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by Gwenny Ichsan Prabowo

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Effect of *Sticophus hermanii* extract on fasting blood glucose and skeletal muscle glut4 on type 2 diabetes mellitus rats modelI Safitri¹, B Purwanto^{2*}, L Rochyani³, G I Prabowo¹ and D Sukmaya⁴¹Medical Biochemistry Department, Faculty of Medicine, Airlangga University²Physiology Department, Faculty of Medicine, Airlangga University³Faculty of Dentistry, Hang Tuah University⁴Faculty of Medicine, Surabaya University

*indrisafitri@yahoo.com

Abstract. The purpose of this study was to prove that *Sticophus hermanii* (SH) extract can lower blood glucose levels and increase skeletal muscle GLUT4 levels in Type 2 Diabetes Mellitus (T2DM) rats model. This research is a laboratory experimental study, with complete randomized design. Thirty rats (Wistar rats) were randomly divided into five groups, a normal control group and four T2DM rat groups by intra peritoneal STZ 50 mg / kg BW. The four T2DM rat groups divided into control positif group (without giving anything), given metformin 100 mg (first-line drugs T2DM), SH 8.5 mg and 17mg / kg BW, respectively, by gastric intubations every day during 2 weeks. After 2 weeks the rats sacrificed to measure blood glucose level with stikNesco multicheck and skeletal muscle GLUT4 level with elisa method. The results of this study were 1) blood glucose levels of T2DM rats decreased significantly, with the giving of SH 8.5 mg / kg body weight and 17 mg / kg body weight and gave the same effect with metformin 100 mg / kg body weight, 2) Skeletal muscle Glut 4 of T2DM rats increased significantly, with the giving of SH 8.5 mg / kg body weight and 17 mg / kg body weight and giving effect equal to metformin 100 mg / kg body weight. The conclusion was administration of SH extract at dosage 8.5 mg / kg body weight or 17 mg / kg body weight in T2DM rats statistically gives the same effect with metformin 100 mg / kg body weight, but it seems that dosing 8.5 mg / kg body weight gives better effect .

Keywords : *Sticophus hermanii* , fasting blood glucose, GLUT 422
1. Introduction

Epidemiological research shows that the incidence of type 2 diabetes mellitus (T2DM) tends to increase. By 2020 there are an estimated 250 million people with T2DM in the world. According to WHO, in Indonesia the number of sufferers in 2000 was 8.4 million, which in 2030 was predicted to be 21.3 million [18]. A high cost is needed for the treatment of T2DM disease, and the many complications that can occur (e.g. cardiovascular disease) with high mortality rates, T2DM disease is a strategic disease that needs to be considered, especially in preventing the emergence or slowing the possibility of complications [12] The results of Indonesia Basic Health Research (Riskesdas) in 2007 found that the proportion of causes of death due to T2DM in the 45-54 year age group in urban areas was ranked 2nd, namely 14.7%. And rural areas, T2DM ranked 6th, which was 5.8%. Basically the complications that occur in people with T2DM are the result of the formation of ROS [7].

The most important management of T2DM is controlling blood glucose levels, because it plays a very important role in preventing DM complications. It is currently believed that oxidative stress plays an important role in the development of vascular complications in diabetes, especially T2DM. According to epidemiological studies, diabetes mortality can be explained mainly by an increase in vascular disease in addition to hyperglycemia [17].

Glycemia control is strictly a top priority in T2DM management, but the fact is that only a small proportion of patients have achieved long-term glycemic targets [16]. Based on this phenomenon and the characteristics of progressive T2DM disease, now a new and more aggressive strategy is used in the long-term use of hypoglycemic drugs. Therefore, the discovery of new drugs that are able to



control the glycemic state and include reducing the occurrence of ROS due to T2DM should be further enhanced, especially the use of natural ingredients as part of nutrigenomic therapy [17].

Sticopus hermanii is widely found in Indonesia, including in East Java. *Sticopus hermanii* contain nutritional compounds such as Vitamin A, Vitamin B1 (thiamine), Vitamin B2 (riboflavin), vitamin B3 (niacin), and minerals, especially chromium, calcium, magnesium, iron, and zinc [6], [2]. In addition, *Sticopus hermanii* also contains bioactive compounds such as triterpene glycosides (saponins), sulfate chondroitin, glycosaminoglycans (GAG), polysaccharides sulfates, sterols (glycosides and sulfates), phenolics, cerberosides, lectins, peptides, glycoproteins, glycosphingolipids and essential fatty acids. High components of active compounds that have therapeutic properties, allowing *Sticopus hermanii* to be used for the treatment of various diseases [15], [2]. Saponins play a role in increasing tyrosine phosphorylation from the insulin subunit β receptor, inhibiting tyrosine phosphatase, and stimulating glucose transport activity, such as GLUT 4 [8]. At present GLUT 4 is often used as a variable in research on the occurrence of T2DM repair / recovery [9], [5]. Phenolic can stimulate an increase in insulin release from pancreatic beta cells [4] and provide protection against cell damage due to oxidative stress associated with free radicals [13], while chromium can increase the number of insulin receptors, so between insulin and cell increases, inhibiting the protein tyrosine phosphatase 1 and activating insulin receptor tyrosine kinase (IRTK) [11], [19].

