Available *online* at : http://ejurnal.stikesprimanusantara.ac.id/

Jurnal Kesehatan

| ISSN (Print) 2085-7098 | ISSN (Online) 2657-1366 |

Effects of Stevia Leaf Extract on Blood Glucose and SOD Activity in Hyperglycemic Rats

Salsa Billa Pratami Zoni[1], *Eti Yerizel*[2], *Rahmatini*[3]
[1]Medical Study Program, Faculty of Medicine, Universitas Andalas, Padang, Indonesia
[2]Departement of Biochemistry, Faculty of Medicine, Universitas Andalas, Padang, Indonesia
[3]Departement of Pharmacology, Faculty of Medicine, Universitas Andalas, Padang, Indonesia

ARTICLE INFORMATION

Received: 08 January 2026
Revised: 25 January 2026
Accepted: 30 march 2026
Available online: 31 March 2026

KEYWORDS

Stevia rebaudiana, oxidative stress, hyperglycemia, blood glucose, Superoxide Dismutase (SOD)

CORRESPONDING AUTHOR

***Corresponding author, email:**

billacaca556@gmail.com

ABSTRACT

Background: Hyperglycemia is characterized by elevated blood glucose levels and may induce oxidative stress through excessive production of reactive oxygen species (ROS) that exceed the capacity of antioxidant defense systems. Stevia rebaudiana leaf extract contains antihyperglycemic and antioxidant compounds, such as polyphenols and steviol glycosides. **Objectives:** This study aimed to investigate the effects of Stevia leaf extract on blood glucose levels and superoxide dismutase (SOD) enzyme activity in hyperglycemic rats (Rattus norvegicus).**Methods:** This experimental study involved 35 rats divided into a negative control group (K−), a positive control group (K+), and three treatment groups (P1, P2, P3) administered Stevia rebaudiana extract at doses of 100, 200, and 400 mg/kg body weight. Hyperglycemia was induced using alloxan. Blood glucose levels were measured using a digital analyzer, while SOD enzyme activity was determined colorimetrically. The data obtained were analyzed using the Kruskal–Wallis test, followed by the Mann–Whitney test. **Results:** The mean blood glucose levels in groups K−, K+, P1, P2, and P3 were 93.2 mg/dL, 371.08 mg/dL, 134.3 mg/dL, 130.42 mg/dL, and 113.22 mg/dL, respectively. The mean SOD enzyme activity in groups K−, K+, P1, P2, and P3 were 14.92 U/mL, 13.53 U/mL, 14.57 U/mL, 14.74 U/mL, and 14.93 U/mL, respectively. The P3 group, which received a dose of 400 mg/kg body weight, showed the most significant effects in lowering blood glucose levels and increasing SOD enzyme activity. **Conclusion:** Stevia rebaudiana leaf extract significantly lowered glucose levels in hyperglycemic rats and tended to increase superoxide dismutase activity, although this increase in SOD activity did not show a statistically significant difference.

INTRODUCTION (CHAPTER)

Hyperglycemia is a metabolic condition characterized by elevated blood glucose levels resulting from impaired insulin secretion, impaired insulin action, or a combination of both.[1] Hyperglycemia is a hallmark of diabetes mellitus, a chronic metabolic disorder whose prevalence is rapidly increasing worldwide. According to the International Diabetes Federation, in 2021 there were more than 537 million adults worldwide living with diabetes, with projections indicating an increase.[2]

Glucose dysregulation in hyperglycemia begins with a decrease in insulin sensitivity in peripheral tissues, particularly skeletal muscle and adipose tissue, leading to reduced GLUT-4 translocation and sustained hepatic glucose production via gluconeogenesis, thereby maintaining high circulating glucose levels.[3] Chronic hyperglycemia activates various abnormal metabolic pathways, including the formation of advanced glycation end products and the activation of protein kinase C, which significantly increases the production of reactive oxygen species beyond the capacity of the endogenous antioxidant system.[4] his excessive oxidative stress subsequently reduces the activity of key antioxidant enzymes such as superoxide dismutase, contributing to pancreatic β-cell dysfunction, impaired insulin secretion, and increased insulin resistance that accelerates the progression of diabetes mellitus.[5]

