Effects of Leadtree Seed (*Leucaena leucocephala*) Extract in Inhibiting the Increase of Postprandial Blood Glucose Level in Alloxan-induced Diabetic Rats

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ABSTRACT

This research aimed to add evidence on the effect of white leadtree seed extract (*Leucaena leucocephala*) on postprandial blood glucose level on white male alloxan induced diabetic rats. This research was an experiment with pretest-posttest control group design. The subjects of this research were 25 white male rats, Wistar strain was divided into 5 groups. Group I was the positive control, which was treated with Acarbose, group II was the negative control, and group III, group IV, and group V were treatment groups and were given white leadtree seed extract of 1.5 g/kg of BW, 3.5 g/kg of BW, and 7.8 g/kg of BW respectively. Blood glucose level was checked before and two hours after treatment. The statistical analysis used one-way ANOVA and Bonferroni post hoc test. The result showed that there were no significant differences between group III, group IV, and group V and the positive control group ($p<0.05$). The best result of inhibition of the increase in blood glucose level was found in 7.8 g/kg of BW (group V) dosage group with average difference of 186.4 mg/dl. In conclusion, white leadtree seed extract could decrease two hour postprandial blood glucose level in white male alloxan-induced diabetic rats and a dosage of 7.8 g/kg of BW was shown to be the most effective.

Keywords: diabetes mellitus, two hour postprandial blood glucose level, white leadtree seed extract

INTRODUCTION

Postprandial hyperglycemia still remained a problem in management of type 2 Diabetes Mellitus (DM) (Fonseca 2003). Postprandial hyperglycemia is marked by a rapid and high increase in blood glucose concentration. In the postprandial phase, there is a possibility of a hyperglycemic surge (Ceriello 2005). This surge phenomenon might induce the endothelial dysfunction, inflammatory reaction, and oxidative stress that could cause organ failure (Node & Inoe 2009). Thus, postprandial hyperglycemia management is pivotal for the treatment of DM type 2 (Dijk *et al*. 2011).

In general, oral hypoglycemic drugs or insulin injections aim to regulate the blood glucose concentration. However, this effort had not been able to fully prevent the occurrence of complications. In addition, the price of synthetic drugs is quite expensive and therefore, alternative drugs are developed (Jasaputra *et al*. 2014). Of all anti-diabetic drugs available, α-glucosidase inhibitor seems to be the most effective in reducing the postprandial hyperglycemia (Derosa

& Maffioli 2012). The excellence of α-glucosidase inhibitor over other drugs is that it has not caused hypoglycemia. One of α-glucosidase inhibitors that are commonly used is acarbose (Ndraha 2014).

One of the traditional medical plants used by Indonesian in treating diabetes is the white leadtree (*Lucaena leucochepala*) (Kuppusamy *et al*. 2014). White leadtree is a shrub plant, containing active substance such as flavonoids, galactomannan, tannin, calcium, phosphorus, and iron, as well as vitamin B1, vitamin C, and vitamin A. The content of flavonoids, tannins, and galactomannan in white leadtree could inhibit the increasing of blood glucose concentration, by inhibiting the activity of α-glucosidase which played role in the process of glucose absoption in brush border cell membrane in small intestine (Silvita 2015).

As a metabolic disorder, the prevalence of Diabetes Mellitus (DM) had increased from around 108 million in 1980 to 422 million in 2014. The increase in prevalence of type 2 DM patients is higher in the middle and low income countries (WHO 2016). International Diabetes

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Federation (IDF 2011) stated that more than 371 million people have DM, 4.8 million people die because of this metabolic disease and 471 billion US dollar was spent for the treatment.

In Indonesia, DM prevalence had increased from 1.1 percent in 2017 to 2.1 percent in 2013. The highest prevalence of DM that was diagnosed by clinicians is in DI Yogyakarta (2.6%), DKI Jakarta (2.5%), North Sulawesi (2.4%), and East Kalimantan (2.3%) (Balitbangkes 2013). DM is serious public health threat, since it might cause various disability, such as blindness, kidney failure, diabetic feet, heart disease, and stroke (Depkes RI 2013).

Various research have been conducted on the role of white leadtree in reducing blood glucose concentration. Silvita *et al.* (2015) stated that the infusion of white leadtree reduced the blood glucose concentration in diabetic mice model. This study used acarbose as positive control, but it used infusion method. Therefore, the active substances produced by white leadtree were unstable and easily polluted.

