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Research Article

Anti-hiperglycemic Effect of *Urena lobata* Leaf Extract by Inhibition of Dipeptidyl Peptidase IV (DPP-IV) on Diabetic Rats

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ABSTRACT
Glucagon Like Peptide-1 (GLP-1) is one of incretin hormone which is proposed as a new therapy for type 2 diabetes (T2DM). However, this hormone is metabolized excessively by Dipeptidyl Peptidase IV (DPP-IV) into inactive form. The inhibition of DPP-IV can prolong GLP-1 bioavailability for regulating blood glucose level on T2DM. *Urena lobata* is a plant which has been used to cure T2DM empirically but the inhibitory activity on DPP-IV has not been tested. The aim of the study was to evaluate anti diabetic effect of *U. lobata* leaf extract through DPP-IV inhibition. *Urena lobata* leaf was extracted in ethanol solvent and hot water then evaporated till pasta form. The object study was used animal model of T2DM which divided into 2 control group and 6 test group (n=4) and then DPP-IV level, GLP-1, insulin and blood glucose AUC were examined after supplemented *U. lobata* leaf extract. All data are expressed as the mean ± SD and analyzed with *one way anova* and then continued with LSD and Dunnet c ($p<0.05$). Both of water and ethanolic extract from *U. lobata* decrease DPP-IV level and blood glucose AUC compared to control group ($p<0.05$) whereas insulin level and GLP-1 are increased ($p<0.05$). It was controlled by stigmasterol, β-sitosterol and mangiferin having anti-diabetic effect by inhibiting DPP-IV. Water extract of *U. lobata* stronger decrease DPP-IV level and blood glucose AUC and also increase insulin level and GLP-1 compared to ethanolic extract ($p<0.05$). The conformation change of active substances result a poor solubility and absorption in ethanol extract contribute to decrease their biology activity.

Keywords: Diabetes mellitus type II, DPP-IV, GLP-1, Insulin, *Urena lobata.*

INTRODUCTION

Nowadays, treatment of type 2 Diabetes mellitus (T2DM) is focused on incretin hormon. Glucagon like Peptide-1 (GLP-1) and Glucose Dependent Insulinotropic Polypeptide (GIP) are a major incretin hormon secreted by intestinal due to oral nutrition induce[1]. GLP-1 play a role to maintain blood glucose level related to their biology action such as to stimulate insulin secretion, increase β-cell proliferation, inhibit glucagon secretion, reduce the rate of gastric emptying and induce satiety[1,2]. In T2DM patient, GLP-1 bioavaibility decrease so that insulin secretion reduce and the clinical effect is hyperglycemic chronic[3].

Incretin hormone especially GLP-1 have a potency to cure T2DM but GLP-1 is metabolized by Dipeptidyl peptidase-IV (DPP-IV) excessively into inactive forms. GLP-1 have a short half life in the body, approximately 2-5 minutes due to DPP-IV activity[2,3]. Inhibition of DPP-IV is effective to treat T2DM so that GLP-1 bioavaibility can be retain so that it was able to regulate blood glucose level[3].

Treatment of T2DM with synthethic chemical drugs such as *incretin like* or DPP-IV inhibitor show less side effect but the use of this drugs is still limited. Adverse reaction of Oral Anti Diabetic (OAD) such as Gastro Intestinal Tract (GIT) disorder, body weight gain and hypoglycemic are seldom in using of DPP-IV inhibitor or incretin like drugs[4]. The less side effect of drugs is affected by GLP-1 activity that could suppress appetite and it does not have insulin secretory effect[3,5]. Generic name of DPP-IV inhibitor are not available in society so that the price of drugs are expensive and it cannot be bought by peoples. The safety of DPP-IV inhibitor for long term use in treatment of T2DM is still under questioned and the data have not been completed[6]. This phenomenon attract people to find medicinal plant as alternative to treat T2DM by DPP-IV inhibition[6,7].