Current diabetes management focuses on glycemic control through lifestyle modifications and pharmacological therapy; however, the challenges of long-term adherence and the need for lifelong medication use underscore the importance of developing complementary therapies based on natural products.[1] Stevia rebaudiana is a non-caloric natural sweetener with a glycemic index of zero that contains steviol glycosides and flavonoids, which have antihyperglycemic effects via insulin-like mechanisms as well as antioxidant activity by increasing endogenous antioxidant enzymes, including superoxide dismutase.[6], [7] Previous studies, including Ahmad et al. (2018), have shown that Stevia rebaudiana leaf extract significantly reduces blood glucose levels in diabetic rat models. However, the existing evidence places greater emphasis on.[8] However, the currently available evidence primarily focuses on glycemic control outcomes without a simultaneous assessment of parameters related to oxidative stress, particularly superoxide dismutase (SOD) activity as the primary endogenous antioxidant enzyme under hyperglycemic conditions. Given that hyperglycemia triggers excessive production of reactive oxygen species that contribute to β-cell dysfunction and insulin resistance, an integrated evaluation of glycemic control and antioxidant status is essential. Therefore, this study aims to elucidate the effects of Stevia rebaudiana leaf extract at doses of 100, 200, and 400 mg/kg body weight on blood glucose levels and SOD activity in hyperglycemic rats, as a scientific basis for the development of natural product-based adjunct therapies for diabetes management.

DOI: http://dx.doi.org/10.35730/jk.v17i1.1603

METHOD

Research Design and Research Sample

This study was conducted as a pure experimental study involving the administration of stevia leaf extract to Wistar rats. The study design used a post-test control-only design with a completely randomized design (CRD) approach. Adult male Wistar rats were randomly divided into five experimental groups, each consisting of seven rats, with five receiving the treatment and two set aside as reserves to anticipate potential subject loss during the study.

Materials

The materials used in this experimental study included Stevia rebaudiana leaves, male Wistar rats that met the inclusion criteria, laboratory-grade alcohol, rat chow, cage cleaning solution, rat blood samples, alloxan monohydrate, 96% ethanol, chloroform, sodium chloride (NaCl), distilled water, glucose test kits, superoxide dismutase (SOD) activity test kits, and control serum.

Tools and Instruments

The equipment and instruments used in this study included animal cages, animal scales, a digital analytical balance (Ohaus), a digital spectrophotometer, a centrifuge (Nasco), 100 µL micropipettes, test tube racks and test tubes, microcuvettes, measuring cups, a vortex mixer, a water bath, an oral gavage device, vial tubes, microtubes, blood collection containers, microhematocrit sets, personal protective equipment (gloves and masks), cotton swabs and alcohol swabs, surgical instruments (scissors and scalpels), syringes, a glucometer (Accu-Chek) with compatible test strips, a blender, a rotary evaporator, and a Mikrolab 300 analyzer.

Research Procedures

Animal Housing and Experimental Treatment

Male Wistar rats (Rattus norvegicus) aged 2 to 3 months and weighing between 200 and 250 grams were used as test subjects. Prior to the experiment, the animals were acclimatized for seven days in conventional laboratory cages equipped with water bottles, standard feed, and rice husk bedding. An intraperitoneal injection of alloxan at a dose of 120 mg/kg body weight was used to induce hyperglycemia. This dose was administered in 0.2 mL.

Preparation and Administration of Stevia Leaf Extract

Fresh stevia leaves (Stevia rebaudiana) were washed under running water to remove surface contaminants. The leaves were then air-dried at room temperature in a well-ventilated area protected from direct sunlight until completely dry. The dried leaves were ground into a fine powder using a blender and sieved to ensure uniform particle size. The powder is then macerated in 96% ethanol for 72 hours. Filtration is performed using flannel cloth to obtain the filtrate. The resulting filtrate is then concentrated using a rotary evaporator to produce a thick extract. Distilled water is used to prepare a homogeneous suspension

DOI: http://dx.doi.org/10.35730/jk.v17i1.1603

suitable for oral administration. The stevia leaf extract is administered orally once daily for 14 consecutive days using the oral gavage method. The administered volume was adjusted to 1% of body weight. Rats weighing 200 grams received a total volume of 2 mL. The animals were carefully restrained, and the extract was slowly administered along the edge of the palate into the esophagus

Blood Serum Collection

Blood samples were collected from Wistar rats on day 14 following administration of stevia leaf extract. Approximately 3 mL of blood was obtained via the intraorbital vein using a hematocrit glass tube. The collected blood was then transferred to a blood collection tube and centrifuged at 3,000 rpm for 10 minutes to separate the serum from the blood cells.

