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The Effect of Gambir Leaf Tea (*Uncaria gambir* Roxb) on Superoxide Dismutase in Diabetic Model Rats

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ABSTRACT

Diabetes mellitus causes dangerous conditions due to hyperglycemia toxicity. Hyperglycemia in diabetes produces reactive oxygen species (ROS) that can deactivate the antioxidant system, leading to oxidative stress. This research aims to examine the effect of gambir leaf tea on superoxide dismutase levels in a diabetic rat model. This research is an experimental study with a post-test only control group design using 36 rats divided into six groups: K(-) received a standard diet and aquadest, K(+) was induced with alloxan, K MET received metformin, and those given gambir leaf (*Uncaria gambir* Roxb.) P1 (1 g/100 ml), P2 (2 g/100 ml), and P3 (4 g/100 ml) for 30 days. The SOD level was measured using an ELISA reader. Data were analyzed using Kruskal-Wallis and Post Hoc Mann-Whitney. The research results indicate that there is no significant effect of administering gambir leaf on the increase of SOD levels ($p>0.05$).

Keywords: Diabetes Mellitus, Hyperglycemia, Superoxide Dismutase Levels, Gambir Leaf Tea.

1. INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disease characterized by elevated blood glucose levels. There are two main types of diabetes mellitus, namely Type-1 and Type-2. Type-2 diabetes occurs when the body becomes resistant to insulin or does not produce enough insulin. Type-1 diabetes, also known as juvenile diabetes or insulin-dependent diabetes, is a chronic condition in which the pancreas produces little or no insulin at all [1].

The International Diabetes Federation reported that in 2021, there were 90 million adults (aged 20-79) living with diabetes in Southeast Asia. This figure is expected to rise to 113 million by 2030 and 152 million by 204 [2]. The prevalence of diabetes mellitus in Indonesia is 19.5 million, ranking fifth in the world for the highest number of sufferers, and is a leading cause of death [2,3]. West Sumatra had a diabetes prevalence of 1.6% in 2018, ranking 21st out of 34 provinces in Indonesia [4]. The number of diabetes cases in West Sumatra in 2018 was 44,280, with the highest number located in the city of Padang, totaling 12,231 cases [5].

Diabetes mellitus causes dangerous conditions due to hyperglycemia toxicity. Hyperglycemia in diabetes produces reactive oxygen species (ROS), which can damage DNA, lipids, and proteins and are considered significant mediators or contributors to the development of diabetes complications [6,7]. Oxidative stress occurs when the concentration of ROS is higher in

the body while the amount of antioxidant enzymes is minimal [8,9]. This imbalance can lead to cellular damage, particularly affecting lipids in cell membranes and disrupting normal physiological functions.

In facing free radical attacks, the body has a protective mechanism: the antioxidant system. Antioxidants can inhibit the oxidation of essential molecules such as proteins, fats, and DNA caused by free radicals by donating their electrons or acting as reducers [10]. There have been many health benefits from antioxidants, particularly their role in combating oxidative stress by reducing the formation of reactive oxygen species, thus playing a part in preventing or treating diabetes and related complications [11, 12]. Superoxide dismutase (SOD) is a primary antioxidant that plays a role in combating free radicals, specifically superoxide anions [13]. Superoxide anions are free radicals that are catalyzed by SOD into hydrogen peroxide and oxygen molecules, allowing them to decompose into less toxic compounds [14].

The gambir plant (*Uncaria gambir* Roxb) has a very high antioxidant content derived from its leaves and branches. Antioxidants in gambir leaves consist of alkaloids and phenolic compounds, including flavonoids that act as antioxidants, such as catechins. This gives gambir various health benefits [15, 16, 17]. Gambir leaf tea is a beverage made from gambir leaves that have been dried using a smoking method and ground into a powder, which is then brewed with hot water, resulting in a tea-like drink with a brownish color. The administration of tea containing catechins can inhibit oxidative stress and repair damage caused by free radicals [18, 19, 20].