Other study by Nugraha and Yusuf (2015) suggested that the use of ethanol extract of white leadtree reduced fasting blood glucose concentration and the level of pancreatic β-cells damage in hyperglycemic rats induced by alloxan. Hypoglycemic ethyl acetate fraction derived from white leadtree was able to reduce the concentration of glucose in wistar rats induced by alloxan. That study used glibenclamide as the positive control, in which its mechanism was to increase insulin and unlike acarbose that inhibits the absorption of glucose in gastrointestinal tract. On the other hand, the study by Utami *et al.* (2015) showed that white leadtree had no effect in reducing the concentration of blood glucose in wistar rats induced by alloxan. That study used insulin as its positive control. Insulin worked directly in blood and therefore, the inhibition of increasing two hour postprandial blood glucose level could not be seen.

Mice and humans had similar metabolism and thus, mice were often used as experimental animals (Febrian 2017). Alloxan was used in this study because of its cytotoxic characteristic to pancreatic β-cell through the formation of free radicals and oxidative stress. Alloxan induced the release of calcium ions from mitochondria so that the process of cell oxidation was disrupted. The release of calcium ion from mitochondria caused homeostatic disorder, which was the beginning of cell death. Alloxans' mechanism in damaging pancreatic β-cells resulted in the decrease of

insulin concentration and disruption of blood glucose homeostasis so that blood glucose increased (Akrom *et al.* 2014).

Based on the scientific information above, there is a need to investigate whether the white leadtree (*Leucaena leucocephala*) have any effect to inhibit the increase of two hour postprandial blood glucose concentration in white male diabetic rats, induced by alloxan.

METHODS

Design, location, and time

This study is a true-experiment with pretest-posttest control group design. This study was conducted in the Department of Pharmacology and Therapy, Faculty of Medicine, Padjajaran University, Bandung. The making of white leadtree extract was carried out in Balai Penelitian Tanaman Rempah dan Obat (BALITRO), Bogor. This study was conducted in September 2016 until August 2017.

Sampling

The sample size of each group was calculated using Federer with n as number of sample, and t as number of group. The following was the formula used,

$$(n-1)(t-1) \geq 15$$

Based on Federer's formula, the sample needed for each group was 5 white male rats. To avoid the reduction of samples' due to death during the treatment, 2 more white rats were added in each group (drop out), so the number of sample for each group was 7 rats and thus, counting for 35 white male rats in total. This research has received ethical approval from Ethics Committee of Faculty of Medicine UPN Veteran Jakarta No: B/1185/IX/2017/KEPK.

Materials and tools

The instruments used were experimental animal cages along with feeding and drinking supplies, animal and digital scales, disposable syringe, glucose strip test Easy Touch®, cotton, alcohol, scissors, knives, rat stomach, rat oral gavage, mortar, measuring cup. The ingredients used were 70% ethanol extract of white leadtree, acarbose, sucrose, 0.5% carboxymethyl cellulose (CMC), alloxan monohydrate, sucrose, and 0.9% physiological solution of NaCl. The experimental animals used in this study were 35 white male wistar rats with sex of male, aged 2–3 months, and weight of 200–250 g the inclusion criteria.

Procedures

Mice were acclimatized in the cage for 7 days, one cage for each mouse. The mice were then given standard food in pellets and drinks in ad libitum. Rat food was provided at night since rats are nocturnal animals that actively eat at night.

On day 8, all rats were weighed and fasted for 8 hours, furthermore their Fasting Blood Sugar (FBS) level were examined. FBS and weight examinations were to ensure that rats used in this study matched the inclusion criteria and were feasible as experimental animals. The examinations were also to determine alloxan doses. Alloxan acts by damaging the essential substances in pancreatic β-cells, causing the reduction of granules in pancreatic the cells (Yuriska 2009). Alloxan with a dose of 125 mg/kg of BW was prepared by dissolving 875 mg of alloxan in 35 ml NaCl, thus 25 mg/ml suspension was obtained. Once the alloxan was ready, alloxan was injected intra-peritoneally based on the doses. The effect would appear for ±3 days while being fed and given drink as usual.

Alloxan that was induced to make normal rats became diabetic had a success rate of ±8%. If diabetic effect did not appear in 5 days after injection, re-injection was done (Efendi *et al.* 2010). Furthermore, the rats were fed with feed pellets and given drink in ad libitum until the day 10.

Day 11 was 3 days post induction of alloxan, every rats was fasted for 8 hours. On day 12, or 4 days post induction of alloxan, FBS concentration examination was conducted. Blood sugar concentration <126 mg/dl was excluded from this study, and the subject of the study was randomized.