The serum fraction was carefully collected using a micropipette and transferred into a microtube. These serum samples were subsequently used for the analysis of blood glucose levels and superoxide dismutase (SOD) enzyme activity.

Blood Glucose Measurement

Blood glucose levels were measured on day 7 after alloxan induction using a portable glucometer with glucose test strips. Blood samples were collected from the lateral tail vein after rats were fasted for 8–12 hours. Tail tips were disinfected with 70% alcohol prior to puncture. Approximately one drop of blood was obtained and immediately applied to the glucose strip inserted into the glucometer. Glucose values were displayed on the device screen within 5 seconds. Rats presenting blood glucose levels greater than 135 mg/dL were classified as hyperglycemic.[9]

Blood glucose levels were measured again on day 14 after administration of stevia leaf extract to assess the effectiveness of the intervention. Blood glucose concentrations were determined using a colorimetric method. Serum samples obtained after centrifugation were used for analysis. Reaction mixtures were prepared by adding 10 µL of distilled water as a blank, 10 µL of serum as a sample, or 10 µL of glucose standard for calibration to separate test tubes. A total of 1,000 µL of glucose reagent was added to each tube.

The reaction mixtures are thoroughly mixed until homogeneous and then incubated for 20 minutes at room temperature or for 10 minutes at 37°C. Absorbance measurements are performed using a Microlab 300 spectrophotometer at a wavelength of 546 nm. Blood glucose concentration is determined by comparing the sample absorbance values to the standard absorbance according to the following equation:

$$\text{Blood glucose (mg/dL)} = \frac{\text{Sample absorbance}}{\text{Standard absorbance}} \times \text{Standard concentration}$$

Measurement of Serum Superoxide Dismutase (SOD) Activity

DOI: http://dx.doi.org/10.35730/jk.v17i1.1603

Serum samples obtained after centrifugation were used to determine superoxide dismutase (SOD) activity. The analysis was performed using a commercial Total Superoxide Dismutase (T-SOD) assay kit based on a colorimetric method. This assay measures SOD activity indirectly by inhibiting the formation of the formazan dye produced during the reaction.

Test wells were prepared by adding 20 µL of serum, while control and blank wells were prepared using distilled water and enzyme buffer according to the assay protocol. Enzyme working solution and substrate solution were added to each well in predetermined volumes. All reaction components were thoroughly mixed until homogeneous. Incubation was performed at 37°C for 20 minutes to allow the enzymatic reaction to proceed. Optical density was then measured using a microplate reader at a wavelength of 450 nm.

The percentage inhibition (i%) was calculated using the absorbance values of the control, sample, and blank according to the following equation:

$$i\% = \frac{(A_{\text{control}} - A_{\text{blank}}) - (A_{\text{sample}} - A_{\text{blank}})}{A_{\text{control}} - A_{\text{blank}}} \times 100\%$$

Serum SOD activity was expressed as units per milliliter (U/mL) and calculated using the following formula:

$$\text{SOD activity (U/mL)} = \frac{i\%}{50\%} \times \frac{V_1}{V_2} \times f$$

where i% represents the percentage of inhibition, V_1 is the total reaction volume (240 µL), V_2 is the sample volume (20 µL), and f is the dilution factor.

Data Analysis

In the data analysis for this study, nonparametric statistical tests were used. The Shapiro-Wilk test was used to assess the normality of blood glucose levels and superoxide dismutase (SOD) activity in each group prior to comparative analysis; data were considered normally distributed if the p-value was greater than 0.05.

The results of the Shapiro-Wilk test for SOD activity and blood glucose levels showed that at least one group had a p-value less than 0.05, indicating a non-normal data distribution. Normality could not be achieved despite efforts to modify the data. Therefore, the Kruskal–Wallis test was used to further analyze the variation in blood glucose levels and SOD activity across groups. Although there were no statistically significant differences in SOD activity across all groups (p = 0.413), the Kruskal–Wallis analysis revealed statistically significant differences in blood glucose levels among the study groups (p = 0.001). The Mann-Whitney U test was then used for post hoc analysis to identify specific differences among these groups.

DOI: http://dx.doi.org/10.35730/jk.v17i1.1603

RESULT AND DISCUSSION

RESULT

Blood Glucose Levels

The mean serum blood glucose levels of experimental rats after 14 days of treatment is presented in Table 1.

