis of plasma proteins, including albumin (10). Under diabetic conditions, increased metabolic burden, lipid accumulation, oxidative stress, and inflammation are associated with hepatic involvement (5, 11). Accordingly, serum AST and ALT levels are considered biochemical markers associated with hepatocellular injury, although AST in particular is not liver-specific. Albumin is a major plasma protein synthesized by hepatocytes and may provide supportive information regarding hepatic protein synthesis capacity; however, because serum albumin is also influenced by extrahepatic factors, it is not a specific marker (12). Evaluating these parameters together with glucose, insulin, and the lipid profile

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contributes to a more comprehensive interpretation of the metabolic and biochemical consequences of STZ-induced diabetes (13, 14).

Regular exercise is a basic lifestyle approach in controlling diabetes-associated metabolic disturbances apart from pharmacological treatment. Exercise acutely increases insulin-independent glucose uptake in skeletal muscle and, long-term, improves insulin sensitivity and glucose transport through mechanisms involving AMPK, Akt, and GLUT4 (15, 16). The effect of exercise in experimental diabetes is not limited to glucose metabolism. In STZ-induced experimental diabetes models, exercise has been reported to improve glucose levels, the lipid profile, aminotransferases, and oxidative stress markers; however, the outcomes vary according to the STZ dose and the type, intensity, and duration of exercise (17, 18).

Plant-derived bioactive compounds are among the complementary experimental approaches investigated for metabolic disorders associated with diabetes. Hawthorn (Crataegus spp.) is a botanical source of flavonoids, phenolic acids, organic acids, and other polyphenolic compounds (19–21). Hawthorn extracts and polyphenol fractions possess antioxidant, anti-inflammatory, hypoglycaemic and hypolipidaemic effects and modulate pathways involved in insulin signalling and lipid homeostasis (22, 23). However, vinegar obtained through the fermentation of hawthorn fruit differs from concentrated extracts in both its production process and chemical composition. Hawthorn vinegar has been reported to contain phenolic compounds such as gallic acid and chlorogenic acid and to exhibit antioxidant capacity and inhibitory activity against alpha-amylase and alpha-glucosidase under in vitro conditions (24, 25). A study in Wistar rats showed that hawthorn vinegar may affect certain lipid and antioxidant markers (26). Nevertheless, a substantial proportion of this evidence was obtained outside diabetic models. Although studies of hawthorn extracts suggest potential improvements in glucose and insulin responses under diabetic conditions, findings obtained with extracts should not be directly generalised to hawthorn vinegar (27).

Therefore, this study aimed to evaluate the separate and combined effects of treadmill exercise and hawthorn vinegar on body weight, glucose metabolism, lipid profile, and liver-related serum biochemical parameters in STZ-induced diabetic rats. It was hypothesized that exercise and hawthorn vinegar, particularly when administered in combination, would improve these outcomes compared with the diabetic control group.

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MATERIALS AND METHODS

Ethical Approval, Experimental Animals and Housing Conditions

This study was approved by the Harran University Local Ethics Committee of Animal Experiments on September 25, 2025 (session number 2025/009, decision number 01-8). Experimental procedures were performed at the Harran University Experimental Animals Application and Research Center.

Male Wistar albino rats aged 8–12 weeks and of similar body weights were used. The animals were housed in standard cages at an ambient temperature of 23 ± 2 °C, approximately 50% relative humidity, and a 12-hour light/12-hour dark cycle; standard rat chow and water were provided ad libitum. The animals were acclimatized to laboratory conditions for one week before the experimental procedures.

Study Design and Experimental Groups

The study was initiated with 46 rats. Animals were randomized into five groups at the beginning, including 6 rats in SK group and 10 rats in the other four groups. Four rats were lost in early stage after STZ administration, and the experimental process was completed with 42 rats. The final groups were SK (n=6), DK (n=9), DE (n=9), DA (n=9) and DEA (n=9).

The SK group received no STZ, exercise, or hawthorn vinegar. No treatment besides STZ was administered to the DK group. The DE group was exposed to exercise, the DA group was treated with hawthorn vinegar and the DEA group was exposed to exercise and hawthorn vinegar after STZ administration.

