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The Antidiabetic Properties of Indonesian *Swietenia mahagoni* in Alloxan-Induced Diabetic Rats

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Abstract**—**Diabetes mellitus (DM) is a metabolic disease that can be indicated by the high level of blood glucose. The objective of this study was to observe the antidiabetic properties of ethanolic extract of Indonesian *Swietenia mahagoni* Jacq. seed on the profile of pancreatic superoxide dismutase and β-cells in the alloxan-experimental diabetic rats. The *Swietenia mahagoni* seed was obtained from Leuwiliang-Bogor, Indonesia. Extraction of *Swietenia mahagoni* was done by using ethanol with maceration methods. A total of 25 male *Sprague dawley* rats were divided into five groups; (a) negative control group, (b) positive control group (DM), (c) DM group that was treated with *Swietenia mahagoni* seed extract, (d) DM group that was treated with acarbose, and (e) non-DM group that was treated with *Swietenia mahagoni* seed extract. The DM groups were induced by alloxan (110 mg/kgBW). The extract was orally administrated to diabetic rats 500 mg/kg/BW/day for 28 days. The extract showed hypoglycemic effect, increased body weight, increased the content of superoxide dismutase in the pancreatic tissue, and delayed the rate of β-cells damage of experimental diabetic rats. These results suggested that the ethanolic extract of Indonesian *Swietenia mahagoni* Jacq. seed could be proposed as a potential anti-diabetic agent.

Keywords**—**β-cell, diabetes mellitus, superoxide dismutase, *Swietenia mahagoni.*

I. Introduction

DM is a common metabolic disease characterized by abnormally high plasma glucose levels (hyperglycemia). Insulin is needed to uptake glucose from blood circulation into the cells. If the damage of β-cells in diabetic condition caused insulin deficiency, then plasma glucose cannot enter into the cells and resulted in hyperglycemia [1]. DM caused by β-cells of pancreatic tissues produces less insulin, or the insulin has low sensitivity, or both. DM interferes with this process, causing impairment of carbohydrate, protein, and lipid metabolism, then resulted in oxidative stress condition. High plasma glucose levels lead to a condition of oxidative stress. Abundance of free radicals causes lesion in some blood vessels especially in kidney, eye, and heart, then gives rise to major complications, such as neuropathy, retinopathy, and cardiovascular disease [2], [3].

The number of DM patients increases every year. International Diabetes Federation [4] reported that there are 415 million DM patients in 2015, and it was estimated that this number will be 642 million people with DM in 2040. Today, Indonesia has 8.5 million DM patients. Indonesia ranks the 7th highest in the world in number of DM patients [4]. Recently, DM has also occurred in dogs and cats in Sweden [5] and United States of Amerika [6]. More than 1.4 million dogs and cats, in USA, are DM with high glucose level [7]. It was reported that DM in dogs increased 200% during last 30 years [8]. Effective control of blood glucose levels is one of key methods for preventing or reversing diabetic complications and improving the quality of life for diabetic patients. Another way is to increase the insulin production or to delay the damage of β-cells in pancreatic tissue.

In order to address the problem of DM in both human and animals, especially to control the blood glucose level and to reduce stress oxidative condition, it is important to search for biochemical compounds that may serve as antidiabetic treatments as well as antioxidative activity. Raptis and Dimitriadis [9] described various mechanisms by which oral hypoglycemic agents may work: as α–glucosidase inhibitors, insulin secretagogues, and insulin sensitizer. It was reported that naturally abundant antioxidant compounds have received considerable attention as potential α-glucosidase inhibitors [10]. Panda et al. [11] reported that Indian *Swietenia mahagoni* has antioxidative and antidiabetic activities in streptozotocin-induced rats. De et al. [12] also suggested that Indian *Swietenia mahagoni* is a good candidate for antidiabetic medicine.

