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Catechin Isolates from Gambir (*Uncaria gambir* Roxb) Maintain Glucose Homeostasis in Diabetic Model Rat

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Abstract: The prevalence of diabetes mellitus is rising globally. Oxidative stress, which can result from hyperglycemia in diabetes, might have negative consequences. An antioxidant is needed to prevent hyperglycemia. Cathechin isolates are derived from gambir, which has many antioxidants. This study examines catechin isolates from gambir (*Uncaria gambir* Roxb.) effect on glucose homeostasis in rats induced by alloxan. For this experiment, 35 male rats were employed. Male rats were given alloxan (150 mg/BW, IP), and after 72 hours, blood glucose levels were assessed. If blood glucose levels exceeded 200 mg/dl, three oral catechin isolates were administered (T1=10 mg/kg/day, T2=20 mg/kg/day, and T3=40 mg/kg/day). Following blood collection on the experiment's last day, fasting blood glucose, glucagon and insulin levels were measured. Catechin isolates decreased blood glucose levels in all treatment groups compared to the positive control group (T1 = 150.750 ± 14.359 mg/dl; T2 = 159.750 ± 15.434 mg/dl, and T3 = 153.375 ± 20.207 mg/dl vs 385 ± 60.989 mg/dl) significantly (p value-0.05). A decrease in glucagon serum level was also observed in the treatment group vs positive control (T1: 193.855 ± 36.009 pg/ml, T2 = 286.689 ± 20.313 pg/ml, and T3 = 319.462 ± 30.060 pg/ml vs 529.825 ± 74.279 pg/ml), significantly. Catechine isolates in the T3 group showed an increase in insulin serum level compared to the positive control group significantly (T3 = 216.640 ± 38.230 µIU/ml vs 69.833 ± 3.071 µIU/ml). In conclusion, catechin isolates from gambir decreased blood glucose levels by reducing glucagon and increasing insulin serum levels.
Keywords: Gambir catechins; glucagon; insulin; rat.

INTRODUCTION

Globally, the quantity of people who have diabetes continues to increase. The International Diabetes Federation (IDF) estimates that 463 million people worldwide have diabetes in 2019 (Saeedi et al., 2019). There will be 537 million adults with diabetes globally in 2021, 643 million in 2030, and 783 million in 2045, according to projections. Indonesia has the fifth-highest number of individuals with diabetes mellitus worldwide in 2021, behind the US, China, India, and Pakistan. The number of Indonesians with diabetes mellitus in 2019 reached 3.9 million (International Diabetes Federation, 2021). This condition causes diabetes mellitus to become a problem not only in the world but also in Indonesia.

A condition known as hyperglycemia occurs when blood glucose levels rise above the usual range. Type 1 or type 2 diabetes typically affects people with this

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condition (Lee & Halter, 2017; Skyler et al., 2017). Oxidative stress from hyperglycemia may result in harmful complications (Davies et al., 2022; Huang et al., 2017; Umpierrez & Pasquel, 2017). Current diabetic mellitus therapies have assisted in overcoming hyperglycemia (Elsayed et al., 2023; Foretz et al., 2023). However, adverse effects from standard treatment are frequently experienced (Ahmad et al., 2020; American Diabetes Association, 2018; Nauck et al., 2021). Therefore, there is a need for alternative treatments that are relatively safe and have minimal side effects. The use of antioxidants to treat oxidative stress in people with diabetes is one potential alternative treatment.

