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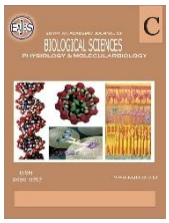
Citation: *Egypt.Acad.J.Biolog.Sci. (C.Physiology and Molecular biology) Vol. 17(2) pp149-158 (2025)*
DOI: 10.21608/EAJBSC.2025.453749

Egypt. Acad. J. Biolog. Sci., 17(2):149-158 (2025)

Egyptian Academic Journal of Biological Sciences
C. Physiology & Molecular Biology
ISSN 2090-0767
www.eajbsc.journals.ekb.eg



Ameliorative Effect of Non-Caloric Sweeteners on Liver Damage of Diabetic Rats and Their Correlation with Mir-122 Gene Expression

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ARTICLE INFO
Article History
Received: 3/8/2025
Accepted: 18/9/2025
Available:22/9/2025

Keywords:
Diabetes, liver damage, stevia, sucralose, oxidative stress, and mir122.

ABSTRACT

Diabetes mellitus is a long-term metabolic disorder marked by an abnormal increase in blood glucose levels due to deficiencies in insulin production, its action, or a combination of both. This research aims to assess the liver-protective potential of two non-caloric sweeteners, stevia, derived from natural plant sources, and sucralose, a chemically synthesized alternative, in diabetic rats induced by streptozotocin. It also evaluates the relationship between these sweeteners and the expression of microRNA-122 (miR-122), a key molecular marker involved in liver function and lipid homeostasis.Twenty-eight adult albino rats were randomly allocated into four separate experimental groups: a normal control group, a diabetic group without treatment, and two diabetic groups that received either stevia (400 mg/kg body weight) or sucralose (15 mg/kg body weight) for 4 weeks. Administration of both sweeteners led to significant decreases in blood glucose, liver enzymes (ALT and AST), total cholesterol, triglycerides, LDL, and malondialdehyde (MDA) levels. Conversely, insulin levels, antioxidant enzymes (SOD and CAT), and HDL showed marked improvement. Moreover, miR-122 was notably suppressed in the diabetic group and showed upregulation after sweetener treatment, indicating its association with liver recovery.

In conclusion, both stevia and sucralose exhibited hepatoprotective effects in diabetic rats, with stevia demonstrating a more pronounced impact, possibly due to its influence on miR-122 expression. These results highlight their potential in supporting liver health under diabetic conditions.

INTRODUCTION

Diabetes mellitus is a long-term metabolic condition marked by consistently elevated blood sugar levels due to insufficient insulin production or reduced sensitivity to insulin, or a combination of both (American Diabetes Association, 2023). The liver is one of the primary organs impacted by diabetes, given its vital role in managing glucose and lipid homeostasis. A key hepatic complication associated with diabetes is non-alcoholic fatty liver disease (NAFLD), which causes liver dysfunction and mortality in diabetic patients (Mantovani *et al.,* 2022; Eslam *et al.,* 2020)

To reduce sugar intake, non-caloric sweeteners (NCSs) such as sucralose and stevia are frequently used as sugar alternatives because they provide sweetness without significantly impacting the blood glucose (Magnuson *et al.,* 2022).

The long-term effect on liver health, particularly under diabetic conditions, remains under ongoing investigation. Stevia is derived from the *Stevia rebaudiana* plant and contains steviol glycosides, which are not metabolized by the human body, thereby offering sweetness with no caloric contribution (Kakleas *et al*., 2020). Due to their antioxidant properties, affordability, and fewer adverse effects, herbal remedies such as stevia are increasingly favored. In traditional medicine, Stevia has shown promise in controlling blood glucose and mitigating diabetic complications (Amin *et al*., 2006). The plant's leaves contain several natural glycosides, including stevioside and rebaudiosides, with stevioside being one of the most potent estimated to be 100 to 300 times sweeter than regular sugar. This compound is widely used across the food, pharmaceutical, cosmetic, and beverage industries (Stoyanova *et al*., 2011). Sucralose, on the other hand, is synthesized by modifying sucrose and is known for its chemical stability and palatability, making it one of the most popular artificial sweeteners (Magnuson *et al*., 2017). Still, some studies have raised concerns about the potential effects of NCSs on hepatic oxidative stress, inflammatory markers, and related gene pathways (Harada *et al*., 2021).