Our previous study examined the potencies of ethanolic extract of *Swietenia mahagoni,* a tree found almost everywhere in Indonesia. The ethanolic extract of *Swietenia mahagoni* seed displayed the presence of bioactive compounds, such as alkaloid, steroids, tannins, saponins, triterpenoids, hidroquinons, and flavonoids [13]. Alkaloids [14], triterpenes [15], and flavonoids [16] have all been reported to exhibit α-glucosidase inhibitor properties. The *Swietenia mahagoni* seed extract is also reported to exhibit antioxidative activity, α-glucosidase inhibitory effect, and hypoglycemic activity properties. The extract decreased the blood glucose level in sucrose-induced hyperglycemic rats [13]. These results suggested that the extract has a potential antidiabetic. It is very important to elucidate these properties in experimental diabetic rats. Besides the blood glucose level, feed consumption, and body weight, other indicators such as the profile of β-cells and antioxidant content in pancreatic tissues should be clearly observed.

The *Swietenia mahagoni* seeds used in this study were

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International Science Index, Animal and Veterinary Sciences Vol:10, No:10, 2016 waset.org/Publication/10005551

obtained from Leuwiliang Bogor, Indonesia. Little is known about the potency of *Swietenia mahagoni,* but we know that bioactive compounds found in plants may depend on the location where they grow. The objective of this study was to observe the antidiabetic and antioxidative activities of ethanolic extract of *Swietenia mahagoni* seed in experimental diabetic rats.

II. Materials and Methods

This study was conducted at the animal laboratory management unit of Faculty of Veterinary Medicine, Bogor Agricultural University, Indonesia. Rat care and experimental procedures in this study were in accordance with Ethical Approval Letter No. 14-2013 IPB from Animal Care and Use Committee, Bogor Agricultural University, Indonesia

A. Swietenia mahagoni Seeds Extraction

Swietenia mahagoni seeds were harvested from the wild in Leuwiliang, Bogor, Indonesia. Sampling was done by using WHO procedure [17]. The seeds were first dried at 50 $_{o}$C, then were ground and filtered with 40 mm mesh. Extraction was carried out by using maceration methods and ethanol as the solvent [13]. The maceration method was as follows: *Swietenia mahagoni* seeds were dried and ground into powder, which was mixed with solvent (1:5) for 24 hours, followed by filtration. The maceration was repeated three times with the same kind of solvent. All of the filtrates were then evaporated by using vacuum evaporator [13].

B. Animal Management and Experimental Design

A total of 25 male *Sprague-Dawley* rats was used in this study. The rats were obtained from Animal Laboratory Unit, Faculty of Veterinary Medicine, Bogor Agricultural University, Indonesia. The rats were divided into five groups; (a) a negative control group, (b) a positive control group (DM), (c) DM group that was treated with *Swietenia mahagoni* seed extract, (d) DM group that was treated with acarbose, and (e) non-DM group that was treated with *Swietenia mahagoni* seed extract. Diabetic condition was obtained by alloxan induction, 110 mg/KgBW [18]-[19]. The extract was orally administrated to diabetic rats for 28 days.

C. Feed Consumption, Body Weight, Blood Glucose, and Pancreatic Tissues Sampling and Analysis

Feed consumption was measured every day, while body weight and blood glucose level of rats was measured by using a Gluko Dr and strip kit every four days. At the end of treatment, rats were anaesthetized by using ketamin and xylasine, then followed by collecting pancreatic tissues and others. The tissues were then processed by using paraffin embedding standard method, and subjected to β-cell analysis and antioxidant copper, zinc-superoxide dismutase (Cu,Zn-SOD) content. The profile of β-cells and the content of antioxidant Cu,Zn- SOD in pancreatic tissues were analyzed by using immunohistochemical technique [18], [20]. Monoclonal Anti-insulin (Sigma I-2018), monoclonal anti-Cu,Zn-SOD (Sigma S2147), and Strar Trek Universal HRP detection (Biocare STUHRP700H-KIT) were used for the immunohistochemical analysis.

D. Statistical Analysis

Feed consumption, number of Langerhans islet, and number of β-cells in the pancreatic tissues were statistically analyzed by using Analysis of Variance (One-way ANOVA). If there was a significant difference between the groups, then the data were analyzed by using Duncan Multiple Range Test (DMRT) (SPSS 21).