Induction of the Diabetes Model

STZ (Focus Biomolecules, Plymouth Meeting, PA, USA) was freshly prepared in 0.1 M sodium citrate buffer at pH 4.5. Rats other than those in the SK group received a single intraperitoneal injection of 50 mg/kg STZ (7, 28). Before STZ administration, the animals were fasted for 12 hours without restricting access to water. During the first 24 hours after injection, water containing 5% glucose was provided to reduce the risk of hypoglycemia.

Blood glucose concentration in fasting blood samples collected from the tail vein 72 hours after STZ injection was measured using a LifeChek Silver GH-82 glucometer (China). Rats with blood glucose levels above 200 mg/dL were considered diabetic and included in the study (29). In addition, body weight and fasting blood glucose levels were measured serially using the same glucometer during weeks 1, 3, 6, and 8 of the intervention period.

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Exercise Protocol

The exercise groups performed running exercise on a specialized treadmill designed for rodents, with separate lanes for each animal and adjustable speed and incline (Ugo Basile, Animal Treadmill, Italy). To reduce acute stress associated with exercise, the rats underwent one week of treadmill familiarization before the main intervention. During this period, the animals ran for 10 minutes/day at 4 m/min and a 0° incline. Following adaptation, the exercise program was continued for eight weeks, five days/week, and 30 minutes/day. Each exercise session consisted of 5 minutes at 8 m/min, 5 minutes at 11 m/min, and 20 minutes at 14 m/min; all sessions were performed at a 0° incline. The speed stages were adapted from the moderate-intensity treadmill protocol reported by Kayacan et al. (30).

Hawthorn Vinegar Administration

Commercially available Temmuz Organik Çiftliği brand hawthorn vinegar was used. Hawthorn vinegar was administered to the DA and DEA groups by oral gavage at a dose of 1 mL/kg, five days/week for eight weeks. In the DEA group, the vinegar was administered approximately one hour before exercise. The dose used was consistent with previous studies in rats (26).

Termination of the Experiment and Preparation of Serum Samples

At the end of the experiment, deep anesthesia was induced in the rats by intraperitoneal administration of ketamine (90 mg/kg) and xylazine (10 mg/kg). Blood samples collected by cardiac puncture were transferred into tubes and centrifuged at 4,000 rpm for 10 min. The resulting serum samples were transferred into Eppendorf tubes, appropriately labeled, and stored at −80 °C until biochemical analysis.

Biochemical Analyses

Serum glucose, insulin, triglyceride, total cholesterol, HDL cholesterol (HDL-C), LDL cholesterol (LDL-C), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and albumin levels were evaluated.

Serum glucose, triglyceride, total cholesterol, HDL-C, LDL-C, AST, ALT, and albumin levels were analyzed using an automated analyzer system (Atellica Solution®, Siemens Healthineers) at the Biochemistry Laboratory of Harran University Hospital.

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Statistical Analysis

Statistical analyses were conducted using procedures compatible with IBM SPSS Statistics for Windows, version 27.0. Data integrity, duplicate animal identifiers, group sizes, and missing observations were checked. Body weight and serial fasting blood glucose were analyzed using a two-way mixed-design repeated-measures analysis of variance to evaluate group, time, and group × time effects. The Greenhouse–Geisser correction was applied to the time and group × time tests, and effect size was reported as partial eta squared (partial η^2). Group comparisons of final measurements and change scores were performed using the Kruskal–Wallis test and, when required, the Holm-adjusted Dunn test.

Because of the small group sizes and distributional characteristics, terminal serum markers were presented as median [interquartile range] and compared using the Kruskal–Wallis test. The false discovery rate across the omnibus p values for nine terminal outcomes was controlled using the Benjamini–Hochberg method. Results with an adjusted $q < 0.05$ were followed by Holm-adjusted Dunn tests covering 10 pairwise comparisons for each marker. Epsilon squared (ε^2) was calculated for the Kruskal–Wallis tests. All tests were two-sided, and p or $q < 0.05$ was considered statistically significant.

RESULTS

A total of 42 rats were included in the analysis. Group sizes were DE (n=9), DA (n=9), DEA (n=9), DK (n=9), and SK (n=6). No missing observations were identified for the analyzed variables.