MicroRNAs (miRNAs) are short, non-protein-coding RNA molecules involved in post-transcriptional regulation of gene expression. Among them, miR-122 is abundantly expressed in hepatic tissue and is essential for the regulation of liver metabolic processes and cellular activities. Changes in its expression levels have been associated with a range of liver diseases and metabolic dysfunctions (Wang *et al*., 2023; Cheung *et al*., 2020).

The current study investigates how stevia and sucralose may protect the liver in a diabetic model using streptozotocin-induced rats, with a specific focus on the modulation of miR-122 expression.

MATERIALS AND METHODS

Sweetener:

The stevia powder used in this study was purchased from the Teyab Shana brand and prepared by dissolving it in distilled water.

Animals:

A total of 28 male albino rats, each weighing approximately 150 ± 10 g, were obtained from the animal facility at the Faculty of Veterinary Medicine, Zagazig University. Before the commencement of the experiment, the animals were allowed to acclimate to the laboratory environment at a temperature of 24 ± 2°C for a period of 10 days

Induction of Diabetes Mellitus:

Based on the method described by Ajiboye *et al*. (2024) and El-Shafey *et al*, (2013), twenty-one rats were initially deprived of food overnight. The following day, each rat was injected into the peritoneal cavity with streptozotocin at a concentration of 45 mg per kilogram of body weight, using a citrate buffer solution (0.01 M, pH 4.5) as the solvent. After 72 hours, blood glucose levels were measured, and only animals exhibiting hyperglycemia above 200 mg/dL were considered diabetic and included in the experimental group.

The rats were randomly assigned to four distinct groups as follows:

- **Group I (Control):** Healthy, non-diabetic animals serving as the baseline group.
- **Group II (Diabetic, untreated):** Diabetic rats that did not receive any therapeutic intervention.
- **Group III (Diabetic + Stevia):** Diabetic rats orally supplemented with stevia powder at a daily dose of 400 mg/kg body weight (Gholizadeh *et al*., 2018) for a duration of four weeks.
- **Group IV (Diabetic + Sucralose):** Diabetic rats treated with sucralose at a concentration of 15 mg/kg body weight per day (Ghasemi *et al*.,2016) in drinking water for four weeks via oral gavage.

Blood Sampling:

All animals were subjected to overnight fasting after the 4 weeks, then anesthetized using isoflurane inhalation. Blood was drawn into plain tubes and left to clot naturally for 1 to 2 hours at 37°C without adding anticoagulants. The samples were then centrifuged at 3000 rpm for 15 minutes, after which the serum was carefully separated and stored at –20°C for later biochemical analysis.

Liver Tissue Preparation:

Liver tissues were excised and washed with ice-cold 0.9% saline solution. Each liver was divided into two portions:

- One portion was preserved at −80 °C for molecular investigations conducted at the Molecular Biology and Biotechnology Unit, Department of Medical Biochemistry.
- The second portion was homogenized in iced phosphate-buffered saline (PBS), centrifuged at 4000 ×g for 5 minutes, and the resulting supernatants were stored for subsequent biochemical analyses.

Biochemical Analyses

- Serum glucose was assessed using enzymatic colorimetric kits (Biodiagnostic, Egypt).
- Serum insulin levels were quantified using ELISA kits specific for rats (Abnova, Taiwan).
- Liver enzymes (ALT and AST) were measured using spectrophotometric methods with Sgmitalia kits.
- The lipid profile including triglycerides, total cholesterol, high-density lipoprotein (HDL), and low-density lipoprotein (LDL)was evaluated using commercial diagnostic kits supplied by Roche Diagnostics. The levels of LDL-C and very low-density lipoprotein cholesterol (VLDL-C) were calculated using the formulas established by Friedewald *et al.* (1972).