Table 1. Blood Glucose Levels in each Experimental Group

Group	Mean ± SD (mg/dL)
K- (Negative Control)	93.20 ± 9.19
K+ (Positive Control)	371.08 ± 113.45
P1 (Stevia 100 mg/kgBW)	134.30 ± 16.33
P2 (Stevia 200 mg/kgBW)	130.42 ± 9.19
P3 (Stevia 400 mg/kgBW)	113.22 ± 19.63

The positive control group (K+) showed significantly higher blood glucose levels, with a mean of 371.1 ± 113.45 mg/dL, indicating successful induction of hyperglycemia, whereas the negative control group (K−) had normal blood glucose levels, with a mean of 93.2 ± 9.19 mg/dL.

Administration of *Stevia rebaudiana* leaf extract resulted in a substantial reduction in blood glucose levels across all treatment groups. The P1 group (100 mg/kg body weight) demonstrated a mean blood glucose level of 134.3 ± 16.33 mg/dL, while the P2 group (200 mg/kg body weight) showed a mean of 130.4 ± 9.19 mg/dL. The P3 group (400 mg/kg body weight) showed the greatest reduction, with an average blood glucose level of 113.2 ± 19.63 mg/dL, which was close to the values in the negative control group. With a tendency for a stronger glucose-lowering effect at higher doses, these results indicate that stevia leaf extract successfully lowers blood glucose levels in hyperglycemic rats.

SOD Enzyme Activity

The mean serum superoxide dismutase (SOD) activity of experimental rats after 14 days of treatment is presented in Table 2.

Table 2. Serum SOD Activity in Each Experimental Group

Group	Mean ± SD (mg/dL)
K- (Negative Control)	14.92 ± 0.31
K+ (Positive Control)	13.53 ± 2.20

DOI: http://dx.doi.org/10.35730/jk.v17i1.1603

P1 (Stevia 100 mg/kgBW)	14.57 ± 0.53
P2 (Stevia 200 mg/kgBW)	14.74 ± 0.22
P3 (Stevia 400 mg/kgBW)	14.93 ± 0.12

The positive control group (K+) had a slightly lower mean value of 13.53 ± 2.20, indicating a decrease in antioxidant activity under hyperglycemic conditions, whereas the negative control group (K−) had a mean SOD activity of 14.92 ± 0.31. After treatment with Stevia rebaudiana leaf extract, SOD activity levels in all treatment groups became similar. The P1 group (100 mg/kg body weight) showed a mean SOD activity of 14.57 ± 0.53, the P2 group (200 mg/kg body weight) exhibited 14.74 ± 0.22, and the P3 group (400 mg/kg body weight) demonstrated 14.93 ± 0.12. Overall, SOD activity in the treatment groups tended to be similar to that of the negative control group.

DISCUSSION

Effect of Stevia Leaf Extract on Blood Glucose Levels in Hyperglycemic Rats

This study demonstrated that administration of Stevia rebaudiana leaf extract significantly reduced blood glucose levels in alloxan-induced hyperglycemic rats ($p = 0.001$; $p < 0.05$). The positive control group (K+) exhibited a significant increase in blood glucose levels compared to the negative control group (K−), confirming the effectiveness of alloxan as a diabetogenic agent through the selective destruction of pancreatic β-cells.[10]

.Alloxan causes an increase of reactive oxygen species (ROS) when it enters pancreatic β-cells through the GLUT-2 transporter.[10] he most deadly type of ROS, hydroxyl radicals (OH•), cause oxidative damage to proteins, DNA, and cell membranes, which results in β-cell necrosis and death.[11] This damage leads to a significant reduction in insulin secretion and, consequently, hyperglycemia. Furthermore, excessive production of reactive oxygen species (ROS) that exceeds the capacity of endogenous antioxidants triggers oxidative stress, which disrupts insulin signaling through increased phosphorylation of IRS-1/IRS-2, inhibits the activation of PI3K and Akt, and disrupts GLUT-4 translocation, ultimately leading to insulin resistance and persistent hyperglycemia.[4], [12] These mechanisms are consistent with findings reported by Ibrahim RM et al. (2023) and Tataru I et al. (2025), who observed significant hyperglycemia, reduced insulin levels, pancreatic β-cell damage, and increased oxidative stress in alloxan-induced rats.[13], [14]

