Majalah Obat Tradisional (Trad. Med. J.), October-December 2025
Vol. 30(3), p 300-306
ISSN-p : 1410-5918 ISSN-e : 2406-9086

Submitted :31-07-2024
Revised : 04-11-2024
Accepted : 10-01-2025

Effect of Diabetes on Cortisol Levels After the Administration of *Stenochlaena palustris* (Burm.) Bedd

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ABSTRACT

Cortisol, is a steroid hormone, that plays a role as a stress hormone and is known to elevate blood sugar levels, leading to hyperglycemia. Hyperglycemia is characterized by high cortisol levels and insulin resistance in type 2 diabetes mellitus *(T2DM*). Kelakai (*Stenochlaena palustris* (Burm.) Bedd) has many health benefits, including its antioxidant content that can reduce blood sugar levels (hypoglycemia). This study aims to evaluate the cortisol level reduction in model rats with T2DM after being treated with *Stenochlaena palustris* (Burm.) Bedd extract by employing a laboratory experimental approach. The blood glucose analysis was performed using pre- and posttest control group designs, while the cortisol measurement followed a posttest control group design. The rats were divided into five groups: KN (normal group), K− (T2DM model rats) which became the control group in this research, K+ (T2DM model rats treated with metformin), and two experimental groups, namely, P1 and P2 (T2DM model rats treated with both metformin and kelakai extract at 400 and 800 mg/kgBW/day doses, respectively, administered through a nasogastric tube for 21 days). Statistics used parametric tests, namely, analysis of variance (ANOVA) with least significant difference post-hoc test. The results of the cortisol levels showed a significant difference ($p \leq 0.05$).
Keywords: Cortisol; *Stenochlaena palustris* (Burm.) Bedd; Stress Cells; T2DM

INTRODUCTION

Y cells define stress as a coordinated neurohormonal process designed to preserve homeostasis, which includes blood glucose level regulation (Chovatiya & Medzhitov, 2014). The adaptive acute stress response is triggered by neurocognitive, catecholaminergic, and immunomodulatory pathways, all of which are further regulated by cortisol. A key aspect of stress response is the sympathoadrenomedullary system, particularly the hypothalamic–pituitary–adrenal (HPA) axis that plays a role in many clinical diseases by establishing a new state of homeostasis known as allostasis. Cardiometabolic conditions, such as type 2 diabetes, may lead to elevated cortisol levels (hypercortisolemia). However, chronic conditions often require treatments that can modify the stress system's function. Accordingly, some researchers have identified a link between elevated blood glucose and serum cortisol levels (Haryono & Handayani, 2021). High cortisol levels are significantly associated with diabetic microangiopathy (Sun & Wang, 2023). Cortisol, which is often referred to as the stress hormone, influences various bodily functions, such as stress response management, metabolism control, inflammation modulation, and immune function support. However, understanding the origins of chronic stress necessitates establishing a clear cause-and-effect link, along with practical applications like treatments that modify the stress system activity. Research indicates that elevated cortisol levels are connected to conditions like hypertension and anxiety, particularly in individuals with type 2 diabetes mellitus (T2DM) (Lee et al., 2024).

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Cortisol and Type 2 Diabetes Mellitus

Cortisol, a glucocorticoid hormone secreted by the adrenal glands, is crucial for numerous physiological functions. Cortisol level imbalances triggered by factors like prolonged stress, aging, or illness can lead to notable impacts on the body. Studies involving experimental animals provide valuable insights into cortisol dynamics during stress, its influence on the immune system's stress response, and its neuroendocrine interactions, along with how it interacts with various physiological factors (Knezevic et al., 2023). Diabetes mellitus is a condition caused by impaired carbohydrate metabolism that disrupts the glycolysis, glycogenesis, and gluconeogenesis pathways (Mills et al., 2022).

