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Combination of Secang (*Caesalpinia sappan* L.) and Glibenclamide in Mice (*Mus Muscullus*) Hyperglycemia

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ABSTRACT

Diabetes is a disease whose sufferers continue to increase in Indonesia. The International Diabetes Federation (IDF) in 2019, estimated that around 463 million people with the disease. This figure is likely to continue to increase, up to 578 million in 2030 and 700 million in 2045. The use of herbal medicines is now growing, one of which comes from the secang woods *(Caesalpinia sappan* L.*)*. The plant is rich in active bioactive components such as flavonoids and tannins. The flavonoids contained in secang have the ability to inhibit the enzyme α-glucosidase, which plays a role in lowering the reabsorption of sugar into the blood. This study aims to determine the antihyperglycemic activity of the combination of sappang *(Caesalpinia sappan* L*)* and glibenclamide in hyperglycemic mice. This research was carried out by providing treatment to the grouped mice. This study was experimental using a pretest-posttest with a control group design. The results showed a significant difference in the average blood sugar levels of mice induced by alloxan in the group given a combination of secang and glibenclamide, namely a decrease in blood sugar levels from 223 mg/dL to 105,92 mg/dL after treatment.

Keywords: Diabetes, Glibenclamide, Secang,

Introduction

Diabetes mellitus (DM) is a long-lasting disease that occurs when the pancreas is unable to produce sufficient amounts of insulin, a hormone that functions to control blood sugar levels, or when the body is unable to use insulin effectively. The consumption of antidiabetic drugs generally lasts for a long time and continuously, so that it stimulates significant side effects of the drug, such as liver disorders, gastrointestinal pain, and kidney disorders. In addition, certain drugs do not always provide optimal therapeutic effects, with the potential for unwanted effects such as weight gain, indigestion, hypoglycemia, non-optimal bone function, vitamin B12 deficiency, and urinary tract disorders (Utomo et al., 2023).

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Sulfonylurea is one of the most commonly used therapeutic classes for DM worldwide. However, treatment with sulfonylurea alone is often not able to maintain glycemic targets and causes side effects. Failure of monotherapy over time indicates the need for a combination of therapies to achieve glycemic target levels. Oxidative stress has been hypothesized to be one of the pathogenic mechanisms in DM.

According to a study, the combination of Glibenclamide with Habbatussauda *(Nigella sativa)* has been shown to be effective in lowering blood sugar levels. This finding is in line with the results of Ali et al, (2021), who showed that the combination of Glibenclamide with Habbatussauda was able to significantly reduce sugar levels, more effectively than the use of Glibenclamide alone.

Combination therapy with herbal plants is one of them, namely Secang *(Caesalpinia sappan L.),* which comes from the family Leguminosae. Secang wood is a plant rich in bioactive components such as terpenoids and saponins. The plant has strong antioxidant activity and anti-inflammatory properties. Previous research has shown that Secang root bark extract can protect pancreatic cells against oxidative damage and inhibit glycation reactions. This shows that Secang has potential in the treatment of diabetes.

Based on the background, we want to evaluate the effect of the combination of secang *(Caesalpinia sappan* L.*)* and Glibenclamide in lowering blood sugar levels of male white mice (Mus musculus) that were induced with aloxan.

Methodology

This study is an experimental study using a "pretest-posttest with control group" design. In this study, the experiment was carried out on experimental animals in the form of mice that were divided into four groups. Each group consisted of six mice.

The plant used in this study was Secang, that were identified in the laboratory of the Mitra Sehat Mandiri Sidoarjo Academy of Pharmacy. This plant was obtained from Krian District, Sidoarjo Regency. After the Secang is taken, the wood is washed thoroughly and then dried in a place protected from direct sunlight, so that the moisture content does not decrease. When the sappan wood is dry, blend it using a blender, then filtered until a fine powder. The next process is to soak the powder with 96% ethanol solvent and then filter it to obtain the filtrate. After the filtrate is obtained, it is evaporated with a rotary evaporator until it becomes a viscous extract.

Glibenclamide used in the study was a tablet with a dose of 5 mg. Two tablets are crushed into a fine powder, then weighed and mixed with a 1% CMC Na solution, which acts as an emulsifier. The mixture is then mixed until homogeneous.

Before treatment, mice were adapted for 5 to 7 days. Keep mice in cages with adequate ventilation and lighting, and lined with wood powder. Before treatment, mice were fasted for 10–12 hours, then weighed, and fasting blood sugar levels were tested to minimize the influence of external factors on glucose levels. DM induction was performed by adding aloxan with a dose of 180 mg/kgBB through intraperitoneal injection. Three days after the injection, blood glucose levels were measured again (pretest).

Mice are grouped into four groups, where each group contains six mice. The first group was a negative control and was given aquadest. Positive controls used glibenclamide at a dose of 0,013 mg/kgBB. The third group received treatment in the form of secang wood extract with a dose of 100,8 mg/kgBB. Finally, the fourth group received a combination of sappang wood extract and glibenclamide. The medication was administered orally using a probe, and the intervention with the secang wood extract lasted for 14 days.

Blood glucose levels were measured before and after the intervention, namely at the pretest and posttest stages. Blood collection was carried out by cutting the tail of a mouse, then the blood was dripped into a blood sugar strip and measured using a glucometer. Data analysis was carried out with the One-Way ANOVA test if the data were normal, while the Kruskal-Wallis test was carried out if the data did not meet the normality assumption.