III. Results

Body Weight and Feed Consumption

During 28-day treatment, all rats showed an increase in their body weight, except rats of positive control group (DM) that was not treated with ethanolic extract of *Swietenia mahagoni* seed (B) (Fig. 1). The negative control group (A) and the non-DM group that was treated with the extract (E) showed the highest in their body weight. The DM groups that were treated with the extract (C) and acarbose (D) showed increased in their body weight, but slightly lower than that of A and E groups. The rats body weight of positive control group (B) showed the lowest level and it did not increase during the treatment. However, feed consumption of this group (B) showed higher than that of negative control group (A) (Table I).

The diabetic rats group that was treated with ethanolic extract of *Swietenia mahagoni* seed (C) showed increased in their body weight compared to that of positive control group (B). The profile of body weight in the diabetic group treated with ethanol *Swietenia mahagoni* seed extract (C) is similar with that of diabetic group treated with acarbose (D). The body weight of non-DM group that only treated with the extract (E) showed similar with that of negative control group (A). The feed consumption of C, D, and E groups did not show a significant not different. The feed consumption of the A, C, and E groups did not show a significant difference (Fig. 1, Table I).

TABLE I
Feed Consumption of Treated Rats

No.	Group	Feed consumption (g)
1	A	666.3 ± 73.8a
2	B	839.0 ± 116.9b
3	C	727.3 ± 31.1ab
4	D	859.7 ± 52.7b
5	E	723.3 ± 69.8ab

A=negative control group, B= positive control group (DM), C=DM group that was treated with *Swietenia mahagoni* seed extract, D=DM group that was treated with acarbose, and E=non-DM group that was treated with *Swietenia mahagoni* seed extract. Values followed by the different superscripts in the same coloum showed significant difference (P<0.05).

Blood Glucose Level

It was reported that normal blood glucose level of rats in range 90-142 mg/dL [21]. While Gulfraz et al. [22] reported normal blood glucose level of rats in range 99-127 mg/dL. In this study, the rats' blood glucose level of negative control group (A) and non-DM group that was treated with the

International Science Index, Animal and Veterinary Sciences Vol:10, No:10, 2016 waset.org/Publication/10005551

ethanolic extract of *Swietenia mahagoni* seed (E) was stable in normal range, about 100 mg/dL, during 28-day treatment (Fig. 2). The profile of rats' blood glucose level in the DM group that was treated with the extract (C) and acarbose (D) showed decrease towards normal range during 28-day treatment (Fig. 2). The rats' blood glucose level pattern of C group is similar to that of D group. During 28-day treatments, the rats' blood glucose level of DM group (B) showed the highest values with respect to the other groups (Fig. 2).

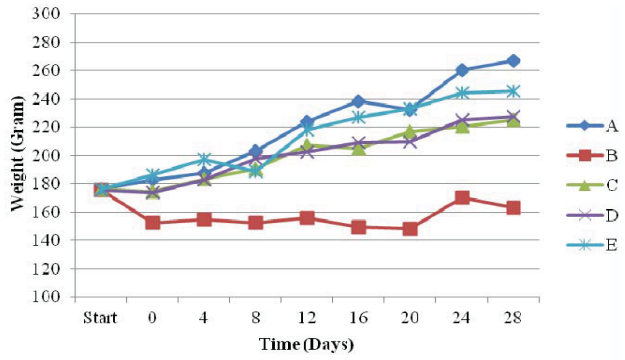


Fig. 1 The body weight of treated rats. *Swietenia mahagoni* seed extract treatment showed increased body weight compare to that of DM group without extract treatment. A=negative control group, B= positive control group (DM), C=DM group that was treated with *Swietenia mahagoni* seed extract, D=DM group that was treated with acarbose, and E=non-DM group that was treated with *Swietenia mahagoni* seed extract