Group I as positive control (acarbose + sucrose). Acarbose inhibits the increasing of post-prandial blood glucose concentration. Group II as negative control (0.5% CMC + sucrose). 0.5% CMC had no effect in inhibits the increasing of post prandial blood glucose concentration. Group III was white leadtree extract 1.5 g/kg of BW + sucrose. Group IV was white leadtree extract 3.5 g/kg of BW + sucrose. Group V was white leadtree extract 7.8 g/kg of BW + sucrose, all of them had similar effect as the acarbose positive control group. Furthermore, acarbose, 0.5% CMC, white leadtree extract was administered orally using rat oral gavage.

Dosage of intervention. The extract dosage was determined based on previous research by Silvita *et al.* (2015), which stated that the infusion of white leadtree at dose of 2.1 g/200g of BW, 3.5 g/kg of BW, and 7.8 g/kg of BW had a postprandial antihyperglycemic effects.

Acarbose as positive control was a hypoglycemic drugs used as diabetic therapy (Ndraha 2014). Acarbose was a type of diabetic drugs as an inhibitor of alpha glycosidase enzyme to present postprandial hyperglycemia. Acarbose binds to α-glucosidase enzyme in gastrointestinal tract, so disaccharide hydrolysis in small instestine is disrupted. This reduces the possibility of glucose absorption in the digestive tract to go into blood. Acarbose is used relatively often in diabetes treatment, its mechanism was similar to the antidiabetic effect of white leadtree (Manaf 2010). The used of acarbose in those who had glucose tolerance disorder was not only associated to 36% reduction of diabetes risk development, but also might reduce the risk of developing new cases of hypertension by 34% and reduce the risk of cardiovascular occurrence, especially silent myocardial infarction by 49% (Ceriello *et al.* 2006). Acarbose therapy dosage used in this study was 50 mg (Willihnganz 2013). Furthermore, that dosage was converted based on Laurance and Bacharach table. Dosage of a 70 kg human to 200 g mice is equivalent to 0.018 times of human dosage. The calculation of the acarbose dosage used in this study was 50 mg x 0.018=0.9 mg/200g of BW.

Meanwhile, 0.5% CMC was used as the negative control. Kristanto and Christofer (2015) described that 0.5% CMC was a thickener, emulsion stabilizer, and neutral, so it did not contain any substance that could produce hypoglycemia. The dose of sucrose used in all groups was 2 g/kg of BW=0.4 g/200g of BW of mice (Parmawati 2014).

Alloxan dosage used was 125 mg/kg of BW. The dosage selection was based on the results of initial research that had been done previously and had ensured that alloxan at a dose of 125 mg/kg of BW might cause pancreatic damage, but not death (Sulistyaini 2015).

Data analysis

Data were presented in mean and SD. The concentration difference between Fasting Blood Glucose Diabetes Mellitus (FBGDM) and 2 Hour Post-Prandial Blood Glucose (2HPBG) was analyzed using one-way ANOVA and followed by Bonferroni post hoc test. Data processing and analysis were carried out using SPSS 2007 version 17 program. Statistical difference was considered significant if $p < 0.05$.
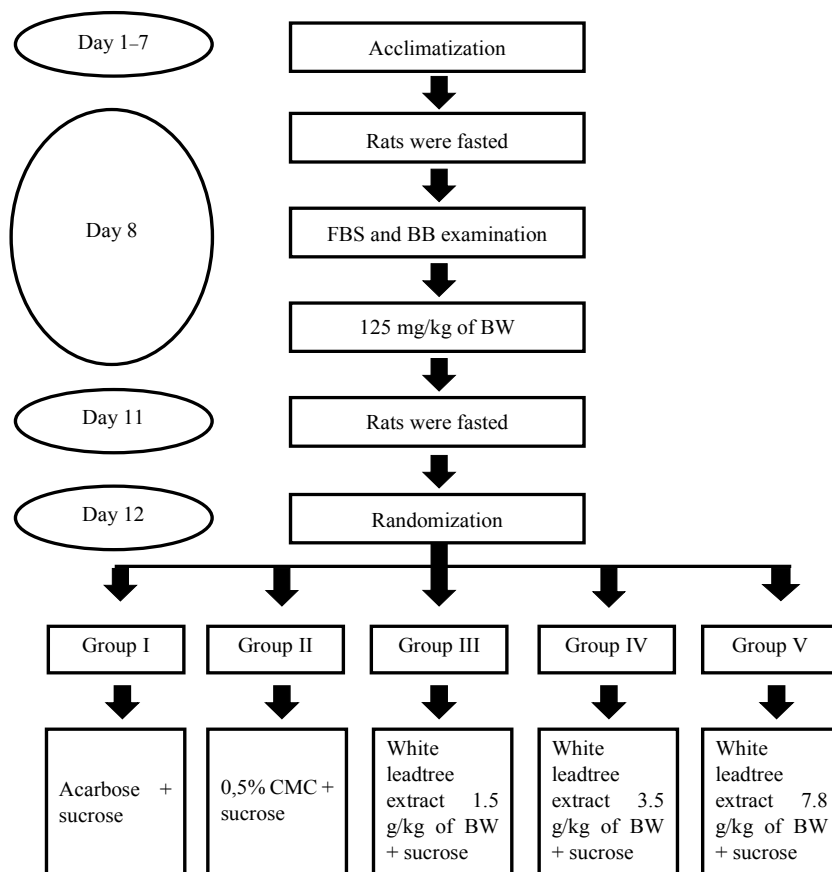
Figure 1. Study procedure