Administration of stevia leaf extract at doses of 100, 200, and 400 mg/kg body weight showed a gradual decrease in blood glucose levels compared to the positive control group, with the most significant decrease occurring at the 400 mg/kg body weight dose (P3), which approached

DOI: http://dx.doi.org/10.35730/jk.v17i1.1603

normal blood glucose levels. This indicates a dose-response antihyperglycemic effect, in which the 400 mg/kg body weight dose was the most effective. These results are consistent with a meta-analysis conducted by Chowdhury et al. (2022), which reported that stevia leaf extract at a dose of 400 mg/kg body weight provided the most optimal blood glucose-lowering effect.[15]

The antihyperglycemic effects of stevia are attributed to its bioactive compounds, particularly steviol glycosides and polyphenols. Polyphenols possess antioxidant activity that helps reduce oxidative stress and protect pancreatic β-cells, thereby supporting insulin secretion.[16] Additionally, steviol glycosides exert an insulin-mimetic effect by enhancing insulin sensitivity through the activation of tyrosine kinase receptors and the PI3K/Akt pathway, which leads to GLUT-4 translocation and increased cellular glucose uptake..[17], [18]

Effect of Stevia Leaf Extract on Superoxide Dismutase (SOD) Activity in Hyperglycemic Rats

This study indicates that administration of Stevia rebaudiana leaf extract tends to increase superoxide dismutase (SOD) activity in alloxan-induced hyperglycemic rats, although no statistically significant differences were found among the treatment groups. A dose-dependent trend was observed, with the highest mean SOD activity observed in the 400 mg/kgBW group (P3), which was slightly higher than that of the negative control group..

The lack of statistical significance observed may be attributed to the biological characteristics of SOD as an intracellular enzyme. SOD1 (Cu/Zn-SOD) is primarily localized in the cytosol, whereas SOD2 (Mn-SOD) is found within the mitochondrial matrix; consequently, serum SOD activity does not accurately reflect intracellular antioxidant status.[19] In the absence of significant tissue damage, only a small amount of SOD enters the circulation, resulting in relatively low, stable serum SOD levels with limited biological variability.[20], [21] Therefore, treatment-related changes in SOD activity may not be strongly reflected in serum measurements.

The increase in SOD activity observed in the group receiving stevia treatment is likely related to the bioactive compounds in stevia leaf extract, particularly steviol glycosides and polyphenols, which exhibit antioxidant effects both directly and indirectly.[22], [23] Direct antioxidant activity involves the scavenging of free radicals through the donation of electrons or hydrogen, whereas indirect mechanisms include the inhibition of ROS-producing enzymes such as NADPH oxidase and xanthine oxidase, as well as the modulation of antioxidant gene expression via the Nrf2 signaling pathway.[18], [24]

DOI: http://dx.doi.org/10.35730/jk.v17i1.1603

Polyphenols also chelate transition metal ions such as Fe^{2+} and Cu^{2+}, which are involved in ROS generation through the Haber–Weiss and Fenton reactions, thereby preventing the formation of highly reactive radicals and protecting cells from oxidative damage.[16], [24] Steviol glycosides have been reported to enhance the activity and expression of antioxidant enzymes, including SOD and catalase, through activation of the PI3K/Akt signaling pathway.[6], [25] Moreover, steviol glycoside derivatives such as rebaudioside A activate the Nrf2–ARE pathway, promoting nuclear translocation of Nrf2 and upregulation of endogenous antioxidant genes such as SOD-1, HO-1, and NQO1, thereby strengthening cellular defense against oxidative stress.[25], [26] These findings are consistent with the meta-analysis by Papaefthimiou et al. (2023), which reported that stevia leaf extract enhances antioxidant defense by increasing SOD, catalase, and GPx activities while reducing oxidative damage biomarkers.[23]

Conclusion

1. Administration of stevia leaf extract significantly reduced blood glucose levels in alloxan-induced hyperglycemic rats, with a dose of 400 mg/kg body weight demonstrating the most pronounced glucose-lowering effect.
2. Administration of stevia leaf extract showed a tendency to increase superoxide dismutase (SOD) enzyme activity in alloxan-induced hyperglycemic rats; however, no statistically significant differences were observed among groups, with the 400 mg/kg body weight dose exhibiting the greatest increase in SOD activity.