LDL-C = Total cholesterol − [HDL-C + (Triglycerides / 5)]

VLDL-C = Triglycerides / 5

Estimation of miR-122 Gene Expression in Liver Tissue:

Total RNA, including microRNAs, was isolated using Trizol reagent (ZYMO RESEARCH CORP., USA; Cat# R2072) following the protocol provided by the manufacturer. RNA yield and purity were determined using a Beckman spectrophotometer. Complementary DNA (cDNA) specific to miRNAs was synthesized using the miScript Reverse Transcription Kit (QIAGEN, Cat# 218061). Quantitative real-time PCR (qPCR) was then carried out using the miScript SYBR Green PCR Kit (QIAGEN, Cat# 218073) on a StepOne Real-Time PCR System (Applied Biosystems, USA). Each PCR reaction (total volume 20 µL) contained 10 µL of 2× SYBR Green Master Mix, 10 ng of cDNA template, and gene-specific primers. The thermal cycling conditions were as follows: initial denaturation at 95°C for 10 minutes, followed by 40 amplification cycles of 95°C for 2 seconds, 60°C for 20 seconds, and 70°C for 10 seconds. The expression of miRNA-122 was normalized against GAPDH or U6 as internal controls and analyzed using the 2^−ΔΔCt method (Table 1).

Table 1: Sequences of primers utilized for evaluating miR-122 gene expression.

	Forward sequence	Reverse sequence	Gene accession number
miRNA 122	GTATACTGGAGTG TGACAATG	GTGCAGGGTCCGA GGT	MI0000891
U6	CTCGCTTCGGCAG CACA	AACGCTTCACGAA TTTGCGT	K00784

Statistical Analysis:

Statistical analysis was carried out using one-way analysis of variance (ANOVA), followed by Duncan's multiple range test (Duncan, 1957) to determine significant differences among groups. Data processing was performed using the Statistical Package for Social Sciences (SPSS, version 20; IBM Corp., Chicago, IL, USA). Results are expressed as mean ±

standard deviation (SD), with each group consisting of seven independent samples

RESULTS

Effect of Stevia and Sucralose on Serum Glucose and Insulin in Diabetic Rats:

As indicated in Table 2, diabetic rats showed a significant rise in serum glucose concentrations ($P < 0.05$) compared to all other experimental groups. In contrast, insulin secretion was substantially decreased in diabetic animals, with the lowest levels detected in the untreated diabetic group. Insulin levels increased progressively in the diabetic + sucralose group, the diabetic + stevia group, and finally reached the highest values in the control group. All these variations were statistically significant ($P < 0.05$).

Table 2: Effects of stevia (400 mg/kg b.w) and sucralose (15 mg/Kg b.w) on serum glucose and insulin in the serum of diabetic rats.

	Group I	Group II	Group III	Group IV
Glucose (mg/dL)	87 ± 6.75^{d}	262.67 ± 5.75^{a}	99.67 ± 4.50^{c}	156 ± 4.73^{b}
Insulin (µIU/mL)	1.48 ± 0.18^{a}	0.78 ± 0.08^{d}	1.17 ± 0.06^{b}	1.05 ± 0.09^{c}

The data are presented as mean ± standard deviation (SD). Group I serves as the control group, Group II includes diabetic rats that received no treatment, Group III consists of diabetic rats administered stevia, and Group IV includes diabetic rats treated with sucralose. In each row, values sharing the same letter indicate no statistically significant difference, while different letters represent statistically significant variations.

Effect of Sweeteners on Liver Injury Biomarkers in Diabetic Rats:

Data in Table 3, reveal that alanine aminotransferase (ALT) activity was significantly elevated in diabetic rats ($P < 0.05$), followed by a gradual decrease in the sucralose-treated group, the stevia-treated group, and the control group. For aspartate aminotransferase (AST), the diabetic group exhibited the highest enzyme activity, while the diabetic + sucralose group showed moderate levels. No significant difference in AST activity was observed between the diabetic + stevia group and the control.

Table 3: Effects of stevia (400 mg/kg b.w) and sucralose (15 mg/Kg b.w) on tissue injury markers in serum of diabetic rats.

