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THE EFFECT OF BITTER MELON (*Momordica charantia*) EXTRACT ON SUPEROXIDE DISMUTASE LEVELS AND IMMUNOHISTOCHEMICAL PROFILE IN THE LIVER OF DIABETIC RATS

Pengaruh Pemberian Ekstrak Buah pare (*Momordica charantia*) terhadap Kadar dan Profil Imunohistokimia Superoksida Dismutase pada Hati Tikus Diabetes

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Abstract

Chronic hyperglycemia in diabetes can trigger oxidative stress and reduce the activity of superoxide dismutase (SOD) as an endogenous antioxidant. Bitter melon (*Momordica charantia*) has bioactive compounds that have the potential to support the antioxidant system. This study aims to determine the effect of bitter melon extract on the levels and immunohistochemical profile of SOD in the liver tissue of diabetic rats. A total of 20 male rats were divided into four groups: normal controls, diabetic controls, and two diabetic groups given bitter melon extract at doses of 50 mg/kg BW and 100 mg/kg BW for 21 days. SOD levels were measured using the ELISA method, while the SOD profile was analyzed through immunohistochemical staining. The results showed that diabetes reduced SOD levels in the liver tissue of rats compared to the normal control group, with values of 3,873 ± 0,298 ng/mL and 1,916 ± 0,220 ng/mL, respectively. Administration of bitter melon fruit extract increased SOD levels, with a higher response at a dose of 100 mg/kg BW (3,089 ± 0,202 ng/mL), compared to 50 mg/kg BW (2,884 ± 0,272 ng/mL). Immunohistochemical analysis showed a stronger intensity of SOD staining expression in liver tissue after administration of the extract, especially at a dose of 100 mg/kg BW. Further research is needed to evaluate other antioxidant enzymes and determine varying doses to enhance the endogenous antioxidant system.

Keywords: Diabetes mellitus, immunohistochemistry, *Momordica charantia*, oxidative stress, superoxide dismutase

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Abstrak

Hiperglikemia kronis pada diabetes dapat memicu terjadinya stres oksidatif dan menurunkan aktivitas superoksida dismutase (SOD) sebagai antioksidan endogen. Buah pare (*Momordica charantia*) memiliki senyawa bioaktif yang berpotensi mendukung sistem antioksidan. Penelitian ini bertujuan untuk mengetahui pengaruh pemberian ekstrak buah pare terhadap kadar dan profil imunohistokimia SOD pada jaringan hati tikus diabetes. Sebanyak 20 tikus jantan dibagi menjadi empat kelompok, yaitu kontrol normal, kontrol diabetes, serta dua kelompok diabetes yang diberi ekstrak buah pare dosis 50 mg/kg BB dan 100 mg/kg BB selama 21 hari. Pengukuran kadar SOD menggunakan metode ELISA, sedangkan profil SOD dianalisis melalui pewarnaan imunohistokimia. Hasil penelitian menunjukkan bahwa keadaan diabetes menurunkan kadar SOD di jaringan hati tikus dibandingkan dengan kelompok kontrol normal, dengan nilai masing-masing 3,873 ± 0,298 ng/mL dan 1,916 ± 0,220 ng/mL. Pemberian ekstrak buah pare meningkatkan kadar SOD, dengan respons lebih tinggi pada dosis 100 mg/kg BB (3,089 ± 0,202 ng/mL), dibandingkan 50 mg/kg BB (2,884 ± 0,272 ng/mL). Analisis imunohistokimia menunjukkan intensitas ekspresi pewarnaan SOD yang lebih kuat pada jaringan hati setelah pemberian ekstrak, terutama dosis 100 mg/kg BB. Penelitian lanjutan diperlukan untuk mengevaluasi enzim antioksidan lainnya dan menentukan dosis pemberian yang bervariasi untuk meningkatkan sistem antioksidan endogen.

Kata kunci: Diabetes mellitus, imunohistokimia, *Momordica charantia*, stres oksidatif. superoksida dismutase.

INTRODUCTION

Diabetes mellitus is a metabolic disorder characterized by hyperglycemia, with incidence rates continuing to rise globally, including in Indonesia (IDF Diabetes Atlas, 2021). Chronic hyperglycemia can increase the formation of reactive oxygen species (ROS), which triggers oxidative stress. Uncontrolled ROS accumulation can damage cell membranes, proteins, lipids, and DNA, thereby causing damage to various body tissues, including the liver (Soviana *et al.*, 2014). The liver plays a crucial role in regulating glucose, lipid, and protein metabolism, as well as serving as a detoxification organ (Ding *et al.*, 2018).