Body Weight

For body weight, the group effect ($F(4, 37)=26.06$; $p<0.001$; partial $\eta^2=0.738$), time effect (Greenhouse–Geisser-adjusted $F(2.94, 108.64)=6.89$; $p<0.001$; partial $\eta^2=0.157$), and group×time interaction (Greenhouse–Geisser-adjusted $F(11.74, 108.64)=2.89$; $p=0.002$; partial $\eta^2=0.238$) were significant. At week 8, body weights in the DE, DA, and DEA groups were lower than in the SK group (Holm-adjusted p values of 0.001, 0.027, and 0.001, respectively); no significant differences were detected between the intervention groups and the DK group (Table 1).

Table 1. Body weight (g) by group during the eight-week experimental period

Time	DE (n=9)	DA (n=9)	DEA (n=9)	DK (n=9)	SK (n=6)
Baseline	343.4 ± 20.8	351.9 ± 23.5	365.6 ± 35.3	370.2 ± 29.9	378.7 ± 17.0
Week 1	310.6 ± 30.6	363.3 ± 6.1	338.6 ± 33.1	375.7 ± 30.7	395.8 ± 13.5

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Week 3	287.8 ± 41.5	331.6 ± 49.8	322.6 ± 22.5	387.7 ± 47.9	405.2 ± 18.3
Week 6	284.2 ± 39.2	339.4 ± 31.9	334.8 ± 33.2	360.8 ± 27.8	382.8 ± 26.1
Week 8	289.1 ± 59.7	314.9 ± 48.0	304.8 ± 11.8	343.8 ± 36.1	427.0 ± 33.3

Note: Data are presented as mean ± standard deviation. DE, diabetes+exercise; DA, diabetes+hawthorn vinegar; DEA, diabetes+exercise+hawthorn vinegar; DK, diabetic control; SK, healthy control.

Fasting Blood Glucose

For fasting blood glucose, the group effect ($F(4, 37)=47.86$; $p<0.001$; partial $\eta^2=0.838$), time effect (Greenhouse–Geisser-adjusted $F(2.84, 105.22)=3.39$; $p=0.023$; partial $\eta^2=0.084$), and group×time interaction (Greenhouse–Geisser-adjusted $F(11.37, 105.22)=1.98$; $p=0.036$; partial $\eta^2=0.176$) were significant. At week 8, fasting blood glucose levels in the DA and DK groups were higher than in the SK group (Holm-adjusted p values of 0.003 and <0.001, respectively). Change scores from the first to the final measurement did not differ among groups ($H(4)=5.30$; $p=0.258$; $\varepsilon^2=0.035$). Therefore, within-group changes were not interpreted as evidence of superiority over the DK group (Table 2).

Table 2. Fasting blood glucose (mg/dL) by group during the experimental period

Time	DE (n=9)	DA (n=9)	DEA (n=9)	DK (n=9)	SK (n=6)
Day 3	404.9 ± 78.8	409.2 ± 97.0	334.1 ± 86.7	384.0 ± 62.1	113.0 ± 12.2
Week 1	323.7 ± 41.9	350.1 ± 82.0	301.6 ± 74.7	365.6 ± 53.8	111.0 ± 7.4
Week 3	314.3 ± 49.5	303.4 ± 67.2	363.9 ± 93.4	336.4 ± 49.6	105.8 ± 4.7
Week 6	279.8 ± 36.7	337.1 ± 112.4	368.3 ± 87.0	392.2 ± 73.2	112.0 ± 6.2
Week 8	299.2 ± 44.8	364.7 ± 92.9	293.9 ± 120.5	385.0 ± 49.6	110.2 ± 5.9

Note: Data are presented as mean ± standard deviation. Abbreviations are defined in Table 1.

Terminal Serum Biochemical Markers

After false discovery rate correction, overall group differences remained significant for serum glucose ($q=0.027$), insulin ($q=0.025$), AST ($q=0.017$), ALT ($q=0.027$), and albumin ($q=0.017$). No significant differences were detected for triglycerides ($q=0.062$), total cholesterol ($q=0.286$), HDL cholesterol ($q=0.091$), or LDL cholesterol ($q=0.197$). All Holm-adjusted pairwise comparisons that reached significance involved the SK group; none of the intervention groups differed significantly from the DK group. Therefore, the terminal findings did not provide evidence that the interventions produced improvement relative to the DK group (Table 3).