Numerous research examined the role of antioxidants in diabetes situations (Ghasemi-Dehnoo et al., 2020; Johansen et al., 2005; Pinela et al., 2023). It has been demonstrated that taking antioxidant supplements helps people with diabetes with hyperglycemia (Balbi et al., 2018; Park & Park, 2021; Yi et al., 2023). Diabetes mellitus can be cured by the many medicinal plants found in Indonesia. One of Indonesia's West Sumatra Province's medicinal plants, gambir (*Uncaria gambir* Roxb), has been shown to provide a variety of benefits for treating illnesses, including diabetes mellitus (Arundita et al., 2020; Mat Saad et al., 2020; Munggari et al., 2022). There have been reports of gambir extract having antihyperglycemic properties (Munggari et al., 2022; Yuniarti & Ramadhani, 2023; Zebua et al., 2018). Catechin is the primary antioxidant component of gambir extract (Anggraini et al., 2011; Aprely et al., 2021; Yanis Musdja et al., 2018). Since there is little information on how catechin isolates from gambir prevent hyperglycemia through hormonal secretion, this study aims to determine how catechin isolates affected the insulin, glucagon, and fasting blood glucose levels in rats administered alloxan. Insulin and glucagon predominantly control glucose homeostasis.

MATERIALS AND METHODS

Animal

The 35 male Wistar rats, ages 8 to 12, were housed in compliance with Andalas University's Faculty of Medicine guidelines. The Research Ethics Committee of the Faculty of Medicine at Universitas Andalas granted ethical clearance for this research, with reference number 518/KEP/FK/2018. Rats were kept in controlled environments with a light-dark cycle, temperature, and humidity. Animals were acclimatized for one week before experiments.

Measurement of Fasting Blood Glucose Level

The Glucose Oxidase-Peroxidase Aminoantypirin (GOD-PAP) method was used to test the fasting blood glucose levels. Rats were fasted 8-10 hours before the experiment. The retroorbital vein collected blood, then centrifuged and separated 10 µl serum. The spectrophotometer (Microlab 300) measured blood glucose serum levels at 505 nm wavelength (Rita et al., 2023).

Induction of Hyperglycemia by Alloxan

As previously reported, alloxan 150 mg/BW was injected intraperitoneally to induce hyperglycemia (Rita et al., 2015, 2023; Safithri & Fahma, 2008). A glucometer (ACCUCHECK) measured the rat's fasting blood glucose after 72 hours. If the level was over 200 mg/dl, the rat was treated with several dosages of catechin isolates. At the end of the experiment, fasting blood glucose levels were measured with insulin and glucagon serum levels.

Preparation of Catechin Isolates From Gambir

Andalas Sitawa Fitolab Company produced catechin isolates from gambir that contained 91.8 percent catechin (Certificate of Analysis No. 01/PE-FP/2017). This

investigation employed three doses of catechin isolate solution (10 mg/kg/day, 20 mg/kg/day, and 40 mg/kg/day) (Alioes et al., 2019; Rahmi et al., 2021).

Experimental Design

Negative control: Normal rat
Positive control: Alloxan 150 mg/kg (intraperitoneal)
Treatment Group 1: Alloxan 150 mg/kg (ip)+ catechin isolates 10 mg/kg/day (per oral), two weeks
Treatment Group 2: Alloxan 150 mg/kg (ip) + catechin isolates 20 mg/kg/day (per oral), two weeks
Treatment Group 3: Alloxan 150 mg/kg (ip) + catechin isolates 40 mg/kg/day (per oral), two weeks
Blood was drawn from the sinus retroorbitalis on the experiment's final day to assess the serum's glucagon and insulin levels.

Measurement of Insulin Serum Level

The sample and 100 µl of the standard are put into the proper well. After covering the well is incubated at room temperature for two and a half hours. Substances that obstruct the interaction between antigens and antibodies are eliminated from the solution by washing it with a wash buffer. Following drying, each well receives 100 µl of biotinylated antibodies, which are then incubated for an hour at room temperature. After that, the solution is thrown away and cleaned once again using a wash buffer. Following drying, each well receives 100 µl of Streptavidin solution, which is then incubated for 45 minutes at room temperature. After discarding the solution and giving it another wash, 100 µl of TMB One-Step Substrate Reagent is added to each well. After 30 minutes of room temperature incubation in dark condition, fill each well with 50 µl of Stop Solution. A 450 nm wavelength spectrophotometer reads the solution instantly (Jayaraman et al., 2021).