Under hyperglycemic conditions, an imbalance between increased ROS production and the capacity of the intracellular antioxidant system leads to hepatocyte damage and impaired liver function (Halliwell & Gutteridge, 2015). One of the endogenous antioxidant enzymes involved in neutralizing ROS is superoxide dismutase (SOD), which converts superoxide radicals into more stable molecules (Ighodaro & Akinloye, 2018). However, under conditions of chronic hyperglycemia, SOD activity tends to decrease in various organs, thereby increasing tissue susceptibility to oxidative stress (Yunarsa & Adiatmika, 2018). Therefore, the administration of exogenous antioxidants is necessary to support the body's antioxidant defense system (Panova & Tatikolov, 2023).

Bitter melon contains bioactive compounds such as charantin, flavonoids, alkaloids, and saponins, which possess antioxidant and antihyperglycemic properties (Puspitasari & Choerunisa, 2021). Bitter melon extract has been reported to lower blood glucose levels and modulate the regulation of GLUT2 and GLUT4, which play a role in maintaining glucose homeostasis (Putri *et al.*, 2025). Additionally, saponins in bitter melon have been reported to increase SOD and CAT enzyme activity in the livers of diabetic rats (Jiang *et al.*, 2020). Another study by Yuniartha *et al.* (2022) showed a decrease in the number of SOD1-positive cells in rat livers as the duration of hyperglycemia increased. However, studies that simultaneously evaluate SOD levels and immunohistochemical profiles in the livers of diabetic rats following administration of bitter melon extract remain limited. Therefore, this study aims

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to determine SOD levels and profiles in the livers of diabetic rats following administration of bitter melon extract.

RESEARCH METHODS

Ethical Approval for Animal Use

All procedures involving the use of laboratory animals have been approved by the Animal Ethics Committee of the Faculty of Veterinary Medicine, Udayana University, as evidenced by Animal Ethics Approval Letter No. B/180/UN14.2.9/PT.01.04/2025.

Research Subjects

The subjects of this study were male Sprague Dawley white rats, approximately 2 months old, weighing 130–140 g. The rats were obtained from the Bio Mice and Rat laboratory animal breeding facility in Denpasar.

Study Design

This study is an experimental study using a completely randomized design (CRD), involving 20 male rats randomly assigned to four treatment groups. Three groups were induced with diabetes using streptozotocin (STZ) at a dose of 60 mg/kg body weight via intraperitoneal injection (Fatmawati, 2013), while one group served as the normal control without STZ induction. Rats were considered diabetic if their blood glucose levels were ≥200 mg/dL (Furman, 2021). Treatments were administered orally via a feeding tube at a volume of 1 mL/day for 21 days (Padang *et al.*, 2020). The treatment groups consisted of P0 (normal control + distilled water), P1 (diabetic control + distilled water), P2 (diabetes + bitter melon fruit extract at a dose of 50 mg/kg body weight), and P3 (diabetes + bitter melon fruit extract at a dose of 100 mg/kg body weight).

Research Variables

Research variables consist of independent variables, dependent variables, and controlled variables. The independent variable was the administration of bitter melon extract at doses of 50 mg/kg body weight and 100 mg/kg body weight. The dependent variables included enzyme levels and the SOD immunohistochemical profile in the livers of diabetic rats. Controlled variables include rat strain, age, sex, body weight, experimental environment, diet, water intake, and STZ dose.

Data Collection Methods

Research data were obtained by measuring superoxide dismutase (SOD) enzyme levels in rat liver tissue using a sandwich-type enzyme-linked immunosorbent assay (ELISA) with an ELISA kit from Bioassay Technology Laboratory (BT LAB). Meanwhile, the SOD profile was analyzed via immunohistochemical staining to assess the distribution and intensity of staining in liver tissue.

Sample Collection

Liver tissue samples were collected on day 22 following treatment administration. Rats were anesthetized with ketamine HCl at a dose of 80 mg/kg body weight via intramuscular injection (Mudiana *et al.*, 2023). After anesthesia, surgery was performed to remove the liver. A portion of the liver tissue was used for SOD level analysis and stored in Eppendorf tubes at -20°C, while the remaining portion was fixed in 10% formalin buffer solution for immunohistochemical analysis.