RESULTS AND DISCUSSION

Table 1 showed the average FBGDM concentration increased in all groups after administration of alloxan. The average 2HPBG concentration decreased in all groups after treatment. The highest difference between FBGDM and 2HPBG was in group V, 190.6 ±8.792 mg/dl.

The One Way ANOVA test result in Table 2 showed that there was a statistically significant difference between groups ($p<0.05$). Therefore, Bonferroni post hoc test was conducted to investigate the significance value between groups.

The result of Bonferroni Post Hoc in Table 3 showed a significant value greater than 0.05 between positive control group (acarbose) and the group treated with white leadtree extract 1.5g/kg of BW, 3.5 g/kg of BW, and 7.8 g/kg of BW, so it could be concluded that there was no significant difference between positive control group and other three groups treated with white leadtree extract. The difference between the negative control group (0.5% CMC), positive control group, and with white leadtree, however, showed a significant value less than 0.05 ($p<0.05$), which could be concluded that there was a significantly difference between negative group, positive control group, and three groups treated with white leadtree extract.

Material used in this study was 70% ethanol extract of white leadtree (*Leucaena leucocephala*). It was used because the active compound in it had been separated from the plants' inactive or inert compounds by solvents, which were used during the extraction process. The purpose of this extract was to achieve maximum therapeutic effect since only active compounds were contained in it (Parmawati 2014). Ethanol was used because of its polar and inert properties. Polar solvent was able to break cells so the compounds in cells could be obtained. Inert properties played role in preventing decomposition (Shofiyullah 2015). The used of ethyl acetate fraction derived from white leadtree 70% ethanol has been proven to reduce blood glucose concentration in wistar rats induced by alloxan (Chahyono *et al.* 2012). White leadtree was used in this study because it is correspondent with the result of previous

Table 1. Blood glucose concentration in pre-treated and post-treated mice (mg/dl)

Treated Groups	Pre-treated		Post-treated	Δ FBGDM and 2HPBG
	NFBG	FBGDM	2HPBG	
	Mean±SD	Mean±SD	Mean±SD	
Group I	94.8±6.535	283.8±24.904	99.2±13.217	184.6±17.530
Group II	103±2.550	286±21.436	181±10.320	105±11.402
Group III	93.4±6.148	278.8±13.103	108.2±11.632	170.6±17.981
Group IV	73.8±7.727	283.4±45.523	106.2±9.884	177.2±47.715
Group V	81±17.507	293.6±13.722	103±11.009	190.6±8.792

NFBG: Normal Fasting Bloog Glucose; FBGDM: Fasting Blood Glucose Diabetes Mellitus; 2HPBG: 2 Hour Post Prandial Blood Glucose; SD: Standard Deviation; Δ: Differences Group I: Positive Control (Acarbose); Group II: Negative control (0.5% CMC); Group III: White leadtree extract 1.5 g/kg of BW; Group IV: White leadtree extract 3.5 g/kg of BW; Group V: White leadtree extract 7.8 g/kg of BW

study, which stated that white leadtree contains flavonoids, tannins, and galactomannans, which are able to inhibit the increasing of blood glucose concentration by inhibiting α-glucosidase activity. Alpha glucoidase played role in glucose absorption process in brush border cell membrane in small intestine (Silvita *et al.* 2015).