Measurement of Glucagon Serum Level

Fasting glucagon serum levels were measured by EIA (Ray Biotech, USA). Each well receives 100 µl of anti-glucagon antibodies and stays at room temperature for 1.5 hours. After discarding the solution, a wash solution buffer is used to wash the well. The well is filled with 100 µl of the standard and 100 µl of the sample, sealed and allowed to incubate at room temperature for two and a half hours. After being thrown away, the solution is cleaned four times. Then, the well is added by 100 µl of HRP-Streptavidin solution to the well and incubated for 45 minutes at room temperature. TMB One-Step Substrate Reagent (100 µl) is applied to each well and kept at room temperature in a dark environment for 30 minutes. Each well receives 50 µl of Stop Solution, then measured at 450 nm wavelength (Desai & Harris, 2014).

Statistical Analyses

Fasting blood glucose, glucagon, and insulin serum were represented as mean ± SEM. A data normality test with Shapiro Wilk shows normal-distributed data ($p > 0.05$). Fasting blood glucose, glucagon, and insulin serum data were analyzed by Oneway Anova and continued by Post Hoc Multiple Comparison Tukey HSD by GraphPad. P-values less than 0.05 were regarded as significant data.

RESULTS AND DISCUSSION

The gambier plant is a medicinal plant that is rich in antioxidants. Catechin is the most abundant antioxidant in gambir. The present study indicated that catechin isolates from gambir (*Uncaria gambir* Roxb) could decrease fasting blood glucose and glucagon serum levels. In contrast, serum insulin levels were increased compared to positive control groups.

Administration of alloxan (150 mg/kg BW, ip) increased fasting blood glucose level in the positive control group vs negative control group (385 ± 60.989 mg/dl vs 76.857 ± 1,883 mg/dl). Catechin isolates of gambir decreased blood glucose levels when compared to the positive control group in all treatment groups and statistically significant ($p < 0.05$) (blood glucose level of Treatment 1 = 150.750 ± 14.359 mg/dl, Treatment 2 = 159.750 ± 15.434 mg/dl, and Treatment 3 = 153.375 ± 20.207 mg/dl vs 385 ± 60.989 mg/dl).

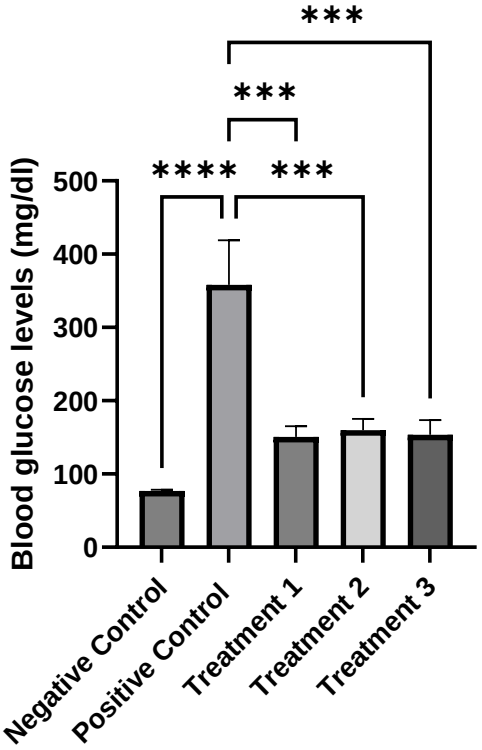

Figure 1. Catechin isolates lowered alloxan-induced rats' fasting blood glucose levels. All treatment groups that received three doses of catechin isolates (Treatment 1/(T1): 10 mg/kg BW/day; Treatment 2/(T2): 20 mg/kg BW/day; and Treatment 3/(T3): 40 mg/kg/day) had significantly higher fasting blood glucose levels than the negative control group. ***p value < 0,001, ****p value < 0.0001; n = 7-8 rats per group; Post-Hoc Tukey HSD