	Group I	Group II	Group III	Group IV
ALT (U/L)	37.83 ± 2.73^{c}	51.5 ± 0.95^{a}	41.8 ± 2.33^{c}	45.43 ± 0.96^{b}
AST(U/L)	117 ± 1.3^{d}	153.33 ± 2.7^{a}	135 ± 2.9^{c}	142.3 ± 1.75^{b}

The data are presented as mean ± standard deviation (SD). Group I serves as the control group, Group II includes diabetic rats that received no treatment, Group III consists of diabetic rats administered stevia, and Group IV includes diabetic rats treated with sucralose. In each row, values sharing the same letter indicate no statistically significant difference, while different letters represent statistically significant variations.

Effect of Stevia and Sucralose on Serum Lipid Profile:

According to Table 4, diabetic rats displayed significantly increased levels of total cholesterol (TC), triglycerides (TG), and low-density lipoprotein cholesterol (LDL-C), followed by the sucralose and stevia groups, with the control group showing the lowest values ($P < 0.05$). On the other hand, high-density lipoprotein cholesterol (HDL-C) was lowest in the diabetic group and showed a stepwise elevation in the sucralose group, stevia group, and control group, respectively, with significant differences among all groups.

Table 4: Effects of stevia (400 mg/kg b.w) and sucralose (15 mg/Kg b.w) on serum lipid profile in STZ-induced liver damage in male albino rats.

	Group I	Group II	Group III	Group IV
TC(mg/dL)	82.47±4.6^{d}	122±2.68^{a}	85.33±3.24^{c}	90.43±2.45^{b}
TG(mg/dL)	70.1±4.04^{d}	287.67±7.17^{a}	76.87±5.9^{c}	123.33±8.50^{b}
HDL(mg/dL)	36.3±1.85^{a}	21.43±1.3^{d}	33.07±1.2^{b}	26±0.90^{c}
LDL(mg/dL)	32.15±2.5^{d}	43.2±1.24^{a}	36.88±1.8^{c}	39.76±4.77^{b}

The data are presented as mean ± standard deviation (SD). Group I serves as the control group, Group II includes diabetic rats that received no treatment, Group III consists of diabetic rats administered stevia, and Group IV includes diabetic rats treated with sucralose. In each row, values sharing the same letter indicate no statistically significant difference, while different letters represent statistically significant variations.

Effect of Stevia and Sucralose on Oxidative Stress Markers:

As shown in Table 5, malondialdehyde (MDA) levels, an indicator of lipid peroxidation, were markedly elevated in diabetic rats and decreased progressively in the sucralose-treated, stevia-treated, and control groups ($P < 0.05$). Conversely, the antioxidant enzymes superoxide dismutase (SOD) and catalase (CAT) showed significantly reduced activity in the diabetic group, with gradual improvements seen in the sucralose and stevia groups, and the highest enzyme activities detected in the control group. All differences among groups were statistically significant.

Table 5: Effects of stevia (400 mg/kg b.w) and sucralose (15 mg/Kg b.w) on oxidative stress markers in STZ-induced liver damage in male albino rats.

	Group I	Group II	Group III	Group IV
MDA(nmol/mg protein)	115±4.47^{d}	197,33±3.61^{a}	161.33±6.28^{c}	176.83±4.99^{b}
SOD(U/mg protein)	49.7±0.97^{a}	21.43±0.90^{d}	33.37±2.29^{b}	29.3±0.82^{c}
CAT(nmol/mg protein)	27.5±1.97^{a}	11.77±0.98^{c}	16.53±2.13^{b}	16.73±0.72^{b}

The data are presented as mean ± standard deviation (SD). Group I serves as the control group, Group II includes diabetic rats that received no treatment, Group III consists of diabetic rats administered stevia, and Group IV includes diabetic rats treated with sucralose. In each row, values sharing the same letter indicate no statistically significant difference, while different letters represent statistically significant variations.

Effect of Stevia and Sucralose on Hepatic miR-122 Expression:

Figure 1 demonstrates a marked upregulation of hepatic miR-122 expression in diabetic rats compared to all other groups ($P < 0.001$). The pattern of expression followed this order: diabetic > diabetic + sucralose > diabetic + stevia > control. Additionally, Figure 2 reveals a strong positive correlation between serum glucose levels and hepatic miR-122 expression, whereas Figure 3 shows a significant negative correlation between insulin levels and miR-122 expression. Rats with lower insulin secretion exhibited increased expression of miR-122. Treatment with non-caloric sweeteners improved insulin levels and concurrently reduced miR-122 expression. These results suggest that miR-122 could serve as a molecular indicator of hepatic dysfunction associated with diabetes, exhibiting an inverse relationship with insulin activity.

