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# Effects of Bitter Melon (*Momordica charantia*) Extract on Glucose Transporters 2 and 4 Levels in Streptozotocin-induced Hyperglycaemic Rats

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## ABSTRACT

Glucose transporters (GLUTs) are essential for regulating glucose metabolism, with GLUT2 and GLUT4 serving as the primary transporters in muscle cells. In diabetic conditions, oxidative stress caused by free radicals damages glucose uptake into cells. Bioactive compounds in bitter melon, including triterpenoids, charantin, and conjugated linoleic acid, have been shown to have hypoglycaemic effects. Therefore, the present study aimed to evaluate the effect of bitter melon extract (*Momordica charantia*) on blood glucose, GLUT2, and GLUT4 in streptozotocin-induced hyperglycemic rats. The present study involved 15 male Wistar rats (white strain), 2 months old, with an average body weight of 130 grams. Diabetes was induced by administering streptozotocin at a dose of 60 mg/kg body weight. The animals were divided into three treatment groups, including the diabetic control group (P0), the diabetic group treated with 50% weight/volume (w/v) bitter melon extract (P1), and the diabetic group treated with 100% (w/v) bitter melon extract (P2). The extract was given orally at a dosage of 1 ml per rat for 14 days. Blood glucose concentrations were determined using a glucometer, whereas serum GLUT2 and GLUT4 levels were quantified with an ELISA kit. The results indicated that treatment P2 significantly lowered blood glucose levels compared to the diabetic control group, decreasing from 414.60 mg/dL (P0) to 223.60 mg/dL (P2). Serum GLUT2 concentrations declined from 21.51 (P0) to 16.50 (P2), and GLUT4 levels decreased from 19.94 (P0) to 17.60 (P2). These changes suggested an adaptive response intended to restore glucose homeostasis. Based on the present results, 100% w/v bitter melon extract concentration demonstrated a significant reduction in blood glucose, GLUT2, and GLUT4 levels in the serum of streptozotocin-induced diabetic rats.

**Keywords:** Bitter melon, Diabetes mellitus, Hyperglycemia, Glucose transporter

## INTRODUCTION

The increasing prevalence of diabetes mellitus is a significant and alarming threat to global health. The IDF (2021) reported that the worldwide number of individuals with diabetes mellitus has reached 537 million and is expected to rise to 643 million by 2030. Diabetes mellitus is characterized by chronic hyperglycemia resulting from impaired insulin secretion, action, or both (Antar et al., 2023). Hyperglycemia increases the amount of glucose in the glycolytic pathway, leading to increased production of free radicals, which heightens oxidative stress in cells. Persistent free radicals within cells also damage cellular macromolecules, including nucleic acids, lipids, and proteins (Rochette et al., 2014).

Glucose is a primary energy source for cellular activity in living organisms. However, due to its hydrophilic property, glucose transport across the cell membrane requires a specific carrier protein. Glucose transporters (GLUTs) are transmembrane proteins that facilitate the movement of glucose across cell membranes (Wang et al., 2020). Elevation of blood glucose level stimulates GLUT2 to transport glucose into β cells and trigger insulin secretion. Increased insulin promotes glucose uptake into muscle and adipose tissues by regulating GLUT4 translocation to the plasma membrane (Leto and Saltiel, 2012). Therefore, GLUT2 and GLUT4 play crucial roles in the progression of diabetes mellitus.

Diabetes mellitus treatment mainly focuses on managing blood glucose levels to prevent complications. However, prolonged use of synthetic antidiabetic medicines poses risks of side effects and toxicity (Wang et al., 2019). Therefore, finding safe, affordable, and effective alternative treatments is essential. One potential plant as an alternative treatment is bitter melon (*Momordica charantia*). Bioactive compounds in bitter melon, including triterpenoids, charantin, and



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conjugated linoleic acid, have been shown to have their hypoglycaemic and antioxidant effects that reduce oxidative stress (Mahmoud et al., 2017; Liu et al., 2021). The reduction in oxidative stress may improve GLUT2 and GLUT4 translocation and regulation, thereby enhancing glucose uptake and homeostasis (Çiçek, 2022).

A previous study by Poovitha and Parani (2017) demonstrated that several compounds in bitter melon enhance GLUT4 translocation through the AMP-activated protein kinase (AMPK) pathway in muscle cells. Furthermore, Malekshahi et al. (2019) reported that bitter melon reduces the expression of GLUT2, leading to decreased glucose reabsorption in the kidneys and increased urinary glucose excretion. Nevertheless, studies investigating the influence of bitter melon on serum GLUT2 and GLUT4 levels in streptozotocin (STZ)-induced diabetic rat models are still scarce. Therefore, the present study aimed to assess the effects of bitter melon *(Momordica charantia*) extract on blood glucose, as well as serum GLUT2 and GLUT4 levels, in STZ-induced hyperglycemic rats.