DOI: 10.22146/mot.98823 | *Majalah Obat Tradisional, 30(3), 2025*

Cortisol and Reactive Oxygen Species

The diabetes mellitus incidence has reached epidemic proportions in adults, and its prevalence continues to increase. It is estimated that by 2030, 438 million people worldwide would be suffering from diabetes. In Indonesia, the number of diabetes cases continues to increase annually. T2DM is often associated with hidden hypercortisolism (HidHyCo). Studies that used meta-analysis to assess the prevalence of HidHyCo in patients with T2DM found a higher HidHyCo prevalence (Aresta et al., 2021). An increase in iNOS in response to psychological stress was also observed both in vivo and in treated cells. Cortisol and norepinephrine can significantly increase levels of reactive oxygen and nitrogen species, and stress can affect breast cancer (Flaherty et al., 2017).

Stenochlaena palustris (Burm.) Bedd Antioxidant

In therapy, no effective drug has yet been discovered for diabetes. With this limitation, natural ingredients with antioxidant properties, which can counteract free radicals, are needed. Among these natural ingredients are tree barks, which are ground and extracted (Miaffo et al., 2019). Research has also been performed on methanol leaf extract as medicine (Gwarzo et al., 2014). Plants have long been used to treat various diseases. For primary health care, people use plants (e.g., plant extracts) as traditional medicine because plants contain bioactive substances with many long-term health benefits. *Stenochlaena palustris* (Burm.) Bedd is also known as fern. It belongs to the Polypodiales ordo and has reddish-green lanceolate leaves. In Kalimantan, this plant is generally a wild plant used therapeutically in medicine as an antimalaria, an antihyperlipidemic, and others (Adawiyah et al., 2023). Previous studies performed phytochemical and in vitro tests using *S. palustris* to investigate its potential for diabetes mellitus treatment by inhibiting the enzyme, alpha glucosidase, and others (Gunawan-Puteri et al., 2021). The ethanol extract of kelakai contains flavonoids, tannins, and saponins (Hidayah et al., 2020). This study aims to determine the decrease in the cortisol and blood glucose levels in DM model rats after receiving *S. palustris* (Burm.) Bedd extract.

Materials and Methods

The tools used in this research are as follows: measuring cup, digital scale, pipette, stirrer, centrifuge machine, spectrophotometer, vortex, enzyme-linked immunosorbent assay (ELISA) kits (Elabscience), glucometer (Autocheck), 3cc syringe (for sonde), and scissors.

The materials and solvents used include the following: *S. palustris* (Burm.) Bedd thick extract, metformin 500 mg, Na-CMC 0.5% solution, *S. palustris* (Burm.) Bedd extract, blood serum, streptozotocin (STZ), and nicotinamide (NA).

An experimental design was formulated, detailing the parameters, groups, and methodology used in the research. Diabetes was induced in Wistar rats by administering chemicals to replicate diabetic conditions. Wistar male rats, which are highly sensitive to STZ, have been used for 60 years to develop rat models of type 1 and type 2 diabetes (Ghasemi & Jeddi, 2023).

A total of 25 Wistar rats were divided into five groups, such that each group had five rats and were treated for 21 days as follows: Group 1 (normal); Group 2 (DM + Na-CMC 0.5%), which became the control group in this research; Group 3 (DM + metformin 45 mg); Group 4 (P1 / DM + *S. palustris* extract (Burm.) Bedd 400 mg/kg); and Group 5 (P2 / DM + *S. palustris* extract (Burm.) Bedd 800 mg/kg). The Wistar rats in groups K–, K+, P1, and P2 were given *S. palustris* extract (Burm.) Bedd through a sonde.

Schematic of Experiment

The experimental scheme illustrated in Figure 1 starts with the first step of obtaining approval from the ethics committee. This certification ensures that the research adheres to ethical standards and guidelines. Subsequently, the kelakai extract was prepared using the appropriate method and solvent.