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Table 3. Terminal serum biochemical markers by experimental group

Marker	DE (n=9)	DA (n=9)	DEA (n=9)	DK (n=9)	SK (n=6)	q	ε^2
Serum glucose (mg/dL)	619.0 [570.0–629.0]	585.0 [520.0–653.0]	529.0 [349.0–598.0]	453.0 [359.0–569.0]	337.5 [281.8–362.5]	0.027	0.224
Serum insulin (mU/L)	0.53 [0.24–2.13]	0.56 [0.35–0.78]	0.44 [0.26–0.61]	0.22 [0.16–0.28]	0.14 [0.08–0.16]	0.025	0.262
Triglycerides (mg/dL)	422.0 [303.0–459.0]	214.0 [155.0–337.0]	192.0 [173.0–502.0]	239.0 [170.0–483.0]	143.0 [136.2–149.0]	0.062	0.161
Total cholesterol (mg/dL)	89.0 [83.0–93.0]	85.0 [71.0–94.0]	79.0 [60.0–87.0]	79.0 [77.0–89.0]	78.0 [71.8–82.8]	0.286	0.027
HDL cholesterol (mg/dL)	39.8 [33.9–42.1]	44.6 [36.8–49.9]	33.8 [31.8–36.0]	36.4 [32.8–40.5]	38.3 [35.6–39.6]	0.091	0.125
LDL cholesterol	14.0 [11.9–19.0]	7.8 [3.3–13.0]	9.5 [4.5–11.0]	11.0 [6.6–19.0]	11.6 [5.8–13.9]	0.197	0.063
AST (U/L)	127.0 [112.0–161.0]	197.0 [173.0–261.0]	133.0 [116.0–148.0]	124.0 [113.0–156.0]	101.0 [95.2–104.5]	0.017	0.310
ALT (U/L)	134.0 [132.0–139.0]	118.0 [102.0–172.0]	98.0 [55.0–124.0]	64.0 [55.0–111.0]	55.0 [50.5–55.8]	0.027	0.228
Albumin (g/dL)	3.00 [2.90–3.20]	3.31 [3.20–3.40]	3.30 [3.20–3.40]	3.20 [3.10–3.50]	3.65 [3.45–3.70]	0.017	0.329

Note: Data are presented as median [interquartile range]. q denotes the Benjamini–Hochberg false discovery rate correction applied to nine Kruskal–Wallis omnibus tests; ε^2 denotes the epsilon-squared effect size. Significant pairwise comparisons were as follows: serum glucose, DE>SK (Holm-adjusted p=0.007); serum insulin, DA>SK (Holm-adjusted p=0.016); AST, DA>SK (Holm-adjusted p=0.002); ALT, DE>SK (Holm-adjusted p=0.013); and albumin, DE<SK (Holm-adjusted p<0.001). No intervention group differed significantly from the DK group. AST, aspartate aminotransferase; ALT, alanine aminotransferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

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DISCUSSION

The present study was designed to evaluate the effects of 8 weeks treadmill exercise, hawthorn vinegar and combined protocol on body weight, glucose metabolism, lipid profile and serum biochemical markers related to liver in STZ-induced diabetic rats. The overall results showed that although some variables were different among groups, none of the intervention groups was statistically significantly superior to the diabetic control group.

Group, time, and group × time effects were significant for body weight. At week 8, body weights in the DE, DA, and DEA groups were lower than in the SK group; however, none of these groups differed significantly from the DK group.

In STZ-induced models characterized predominantly by insulin deficiency, weight loss or inadequate weight gain may occur, and the severity of this phenotype may vary according to the STZ dose, administration protocol, and animal characteristics (8, 14). Moura et al. (31) reported that eight weeks of swimming and treadmill exercise improved exercise tolerance, muscle glycogen, and certain indices of muscle morphology in diabetic rats. However, functional and tissue-level improvements do not necessarily indicate normalization of body weight relative to a diabetic sedentary group. The present findings indicate that the applied protocols did not produce a statistically confirmed modification of diabetes-related weight changes relative to the DK group.