Much experimental research has reported alloxan-induced Hyperglycemia (Banda et al., 2018; Ighodaro et al., 2017; Yin et al., 2018). Alloxan significantly increased fasting blood glucose in this study compared to the negative control group. Alloxan selectively damages rodent pancreatic beta cells (Singh et al., 2020). This condition causes animal insulin-dependent diabetes (Ighodaro et al., 2017; Yimam et al., 2014). Reactive oxygen species (ROS) production and the redox cycle mediate the cytotoxic impact of alloxan, which harms pancreatic beta cells. This causes a severe increase in the calcium concentration in the beta cell's cytosol, damaging the pancreatic beta cells and increasing blood glucose levels. (Ighodaro et al., 2017). Administration of catechin isolates from gambir decreased fasting blood glucose levels in all treatment groups compared to the positive control group. The decrease in blood glucose values in each treatment group was caused by the effect of gambier catechin, which overcame oxidative stress caused by alloxan induction. Catechin is a potent antioxidant that can overcome oxidative stress in pancreatic beta cells to reduce blood glucose levels. (Wen et al., 2022; Yuniarti & Ramadhani, 2023) This result confirmed

a previous study that found the antihyperglycemic effect of gambir extract (Munggari et al., 2022; Yuniarti & Ramadhani, 2023; Zebua et al., 2018).

The glucagon level in the negative control group was 283.678 ± 35.962 pg/ml. Alloxan administration enhanced glucagon serum level in the positive control group (529.825 ± 74.279 pg/ml), and catechin isolates decreased glucagon serum level (T1: 193.855 ± 36.009 pg/ml, T2 = 286.689 ± 20.313 pg/ml, and T3 = 319.462 ± 30.060 pg/ml). The glucagon levels of all treatment groups and the positive control group varied significantly.

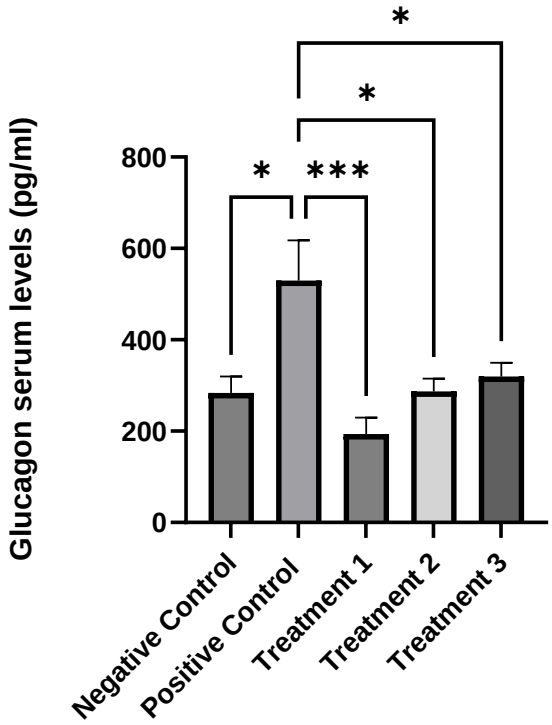

Figure 2. Alloxan raises glucagon serum levels in the positive control group relative to the negative control group, and catechine isolates decreased glucagon levels in all treatment groups relative to the positive control group. Post Hoc Tukey HSD, *p-value < 0,05, ***p value < 0.001; n = 5-8 rats per group Catechine isolates significantly reduced glucagon levels in all treatment groups relative to the positive control group.

Compared to the negative control group, the positive control group's fasting insulin level was lower (69.833 ± 3.071 µIU/ml vs 194.794 ± 31.418 µIU/ml). In all treatment groups, gambir catechin isolates increased fasting insulin levels. (T1 = 76.928 ± 18.005 µIU/ml, T2 = 143.345 ± 14.029 µIU/ml, T3 = 216.640 ± 38.230 µIU/ml), But only T3, and there were notable differences in the positive control group (p-value < 0.001)

One way to determine the mechanism of decreasing blood glucose levels caused by alloxan is by examining insulin and glucagon hormone levels. These two hormones significantly influence the homeostasis of glucose. Rats given alloxan had elevated serum glucagon levels. Other forms of diabetes, including type 1 diabetes, have been shown to have elevated glucagon levels (Cryer, 2012; Hughes & Narendran, 2014). According to other research, type 1 diabetes impairs the glucagon response to hypoglycemia circumstances (Bisgaard Bengtsen & Møller, 2021). The intraislet connection between alpha cells and pancreatic beta cells demonstrates that insulin inhibits the secretion of glucagon by pancreatic alpha cells (Cryer, 2012; Wang

et al., 2013). Administration of gambir catechin significantly reduced serum glucagon levels compared to the positive control.