REFERENCES

[1] Perkumpulan Endokrinologi Indonesia, *Pedoman Pengelolaan dan Pencegahan Diabetes Melitus Tipe 2 Dewasa Di Indonesia 2021*, 1st ed. Perkumpulan Endokrinologi Indonesia, 2021. Accessed: Mar. 08, 2025. [Online]. Available: https://pbperkeni.or.id/wp-content/uploads/2021/11/22-10-21-Website-Pedoman-Pengelolaan-dan-Pencegahan-DMT2-Ebook.pdf

[2] International Diabetes Federation, *International Diabetes Federation Diabetes Atlas 10th edition*, 10th ed. 2021. [Online]. Available: www.diabetesatlas.org

[3] S. Jiang, J. L. Young, K. Wang, Y. Qian, and L. Cai, "Diabetic-induced alterations in hepatic glucose and lipid metabolism: The role of type 1 and type 2 diabetes mellitus (Review)," Aug. 01, 2020, *Spandidos Publications*. doi: 10.3892/mmr.2020.11175.

[4] P. González, P. Lozano, G. Ros, and F. Solano, "Hyperglycemia and Oxidative Stress: An Integral, Updated and Critical Overview of Their Metabolic Interconnections," Jun. 01, 2023, *Multidisciplinary Digital Publishing Institute (MDPI)*. doi: 10.3390/ijms24119352.

[5] N. Eguchi, N. D. Vaziri, D. C. Dafoe, and H. Ichii, "The role of oxidative stress in pancreatic β cell dysfunction in diabetes," Feb. 02, 2021, *MDPI AG*. doi: 10.3390/ijms22041509.

[6] C. Prata *et al.*, "Glycosides from Stevia Rebaudiana Bertoni Possess Insulin-Mimetic and Antioxidant Activities in Rat Cardiac Fibroblasts," *Oxid Med Cell Longev*, Aug. 2017, doi: 10.1155/2017/3724545.

[7] I. A. P. Widiasriani, N. N. W. Udayani, G. A. P. Triansyah, N. P. E. M. K. Dewi, N. L. W. E. Wulandari, and A. A. S. S. Prabandari, "Artikel Review: Peran Antioksidan Flavonoid dalam