The significant group, time, and group×time effects for serial fasting blood glucose indicated that the glycemic trajectories differed among groups. Nevertheless, no intervention group differed from the DK group at week 8, and change scores from the first to the final measurement were not significant among groups. Therefore, lower mean values observed at specific weeks cannot be interpreted as a sustained and superior glycemic response relative to the DK group. This finding differs from some experimental studies reporting exercise-related benefits. In a small sample study Olufunmilayo and Mojirade (32) showed changes in glucose and some lipid markers after 4 weeks of swimming. The differences indicate that the response to exercise is sensitive to the model and protocol characteristics. One potential explanation for the divergence among studies is the model of diabetes used. Cao et al. (15) reported that chronic and acute exercise reduced glucose and modulated signaling components associated with AMPK, Akt, and GLUT4 in a model induced by a high-fat diet and 30 mg/kg STZ. Lin et al. (33) also showed that eight weeks of treadmill exercise improved hyperglycemia, hyperlipidemia, and insulin resistance in a high-fat diet plus low-dose STZ model. In the present study, however, a single

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50 mg/kg dose of STZ was administered without a high-fat diet, and glucose levels remained elevated. Because STZ dose, rat age, and residual functional beta-cell mass may alter the balance between insulin deficiency and insulin resistance, a high-fat diet plus low-dose STZ model and a single higher-dose STZ model cannot be considered the same pathophysiological condition (8, 34). Exercise loads also differed: the present protocol lasted 30 minutes, whereas Ceylan et al. (17) used 45 minutes of running at 20 m/min and Moura et al. (31) applied longer swimming or treadmill sessions. These differences are plausible explanations; however, the present study did not directly test their relative contributions.

The finding that terminal serum glucose was higher only in the DE group than in the SK group, whereas serum insulin differed only between the DA and SK groups, does not demonstrate glycemic or pancreatic superiority of the interventions relative to the DK group. Because the higher insulin level in the DA group did not differ significantly from that in the DK group, it cannot be interpreted as improved beta-cell function. Although exercise may support insulin-independent glucose uptake in skeletal muscle and GLUT4-mediated transport over the long term, it does not necessarily increase serum insulin (15, 16). Studies of insulin responses to hawthorn have been inconsistent. Jouad et al. (35) reported that an aqueous hawthorn leaf extract reduced glucose without altering basal insulin in STZ-diabetic rats, whereas Aierken et al. (27) reported that hawthorn extract reduced glucose while increasing plasma insulin in a high-fat diet plus STZ model.

Findings obtained with hawthorn vinegar should be evaluated separately from studies of hawthorn extracts or purified polyphenols. Liu et al. (23) reported improvements in total cholesterol, triglycerides, insulin, and indices of insulin resistance, together with modulation of the IRS1/PI3K/Akt/GLUT4 and SIRT1/AMPK/NF-κB pathways, following administration of 300 mg/kg hawthorn polyphenol extract in a high-fat diet plus STZ model. Jouad et al. (35) and Aierken et al. (27) also identified glucose-lowering effects with hawthorn extracts. In contrast, the present study used commercially available hawthorn vinegar produced by fermentation, and this product cannot be assumed to have the same bioactive concentration or bioavailability as extracts. Özdemir et al. (25) reported the presence of different phenolic and volatile compounds in hawthorn vinegar, while Akgün et al. (24) identified in vitro inhibition of alpha-amylase and alpha-glucosidase. However, in vitro enzyme inhibition does not constitute direct evidence of a glycemic effect in vivo. Because the phenolic, flavonoid, and organic acid profile of the vinegar used in the present study was not measured, it was not possible to determine whether biologically sufficient exposure was achieved.

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With respect to the lipid profile, no significant group differences were found for triglycerides, total cholesterol, HDL-C, or LDL-C after false discovery rate correction. The absence of a clear terminal lipid separation between the DK and SK groups suggests that a robust and homogeneous dyslipidemic phenotype, against which an intervention effect could be evaluated, was not established. Ceylan et al. (17) reported increased total cholesterol, LDL, and triglycerides and decreased HDL in the diabetic group after 60 mg/kg STZ administration. Although DE values in that study were numerically intermediate between the diabetic and control groups, the published letter groupings did not confirm direct superiority of DE for many markers. By contrast, Karimi et al. (36) reported that swimming and treadmill exercise reduced LDL and triglycerides; Olufunmilayo and Mojirade (32) found that swimming reduced total cholesterol, LDL, and triglycerides while increasing HDL; and Lin et al. (33) reported amelioration of hyperlipidemia in a high-fat diet plus low-dose STZ model. The divergence of the present results may be related to differences in baseline and terminal lipid phenotypes, model characteristics, diet, and within-group variability.