Research conducted by Alexandra in 2023 studied the effects of *Uncaria gambir* Roxb. extract on antihyperglycemic activity, the antioxidant enzyme SOD, and MDA levels in rats induced with streptozotocin. The results demonstrated that the administration of ethanol extract of *Uncaria gambir* could enhance SOD activity in rats induced with streptozotocin [21]. Based on the background above, this research was conducted to determine the effect of giving gambir leaf tea (Uncaria gambir Roxb.) on the levels of SOD in diabetic model rats, thereby providing scientific information about the antioxidant effects of gambir leaves on diabetes mellitus.

2. MATERIALS & METHODS

2.1. Place and Time

This research was conducted at the Biochemistry Laboratory of the Faculty of Medicine, the Biomedical Laboratory of the Faculty of Medicine, and the Animal House of the Pharmacy Laboratory of Andalas University from November 2023 to July 2024.

2.2. Materials

Standard feed, rice husk, alloxan, aqua dest, gambir leaf powder, NaCl, metformin, a serum sample, Rat Superoxide Dismutase, Cu-Zn, and SOD1 ELISA Kit from BT Lab.

2.3. Experimental Animals

This research uses Wistar rats aged approximately 8 weeks, weighing around 200 grams, obtained from the Pharmacy Laboratory of the Faculty of Pharmacy at Andalas University. The maintenance of mice is carried out in a laboratory with adequate ventilation and lighting, without direct sunlight, and with a light and dark cycle maintained every 12 hours. This research has received approval from the Ethics Commission of the Faculty of Medicine at Andalas University with permit number 58/UN.16.2/KEP-FK/2023.

2.4. The Production of Gambir Leaf Tea

Gambir leaf tea is made using dried gambir leaves that have been smoked and ground into a powder, which is then steeped in hot water at 70° – 90 °C for about 3 minutes.

2.5. Treatment

The rats were acclimatized for 7 days before the treatment and then randomly divided into six treatment groups. The negative control group (K-) was only given a

standard diet and aquadest. The positive control group (K+) was induced with alloxan (Dose 125 mg/kg body weight) without being given gambir leaf tea. The K MET group consisted of rats induced with alloxan and then given metformin. The treatment groups 1, 2, and 3 were rats induced with alloxan and then given gambir leaf tea at doses of 1 gram/100 ml, 2 grams/100 ml, and 4 grams/100 ml for 30 days. After that, the levels of superoxide dismutase were examined in the serum samples of the rats.

2.6. Measurement of SOD Levels

The examination of SOD levels uses the Rat Superoxide Dismutase, Cu-Zn, SOD1 ELISA Kit from BT Lab. The device used for the SOD examination is the Bio-Rad ELISA reader. The principle of the SOD examination is that the plate has been pre-coated with Rat SOD1 antibodies. SOD1 present in the sample will bind to the antibodies coated on the wells. The addition of biotinylated Rat SOD1 Antibody leads to the binding with SOD1 in the sample. Next, Streptavidin-HRP will be added, binding to the biotinylated SOD1 antibody. After incubation, unbound Streptavidin-HRP is removed during the washing stage. The substrate solution is then added, and a color change occurs that is proportional to the amount of Rat SOD1. The reaction is terminated by adding an acid-stop solution, and the absorbance is measured at a wavelength of 450 nm.

STATISTICAL ANALYSIS

All data analysis is done using computers. The results of the measurements of serum SOD levels are presented as mean ± standard deviation (mean ± SD). Data were analyzed using the Kruskal-Wallis test. Significant data ($p < 0.05$) were followed by post-hoc Mann-Whitney analysis to determine the significance of the differences in the research results.

RESULT

The average SOD levels are K- (6.59 ± 0.66 U/mL), K+ (5.92 ± 1.82 U/mL), K MET (6.88 ± 0.68 U/mL), P1 (6.19 ± 1.52 U/mL), P2 (7.17 ± 1.72 U/mL), and P3 (7.53 ± 1.00 U/mL). The Kruskal-Wallis test showed no significant differences between the treatment groups. However, there is a trend of increasing SOD levels in the P1, P2, and P3 groups.