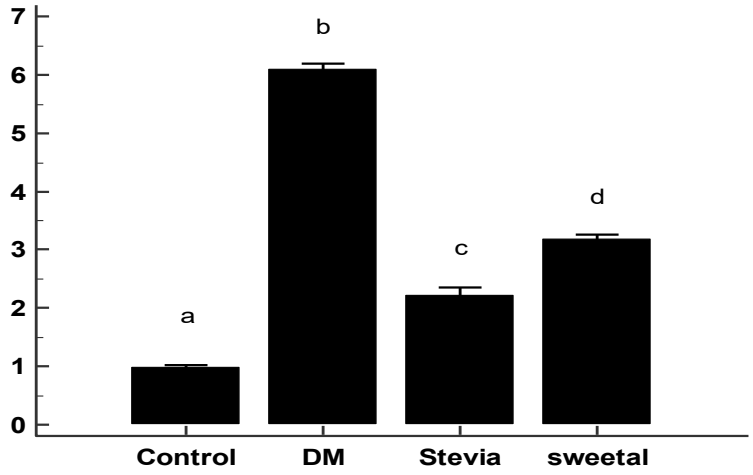

Fig.1: mRNA 122 gene expression level in different studied groups.

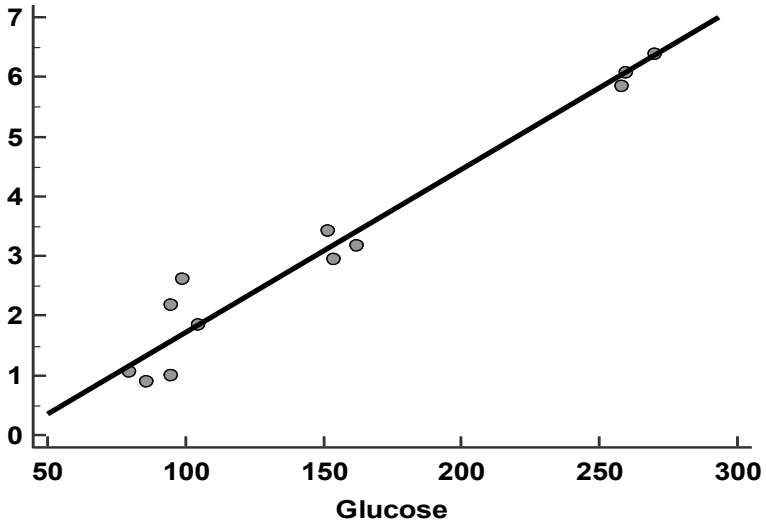

Fig.2: Correlation between blood glucose levels and hepatic miRNA-122 expression.

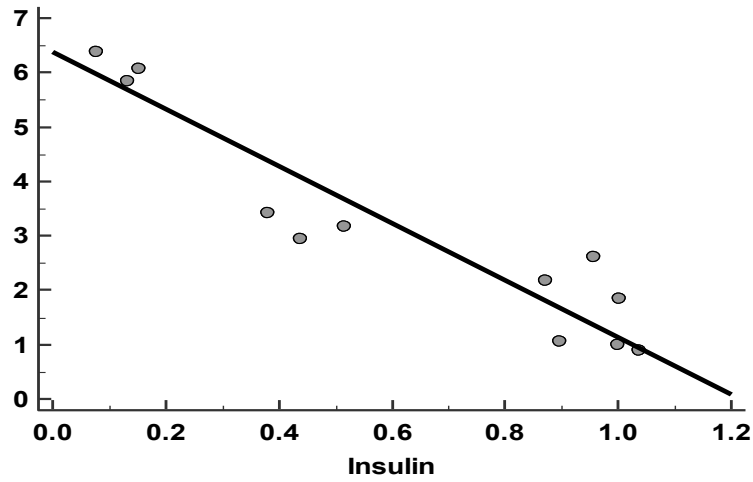

Fig.3: Correlation between blood insulin levels and hepatic miRNA-122 expression.