One of traditional plants which have anti-diabetic effect is Pulutan (*Urena lobata*). Root and leaf extract of *U. lobata* have been used empirically by Nigeria people to treat DM. Preclinical test of *U. lobata* root extract show anti hyperglycemic effect on streptozotocin-induced rat[8]. Bioactivity of *U. lobata* is regulated by its active substances such as sterol, alkaloid and flavonoid. Some study have showed anti diabetic potency of *U. lobata* but the mechanism of herbs on GLP-1 activity with DPP-IV

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Table 1: Body weight, food consumption and blood glucose of diabetic rats at 8th week

	Normal group	Diabetic group	AEU-250	AEU-500	AEU-1000	EEU-250	EEU-500	EEU-1000
Body weight (g)	298.0 ± 13.5#	229.5 ± 8.9*	223.0±10.5*	222.0±9.3*	239.0±6.8*	235.0±8.2*	232.0±11.1*	218.0±9.6*
Food consumption (%)	100.0 ± 0.0	97.0 ± 6.5	55.6 ± 3.7#	51.0 ± 4.9#	79.0 ± 5.5#	98.0 ± 7.9	96.0 ± 8.6	87.0± 6.9#
Fasting Blood Glucose (mg/dL)	101.0 ± 11.8#	129.0 ± 9.6*	96.0± 10.5#	86.7 ± 9.5#	91.5± 11.7#	91.7 ± 7.9#	91.7± 6.8#	103.3±7.4#
Random Blood Glucose (mg/dL)	127.3 ± 10.4#	182.3±11.5*	133.3± 9.8#	118.7± 8.4#	114.0± 7.9#	114.0± 6.7#	129.8±7.5#	162.3 ±9.9*

Result are expressed as means ± SD, n=5
* different compared to normal group (p<0.05, LSD test)
# different compared to diabetic group (p<0.05, LSD test)

inhibition not yet investigated[8-10]. Therefore we examine anti-diabetic effect of *U. lobata* leaf extract with DPP-IV inhibition.

MATERIAL AND METHODS

Preparation of U.lobata leaf extract

U.lobata leaf powder were obtained from Balai Materia Medika Batu Malang with certificate number 074/027/101.8/2015. In brief, the *U.lobata* leaf powder (50 g) was extracted according to decoctation method in 250 ml hot water at 90ºC for 30 minutes. The other *U.lobata* leaf powder (50 g) was extracted by digestion method in 250 ml ethanol for five hours using shaker waterbath and repeated every two times using fresh solvent. Both of extract were evaporated until resulting concentrated extract.

Animals and treatments

Male Sprague-Dawley (SD) rats (180-200 g) were obtained from Gajah Mada University Yogyakarta Indonesia. They were conducted according to the ethical guidelines which were approved by the Commision of Ethical Research Brawijaya University Malang Indonesia with certificate number 245-KEP-UB. SD rats were separately housed in automatically controlled animal room at 25 ± 1º C on a 12:12-h light–dark cycle. They were fed by standard food, water *ad libitum* and fasted overnight before the experiments. Normal diet (ND) and a high-fructosa diet (HFD) food were freshly mixed in every two days. Diabetic rats were induced by HFD (65% fructose and 35% ND food) and single dose of streptozotocin 25 mg/kg BB intra peritoneal. Rats were stated diabetic if fasting blood glucose more than 126 mg/dL[24] . The experimented rats were assigned into eight groups for four rats each. For eight weeks, the control group received ND and the diabetic and treatment groups received HFD. The treatment groups divided into two, the first was given water extract of *U.lobata* and the second was given ethanol extract, at a dose of 250 mg/kg, 500 mg/kg, and 1000 mg/kg for four weeks. Body weight and food intake were monitored weekly. Blood samples were obtained 15 minutes after glucose stimulation and taken from tail vein after overnight fasted. Blood sample were immediatley centrifuge 4500 rpm. The serum was separated and saved under -20 ºC.

DPP-IV assay

DPP-IV serum level was analysed by rat DPP-IV ELISA kit (Elabscience E-EL-R0337). 100 µl samples were incubated for 90 minutes at 37 ºC, added 100 µl Biotinylated detection Ab and then incubated for 60 minutes at 37 ºC. After aspirating and washing then sample was added 100 µl HRP conjugate and incubated for 30 minutes at 37 ºC. Added 90 µl substrat reagent then was added 50 µl *stop solution*. Samples were read with microplate reader at λ = 450 nm.