Based on Table 1, laboratory study showed that blood glucose concentration between pre-treated group (FBGDM) and post-treated group (2HPBG) was decreased in all groups. The decreased of blood glucose concentration was due to incretin effect in small intestine. The incretin effect was played by two main hormones, Glucagon-like polypeptide-1 (GLP-1) and Glucose-dependent insulinotropic polypeptide (GIP) or gastric inhibitory polypeptide. Incretin hormones were then broken by the present of Dipeptidyl Peptidase-4 (DPP-4) enzymes, so they only worked for a few minutes (Balitbangkes 2013). GIP and GLP-1 were secreted from intestines during the sucrose consumption to stimulate secretion of insulin from pancreas β-cell. GIP and GLP-1 can give incretin effect by binding to their specific receptor, GIP Receptor (GIPR) and GLP-1 Receptor (GLP-1R). Receptor binding activated and increased intracellular cyclic adenosine monophosphate in pancreas cell so it could stimulate insulin secretion (Yutaka *et al*. 2010). In addition to stimulating the insulin secretion, GLP-1 also contributes in decreasing glucose by inhibiting glucagon secretion, slowing the gastric emptying time, and inducing

the feeling of fullness (Aravind *et al.* 2015). Laboratory study result showed that the average blood glucose concentration differences between FBGDM and 2HPBG in negative control groups (105±11.402 mg/dl) was lower than in the control groups treated with white leadtree extract 1.5 g/kg of BW (170.6±17.981 mg/dl), 3.5 g/kg of BW (177.2±47.715 mg/dl), 7.8 g/kg of BW (190.6±8.792 mg/dl) and positive control group (184.6±17.530 mg/dl). Rats in negative control groups experienced lower inhibition response in increasing blood glucose concentration compared to three groups treated with white leadtree extract and positive control group. Based on the data, it can be concluded that the groups treated with white leadtree extract and positive control group experienced a hypoglycemic effect, since the treatments were better in inhibiting the increase of blood glucose concentration compared to the negative control.

The result of one-way ANOVA test showed that there was a significant change in average blood glucose concentration between groups. The data analysis followed was continued with Bonferroni post hoc to investigate the significance between groups. The result of Bonferroni post hoc analysis showed a significant difference between negative control group with positive control group and all three groups treated with white leadtree extract ($p < 0.05$). The result of Bonferroni post hoc test analysis also showed that there was no significant difference between positive control group and three groups

Table 2. Change in blood glucose concentration

	Sum of squares	df	Mean square	F	Sig.
Between groups	23833.360	4	5958.340	9.565	.000
Within groups	12458.400	20	622.920		
Total	36291.760	24			

One-way ANOVA test, significant at $p < 0.005$

Table 3. Post hoc comparisons between control group and the group treated with white leadtree extract

Groups	Groups	Sig.
Positive control	Negative control	0.001*
	1.5 g/kg of BW	1.000
	3.5 g/kg of BW	1.000
	7.8 g/kg of BW	1.000
Negative control	Positive control	0.001*
	1.5 g/kg of BW	0.001*
	3.5 g/kg of BW	0.002*
	7.8 g/kg of BW	0.000*
1.5 g/kg of BW	Positive control	1.000
	Negative control	0.001*
	3.5 g/kg of BW	1.000
	7.8 g/kg of BW	1.000
3.5 g/kg of BW	Positive control	1.000
	Negative control	0.002*
	1.5 g/kg of BW	1.000
	7.8 g/kg of BW	1.000
7.8 g/kg of BW	Positive control	1.000
	Negative control	0.000*
	1.5 g/kg of BW	1.000
	3.5 g/kg of BW	1.000

Bonferroni post hoc test significantly diferent $p < 0.05$

treated with white leadtree extract ($p > 0.05$). This might happen because white leadtree contains hypoglycemic active compounds, such as flavonoids, tannins, and galactomanans that inhibit α-glucosidase enzymes so the glucose absorption in intestinal brush border membrane was disrupted. In addition, tannin contained in white leadtree can induce the regeneration of pancreatic β-cells. Furthermore, flavonoid compounds in white leadtree in the form of isoflavones could act as antioxidant, which plays a role in inhibiting the damage that might occur in Langerhans islets of the pancreatic β-cells (Suryanti *et al.* 2016).

The results of this study were parallel with the study by Silvita *et al.* (2015), which described that white leadtree infusion inhibited the increasing of postprandial blood glucose concentration in diabetic mice model, and parallel with the study conducted by Nugraha and Yusuf (2015), which stated that white leadtree extract was effective in reducing the blood glucose concentration in hyperglycemic rats induced by alloxan, marked with changes in Langerhans islets diameter size and the number of the β-cells.

CONCLUSION

The three white leadtree extract dosages were able to inhibit the increase of the two-hour postpandrial blood glucose concentration. There was no significant statistical difference between the positive control of acarbose treatment and the groups of white leadtree treatments of 7.8 g/kg of BW, 1.5 g/kg of BW and 3.5 g/kg of BW. However, the white leadtree extract of 7.8 g/kg of BW showed the best inhibition effect. This result was due to mixed effect of several active compounds in the white leadtree extract, which cause a synergistic effects.

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