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KAYU ULAR (*STRYCHNOS LIGUSTRINA*) DRY EXTRACT PREVENTS FROM HYPERGLYCEMIA IN CHRONIC DIABETES INDUCED BY STREPTOZOTOCIN

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Abstract – Kayu Ular or *Strychnos ligustrina* have been traditionally used in Indonesia as an anti diabetic agent. The objective of this study was to determine anti-hyperglycemic agent activities of Kayu Ular extracts which are traditionally used in the treatment of diabetes in Indonesia. Diabetic rat were given Kayu Ulardry extract orally once a day with the dose of 8,5 mg/kg BW for 84 days. Blood glucose level were evaluated on the day 1, 28, 56 and 84. Daily decoction of Kayu Ulardry extract significantly reduced blood glucose level in streptozotocin (STZ)-induced diabetic rats, suggesting the further potential of Kayu Ularas diabetic drug.

INTRODUCTION

Diabetes mellitus is one of the major health problems in the world today. Diabetes mellitus covers many metabolic disturbances as a result of insulin resistance or lack of insulin at the pancreas. The main sign of diabetes is high blood glucose level known as hyperglycemia.

Since ancient times, medicinal plants have always been use as traditional medicine for the treatment of ailments. Most of the people in developing countries depending on traditional medicine, and between 60 and 80% of people worldwide rely mainly on traditional herbal medicine to meet their primary healthcare needs (Aguilar-Støen and Moe, 2007). *Strychnos ligustrina* commonly known as Kayu Ular in Indonesia, has been mentioned in the Indonesian traditional system of medicine but it has never been analyzed in any experimental or clinical anti-diabetic activity. Kayu Ular has been reported to be used in numerous complementary and alternative medicine systems of Indonesia for the treatment of malaria, diarrhoea, fever, skin infections, diabetes, high blood pressure and cancer (Murningsih *et al*., 2006; Sarmento *et al*., 2015; Gusmailina and Komarayati, 2015). In other study applying another *Strychnos* species, the authors found that methanolic extract of Strychnos nuxvomica had properties as an antidiabetic and antioxidant (Chitra *et al*., 2010).

MATERIALS AND METHOD

Model of Diabetic Rat

Eight weeks-oldnormal Sprague Dawley rats was induced by single injecting streptozotocin (STZ, Nacalai Tesque, Inc., Kyoto, Japan) intraperitoneally at a dose of 50 mg/kg body weight. Rats with fasting blood glucose levels higher than 250 mg/dL were considered diabetic rats and were maintained for 84 days for chronic protocol in this study.One week after the induction of diabetes, half of the diabetic rats were randomly selected and treated with *Strychnos ligustrina* dry extract at the dose of 8.5 mg/kg BW for 84 days (DSL, n=4). The remaining age-matched diabetic rats were treated with distilled water alone as the positive control (D, n=4). Additionally, half of normal rats (N, n=4) received distilled water, was used as negative control. The remaining normal rats received *Strychnos ligustrina* dry extract were added to analyze the effect of *Strychnos ligustrina* in the normal rats (NSL, n=4). All rats were allowed to free access of standard rat chow

and water ad libitum. After 84 weeks of the day of experiments,all rats were sacrificed under deep anesthesia. All protocols were done in accordance with legal ethical guideline for animal experiment in our faculty.

Extract of Strychnos ligustrina

Strychnos ligustrina was determined and extracted by Institute Pertanian Bogor (IPB). In brief, the methanolic extract of *Strychnos ligustrina* was mixed with maltodextrin to form a dry extract of *Strychnos ligustrina*. *Strychnos ligustrina* dry extract was orally given once a day with the dose of 8.5 mg/kg BW for 84 days for randomly selected rats.

Metabolic parameters measurement

Regular checks of peripheral blood glucose level were done on the day 1, 28, 56 and 84 at all groups. In brief, the blood was collected from the rat-tail by puncturing the 27G needle to the tip of the tail. The blood glucose was then analyzed using Medi-safe chips as instructed by the protocol (Terumo, Inc., Tokyo).

Statistical analysis

Blood glucose data were expressed as means and standard of deviation (SD). Student's t-test or one-way analysis of variance (ANOVA), wherever applicable, was used to compare differences of mean among groups. Significant differences were defined as probability (p) value < 0.05.