Preparation of Type 2 DM Rats with STZ–NA

To prepare the type 2 DM rats, Wistar rats were put in a state of fasting for 7 h, and then induced by using STZ–NA (Dewi et al., 2020). NA induction was performed first, followed by STZ induction intraperitoneally 15 min later (Yan, 2022). The dose given to Wistar rats was 65 mg/200 gBW of STZ and 110 mg/200 g NA (Ghasemi et al., 2014). STZ was dissolved in a citrate buffer solution (0.01 M, pH = 4.5). After 30 min, all Wistar rats received water and food ad libitum. The diabetic condition was achieved if the whole blood glucose (GDS) level was ≥200 mg/dL (Furman, 2021a), which was checked after 72 h of STZ–NA induction.

Administration of Kelakai Extract and Metformin Drug

The administration of kelakai extract was given to Group P1 with 400 mg/kgBW/day of

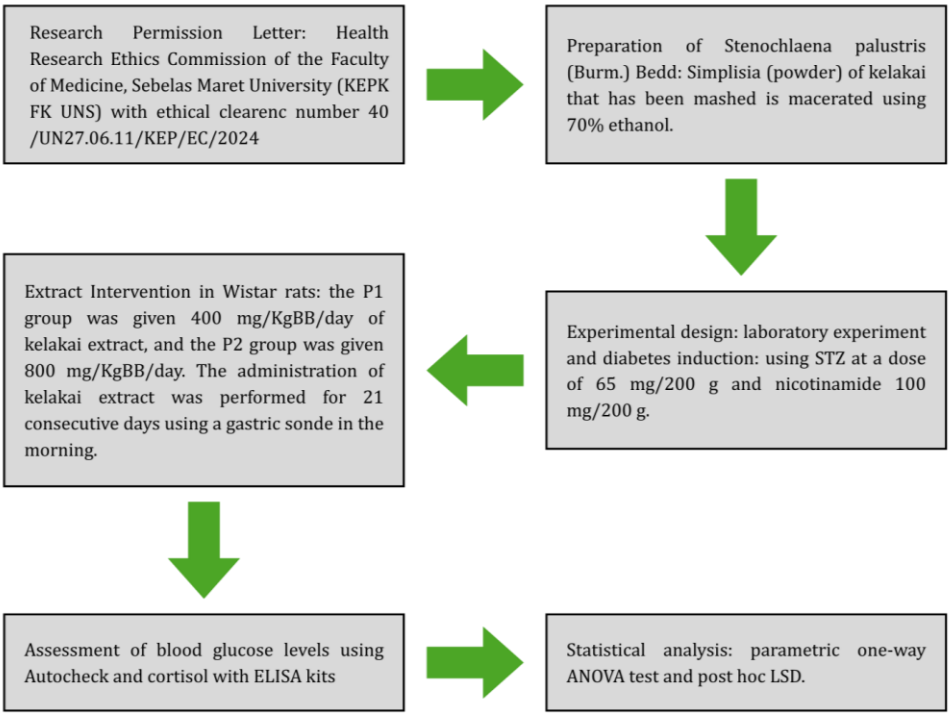

Figure 1. Schematic of the experiment

S. palustris (Burm.) Bedd extract and Group P2 with 800 mg/kgBW/day of *S. palustris* (Burm.) Bedd extract, performed for 21 consecutive days using a gastric sonde in the morning. Standard feed and drink were given sufficiently to all groups (i.e., normal, negative, positive, P1, and P2 groups). The metformin dose was determined based on the therapeutic dose of DM in humans, which is 500 mg/day, and according to Ref. (Pingkan et al., 2020) with a 0.018 conversion rate.

Blood Glucose Level Measurement

The initial blood glucose level measurement was performed to determine if the Wistar rats were normal (nondiabetic). Three days later, the glucose levels were measured (pretest) to ensure that Wistar rats had hyperglycemia >200 mg/dL (Furman, 2021b). Subsequently, treatment was given for 21 days. Blood glucose was measured (*posttest*) on the 22nd day. The glucometer measured the blood glucose levels by first smearing the tail of the Wistar rat with sterile cotton and piercing it using sharp scissors. The blood droplets were then put into a test strip, and the number on the glucometer was read. The glucometer method is widely used in diabetes research on animal models to measure the blood glucose levels. Measurements can easily be done with a few microliters of blood. The device must also be calibrated (Togashi et al., 2016).