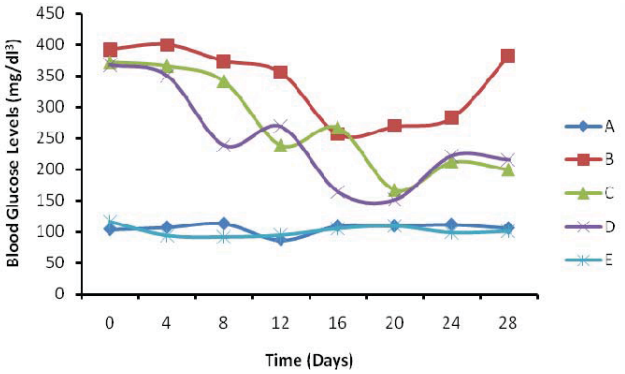


Fig. 2 The blood glucose level of treated rats. *Swietenia mahagoni* seed extract treatment showed decreased blood glucose level compare to that of DM group without extract treatment. A=negative control group, B= positive control group (DM), C=DM group that was treated with *Swietenia mahagoni* seed extract, D=DM group that was treated with acarbose, and E=non-DM group that was treated with *Swietenia mahagoni* seed extract

The Number of Langerhans islet

The number of Langerhans islet in the DM group that was treated with ethanolic extract of *Swietenia mahagoni* seed (C) was not significantly different (P>0.05) from negative control group (A), and the non-DM group that was treated with the extract (E). The number of Langerhans islet in these groups (A, C, and E) was significantly (P<0.05) higher than that of DM group that was not treated with the extract (B) and DM group that was treated with acarbose (D). The number of Langerhans islet in the DM group (B) was not significantly different (P>0.05) from that of DM group treated with acarbose (D) (Table II).

The Number of β-cell in Pancreatic Langerhans Islet

The number of β-cell in negative control group (A) and the non-DM group that was treated with the extract (E) showed significantly (P<0.05) the highest compare to that of other groups. The number of β-cell in positive control group (B) showed the lowest compare to that of other groups. The DM group that was treated with acarbose (D) showed the number of β-cell not significantly different (P>0.05) with both B group and DM group that was treated with the extract (C). The number of β-cells in DM group that was treated with the extract (C) was significantly (P<0.05) higher than that of B group, but it is still significantly lower than that of A group (Table III and Fig. 3).

TABLE II
THE NUMBER OF LANGERHANS ISLET (LI) IN THE PANCREATIC TISSUES OF RATS (PER VIEW OF 100X MAGNIFICATION)

No	Group	The number of Langerhans islet (LI)
1	A	3.10 ± 0.99b
2	B	0.80 ± 0.63a
3	C	2.50 ± 1.35b
4	D	1.50 ± 0.53a
5	E	3.00 ± 1.15b

A=negative control group, B= positive control group (DM), C=DM group that was treated with *Swietenia mahagoni* seed extract, D=DM group that was treated with acarbose, and E=non-DM group that was treated with *Swietenia mahagoni* seed extract. Treatment of the extract in DM rats showed the number of LI was significantly higher than that of DM rats without extract treatment. Values followed by the different superscripts in the same coloum showed significant difference (P<0.05).

TABLE III
THE NUMBER OF β-CELLS IN LANGERHANS ISLET (LI) OF RATS PANCREATIC TISSUES

No	Group	The number of β-cells per LI
1	A	85.20 ± 45.06c
2	B	9.00 ± 3.33a
3	C	35.60 ± 28.58b
4	D	25.10 ± 11.65ab
5	E	79.50 ± 20.92c

A=negative control group, B= positive control group (DM), C=DM group that was treated with *Swietenia mahagoni* seed extract, D=DM group that was treated with acarbose, and E=non-DM group that was treated with *Swietenia mahagoni* seed extract. Treatment of the extract in DM rats could significantly delay the damage of β-cells. Values followed by the different superscripts in the same coloum showed significant difference (P<0.05).

Antioxidant Cu,Zn-SOD content in Pancreatic tissues of experimental diabetic rats

The positive reaction of antioxidant Cu,Zn-SOD is shown by brown colour in the pancreatic tissues. Ethanolic *Swietenia mahagoni* seed extract showed increase in the content of antioxidant Cu,Zn-SOD in the pancreatic tissues of experimental diabetic rats. Fig. 4 showed the immunohistochemical localization of antioxidant Cu,Zn-SOD in pancreatic tissues of the rats. The antioxidant content in the pancreatic tissues of positive control group, diabetic condition (B), showed the lowest values compared to that of the other groups. Both diabetic rat groups that were treated with ethanol

Swietenia mahagoni seed extract (C) and acarbose (D) showed higher content of the SOD than that of diabetic/positive control group (B). The content of Cu,Zn-SOD in DM group treated with the extract (C) was slightly higher than that of DM group treated with acarbose (D). The non-DM group that was treated with the extract (E) showed SOD content in the pancreatic tissues as high as negative control group (A) (Fig. 4).