DISCUSSION

Diabetes mellitus is marked by increased blood glucose concentrations and is frequently associated with heightened oxidative stress., which contributes significantly to the development of diabetic complications. This stress arises primarily from the overproduction of reactive oxygen species (ROS), resulting from disrupted glucose metabolism and mitochondrial dysfunction (Giacco & Brownlee, 2020). The liver, being a central metabolic organ, is especially susceptible to damage under diabetic conditions due to lipid accumulation and increased oxidative load (Sinha *et al.,* 2021).

In this study, diabetic rats exhibited clear signs of metabolic disruption, including hyperglycemia and reduced insulin levels. These effects are consistent with streptozotocin's (STZ) known ability to impair pancreatic β-cells (Szkudelski, 2021). Interestingly, treatment with stevia and sucralose significantly restored insulin levels and reduced blood glucose, suggesting their role in modulating glucose metabolism. This effect may stem from their antioxidant potential, enhancement of β-cell function, and regulation of hepatic gluconeogenesis (Fuchs *et al.,* 2020 and Barakat *et al*.,2023).

The increased activities of ALT and AST detected in diabetic rats indicate liver damage, which was notably improved upon administration of stevia and sucralose. These changes were reversed upon treatment with stevia and sucralose, highlighting their protective influence on liver function. Stevia's bioactive compounds are known to stabilize liver membranes and reduce oxidative stress, while sucralose may exert indirect hepatoprotective effects through its limited metabolic processing (Elbandy *et al.,* 2022; Moeini *et al.,* 2020).

Disturbances in lipid profile were evident, characterized by elevated cholesterol, triglycerides, and LDL levels, accompanied by a reduction in HDL, which are hallmark features of diabetes-related dyslipidemia. These imbalances likely reflect insulin deficiency and impaired lipid metabolism (Al-Suhaimi & Shehzad, 2021). Treatment with stevia and sucralose helped normalize lipid levels, possibly by activating nuclear receptors such as PPAR-α and PPAR-γ, which regulate lipid synthesis and breakdown (Khan *et al.,* 2023).

Oxidative stress markers were also significantly altered in the diabetic group, elevated MDA levels alongside decreased SOD and CAT enzyme activities pointed to increased oxidative damage. Supplementation with stevia and sucralose ameliorated these effects, suggesting an upregulation of antioxidant defenses and suppression of ROS formation (Bashir *et al.,* 2022; Wang *et al.,* 2021).

MiR-122 is a key regulator of hepatic gene expression, contributing significantly to lipid homeostasis and inflammation-related signaling.. In the diabetic rats of this study, miR-122 was markedly upregulated, aligning with previous findings that link elevated glucose and oxidative stress to increased miR-122 expression (Zhang *et al.,* 2021). This upregulation is known to worsen hepatic lipid accumulation and insulin resistance (Xiao *et al.,* 2023).

Using stevia and sucralose, the levels of miR-122 were significantly reduced. This suggests that these non-caloric sweeteners not only improve metabolic markers but may also exert regulatory effects at the molecular level, possibly through antioxidant mechanisms (Koyani *et al.,* 2020). A strong positive correlation was observed between blood glucose levels and hepatic miRNA-122 expression, indicating that as glucose concentration increases, a proportional elevation in miRNA-122 expression occurs. This finding suggests that hyperglycemia is associated with upregulation of miR-122, indicating its potential role in the pathophysiology of diabetic liver injury. Downregulation of miR-122 has been shown to improve insulin responsiveness and reduce liver fat accumulation (Li *et al.,* 2022), suggesting its role as a therapeutic candidate in diabetic liver disease. In this study, hepatic

miR-122 levels were inversely correlated with insulin concentrations, with higher miR-122 expression observed in insulin-deficient diabetic rats. Therefore, treatment with non-caloric sweeteners improved insulin levels and concurrently decreased miR-122 expression. This suggests an inverse regulatory relationship between insulin activity and miR-122 expression, highlighting its potential role as a molecular indicator of liver dysfunction under diabetic conditions.