## MATERIALS AND METHODS

### Ethical approval

Ethical approval for the present study was granted by the animal ethics committee of the Faculty of Veterinary Medicine, Udayana University, Bali, Indonesia (No. B/M.145/UN14.2.9/PT.01.04/2024). All experimental procedures were carried out in strict accordance with animal welfare principles.

### Extract preparation

The extraction process was performed traditionally with a blender, incorporating the method outlined by Jenie and Indraswari (2021) with some modifications. Bitter melon samples were sourced from the Jimbaran traditional market in Badung Regency, Bali, Indonesia. The procedure began by selecting fresh, green fruits, which were then washed and sliced into small pieces. A total of 100 g (wet weight) of bitter melon was blended, and the resulting extract was filtered using cheesecloth and transferred into a volumetric flask. Distilled water was added to increase the volume to 100 mL, resulting in a 100% w/v solution concentration. To prepare a 50% w/v concentration, 50 mL of the 100% extract was diluted with distilled water to a final volume of 100 mL. The extracts at both 50% and 100% w/v concentrations were stored in clean bottles and refrigerated at 4°C to preserve their stability.

### Animals and treatments

Fifteen males white Wistar rats, approximately 2 months old, with an average body weight of 130 g, were used in the current experiment. Wistar rats were divided into three treatment groups, each consisting of five rats with five repetitions. The experimental animals were fasted for 12 hours before being induced intraperitoneally with STZ (Merck KGaA, Germany) at a dose of 60 mg/kg body weight (Gavaher et al., 2022). Bitter melon extract was administered after the rats exhibited blood glucose levels reached 200 mg/dL (Furman, 2021). The extract was administered on day 7 post-STZ induction, with every group receiving the same amount of 1 mL doses/day orally. In the control group, the rats were given water without the extract (P0). In the P1 treatment group, the rats were given bitter melon extract at a 50% w/v concentration. In the P2 treatment group, the rats were given bitter melon extract at a 100% w/v concentration every day for 14 days of treatment. Serum collection was performed on day 14 post-treatment, followed by the sandwich ELISA method (Kohrain Biotech, China) to analyze the levels of GLUT2 and GLUT4 in the rat serum.

### Measurement of glucose transporter concentration

For the GLUT2 and GLUT4 level analysis methods, the procedures listed on the ELISA Kit were used. Rat serum samples were analyzed using the rat glucose transporter 2 (GLUT2 ELISA Kit, E1058Ra, Zhejiang, China) and rat glucose transporter 4 (GLUT4 ELISA Kit, E0499Ra, Zhejiang, China) from the bioassay technology laboratory.

### Sample processing

The sample collection began 14 days after the treatment; every rat was fully anesthetized using ketamine-HCl doses of 50 mg/kg body weight (Wellington et al., 2013). The blood samples were obtained from the orbital vein using a capillary pipette and collected into 3 mL plain Vacutainer tubes. The rats were subsequently euthanized by the cervical dislocation method. The collected blood was then centrifuged at 2000 rpm for 20 minutes. The serum samples were thereafter delivered to the Biochemistry Laboratory, Faculty of Medicine, Udayana University, Bali, Indonesia, for further analysis. Blood glucose levels were measured on day 0 before injection as baseline data, 7 days after STZ induction, and at 14 days after the treatment (end of the treatment). Blood glucose levels of the experimental rats were measured using a glucometer (Allmedicus, South Korea). The rats were categorized as diabetic when the blood glucose level reached a minimum of 200 mg/dL after STZ induction (Furman, 2021).

**Statistical analysis**

Blood glucose and GLUT2 and GLUT4 levels were analyzed by analysis of variance (ANOVA) using data processing software SPSS Statistics 26.0 (IBM, USA). For the significant values, post-hoc Duncan tests were performed. The data were presented as means ± standard deviation, and a p-value less than 0.05 was considered statistically significant.

## RESULTS

The average results of blood glucose, GLUT2, and GLUT4 levels are presented in Table 1. Blood glucose levels differed significantly among the treatment groups ($p < 0.05$). The control group (P0) indicated the highest level of blood glucose (414.60 ± 17.67 mg/dL), followed by P1 (370.80 ± 19.60 mg/dL) and P2 (223.60 ± 12.52 mg/dL). This difference indicated that the administration of bitter melon extract at a 100% concentration (P2) significantly reduced blood glucose levels compared to the 50% concentration group (P1) and the control group.