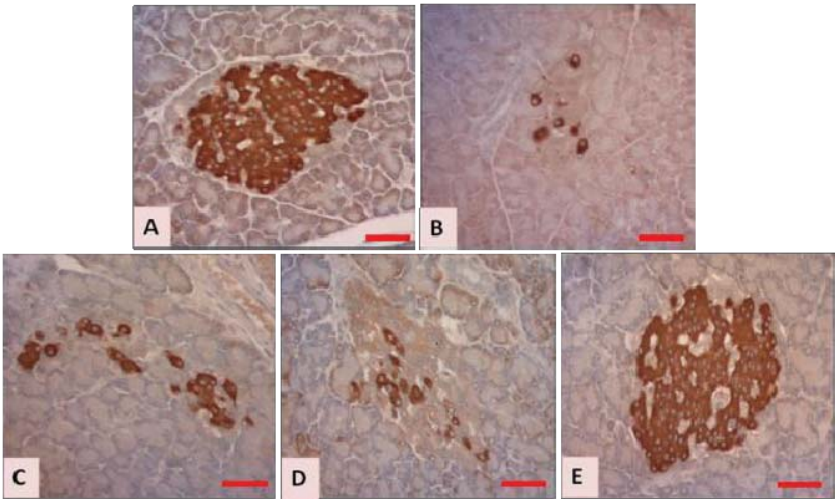


Fig. 3 Photomicrograph of immunohistochemical localization of β-cells in the pancreatic tissue of rats. The content number of β-cells in pancreatic tissue of experimental diabetic rats that were treated with ethanol *Swietenia mahagoni* seed extract (C) showed higher than that of diabetic rats (B). A = Negative control negatif (non-DM), B = Positive control (DM), C = DM + *S. mahagoni* extract; D = DM + glucobay; E = non-DM + *S. mahagoni* extract, Scale = 50 μm

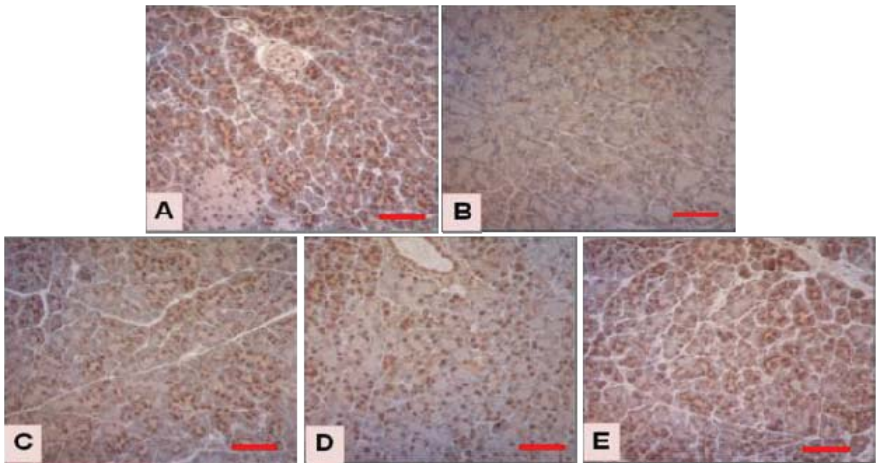


Fig. 4 Photomicrograph of immunohistochemical localization of antioxidant Cu,Zn-SOD in the pancreatic tissue of rats. The content of antioxidant Cu,Zn-SOD in pancreatic tissue of diabetic rats that were treated with ethanol *Swietenia mahagoni* seed extract (C) showed higher than that of diabetic rats (B). A = Negative control negatif (non-DM), B = Positive control (DM), C = DM + *S. mahagoni* extract; D = DM + glucobay; E = non-DM + *S. mahagoni* extract, Scale = 50 μm