Result and Discussion

The results of this study showed that the blood sugar levels in mice that have been induced by alloxan.

Table 1. Results of the blood sugar levels in pre-test mice.

Group	N	Min (Mg/dL)	Max (Mg/dL)	Average ±SD
K (+)	6	211	250	233,71 ±15,51
K (-)	6	215	241	228,13 ±11,17
Extract	6	217	243	227 ±10,03
Combination treatment	6	209	257	223 ±19,08

Based on Table 1, the average post-test blood glucose levels varied across the different groups. The positive control group had an average level of 233.71 mg/dL, compared to 228.13 mg/dL for the negative control. In contrast, the extract treatment group average 227 mg/dL, whlie the combination treatment group had a mean of 223 mg/dL.

Table 2. Results of the blood sugar levels in post-test mice.

Group	N	Min (Mg/dL)	Max (Mg/dL)	Average ±SD
K (+)	6	120	151	137,01 ±11,17
K (-)	6	192	218	199,99 ±11,52

Extract	6	111	127	118 ±5,21
Combination treatment	6	94	124	105,92 ±10,02

Based on Table 2, the average post-test blood glucose levels varied across the different groups. The positive control group exhibited an average of 137,01 mg/dL, the negative control group showed 199,99 mg/dL, the extract group recorded 118 mg/dL, and the combination group had an average of 105,92 mg/dL.

The analysis of blood glucose levels inmice involved pretest and posttest assessments for the positive control, negative control, and extract groups, followed by normality and homogeneity tests for tests for the combination groups. The analysis results indicated a p-value greater than 0.05, suggesting that the data met the requirements of parametric statistical testing due to its normal distribution. To compare blood glocose levels between pretest and posttest, *a paired samples* t-test was conducted. Additionally, a One-way ANOVA was performed to analyze the post-test glucose levels among the groups. The results of the One-way ANOVA revealed significant differences in posttest blood glucose.

Table 3. Results of Bonferroni's Post-hoc test in the Post-test blood glucose group

Group	K(-)	K(+)	Extract	Combination treatment
K (+)		0,000	0,000	0,000
K (-)			1,000	1,000
Extract				0,972
Combination treatment				

Based on Table 3, there was no difference in the positive control group, however in the negative control group and the other groups, there was a significant difference in results.

The results of the analysis of blood glucose levels in pre-test mice induced by alloxan showed an average glucose concentration of more than 200 mg/dL. This increase in glucose levels in all alloxan-induced groups was due to the mechanism of alloxan in inhibiting glucokinase activity, an enzyme that is important for regulating glucose levels and insulin production. Meanwhile, Alloxan also causes the formation of reactive oxygen species (ROS) which causes pancreatic beta gland necrosis. This damage can cause DM in mice.

Blood glucose in post-test mice showed significant differences across groups. The negative control group showed an average of 199.99 mg/dL, the positive control group at 137.01 mg/dL, the extract group at 118 mg/dL, and the combination group at 105.92 mg/dL. Then, the positive control group treated with glibenclamide showed a good blood glucose range of 62.8–176 mg/dL, which was due to glibenclamide's ability to increase insulin secretion from its granules by interacting with ATP-sensitive K channels in the cell membrane. This interaction then opens the Ca2+ ion channel, allowing ions to flow into beta cells and stimulate insulin production. Meanwhile, the negative control group given distilled water recorded a high average glucose, because distilled water served as a negative control in the study and did not affect blood sugar levels. In contrast, the group treated with secang extract showed an average blood glucose level within a safe range, which was associated with the presence of bioactive compounds in secang, such as Brazilian, saponins, tannins, and alkaloids. Flavonoids in this extract are also known for their effects in lowering blood sugar levels through mechanisms such as inhibiting sugar absorption and increasing blood glucose reabsorption, in addition to regulating carbohydrate metabolism enzymes.

The results of the t-dependent test analysis comparing pre-test and post-test blood glucose levels showed significant differences in all groups, indicating that pre-test and post-test measurements contributed effectively to stabilizing blood glucose levels. Meanwhile, the results of the blood glucose comparison analysis with the One-Way ANOVA test showed differences between groups, so it could be continued with the Bonferroni post hoc test. Based on the results of the Bonferroni post hoc test, there was no significant difference in the positive control group. However, the combination treatment group experienced a more substantial and significant decrease in blood glucose levels.

The administration of a combination of glibenclamide and sappanwood extract for 14 consecutive days showed good positive changes. However, statistically there was no significant change in blood sugar levels. This lack of significance may be due to insufficient treatment duration. According to Marwan et al. (2020), factors that can affect research results are the cleanliness of the mouse environment, availability of food and water, air circulation, lighting, and room temperature can trigger stress and disrupt animal metabolism. (Marwan et al., 2020).

Conclusion

In this study, the treatment of secang extract *(Caesalpinia sappan* L.*)* combined with glibenclamide shows antihyperglycemic activity. Combination of secang extract *(Caesalpinia sappan* L.*)* and glibenclamide in male white mice (Mus musculus), which were induced by alloxan, was shown to be effective for lowering blood glucose levels.

Declaration of Competing Interest

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