Analysis of GLUT2 levels demonstrated that administration of 100% bitter melon extract (P2) resulted in a value of 16.50 ± 3.65, which was lower and significantly different ($p < 0.05$) compared to the control group (P0, 21.51 ± 3.31), but not significantly different compared to the P1 group (19.11 ± 3.3, $p > 0.05$). Meanwhile, the GLUT4 level in P2 was 17.6 ± 1.25, lower and significantly different ($p < 0.05$) compared to the P0 (19.94 ± 1.1), but not significantly different compared to P1 (18.97 ± 1.16, $p > 0.05$).

**Table 1.** Blood glucose, Glucose transporters 2 and 4 levels in rats after 14 days of treatment

| Treatment | Blood glucose | Glucose transporters 2 (GLUT2) | Glucose transporters 4 (GLUT4) |
|---|---|---|---|
| P0 | $414.60 \pm 17.67^{c}$ | $21.51 \pm 3.31^{b}$ | $19.94 \pm 1.10^{b}$ |
| P1 | $370.80 \pm 19.60^{b}$ | $19.11 \pm 0.96^{ab}$ | $18.97 \pm 1.16^{ab}$ |
| P2 | $223.60 \pm 12.52^{a}$ | $16.50 \pm 3.65^{a}$ | $17.60 \pm 1.25^{a}$ |

[a,b,c] Different superscript letters differ significantly ($p < 0.05$), and the values are presented as means ± standard deviation. P0: Diabetes control group; P1: Diabetes group received bitter melon extract 50% w/v; P2: Diabetes group received bitter melon extract 100% w/v.

## DISCUSSION

The current results demonstrate that the administration of bitter melon extract in diabetic mellitus rats significantly reduced blood glucose levels, with a statistically significant difference compared to the positive control group. However, the blood glucose levels did not reach normal values (50-130 mg/dL) as reported by Hidayaturrahman et al. (2020). This blood glucose-lowering effect may be due to the active compounds in bitter melon, namely phenols and flavonoids (Rezaeizadeh et al., 2011). Several studies stated that secondary metabolites in bitter melon, including charantin, polypeptides, alkaloids, momordicin, flavonoids, and cucurbitane-type triterpenoids, play crucial roles in reducing blood glucose levels (Pahlavani et al., 2019; Xu et al., 2022).

One of the main types of saponins in bitter melon is triterpenoids, which are divided into two main types, oleanane and cucurbitane. According to Çiçek (2022), eight types of cucurbitane triterpenoids promote GLUT4 translocation in L6 myotubes and 3T3-L1 adipocytes by activating the AMPK pathway, thereby improving fatty acid oxidation and glucose uptake. The AMPK is an energy-sensing protein kinase activated by the phosphorylation of Thr172 on its catalytic α-subunit. The AMPK facilitates glucose uptake into cells independently of insulin signalling and Akt activation (Chang et al., 2021). The AMPK activation can occur through multiple mechanisms, including the canonical pathway regulated by the adenine nucleotide ratio, the non-canonical pathway involving binding at the AdaM site, and the Ca2+-dependent pathway mediated by Ca2+/calmodulin-stimulated protein kinase beta (CaMKKβ). A study conducted by Iseli et al. (2013) noted that triterpenoid compounds in bitter melon activate AMPK via the CaMKKβ pathway.

The bioactive compounds found in bitter melon play vital roles in reducing blood glucose levels. Specifically, charantin, which inhibits the α-glucosidase and α-amylase enzymes (Ahamad et al., 2019), whereas alkaloid compounds act through an insulin-like mechanism (Mahwish et al., 2023). Furthermore, the conjugated linoleic acid present in bitter melon enhances insulin sensitivity by promoting adipogenesis via lipoprotein lipase activation (Gadang et al., 2011). Bitter melon contains two main types of polypeptides, including P-insulin and peroxidase. P-insulin is a carbohydrate-binding protein that can help lower blood glucose levels, facilitating cell recognition and mediating adhesion reactions (Richter et al., 2023). This protein mimics insulin activity by binding to Insulin (INS) receptors. Meanwhile, peroxidase contributes to reducing oxidative stress and detoxifying peroxides by converting them into non-toxic substances. Xu et

al. (2022) further demonstrated that bitter melon extract remarkably increases pancreatic β-cell populations by regenerating and restoring partially damaged β-cells in STZ-induced diabetic rats.