IV. Discussion

In the experimental diabetic rats, the rats were induced with alloxan to damage β-cells in rat pancreatic tissues. The insulin production in this diabetic rat then decreases, and after blood glucose, it could not be uptaken from blood circulation in to cells. Subsequently, the blood glucose level in diabetic rats group (B) showed the highest values during 28-day treatment (Fig. 2). This mechanism was supported by the number of Langerhans islet, and the number of β-cells in experimental diabetic rats group (B) significantly decreased compared to that of negative control group (A) (Tables II, III and Fig. 3). Karunakaran et al. [23] reported that hyperglycemic-induced oxidative stress plays an important role in diabetic complication, especially β-cell dysfunction and failure. The experimental diabetic rats consumed more feed (Table I) but it could not be utilized, so energy was created from glycogen breakdown, glycogenolisis, and also gluconeogenesis. These metabolisms resulted in the loss of their body weight (B) as shown in Fig. 1. Febrinda et al. [24] also reported that body weight of experimental diabetic rats decreased during 28-day treatment.

The ethanolic extract of *Swietenia mahagoni* seed may

International Science Index, Animal and Veterinary Sciences Vol:10, No:10, 2016 waset.org/Publication/10005551

International Science Index, Animal and Veterinary Sciences Vol:10, No:10, 2016 waset.org/Publication/10005551

stimulate insulin production in experimental diabetic rats. The stimulation may be done by flavonoid in the extract [13], as antioxidant to delay the β-cell damage of experimental DM rats. The number of β-cell in C group was significantly higher ($P<0.05$) than that of B group (Table III, Fig. 3). Furthermore, the rats may produce more insulin and they can uptake more glucose from the blood circulation. They could maintain their body weight. It is shown by the profile of body weight of the diabetic rats group treated with the extract (C) higher than that of experimental diabetic rats group (B), although feed consumption of rats in C group was not significantly different from that of group (B).

The profile of body weight in the DM group that was treated with the extract (C group) and acarbose (D group) showed similar, increased during 28-day treatment. Although these body weights are still slightly lower than that of negative control group (A). These results showed that the extract and acarbose treatments have similar effect on body weight and feed consumption in experimental diabetic rats (Table I, Fig. 1).

The non-DM group that was treated with the extract (E group) showed increased in their body weight during the treatment, similar with that of A group (Fig. 1). Feed consumption of rats in non-DM group that only treated with the extract (E) also showed similar with that of negative control group (A). It showed that the extract has no effect on body weight and feed consumption in non-DM rats.

It was reported that alkaloid [14], triterpenes [15], and flavonoids [16] have all been reported to exhibit alpha-glucosidase inhibitor properties. The *Swietenia mahagoni* extract decreased the blood glucose level of diabetic rats group (C) (Fig. 2). It may be caused by the alkaloid, triterpenes, and flavonoid content in the extract that acts as inhibitors of alfa-glucosidase in the intestine as reported by Wresdiyati et al. [13], subsequently it disturbs the carbohydrate metabolism [25]. Wresdiyati et al. [13] also reported that the extract showed hypoglycemic effect in sucrose-hyperglycemia rats. Another way is related to the Langerhans islet and β-cells condition. The extract delayed the damage of Langerhans islet and β-cells in pancreatic tissues of DM rats (Tables II, III and Fig. 4), so the rats produce more insulin and more blood glucose can be uptaken into cells from circulation. Suryani et al. [26] reported that methanolic extract of *Swietenia mahagoni* seed also decreased the blood glucose level in DM rats. Acarbose also showed decrease in the blood glucose level of DM rats (D) (Fig. 2). Sivakumar et al. [27] reported that acarbose also inhibits alpha-glukosidase.