Menghambat Radikal Bebas," *Journal Syifa Sciences and Clinical Research (JSSCR)*, vol. 6, no. 2, pp. 188–197, 2024, doi: 10.37311/jsscr.v6i2.27055.
[8] U. Ahmad and R. S. Ahmad, "Anti Diabetic Property of Aqueous Extract of Stevia Rebaudiana Bertoni Leaves in Streptozotocin-Induced Diabetes in Albino Rats," *BMC Complement Altern Med*, vol. 18, no. 1, pp. 2–11, Jun. 2018, doi: 10.1186/s12906-018-2245-2.
[9] Y. Jiwintarum, I. Eliza, E. Yustin Tatontos, and J. Analis Kesehatan Politeknik Kesehatan Kemenkes Mataram, "Tea Bag Biji Alpukat (Persea Americana Mill) terhadap Kadar Gula Darah Tikus Putih (Rattus Norvegicus)," 2017.
[10] O. M. Ighodaro, A. M. Adeosun, and O. A. Akinloye, "Alloxan-Induced Diabetes, a Common Model for Evaluating the Glycemic-Control Potential of Therapeutic Compounds and Plants Extracts in Experimental Studies," Jan. 01, 2017, *Elsevier B.V.* doi: 10.1016/j.medici.2018.02.001.
[11] R. Vieira *et al.*, "Sugar-lowering drugs for type 2 diabetes mellitus and metabolic syndrome—strategies for in vivo administration: Part-II," Sep. 01, 2019, *MDPI*. doi: 10.3390/jcm8091332.
[12] S. Tangvarasittichai, "Oxidative stress, insulin resistance, dyslipidemia and type 2 diabetes mellitus," *World J Diabetes*, vol. 6, no. 3, p. 456, 2015, doi: 10.4239/wjd.v6.i3.456.
[13] R. M. Ibrahim, H. M. Abdelhafez, S. A. E. M. EL-Shamy, F. A. Eid, and A. Mashaal, "Arabic gum ameliorates systemic modulation in Alloxan monohydrate-induced diabetic rats," *Sci Rep*, vol. 13, no. 1, Dec. 2023, doi: 10.1038/s41598-023-31897-x.
[14] I. Tătaru *et al.*, "Multilevel Assessment of Glycemic, Hormonal, and Oxidative Parameters in an Experimental Diabetic Female Rat Model," *Biomedicines*, vol. 13, no. 4, Apr. 2025, doi: 10.3390/biomedicines13040922.
[15] A. I. Chowdhury, M. Rahanur Alam, M. M. Raihan, T. Rahman, S. Islam, and O. Halima, "Effect of Stevia Leaves (Stevia Rebaudiana Bertoni) on Diabetes: A Systematic Review and Meta-Analysis of Preclinical Studies," Sep. 01, 2022, *John Wiley and Sons Inc*. doi: 10.1002/fsn3.2904.
[16] F. Caruso, S. Incerpi, J. Pedersen, S. Belli, S. Kaur, and M. Rossi, "Aromatic Polyphenol π-π Interactions with Superoxide Radicals Contribute to Radical Scavenging and Can Make Polyphenols Mimic Superoxide Dismutase Activity," Nov. 01, 2022, *MDPI*. doi: 10.3390/cimb44110354.
[17] L. Kang *et al.*, "Effects and Mechanisms of Steviol Glycosides on Glucose Metabolism: Evidence From Preclinical Studies," *Mol Nutr Food Res*, vol. 69, no. 10, p. e70014, May 2025, doi: https://doi.org/10.1002/mnfr.70014.
[18] A. M. Orellana-Paucar, "Steviol Glycosides from Stevia rebaudiana: An Updated Overview of Their Sweetening Activity, Pharmacological Properties, and Safety Aspects," Feb. 01, 2023, *MDPI*. doi: 10.3390/molecules28031258.
[19] S. Wahjuni, *Superoksida Dismutase (SOD) Sebagai Prekursor Antioksidan Endogen Pada Stress Oksidatif*, 1st ed. Bali, 2015. Accessed: Mar. 21, 2025. [Online]. Available: https://repositori.unud.ac.id/protected/storage/upload/repositori/79c4b32a65502f63e70df23dd224f476.pdf
[20] M. Zheng, Y. Liu, G. Zhang, Z. Yang, W. Xu, and Q. Chen, "The Applications and Mechanisms of Superoxide Dismutase in Medicine, Food, and Cosmetics," Sep. 01, 2023, *Multidisciplinary Digital Publishing Institute (MDPI)*. doi: 10.3390/antiox12091675.
[21] M. Ściskalska, M. Ołdakowska, G. Marek, and H. Milnerowicz, "Changes in the activity and concentration of superoxide dismutase isoenzymes (Cu/zn sod, mnsod) in the blood of healthy subjects and patients with acute pancreatitis," *Antioxidants*, vol. 9, no. 10, pp. 1–16, Oct. 2020, doi: 10.3390/antiox9100948.
[22] A. Blinstrubiene, N. Burbulis, N. Juškevičiute, N. Vaitkevičiene, and R. Žukiene, "Effect of growth regulators on Stevia rebaudiana bertoni callus genesis and influence of auxin and proline to steviol glycosides, phenols, flavonoids accumulation, and antioxidant activity in vitro," *Molecules*, vol. 25, no. 12, pp. 2–15, Jun. 2020, doi: 10.3390/molecules25122759.
[23] M. Papaefthimiou, P. I. Kontou, P. G. Bagos, and G. G. Braliou, "Antioxidant Activity of Leaf Extracts from Stevia rebaudiana Bertoni Exerts Attenuating Effect on Diseased Experimental Rats:

A Systematic Review and Meta-Analysis," Aug. 01, 2023, *Multidisciplinary Digital Publishing Institute (MDPI)*. doi: 10.3390/nu15153325.

[24] S. Amin and Z. Assafa, "Peran Senyawa Polifenol dalam Mekanisme Antioksidan: Tinjauan dari Aspek Kimia Medisinal," *Jurnal Imliah Ilmu Kesehatan*, vol. 3, no. 2, p. 2025.

[25] L. Zhao *et al.*, "Stevia residue extract ameliorates oxidative stress in d-galactose-induced aging mice via Akt/Nrf2/HO-1 pathway," *J Funct Foods*, vol. 52, pp. 587–595, Jan. 2019, doi: 10.1016/j.jff.2018.11.044.

[26] Y. Wang *et al.*, "New application of the commercial sweetener rebaudioside a as a hepatoprotective candidate: Induction of the Nrf2 signaling pathway," *Eur J Pharmacol*, vol. 822, pp. 128–137, 2018, doi: https://doi.org/10.1016/j.ejphar.2018.01.020.