Findings regarding the lipid profile of hawthorn-derived products also vary by preparation. Aierken et al. (27) found decreased triglycerides and total cholesterol with hawthorn extract, and Liu et al. (23) reported improved levels of these parameters with hawthorn polyphenol extract. Han et al. in non-diabetic models (37) showed that hawthorn polyphenol fractions reduced total cholesterol, triglycerides, and LDL and increased HDL in mice fed a high-fructose diet; Feng et al. (38) showed that hawthorn fruit acids reduced triglycerides, cholesterol and glucose in hyperlipidemic rats. These studies were carried out with concentrated preparations. Karakçı et al. (26), who directly investigated hawthorn vinegar in healthy female rats, observed more pronounced changes in LDL and several antioxidant markers but found no significant differences in total cholesterol, triglycerides, or HDL. The absence of a lipid effect in the present study is partially consistent with this limited and marker-dependent evidence on vinegar.

Overall group differences in the liver-related markers AST, ALT, and albumin remained significant; however, all significant pairwise comparisons involved the SK group, and no intervention group differed from the DK group. Rehman et al. (13) reported elevations of AST, ALT and ALP after a single dose of 65 mg/kg STZ, but care should be taken when defining a single high dose STZ model as type 2 diabetes. Sedik et al. (14) showed that 45 and 60 mg/kg STZ increased AST and ALT and that the disturbances were more severe at 60 mg/kg. In the study by Ceylan et al. (17), AST and ALT values in the DE group were numerically lower than

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those in the diabetic group, but the letter groupings did not confirm direct superiority. In contrast, Oliveira et al. (39) detected no group differences in ALT or AST in a high-fat diet plus 25 mg/kg STZ model and reported hepatic lipid accumulation in the exercised diabetic group. These findings indicate that the effect of exercise on aminotransferases may vary according to the model and the resulting hepatic phenotype.

A substantial proportion of studies reporting hepatoprotective effects of hawthorn preparations differ from the present diabetic hawthorn vinegar model. Han et al. (37) reported that hawthorn polyphenol fractions reduced ALT, AST, ALP, inflammation, and oxidative stress in mice fed a high-fructose diet, whereas Wang et al. (40) reported that hawthorn fruit extract attenuated increases in aminotransferases, oxidative stress, and apoptosis in a microcystin-LR hepatotoxicity model. Neither study used STZ-induced diabetes or hawthorn vinegar. In the hawthorn vinegar study conducted by Karakçı et al. (26) in healthy rats, no significant differences were found for ALT or AST. The lower albumin level in the DE group than in the SK group in the present study does not, by itself, indicate impaired hepatic synthetic capacity due to exercise, because there was no difference between the DE and DK groups. Given the non-specific nature of albumin, this result should be interpreted together with other clinical and biochemical markers (12).

The DEA group did not differ significantly from the DK group or from either single-intervention group for any outcome; therefore, an additive or synergistic effect cannot be claimed. Although studies combining exercise with other plant-derived compounds have reported biological effects, they do not provide direct evidence for the present combination. Akbari et al. (41) reported lower aminotransferase levels in exercise, stevia, and exercise+stevia groups than in the diabetic control group in STZ-diabetic rats; however, this finding alone does not demonstrate that the combined group was superior to the single interventions. Pourmousavi et al. (42) reported that treadmill exercise and crocin, administered separately and together, reduced cardiac oxidative stress and apoptosis markers; differences in the target organ and plant-derived compound limit direct comparison.

From an experimental perspective, the findings indicate that the applied exercise and hawthorn vinegar protocols were insufficient to improve the evaluated metabolic and liver-related serum parameters under the present conditions. Given the limitations of the animal model and experimental conditions, these results should not be directly extrapolated to clinical practice.

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CONCLUSION

In conclusion, under the present experimental conditions, eight weeks of treadmill exercise, hawthorn vinegar administration, and their combination did not produce statistically significant improvements in glycemic control, lipid profile, or liver-related serum parameters compared with the diabetic control group.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Ethics Approval and Consent

The study was conducted with the approval of the Harran University Local Ethics Committee for Animal Experiments dated September 25, 2025, session number 2025/009, decision number 01-8.

Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

All authors contributed equally to the work

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