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SOD Assay

Liver tissue weighing ±0.1 grams was homogenized in PBS solution; the homogenate was centrifuged at 3000 rpm for 15 minutes at 4°C, and the resulting supernatant was used as the sample. Standard solutions and samples were added to wells of a microplate coated with specific antibodies. After adding the detector antibody and streptavidin-HRP, the plate was incubated at 37°C for 60 minutes. Next, washing with wash buffer was performed, a chromogenic substrate was added to each well, and the plate was incubated for 10 minutes in the dark. The reaction was stopped by adding a stop solution, and absorbance was read with an ELISA reader at a wavelength of 450 nm.

SOD Immunohistochemical Staining

Immunohistochemical staining was performed according to the method reported by (Suarsana *et al.*, 2021). Liver tissue fixed in 10% formalin buffer was processed through a series of dehydration steps using graded alcohol, clearing with xylene, and embedding in paraffin. Paraffin blocks were sectioned to a thickness of 5 µm, followed by deparaffinization with xylene and rehydration. Antigen retrieval was performed using citrate buffer at 95°C for 20 minutes, followed by blocking of endogenous peroxidase using 3% H_2O_2, and nonspecific blocking with bovine serum albumin (BSA). The sections were incubated with anti-SOD primary antibody and horseradish peroxidase (HRP)-labeled secondary antibody. Visualization was performed using diaminobenzidine (DAB) substrate, followed by hematoxylin counterstaining, dehydration, mounting, and observation under a microscope at 400x magnification.

Data Analysis

SOD level data were analyzed using analysis of variance (ANOVA) with the aid of SPSS software. If significant differences were found ($P < 0.05$), the analysis was continued with Duncan's test to determine differences among treatment groups. Meanwhile, the SOD profile in liver tissue was analyzed descriptively based on the results of immunohistochemical staining by assessing the intensity of brown staining indicating a positive reaction to SOD.

RESULTS AND DISCUSSION

Results

The mean superoxide dismutase (SOD) levels in each treatment group are presented in Table 1. The normal control group (P0) showed the highest SOD level (3.873 ± 0.298 ng/mL), while the diabetic control group (P1) had the lowest SOD level (1.916 ± 0.220 ng/mL). Administration of bitter melon fruit extract to diabetic rats in groups P2 and P3 increased SOD levels to 2.884 ± 0.272 ng/mL and 3.089 ± 0.202 ng/mL, respectively. A comparison of the mean SOD levels across groups is shown in Graphic 1, indicating an increase in SOD levels in the P2 and P3 groups administered bitter melon fruit extract compared to the diabetic control group (P1). Results of the ANOVA analysis indicated significant differences among treatment groups ($P < 0.05$). Duncan's post-hoc test indicated that SOD levels in groups P2 and P3 were not significantly different from each other ($P > 0.05$), but both were significantly different from groups P0 and P1 ($P < 0.05$).

Analysis of SOD protein expression via immunohistochemical staining is presented in Figure 1. In the normal control group (P0), positive SOD expression was observed in the cytoplasm and cell nucleus with very strong brown staining intensity. In contrast, the diabetes control group (P1) showed weak brown staining intensity. In groups P2 and P3, which were administered bitter melon extract, the intensity of brown staining increased compared to P1, with stronger expression observed in group P3.

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Discussion

This study shows that superoxide dismutase (SOD) levels in the liver tissue of diabetic rats are lower than those in the normal control group. These findings are also supported by immunohistochemical results showing weak SOD expression in the diabetic group, as indicated by the low intensity of brown staining in the liver tissue. The decrease in SOD levels and expression indicates a disruption of the liver's antioxidant system due to diabetes (Caturano *et al.*, 2023). Chronic hyperglycemia in diabetes increases the formation of reactive oxygen species (ROS) through various metabolic pathways, such as glucose autooxidation, the polyol pathway, and the formation of advanced glycation end products (AGEs) (Chen *et al.*, 2024). ROS accumulation triggers oxidative stress, which can damage cells and tissues in various organs, including the liver (Halliwell & Gutteridge, 2015). The body possesses an antioxidant defense system, one of which is superoxide dismutase (SOD), which functions to convert superoxide radicals into hydrogen peroxide and oxygen (Ighodaro & Akinloye, 2018). However, under conditions of oxidative stress, the activity of antioxidant enzymes tends to decrease in various tissues (Yunarsa & Adiatmika, 2018). A decrease in SOD activity and expression in diabetic conditions has also been reported by (Wresdiyati *et al.*, 2010).