Based on the content contained in the *Sticopus hermanii* mentioned above, it is hoped that the *Sticopus hermanii* can be used as a treatment for T2DM. To prove this, a study was conducted "Analysis of changes in blood glucose levels and GLUT 4 in the T2DM rat model which was given extract of *Sticopus hermanii*". This research was conducted on experimental animals made by T2DM [1], because it is not ethical if it is directly applied to humans. The dose given at 8.5 mg / kg body weight and 17 mg / kg body weight refers to previous studies which found that the antioxidant effect of *Sticopus hermanii* would be significant in Wistar rats exposed to cigarette smoke at these doses [14]

2. Experimental Methods

2.1 Extraction of *Sticopus hermanii*

Sticopus hermanii fresh in weight of 9 kg were taken from Sumenep, Madura island. *Sticopus hermanii* were cleaned, removed inside and cut into pieces with a size of 3-10 cm and dried in an oven at 50 ° C until dry. The dried *Sticopus hermanii* mashed with a blender into powder and obtained weight of 1.3 kg. The *Sticopus hermanii* powder was macerated by stirring repeatedly for 8 hours and soaked in 80% ethanol solution for 24 hours, after 24 hours 80% ethanol solution was collected and the *Sticopus hermanii* pulp was remacerated with 80% ethanol in the same way (total ethanol solution used as much as 5.5 liters). The 80% ethanol solution obtained was evaporated with a water temperature of 50 ° C until the ethanol solution evaporated and obtained a thick extract of 242.5 grams of *Sticopus hermanii* (Ridzwan et al., 2001).

2.2 Making T2DM rat models

The experimental animals used were thirty of male rat (*Wistar novergicus* strains) aged 3-4 months with a body weight of 150-200 grams. After acclimatizing for 7 days, the rats were fastened for 4 hours before induction began. Rat were injected with a single dose of STZ 50 mg / kg body weight by i.p. The STZ solution was prepared by diluting STZ with a citrate buffer solution according to the specified dose, and the amount injected 0.2 ml. Significant hyperglycemia will occur three days after induction. Blood glucose levels are calculated using a glucometer. Rat were diagnosed with T2DM if blood glucose levels were ≥ 200 mg / dl (Al-awar et al., 2016).

2.3 Treatment

A total of 30 rats after acclimatization for 1 week were divided randomly into 5 groups. A negative control group (normal rat), control positive groups (T2DM rat without treatment), group of T2DM given metformin 100 mg (first-line drugs T2DM), SH 8.5 mg and 17mg / kg body weight, respectively, by gastric intubations every day during 2 weeks. Metformin and extract of *Sticopus hermanii* were dissolved in CMC Na 1%. On the 15th day after giving metformin / extract of *Sticopus hermanii*, the rats were fasted for 8 hours and then sacrificed to examine blood glucose levels with the Nesco multichex stick and taken by skeletal muscles to check GLUT4 muscle levels

by Elisa. In this study also used metformin which will be used as a control because currently metformin is used as the first line of T2DM treatment.

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2.4 Measuring blood glucose levels

Blood glucose levels are the amount of blood glucose of mice which has been satisfied for 8 hours and measured with a Nesco multichex stick.

2.5 Measuring muscle GLUT 4 levels

Muscle GLUT4 levels are GLUT4 levels in the skeletal muscles of mice which were measured by the elisa method with pg / mg muscle tissue, using Rat Glucose Transporter 4 (GLUT4) ELISA Kit Cat.No: MBS005996.

3. Results and discussion

Research has been conducted on "Analysis of changes in blood glucose levels and GLUT 4 in the Diabetes Mellitus rats model which was given a *Sticophus hermanii* extract" The experimental animals used in this study were 30 rats (*Rattus norvegicus*), body weight ranging from 120 - 170 grams which were kept in the Department of Medical Biochemistry, Faculty of Medicine, Airlangga University. After acclimatization the rats were divided into 5 groups:

1. Group 1: negative control group
2. Group 2: positive control group (only given STZ, to make T2DM rats)
3. Group 3: T2DM rats group and metformin 100 mg / kg BW / day
4. Group 4: T2DM rats group with *Sticophus hermanii* extract 8.5 mg / kg BB / day
5. Group 5: T2DM rats group with *Sticophus hermanii* extract 17 mg / kg BW / day

At 3 days after induction with STZ, group 3 was given metformin, group 4 was given low-dose *Sticophus hermanii* extract, and group 5 was given high-dose *Sticophus hermanii* extract with a duration of 2 weeks. On the 15th day after being fasted for 8 hours, the rats were sacrificed for blood and gastrocnemius muscle. Blood glucose levels are checked with a simple glucose strip. In addition to examining GLUT 4 muscles, it also examined muscle glucose levels from muscle homogenate. GLUT 4 levels were examined by Elisa using the Rat Glucose Transporter 4 (GLUT 4) Elisa Kit. The results obtained are analyzed by SPSS and get the following results.