Cortisol Level Measurement

Examination of cortisol levels using blood serum, rats were fasted for 8–12 hours. Blood was taken from the orbital sinus with a 0.5 ml haematocrit pipette and collected in a *microtube*. Measured by ELISA using *rat* cortisol test kit. Measurement of cortisol hormone levels was done after treatment. In general, cortisol levels in the blood increase in the morning (highest around 8 am) and slightly decrease at night and in the early phase of sleep. Therefore, the timing of blood sampling is very important (D. Y. Lee et al., 2015).

Glucose and Cortisol Level Analysis

The blood glucose levels were measured thrice: 1) H- (before STZ–NA induction); H0 (3 days after STZ–NA induction and not given kelakai extract); and H21 (21 days after receiving *S. palustris* (Burm.) Bedd extract. To determine the effect of *S. palustris* (Burm.) Bedd extract on the blood glucose levels, statistical tests were performed to compare the blood glucose levels before and after treatment with the paired *t*-test.

The cortisol levels were measured once at the end of the research (H21) with one-way ANOVA test comparing the cortisol levels between groups KN, K−, K+, P1, and P2. A significant difference was found at $p \leq 0.05$. The analysis was continued with the least significant difference

Table I. Blood glucose levels of the Wistar rats

Group	Mean ± SD (mg/dL)			
	H-	H0	H21	*p*
N	89.40 ± 10.38	94.80 ± 7.29	97.40 ± 7.127	0.651[c]
K–	91.20 ± 12.89	433.40 ± 82.34	308.60 ± 106.63	0.138[d]
K+	90.81 ± 4.51	539.80 ± 4.82	284.60 ± 108.65	0.007*[c]
P1	104.20 ± 3.83	427.80 ± 29.12	133.60 ± 21.92	0.000*[c]
P2	97.40 ± 6.95	432.80 ± 75.06	215.80 ± 126.72	0.008*[c]
p	0.055[a]	0.000*[b]	0.003*[a]	

Description: KN = normal; K(−) = DM; K(+) = DM and given metformin 0.45 mg/kgBW/day; P1 = DM rats given 400 mg/kgBw/day extract; P2 = DM rats given 800 mg/kgBW/day extract; H(−) = before STZ–NA induction; H0 = 3 days after STZ–NA induction; H21 = 21 days after receiving kelakai extract; *Significant difference ($p < 0.05$);[a]Kruskal–Wallis test; [b]One-way ANOVA test; [c]Paired *t*-test; [d]Wilcoxon test.

(LSD) post-hoc test,and the results of which are presented in Table III.

RESULTS

Blood Glucose Levels

The mean GDS levels of the Wistar rats at H-, H0, and H21 in each group are listed in Table I.

Table I shows that the blood glucose levels at H- in groups N, K–, K+, P1, and P2 showed no significant difference ($p \geq 0.05$). In all groups, H0 and H21 (after 21 days of extract administration) showed significant differences of $p \leq 0.05$ and $p \leq 0.05$, respectively. In Group N, the blood glucose levels were within the normal limits at H-, H0, and H21, while in Group K–, the blood glucose levels at H0 and H21 showed high levels of more than 200 mg/dL.

The effect of the *S. palustris* (Burm.) Bedd extract on the blood glucose levels determined by the paired *t*-test and Wilcoxon statistical tests showed that the blood glucose levels in groups K+, P1, and P2 between H0 (before administration of the kelakai extract) and H21 (after 21 days of extract administration) showed a significant difference ($p \leq 0.05$).

Cortisol Level Results

The cortisol levels were measured once at the end of the research (H21). The mean cortisol levels of the Wistar rats in each group are presented in the table II.