GLP-1 assay

GLP-1 serum level was analyzed by rat GLP-1 ELISA kit (USCN CEA804). 50 µl samples were added 50 µl Detection reagent A and then incubated for 60 minutes at 37 ºC. After aspirating and washing, samples were added 100 µl detection reagent B and incubated for 30 minutes at 37ºC. Added 90 µl substrat reagent then was added 50 µl *stop solution*. Samples were read with microplate reader at λ = 450 nm.

Insulin assay

Insulin serum level was analyzed by rat insulin ELISA kit (Elabscience E-EL-R0023). 50 µl samples were added 50 µl Biotinylated detection Ab and incubated for 45 minutes at 37 ºC. After aspirating and washing then samples were added 100 µl HRP conjugate and incubated for 30 minutes at 37ºC. Added 90 µl substrat reagent then incubated for 15 minutes at 37ºC. 50 µl *stop solution* was added then read with microplatereader at λ = 450 nm.

Oral Glucosa Tolerance Test

For glucose tolerance test, the glucose were administered orally in a dose of 2g/kg body weight after overnight fasting. The blood samples were collected from the tail

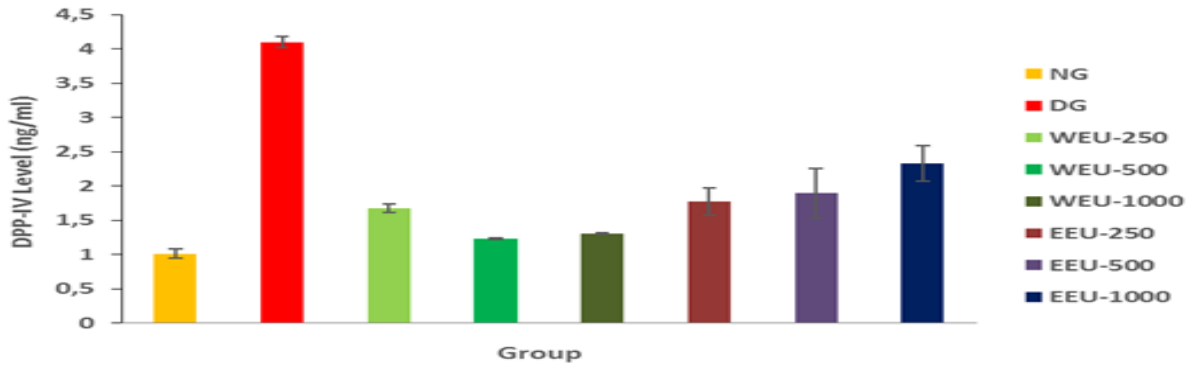

Figure 1: DPP-IV level supplemented *U.lobata* extract; a, b, c etc. showed the differences of potency (p<0.05, Dunnet C test)

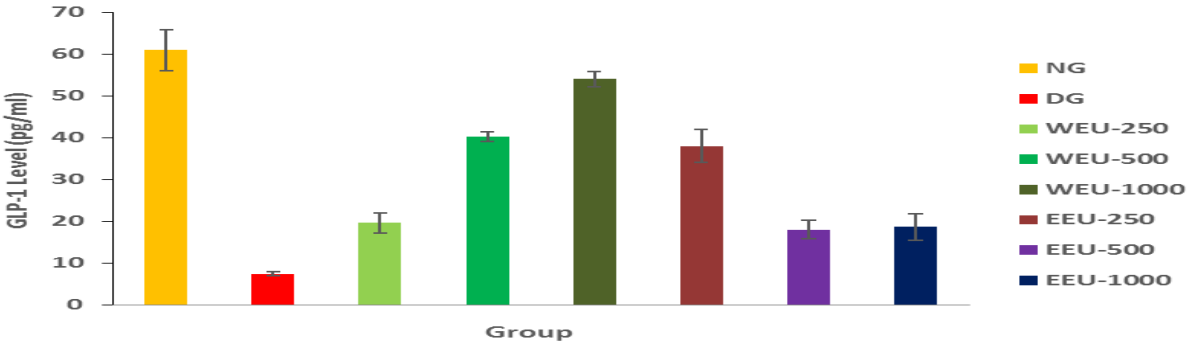

Figure 2: GLP-1 level supplemented *U.lobata* extract; a, b, c etc. showed the differences of potency (p<0.05, Dunnet C test)