Conclusion:

Stevia and sucralose improved glucose metabolism, liver function, and oxidative balance in the STZ-treated rats. Their impact was linked to the downregulation of hepatic miR-122, suggesting a molecular mechanism behind their protective role. Notably, Stevia exerted more pronounced beneficial effects than sucralose, highlighting its superior potential as a natural non-caloric sweetener. These findings support the potential of non-caloric sweeteners as adjunctive agents in managing diabetic liver complications.

Declarations:

Ethical Approval: The study was conducted according to approval No. 0018122017/ Certificate no.1017 from the Research Ethics Committee of the Faculty of Medicine, Benha University

Competing interests: The authors have no competing interests to declare that are relevant to the content of this article. **Authors' Contributions:** I hereby verify that all authors mentioned on the title page have made substantial contributions to the conception and design of the study, have thoroughly reviewed the manuscript, confirm the accuracy and authenticity of the data and its interpretation, and consent to its submission.

Funding: This work has received no external funding.analysis, and manuscript. **Acknowledgments:** Not applicable.

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ARABIC SUMMARY

الدور الوقائي لاثنين من المحليات الخالية من السعرات الحرارية (ستيفيا وسكرالوز) ضد تلف الكبد في الفئران المصابة بداء السكري

دعاء اسماعيل محمد محمود[1]؛ ياسمين محمد مرعي[2]؛ أفنان ابراهيم الجندي[3] وعزة محمد عبد الرحمن مرعي[1]

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[2]قسم الكيمياء الحيوية والبيولوجيا الجزيئية، كلية الطب، جامعة بنها، القليوبية، مصر.

[3]قسم الفسيولوجيا، كلية الطب، جامعة بنها، القليوبية، مصر.

يُعد مرض السكري من الأمراض الأيضية المزمنة التي تؤدي إلى ارتفاع مستويات السكر في الدم نتيجة لخلل في إفراز الإنسولين، أو في وظيفته، أو كليهما معًا. يهدف هذا البحث إلى تقييم التأثير الوقائي للكبد لكل من المُحلّيين غير السُّعريين: الستيفيا، المُستخلص من مصادر نباتية طبيعية، والسكرالوز، المُركب كيميائيًا، وذلك في فئران أُصيبت بالسكري باستخدام مادة الستربتوزوتوسين. كما يتناول البحث العلاقة بين استخدام هذه المُحلّيات وتعبير الجين الخاص بالميكرو (miR-122)، وهو مؤشر جزيئي أساسي مرتبط بوظائف الكبد وتنظيم توازن الدهون في الجسم.

تم توزيع 28 فأرًا أبيض بالغًا من نوع ألبينو عشوائيًا إلى أربع مجموعات (عدد كل مجموعة = 7): مجموعة تحكم سليمة، مجموعة مصابة بالسكري غير معالجة، ومجموعتان مصابتان بالسكري عولجتا إحداهما بالستيفيا (400 ملغم/كغم من وزن الجسم) والأخرى بالسكرالوز (15 ملجم/كجم من وزن الجسم) لمدة أربعة أسابيع. أظهرت المعالجة بكلا المُحلّيين انخفاضًا ملحوظًا في مستويات سكر الدم، وإنزيمات الكبد (ALT وAST)، والكوليسترول، والدهون الثلاثية، وLDL، والمالونديالدهيد (MDA). وفي المقابل، حدث تحسن ملحوظ في مستويات الإنسولين، وإنزيمات مضادات الأكسدة (SOD وCAT). وHDL. علاوة على ذلك، لوحظ انخفاض واضح في تعبير miR-122 لدى المجموعة السكرية غير المعالجة، مع عودة جزئية في التعبير بعد استخدام المُحلّيين، مما يشير إلى ارتباطه بعملية تعافي الكبد.

وبالتالي، أظهر كل من الستيفيا والسكرالوز تأثيرًا وقائيًا للكبد في الفئران المصابة بالسكري، حيث كان تأثير الستيفيا أكثر وضوحًا، ويُحتمل أن يكون ذلك مرتبطًا بتأثيره على تعبير miR-122. وتبرز هذه النتائج إمكانيتهما في دعم صحة الكبد في ظل الظروف السكرية.