Oxidative stress is a redox imbalance characterized by increased production and accumulation of free radicals, accompanied by impaired antioxidant function in cells or tissues (An et al., 2023). Free radicals play important roles in intracellular signalling, cell activity regulation, apoptosis induction, and immune responses. Additionally, free radicals stimulate inflammatory responses through protein kinase activation, transcription factor regulation, and the expression of pro-inflammatory genes (Darenskaya et al., 2021). Free radical-induced cell damage can lead to the release of intracellular substances into the bloodstream (González et al., 2023), including GLUT.

The current findings indicated that diabetic mellitus rats treated with bitter melon extract had lower serum levels of GLUT2 and GLUT4 compared to the control group. This mechanism may be due to the phenolic, flavonol, and flavonoid components in bitter melon, which act as antioxidants that bind to free radicals, inhibiting chain reactions and preventing further cell damage (Tan et al., 2016). Furthermore, bitter melon possesses antiglycation properties that prevent the formation of advanced glycation end-products (AGEs), which are key contributors to diabetic complications (Aljohi et al., 2016). Under hyperglycemic conditions, the elevated production of AGEs triggers the generation of free radicals and pro-inflammatory molecules, thereby disturbing the homeostasis of endothelial cells (An et al., 2023).

During the present study, the control group exhibited the highest levels of GLUT2 and GLUT4, possibly due to STZ triggering oxidative stress and lipid peroxidation, which led to hyperglycemia (Soliman, 2016). β-cells are particularly vulnerable to oxidative stress because they contain low concentrations of endogenous antioxidant enzymes, including catalase and glutathione peroxidase (Rochette et al., 2014). However, in the group receiving the bitter melon extract at a 100% concentration, the blood glucose levels, GLUT2, and GLUT4 demonstrated considerable decreases compared to the control group. This effect might be due to the incomplete β-cell destruction caused by STZ, allowing the antioxidant compounds in bitter melon extract to prevent further chain reactions of free radicals and cellular damage. The present findings aligned with those of Bortolotti et al. (2019), who demonstrated that the antioxidant properties of bitter melon function by alleviating oxidative stress, neutralizing free radicals, and preventing lipid peroxidation. By preventing cellular damage, intracellular substances such as GLUT remain preserved within the cells.

The release of GLUT into the bloodstream can affect the amount of glucose entering cells. The GLUT2 is a transporter protein that not only facilitates passive glucose transport into pancreatic β-cells but also functions as a glucose homeostasis sensor (Kahraman et al., 2015). When blood glucose levels increase, GLUT2 triggers insulin secretion (Berger and Zdzieblo, 2020). Insulin is released into the bloodstream, then binds to its receptor and promotes the translocation of insulin-sensitive GLUT4 to the cell membrane surface. At the cell surface, GLUT4 binds and fuses to form a channel, allowing glucose to enter the cell. Conversely, when there is no insulin stimulation, GLUT4 returns to the cytosol (Wang et al., 2020). Disruptions in GLUT2 and GLUT4 expression and function can prevent glucose from entering cells, leading to prolonged hyperglycemia. This condition can progress to diabetes-related complications such as vascular endothelial damage, hepatic impairment, diabetic ketoacidosis, diabetic retinopathy, diabetic nephropathy, and diabetic neuropathy (Ofuegbe et al., 2020; An et al., 2023).

## CONCLUSION

The administration of bitter melon extract at a more optimal concentration of 100% can reduce blood glucose, GLUT2, and GLUT4 levels in STZ-induced diabetic rats. It is recommended to evaluate the effects of bitter melon administration on GLUT2 and GLUT4 levels using multipolar solvents. Additionally, future studies should consider measuring GLUT levels in different organs, such as the liver, pancreas, muscles, intestines, and brain.

## DECLARATIONS

### Availability of data and materials

All data supporting this study's findings are included within the article's materials, and no additional supporting datasets are available.

### Authors' contributions

Dahlia Putri contributed to conducting the experiments, analyzing the data, and drafting the manuscripts. I Gusti Ayu Agung Suartini contributed to supervision, revised the manuscript, and validated it. I Nyoman Mantik Astawa, Hamong Suharsono, and Anak Agung Sagung Kendran contributed to the supervision and validation of the experiment and manuscript. I Nyoman Suarsana contributed to designing the research project, supervised the study procedure, revised the manuscript, and validated the manuscript. All authors read and approved the final edition of the manuscript.

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**Competing interests**

The authors declared no conflict of interest.

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**Ethical considerations**

The manuscript is original, and it has not been published elsewhere. All authors reviewed the original content of the manuscript. No AI tools was used during the study and writing the manuscript.

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