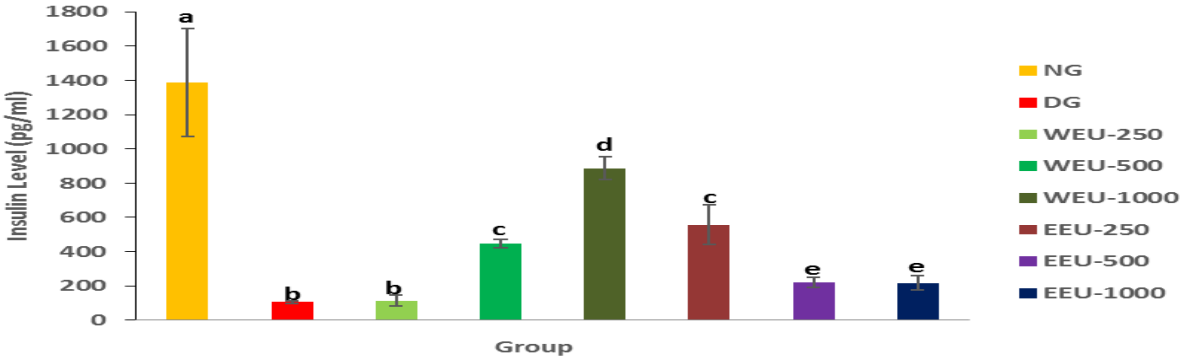

Figure 3: Insulin level supplemented *U.lobata* extract; a, b, c etc. showed the differences of potency (p<0.05, LSD test)

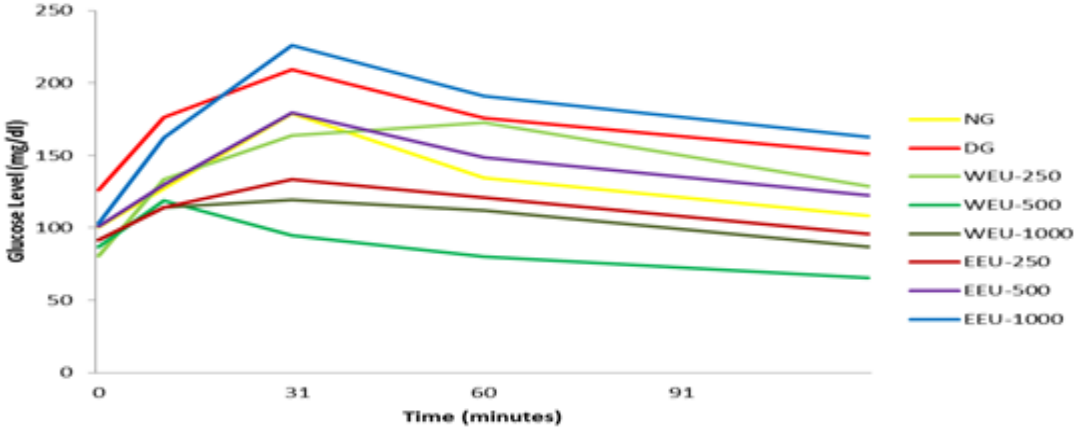

Figure 4: Test of Oral Glucose Tolerance supplemented *U.lobata* extract

vein at 0 (before glucose administered), 15, 30, 60, 90 and 120 min after glucose administered. They were measured immediately using a commercially available glucometer. The integrated area under the postprandial glucose curves (AUCs) was calculated by the trapezoidal method.

Statistical Analysis

The data were expressed as means ± S.E.M. Statistical analysis was performed by one-way ANOVA. The least significant difference (LSD) test and Dunnet C were used for mean comparisons and then $P < 0.05$ was considered to be statistically significant.