Administration of bitter melon (*Momordica charantia*) extract to diabetic rats showed an increase in superoxide dismutase (SOD) levels in the liver compared to the diabetic control group ($P<0.05$), with a better response observed at a dose of 100 mg/kg body weight. These findings are consistent with previous reports that antioxidant compounds in bitter melon can suppress oxidative stress in diabetic conditions and have a protective effect on hepatic tissue through enhanced antioxidant defense (Ayoub *et al.*, 2019; Semiz & Sen, 2007). Immunohistochemical analysis revealed increased SOD protein expression following administration of bitter melon extract, characterized by stronger brown staining intensity in the cytoplasm and cell nuclei. This finding is likely related to the antioxidant compounds in bitter melon fruit, which can enhance SOD expression in liver tissue (Lee *et al.*, 2015).

The protective effects of bitter melon fruit extract on the liver's antioxidant system are thought to be related to its bioactive compounds, such as flavonoids, charantin, saponins, and polypeptide-p (Puspitasari & Choerunisa, 2021; Saeed *et al.*, 2021). Flavonoids are potent antioxidants that directly scavenge free radicals and enhance the activity of endogenous antioxidant enzymes (Kusuma & Maesaroh, 2020). Additionally, charantin has been reported to enhance insulin sensitivity by increasing the expression of glucose transporter-4 (GLUT-4) in skeletal muscle and insulin receptor substrate-1 (IRS-1) in the liver, thereby helping to reduce hyperglycemia and indirectly suppressing ROS formation (Oyelere *et al.*, 2022; Wang *et al.*, 2014).

Alkaloids and tannins possess the ability to neutralize ROS by donating electrons or hydrogen to oxidizing molecules, thereby halting oxidative reactions, inhibiting chain reactions, and reducing lipid peroxidation (Fraga-Corral *et al.*, 2021). Additionally, bitter melon fruit extract has been reported to increase pancreatic β-cell numbers by regenerating and restoring partially damaged β-cells in STZ-induced diabetic rats (Xu *et al.*, 2022). The increase in SOD levels and improvement in SOD expression in the liver tissue of diabetic rats administered bitter melon fruit extract suggest that this extract has the potential to be used to reduce oxidative stress in diabetic conditions.

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CONCLUSIONS AND SUGGESTIONS

Conclusion

Administration of bitter melon (*Momordica charantia*) extract increased levels and improved the expression of the enzyme superoxide dismutase (SOD) in the liver tissue of diabetic rats. The highest increase in SOD levels was observed at a dose of 100 mg/kg body weight (3,089 ± 0.202 ng/mL), with values approaching those of the normal control group (3,873 ± 0.298 ng/mL). Immunohistochemical results showed increased brown staining intensity in liver tissue in the group administered bitter melon extract, indicating improved expression of the SOD enzyme protein.

Suggestions

Further research is needed to evaluate other antioxidant enzyme parameters and to test a wider range of dosages of bitter melon extract in order to gain a more comprehensive understanding of its effects on the endogenous antioxidant defense system.

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Table

Table 1. Mean liver superoxide dismutase (SOD) levels in rats in each group after 21 days of treatment.

Groups	n	Mean ± SD (ng/mL)
P0	5	3.873 ± 0.298^{c}
P1	5	1.916 ± 0.220^{a}
P2	5	2.884 ± 0.272^{b}
P3	5	3.089 ± 0.202^{b}

Note: Different superscript letters in the same column indicate a significant difference ($P < 0.05$) based on Duncan's test. P0 (normal control); P1 (diabetes control); P2 (diabetes + bitter melon fruit extract at a dose of 50 mg/kg body weight); P3 (diabetes + bitter melon fruit extract at a dose of 100 mg/kg body weight)