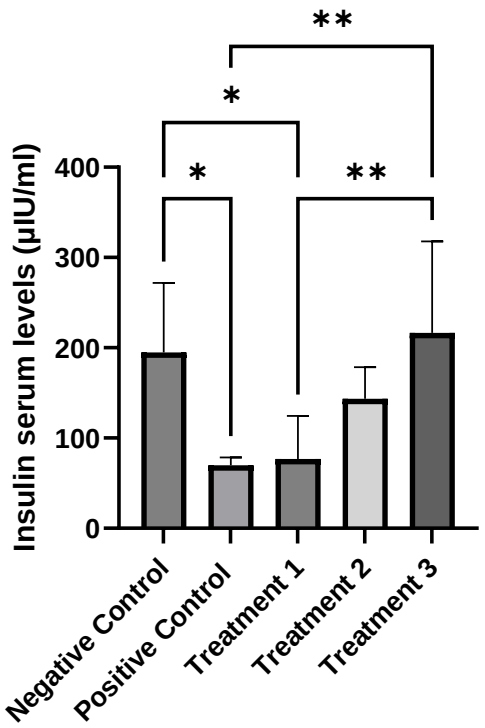

Figure 3**.** Catechin isolates increased insulin serum levels in rats induced by alloxan. Alloxan injection decreased serum levels of insulin in the positive control group as opposed to the negative control group (69.833 ± 3.071 µIU/ml vs 194.794 ± 31.418 µIU/ml. Catechine isolates increase insulin serum levels in a dose-dependent manner (T1 = 76.928 ± 18.005 µIU/ml, T2 = 143.345 ± 14.029 µIU/ml, T3 = 216.640 ± 38.230 µIU/ml). Post Hoc Tukey HSD, *p value < 0,05, **p value < 0.01; n = 5-8 rats per group.

The positive control group in this study had lower serum insulin hormone levels than the negative control group. Alloxan injection significantly harms pancreatic beta cells, lowering insulin levels (Eriani et al., 2021; Ighodaro et al., 2017; Kumar Sharma et al., 2010). Giving gambir catechin isolate 40 mg/kg/day was able to return serum insulin levels to close to normal levels. These findings are consistent with those of the group that received gambier catechin isolate, which had lower blood glucose levels. Gambir catechin can normalize serum insulin levels to reduce blood glucose after alloxan induction. Research shows that Epigallocatechin gallate (EGCG) can preserve the function of pancreatic β-cells by reducing reactive oxygen species (ROS) (Meng et al., 2019). Additionally, it has been claimed that EGCG can protect pancreatic beta cells by lowering iNOS production (Meng et al., 2019; Zhu et al., 2022). The remaining pancreatic beta cells are protected, so insulin levels return to normal.

Taken together, insulin and glucagon are crucial in preserving blood glucose levels. In diabetes, a defect in insulin and glucagon secretion leads to hyperglycemia. Administration of catechin isolates from gambir in diabetic conditions enhances insulin levels and decreases glucagon levels, leading to decreased blood glucose levels. This result suggested that catechin isolates from gambir maintained blood glucose homeostasis in diabetic conditions. This study's limitation is that it focuses only on insulin and glucagon hormones. Many other hormones are involved in glucose

homeostasis, such as incretin hormones (GLP-1 and GIP), growth hormone, amylin, cortisol, and epinephrine.

CONCLUSION

Catechin isolates from Gambir are crucial for preserving glucose homeostasis in diabetes. Glucose homeostasis is maintained by decreasing glucagon and increasing insulin levels. In the future, it is important to elucidate further the effect of catechin isolates on other hormones related to glucose homeostasis.

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CONFLICT OF INTEREST

No conflict of interest exists.

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