RESULTS

The effect of U. lobata leaf extract on body weight, food consumption and glucose level of diabetic rats

Body weight, food consumption and blood glucose level of diabetic rat supplemented *U.lobata* leaf extract can be shown Tabel 1. In the end of study, there is not a significant decrease of body weight on test group compared to diabetic group ($p>0.05$) meanwhile food consumption is decreased ($p<0.05$). The oral administration of *U. lobata* leaf extract decrease both of fasting blood glucose level and random compared to diabetic group ($p<0.05$)

The Effect of U. Lobata Leaf Extract on DPP-IV Serum Level of Diabetic Rats

DPP-4 serum level of diabetic rat supplemented *U.lobata* leaf extract can be shown at Figure 1. The diabetic group shows significant increase in DPP-IV level, which is about 4-fold from the normal group ($p<0.05$). Administration of water extract *U. lobata* 250 mg/kg, 500 mg/kg and 1000 mg/kg bw can decrease DPP-IV level respectively about 60%, 70% and 70% compared to diabetic group ($p<0.05$) whereas ethanolic extract 60%, 50% and 40%. At the same dose, water extract from *U.lobata* is able to decrease more DPP-IV level compared to ethanolic extract ($p<0.05$).

The Effect of U. Lobata Leaf Extract on GLP-1 Serum Level of Diabetic Rats

GLP-1 serum level of diabetic rat supplemented *U.lobata* leaf extract can be shown Figure 2. There is a significant decrease of GLP-1 levels on diabetic group about 8-fold compared to normal group observed ($p<0.05$). Water extract of *U. Lobata* in doses 250 mg/kg bw, 500 mg/kg bw and 1000 mg/kg bw can prevent degradation of GLP-1 respectively about 3-fold, 5-fold and 7-fold compared to diabetic group ($p<0.05$) whereas supplementation of ethanolic extract which show respectively about 5-fold, 2-fold and 2.5-fold ($p<0.05$). At the same dose, water extract from *U.lobata* is able to inhibit more the degradation of GLP-1 compared to ethanolic extract ($p<0.05$) except ethanolic extract of *U.lobata* in dose 250 mg/kg bw.

The Effect of U. Lobata Leaf Extract on Insulin Serum Level of Diabetic Rats

Insulin serum level of diabetic rat supplemented *U.lobata* leaf extract can be shown at Figure 3. There is a significant decrease of insulin levels on diabetic group approximately 14-fold compare to normal group observed ($p<0.05$). The administration of water extract *U.lobata* 250 mg/kg bw cannot increase more insulin level, whereas the dose of 500 and 1000 mg/kg bw will increase insulin level 4-fold, 8-fold respectively compared to diabetic group ($p<0.05$). The ethanolic extract dose of 250 mg/kg bw, 500 mg/kg bw and 1000 mg/kg bw increase respectively about 5-fold, 2-fold and 2-fold ($p<0.05$). The more increase dose of water extract *U. lobata*, the more insulin level escalate, contrally, the ethanolic extract *U. lobata* will reduce the insulin secretion.

The Effect of U. Lobata Leaf Extract on Glucose Tolerance Test of Diabetic Rats

Blood glucose level of rat supplemented *U.lobata* after stimulating glucose can be shown at Figure 4 and 5. Based on these results, there is a significant increase at AUC glucose on diabetic group up to 70% compared to normal group observed ($p<0.05$). The suplementation of water extract *U.lobata* in dose of 250 mg/kg bw, 500 mg/kg bw and 1000 mg/kg bw can decrease AUC glucose respectively 50% ,60% and 50% compare to diabetic group ($p<0.05$) whereas ethanolic extract respectively 50%, 40% and 20% ($p<0.05$). Water extract of *U.lobata* stronger control AUC glucose compared to ethanolic extract ($p<0.05$) after glucose stimulation.

DISCUSSION

The Effect of U. Lobata Leaf Extract on DPP-IV Serum Level of Diabetic Rats

Both of water and ethanolic from *U.lobata* significantly can inhibit DPP-IV activity of diabetic rats. The effects are regulated by active the compounds of *U.lobata* such as mangiferin, stigmasterol and β-sitosterol. Based on in-silico study, the active compounds above have a strong inhibition constanta, thus they act as a good DPP-IV inhibitory[11]. Beside that, they also have a strong affinity binding and surface interaction with DPP-IV until it result a good inhibitory activity on DPP-IV.