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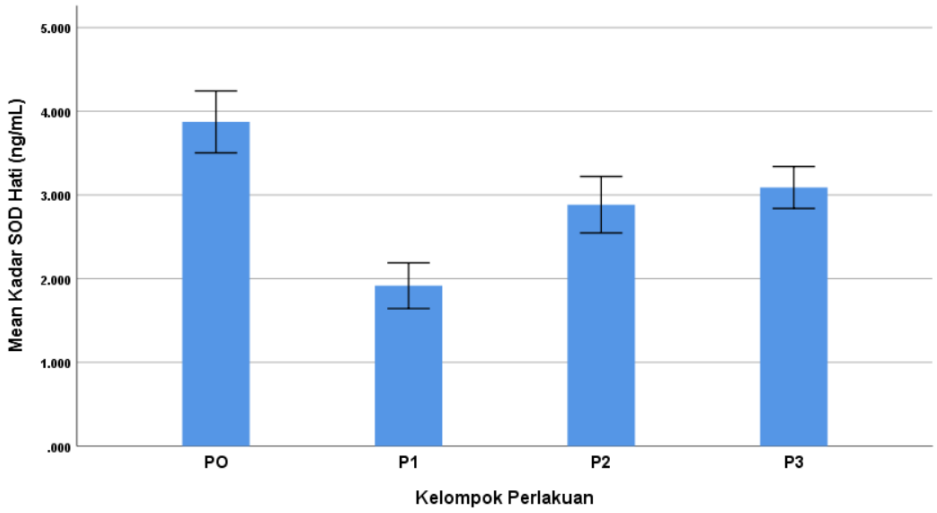
Graph



Graph 1. Mean liver SOD levels in rats in each group after 21 days of treatment. P0 (normal control); P1 (diabetes control); P2 (diabetes + bitter melon fruit extract at a dose of 50 mg/kg body weight); P3 (diabetes + bitter melon fruit extract at a dose of 100 mg/kg body weight)

Figure

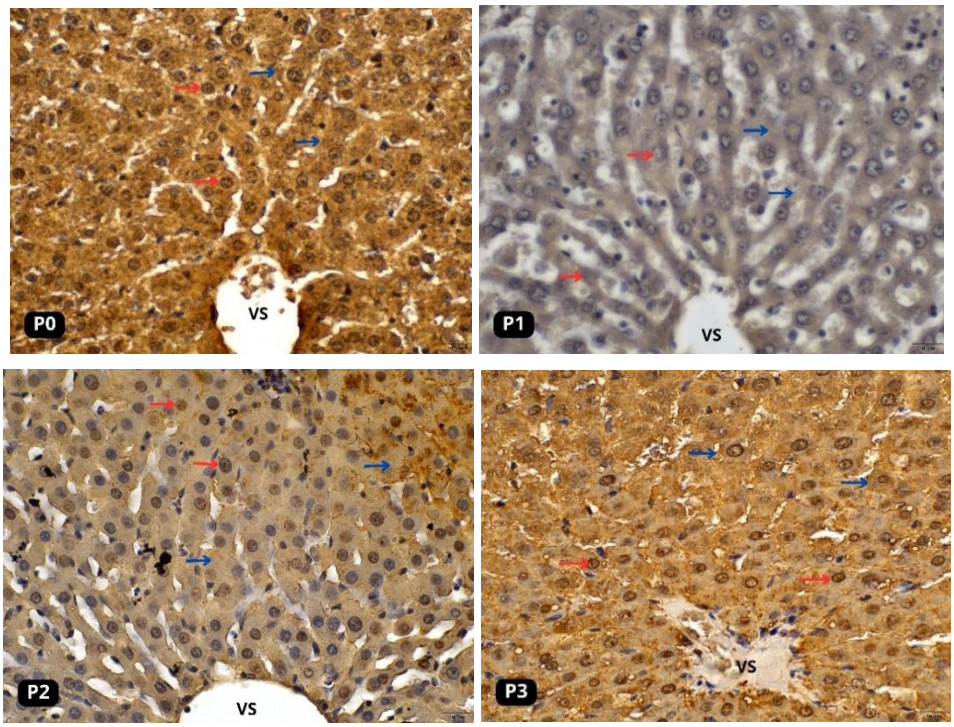


Figure 1. Immunohistochemical staining for SOD in liver tissue. SOD expression in the cell nucleus (red arrow) and cytoplasm (blue arrow) appears brown, indicating a positive reaction. P0 (normal control); P1 (diabetes control); P2 (diabetes + bitter melon extract 50 mg/kg body weight); P3 (diabetes + bitter melon extract 100 mg/kg body weight); VS (central vein). Scale bar 10 μm.

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