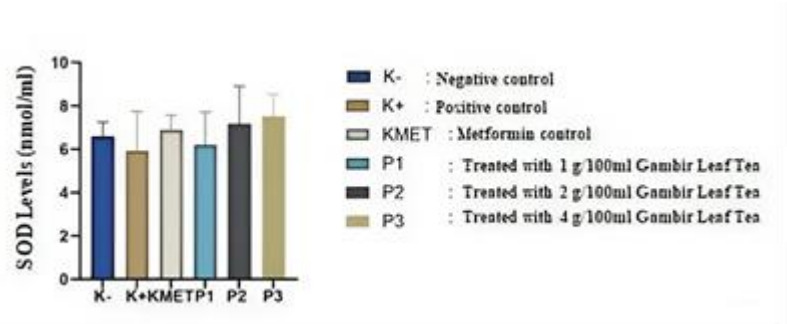

Figure 1 Graph of SOD Levels (nmol/mL) in All Groups

DISCUSSION

The results of the SOD level measurements in Figure 1 show no significant differences in the average superoxide dismutase (SOD) levels across all groups. Although there were no significant differences between groups, there was an increase in the average SOD levels in the treatment group 1 (P1), treatment group 2 (P2), and treatment group 3 (P3), which were 6.19 ± 1.52 U/mL, 7.17 ± 1.72 U/mL, and 7.53 ± 1.00 U/mL, respectively, compared to the positive control group (K+) with an average SOD level of 5.92 ± 1.82 U/mL. The average SOD level in the DM control group (K MET) showed no significant difference, measuring 6.88 ± 0.68 U/mL compared to

the positive control group (K+) with an average SOD level of 5.92 ± 1.82 U/mL.

The decrease in SOD levels in the positive control group (+) is caused by the administration of alloxan, which leads to oxidative stress conditions in hyperglycemic rats, resulting in an increased rate of lipid peroxidation that contributes to the production of free radicals, including the formation of superoxide anions, thereby causing oxidative modifications that lead to the inactivation of SOD [21].

Rats in treatment group 1 (P1), treatment group 2 (P2), and treatment group 3 (P3), which were given gambir leaf tea at doses of 1 g/100 ml, 2 g/100 ml, and 4 g/100 ml, experienced an increase in the average SOD levels compared to the positive control group (K+). However, this increase has not yet reached statistical significance. The insignificant increase in SOD levels may be due to the limited dosage of gambir leaf tea used. The increase in SOD levels occurs because gambir leaf tea contains flavonoid compounds that can reduce oxidative stress by donating one electron from its phenolic hydroxyl group to free radicals, resulting in stable compounds [22]. This antioxidant can also enhance the regulation of antioxidant enzymes, particularly SOD, and inhibit pro-oxidant enzymes such as cyclooxygenase (COX) and inducible nitric oxide synthase (iNOS). Both of these enzymes are active in producing ROS, thus helping to prevent lipid peroxidation and cell and tissue damage [22, 23, 24].

Alexandra et al., in 2023, studied the effects of Uncaria gambir Roxb. extract on antihyperglycemic activity, antioxidant enzyme SOD, and MDA levels in streptozotocin-induced rats. The research was conducted by administering gambir extract at 100 mg/kg body weight, 200 mg/kg body weight, and 400 mg/kg body weight. This demonstrated that the administration of ethanol extract of Uncaria could enhance SOD activity in streptozotocin-induced rats. The higher the dose of *Uncaria gambir* Roxb. extract, the greater the SOD activity produced [21].

The DM control group (K MET) that was given metformin showed an increase in SOD levels compared to the positive control group (K+), but there was no significant difference. Metformin is an antidiabetic medication from the biguanide class, and it also has antioxidant effects [25]. Metformin can reduce ROS production by capturing hydroxyl radicals, which are highly reactive free radicals, by donating electrons to neutralize them. Additionally, metformin enhances the endogenous antioxidant defense system by increasing the levels of antioxidant enzymes such as superoxide dismutase and catalase. This enzyme effectively neutralizes free radicals that can reduce oxidative stress [26].

CONCLUSION

The administration of gambir leaf tea does not increase endogenous antioxidants in the form of SOD in rats with diabetes mellitus.

Declaration by Authors

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