Antioxidant Cu,Zn-SOD contained in pancreatic tissue of experimental diabetic rats (B) showed the lowest values compared to that of the other groups (Fig. 4). It was also reported that the antioxidant Cu,Zn-SOD decreased in the liver of experimental diabetic Macaca fascicularis and rats [19], [28], and in pancreatic tissues of experimental diabetic rats [18], [20]. These reports showed a status of stress oxidative in diabetic condition. Diabetic condition produces more free radicals through several pathways. Giacco and Brownlee [29] reported that metabolic abnormalities in diabetes increased the intracellular free radicals-reactive oxygen species (ROS). First, diabetes condition increased mitochondrial superoxide production in endothelial cells of blood vessels. The condition then activates certain pathways such as polyol pathway flux, increased AGEs, increased expression of AGEs receptor, activate protein kinase C isoform, overactivity of the hexosamine pathway, and also inactivates the endothelial nitric oxide synthase and prostacyclin synthase. All these pathways generate the intracellular free radicals-reactive oxygen species (ROS) [29]. Tsuruta et al. [30] also reported that hyperglycemia enhanced superoxide anion radical generation in blood and exacerbated oxidative stress. Then, more antioxidant Cu,Zn-SOD were needed to scavenge the abundant free radicals. Subsequently the SOD decreased, as showed in diabetic group (B) in this study.

The treatment of ethanolic extract of *Swietenia mahagoni* seed in experimental diabetic rats (C) showed higher values in their content of Cu,Zn-SOD in pancreatic tissues compared to that of experimental diabetic rats group (B) (Fig. 4). These results are related to flavonoid contain in the extract. The flavonoid plays a role as antioxidant to scavenge the free radicals. Another mechanism is that the extract inhibits alpha glucosidase [13], and then, the blood glucose level could be maintained. The extract also delayed the damage of β-cells (Table III, Fig. 3), then insulin production increased and more blood glucose could be uptake from circulation into cell. Overall, the free radical production may decrease in the C group, then the content of antioxidant Cu,Zn-SOD could be maintained in higher level.

The treatment of acarbose in experimental diabetic rats (D group) also showed higher Cu,Zn-SOD content in pancreatic tissues than that of diabetic rat group (B). The antioxidant content in the tissue of D group was slightly lower than that of DM group treated the extract (D), because of there is no any antioxidant property in acarbose.

The treatment of ethanolic extract of *Swietenia mahagoni* seed in non-DM rats (E group) showed no effect on the content of Cu,Zn-SOD in pancreatic tissues. The antioxidant content in E group was as high as in negative control group (A). This result is supported by the profile of blood glucose level. The blood glucose level of both groups was similar at normal range during 28-day treatment. The number of Langerhans islet and β-cells in E group was not significantly different from that of negative control group (A).

This study concluded that ethanolic extract of *Swietenia mahagoni* Jacq. seed increased the body weight, decreased the blood glucose level, delayed the β-cells damage, and increased the content of antioxidant Cu,Zn-SOD in pancreatic tissues of alloxan induced diabetic rats. The *Swietenia mahagoni* seed can be proposed as a potential antidiabetic agent.

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International Science Index, Animal and Veterinary Sciences Vol:10, No:10, 2016 waset.org/Publication/10005551

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1. T. Wresdiyati, S. Sa'diah, A. Winarto. 2015. Alpha-glucosidase inhibition and hypoglycemic activities of *Swietenia mahagoni* seed extract. Hayati Journal of Bioscience 2015, vol. 55, no. 22, pp. 73-78
2. T. Wresdiyati, A. Karmila, M. Astawan, R. Karnila. 2015. Sea cucumber increased antioxidant superoxide dismutase in the pancreatic tissues of experimental diabetic rats. Journal Veteriner 2015, vol. 16, no. 1, pp. 145-151
3. AE. Febrinda, ND Yuliana, E Ridwan, T Wresdiyati, M. Astawan. 2014. Hyperglycemic control and diabetes complication preventive activities of Bawang Dayak (*Eleutherine palmifolia* L. Merr.) bulbs extracts in alloxan-diabetic rats. International Food Research Journal. 2014, vol. 21, no. 3, pp. 1405-1411.

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1. T. Wresdiyati, S. Sa'diah, A. Winarto. Alpha-glucosidase inhibition and hypoglycemic activities of Swietenia mahagoni seed extract. Hayati Journal of Bioscience 2015, vol. 55, no. 22, pp. 73-78
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