Table II shows the results of the one-way ANOVA test comparing the cortisol levels between groups KN, K–, K+, P1, and P2. A significant difference was found at $p = 0.05$. Thus, the analysis can be continued with the LSD post-hoc test, the results of which are shown in Table III. “Post-hoc” is used to compare the mean between groups to know which group is more meaningful (Hadiyantini et al., 2022).

Table III. shows that the cortisol levels at H21 in the KN, K+, and P2 groups showed significantly lower cortisol levels than in the K– group

DISCUSSION

S. palustris and its phytocomponents have α-glucosidase and α-amylase inhibition activities, with IC50 values ranging from 40 to 250 μg/mL (Hendra et al., 2024). However, this research was conducted in vitro; hence, the researchers were interested in continuing the research in vivo in diabetic Wistar rats. Some studies on *S. palustris* (Burm.) Bedd included *S. palustris* as antihyperlipidemia (Adawiyah et al., 2020) and antimalaria (Azizah et al., 2022). *S. palustris* can improve changes in glucose metabolism by Cd (Suhartono et al., 2020) and contains antioxidant, anti-inflammatory, and biological activities (Dvorakova et al., 2024). With its phytochemical content, it can also inhibit cholinesterase against Alzheimer’s disease (Chear et al., 2016).

Our results showed that *S. palustris* extract can reduce the blood glucose levels for 21 days, with statistical results showing significant differences ($p = 0.05$). Similarly, the cortisol levels at H21 showed a significant difference ($p = 0.05$). In the KN, the K+ and P2 groups showed significantly lower cortisol levels compared with that in the K– group. Higher cortisol levels were found, indicating stress (stress hormone cortisol) (Jameel et al., 2014).

In diabetic rats, hyperglycemia leads to impaired hippocampal function as a result of neuronal apoptosis. Elevated glucose levels disrupt the hippocampus’ ability to regulate the HPA axis, causing a prolonged activation of the axis and an increase in the CRH, ACTH, and cortisol levels. A high cortisol level negatively affects GLUT4, reducing insulin production, which prevents glucose from being absorbed into the muscles.

Table II. Mean cortisol levels of the Wistar rats at H21

Group	Mean ± SD (nmol/mL)	*p*
KN	209.148 ± 40.61	
K–	320.90 ± 32.42	
K+	221.53 ± 70.69	0.035*
P1	256.57 ± 54.27	
P2	248.05 ± 63.69	

Source: Primary data, 2024
Description: KN = normal control; K(−) = DM; K(+) = DM and given metformin 0.45 mg/kgBW/day; P1 = DM rats given 400 mg/kgBW/day extract; P2 = DM rats given 800 mg/kgBW/day extract; and *significant difference ($p < 0.05$) in one-way ANOVA test.

Table III. Summary of the post-hoc test results

Intergroup comparison	*p*-Value
KN–K (−)	0.004*
KN–K+	0.722
KN–P1	0.182
KN–P2	0.270
K (−)–K+	0.009*
K (−)–P1	0.075
K (−)–P2	0.046*
K+–P1	0.319
K+–P2	0.448
P1–P2	0.806

Source: Primary data, 2024
Notes: *Significant difference ($p < 0.05$) using LSD

This results in elevated blood glucose levels and promotes the conversion of amino acids into glucose in the liver through gluconeogenesis (Joseph & Golden, 2017).

Further research is still required to determine its potential as a therapy or supplementary treatment. Under hyperglycemic conditions, an imbalance between antioxidants and reactive oxygen species production leads to oxidative stress, which contributes to the progression of diabetes and related complications in adults. Numerous studies involving natural plants with bioactive compounds conducted both in vivo and in vitro have demonstrated antioxidant properties that may help mitigate diabetes and its associated complications (Bhatti et al., 2022). Diabetes mellitus and psychological stress have short- and long-term effects under stressful conditions (Cheung et al., 2019).

CONCLUSION

A significant reduction in both the blood glucose and cortisol levels ($p = 0.05$) was observed in type 2 diabetes mellitus model rats following the administration of *S. palustris* (Burm.) Bedd extract, with notable effects continuing up to Day 21.

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