RESULTS

Chronic diabetic rat model

One week after the STZ injection, blood glucose levels were evaluated and rats with blood glucose level higher than 250 mg/dl were determined as diabetes mellitus. Randomly, the diabetic rats were divided into two groups, which are the diabetic group (D) and the diabetic group with extract (DSL). At the average of blood glucose levels in the D and the DSL group are 491.67±135.80 mg/dl and 497.75±82.81, respectively (Table 1). There is no significant difference of blood glucose levels between the N and the NSL group. As the positive control for diabetes, the blood glucose level of the D group is persistently high from day 1 to day 84 (Table 1).

Effect of *Strychnos ligustrina* or kayu Ularon blood glucose level

In this recent study, we found that daily decoction of kayu Ular significantly decreased blood glucose level started on day 56 (Table 1). In brief, blood glucose level in the DSL group on day 56 is 469.50± 74.31 mg/dl compared to 586.00±24.25 mg/dl in the D group. Significant prominent reduction of blood glucose level was observed on day 84. In detail,

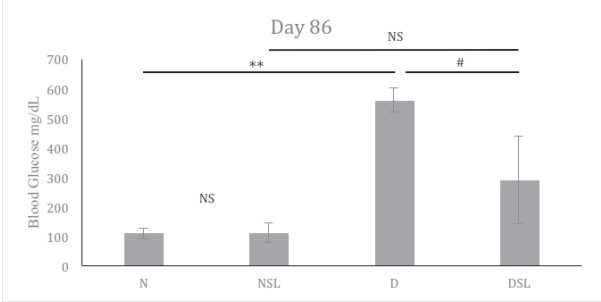

Fig. 1. Effect of *Strychnos ligustrina* dry extract 8.5 mg/kg BW on glucose level at day 84
All values are expressed as the mean ± S.D.
N = normal rat (negative control); NSL = normal rat received *Strychnos ligustrina* extract;
D = diabetic rat received vehicle (positive control); DSL = diabetic rat received *Strychnos ligustrina* extract.
=**p<0.05 compared to the N group

Table 1. Blood glucose level and diabetic model

	Day 1	Day 28	Day 56	Day 84
Group	Blood glucose level (mg/dl)	Blood glucose level (mg/dl)	Blood glucose level (mg/dl)	Blood glucose level (mg/dl)
N	105.25±28.29	109.00±16.87	107.75±17.46	100.50±19.12
NSL	110.25±19.6249	108.00±8.29	109.50±13.00	120.00±26.27
D	1.67±135.80**	370.00±105.43**	586.00±24.25**	559.00±40.51**
DSL	497.75±82.81	394.00±146.44	469.50±74.31#	289.00±147.50#

N = normal rat (negative control); NSL = normal rat received *Strychnos ligustrina* extract;
D = diabetic rat received vehicle (positive control); DSL = diabetic rat received *Strychnos ligustrina* extract.
**p<0.05 compared to the N group
#p<0.01 compared to the D group

blood glucose level in the DSL group was 289.00±147.50 mg/dl compared to 559.00±40.51 mg/dl in the D group.

DISCUSSION

Streptozotocin (STZ) and alloxan are the two drugs that are most commonly used for the induction of diabetes in animal models. STZ enters the cell via the GLUT-2 transporter membrane, inside the cell; STZ causes alkylation of DNA, in addition to the release of nitric oxide. As a result, pancreatic â-cells are destroyed by necrosis (Lukas *et al*., 2016). Both drugs are administered parenterally and the doses administered depend on the species used in the experiment.

There are many substances extracted from plants that offer anti diabetic potential. These results had shown the possible role of *Strychnos ligustrina* pharmacological activity as an anti-diabetic agent. To the extent of our study, this is the first evidence that shows the beneficial role of *Strychnos ligustrina* dry exctract in the diabetes mellitus.

CONCLUSION

The result of present study showed daily decoction of *Strychnos ligustrina* dry extract when compared to untreated diabetic rats, showed significant decrease in blood glucose level in STZ-induced diabetic rats, suggesting the further potential as diabetic drug. However, the exact mechanism via which *Strychnos ligustrina* exerts its anti-diabetic effect in STZ-induced diabetic rats is not clear and has to be clarified. Further investigations of active ingredients in *Strychnos ligustrina* extract are needed to explore for the possible mechanisms that are involved in this effect.

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