DPP-IV or CD26 is an unique serine protease that is widely distributed in numerous tissues. DPP-IV is hydrolase enzyme and also exists as a soluble circulating form in plasma and significant DPP-IV-like activity is detectable in plasma from humans and rodents[12]. DPP-IV (CD26) exerts its biological effects via two distinct mechanisms of action. First, DPP-IV/CD26 is expressed on T cells, plays a functional role in T cell activation, and activation of CD26 sets in motion a well-defined signaling cascade in the T cell. CD26 associates with CD45, and modulation of CD26 activity is frequently associated with enhanced T cell proliferation in immune system. Secondly, the principal biological activity of DPP-IV/CD26 is its enzymatic function. The enzymatic activity of CD26 is exhibited by the membrane-spanning form of the molecule, and the slightly smaller circulating soluble form[14]. The enzim contribute to carbohydrate metabolisms by destructing incretin hormone like GLP-1 and GIP[13].

The substrates of CD26/DPP-IV are not specific to a certain peptides. Proline or alanine containing peptides are the substrates of DPP-IV and include growth factors,

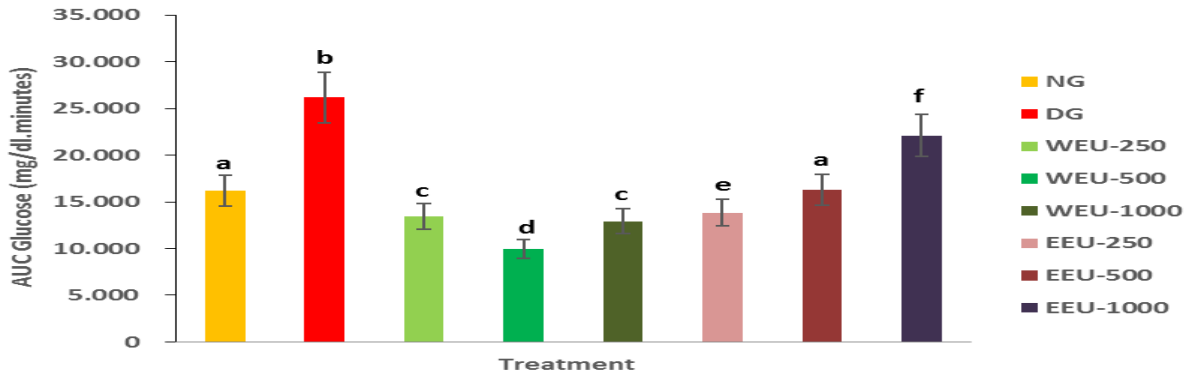

Figure 5:AUC of glucose supplemented *U.lobata* extract; a, b, c etc. showed the differences of potency ($p<0.05$, LSD test)

chemokines, neuropeptides and vasoactive peptides[12]. DPP-IV prefers substrates with an amino-terminal proline or alanine at position 2, but may also cleave substrates with non-preferred amino acids at position 2[12,15]. The structure of incretin hormone such as GLP-1 and GIP reveals a highly conserved to alanine at position 2, rendering these peptides ideal putative substrates for the aminopeptidase DPP-4[15].

DPP-4 inhibitor prevents the degradation of active GLP-1 but does not increase the levels of circulating total GLP-1 and does not prevent the kidney from rapidly clearing GLP-1. DPP-IV inhibition also acutely reduces L cell secretion of GLP-1, likely via negative feedback on the L cell[16]. Using DPP-4 inhibitors, primarily for the treatment of diabetes, related to the potential effects of these inhibition on immune function. CD26/DPP-4 plays an important role in tumor biology, and is useful as a marker for various cancers, with its levels either on the cell surface or in the serum increased in some neoplasms and decreased in others[17]. It is related to the inhibition of T cell proliferation in immune system so that lose their biological activity to protect against neoplasm[14,17].

The increase doses of water extract *U.lobata* more inhibit DPP-4 activity whereas ethanolic extract increase DPP-4 precisely. It is caused by the conformation shift of active compounds particulary sterol group in ethanolic extract, so they were formed complex compounds in post binding[18,19]. The change of active compounds structure can alter the solubility of active substances and absorption so that modulate inhibitory activity on DPP-4[18].

Water extract of *U.lobata* more inhibit DPP-4 activity than ethanolic extract. Complex form of active substances in water extract of *U.lobata* fasciltate inhibitory activity on DPP-IV. Some of active compound in water extract of *U.lobata* have synergistic interaction so that reinforce their inhibitory activity on DPP-IV[4]. DPP-IV inhibition activity will increase the bioavaibility of incretin hormone to contribute in carbohydrate metabolism[3].