3.1 Blood glucose level.

Based on the results obtained, the mean intergroup test showed significant differences between the normal control group and the T2DM group, between the T2DM group and T2DM plus metformin, between the T2DM group and T2DM + *Sticophus hermanii* extract 8.5 mg / kg body weight, and between the T2DM groups with T2DM + *Sticophus hermanii* extract 17 mg / kg body weight ($p < 0.05$). This shows that administration of *Sticophus hermanii* extract 8.5 mg mapun and 17 mg / kg body weight can reduce blood sugar levels such as with metformin. There were no significant differences between the negative control group and T2DM with metformin, *Sticophus hermanii* extract 8.5 mg / kg body weight, and *Sticophus hermanii* extract 17 mg / kg body weight.

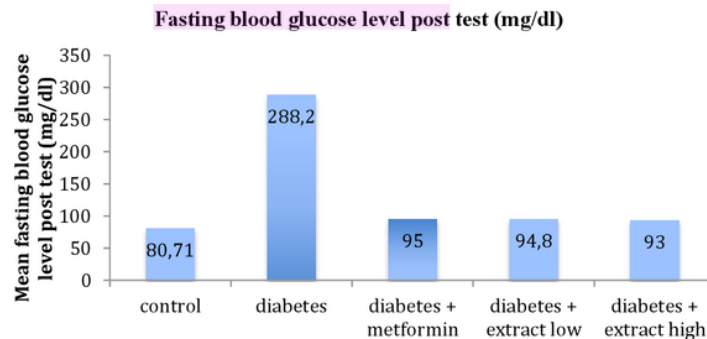


Figure 1. Fasting blood glucose levels after treatment.

3.2 Muscle GLUT 4 Level

Based on the results obtained, the mean intergroup test showed significant differences between the normal control group and the T2DM group, between the T2DM group and T2DM plus metformin, between the T2DM group and T2DM + *Sticophus hermanii* extract 8.5 mg / kg body weight, and between the T2DM groups with T2DM + *Sticophus hermanii* extract 17 mg / kg body weight ($p < 0.05$). There were no significant differences between the negative control group and T2DM with metformin, *Sticophus hermanii* extract 8.5 mg / kg body weight, and *Sticophus hermanii* extract 17 mg / kg body weight. There was an increase in GLUT 4 levels in DM animals who were given a *Sticophus hermanii* extract dose of 8.5 mg / kgBB. Although this was lower than the negative control, it was higher compared to the administration of metformin and the administration of *Sticophus hermanii* extract 18 mg / kg BB.

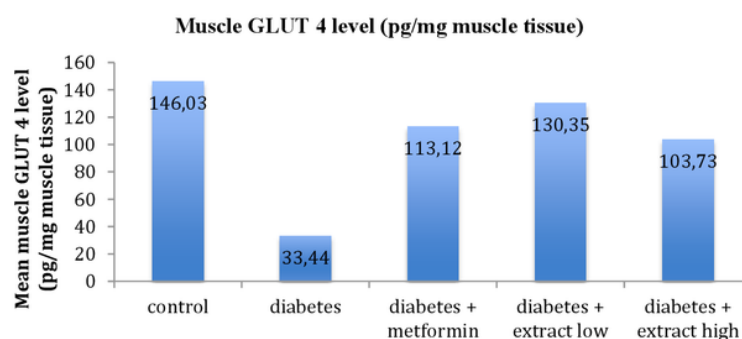


Figure 2. GLUT levels of 4 gastrocnemius muscles after treatment.

In patients with DM there is an increase in oxidant levels (Chikezie et al, 2015), so that antioxidant administration will improve the condition of T2DM [7]. Because the extract of *Sticophus hermanii* has been shown to function as an oxidant (Revianti et al, 2016), then in this study it was proven that the administration of *Sticophus hermanii* can improve the condition of DM.

4. Conclusions

1. Giving extract of *Sticophus hermanii* dose 8.5 mg / kg body weight in T2DM rats can reduce fasting blood glucose levels such as by giving metformin 100 mg / kg body weight, as well as giving *Sticophus hermanii* extract 17 mg / kg body weight, it's just not as good as giving 8.5 mg / kg body weight.
2. Giving extract of *Sticophus hermanii* dose 8.5 mg / kg body weight in T2DM rats can increase muscle glucose levels such as by giving metformin 100 mg / kg body weight, as well as giving *Sticophus hermanii* extract 17 mg / kg body weight, it's just not as good as giving 8.5 mg / kg BB.
3. The administration of *Sticophus hermanii* extract dose of 8.5 mg / kg body weight in T2DM rats can increase GLUT 4 levels of muscles such as the administration of metformin 100 mg / kg BB, as well as the administration of *Sticophus hermanii* r extract 17 mg / kg BB, it's just not as good as giving 8.5 mg / kg BB.

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