The Effect of U. Lobata Leaf Extract on GLP-1 Serum Level of Diabetic Rats

Both suplementation of water and ethanolic extract from *U.lobata* significantly maintain GLP-1 bioavaibility of diabetic rats. Mangiferin, stigmasterol and β-sitosterol in the extract are able to prevent degradation of GLP-1 by DPP-IV. Based on our previous study, active compounds in *U.lobata* above act as DPP-IV inhibitor. DPP-IV inhibition prevents the degradation of active GLP-1 but does not increase the levels of total circulating GLP-1 and does not prevent the kidney from rapidly clearing GLP-1[2].

GLP-1 is incretin hormone produced by L cell intestine and the secretion depends on oral nutrition. GLP-1 has a potency for T2DM therapy but it is metabolized excessively by DPP-IV into inactive form[3,7]. GLP-1 has a short half-life, approximately for 2-5 minutes, it is caused of DPP-IV activity[3,6]. The active form of GLP-1 are GLP-1 (7-36) amides and GLP-1 (7-37) which are rapidly inactivated by DPP-IV through cleave N-terminal dipeptide His-Ala. It produces inactive form of GLP-1, they are GLP-1 (9-36) amide and GLP-1 (9-37) isopeptides[6,7]. A number study showed that the importance of DPP-IV mediated inactivation of GLP-1 as a key determinant of GLP-1 and GIP bioactivity[20].

The water extract of *U.lobata* maintain more GLP-1 bioavaibility compared to ethanolic. It is caused by the difference of active compounds which inhibit GLP-1 degradation by DPP-IV. It also relate to DPP-IV inhibitory activity of active compound both in water extract and ethanol from *U.lobata*. The effect is regulated by DPP-IV inhibitory activity due to a synergistic interaction of active compounds and production of complex compound in water extract[4]. As the result, inhibition of DPP-IV will prevent GLP-1 metabolism from inactivation so that their bioavaibility is able to retain.

GLP-1 is a super family peptide of glucagon which have a similarity degree about 48 %. The similarity of amino acid sequence between GLP-1 and glucagon became one of this causa. Pro glucagon gen was located at chromosome 2q36-q37 and only found in some tissues whereas the messenger RNA (mRNA) of pro glucagon was met at α-cells pancreas, L cells intestine and brain in hypothalamus part. Proglucagon production was started from transcription of preproglucagon gen and then was continued translation process. The regulation of GLP-1 release from L cells intestine are a complex mechanism that involve combinations of nutrition, hormone and neural stimuli[21]. GLP-1 receptor is classified in *G protein-coupled* receptor that is found at liver, muscle and

pancreas cells. This receptor have a specific character by activation of adenilcyclase and result cAMP. After GLP-1 binding with the receptor, it will activate cAMP and Mitogen Activated Protein Kinase (MAPK).

The biological activities of GLP-1 are various and depend on the organ target. GLP-1 activity in pancreas has functions in stimulating the secretion of insulin by cAMP activation, increasing β-cell masses by MAPK pathway, and inhibiting the secretion of glucagon[21]. In brain, it will reduce the rate of gastric-emptying, inducing satiety and neuroprotection. In heart, it will decrease fatty acid metabolism, increasing glucose utilization and cardioprotection. All of them contribute to maintain blood glucose level in T2DM[2].

The Effect of U. Lobata Leaf Extract on Insulin Serum Level of Diabetic Rats

Ethanolic and water extract of *U.lobata* significantly increase insulin synthesis of diabetic rats. It is controlled by active compounds in the extract through biological activity of GLP-1. The supplementation maintains GLP-1 bioavaibility so that the insulin biosynthesis can be increased. GLP-1 has a potency to retain the insulinotropic activity for treating T2DM [5,6].

GLP-1 stimulates pro insulin biosynthesis and transcription of pro insulin gene. GLP-1 contributes to provide insulin deposition which loses from β-cells trough biosynthesis process. GLP-1 is different with oral anti-diabetic sulphonylurea in stimulating insulin formation because the sulphonylurea only stimulate insulin, not the biosynthesis of insulin[4,21]. GLP-1 is incretin hormone which is potential to increase β-cells proliferation and prevent apoptosis of β-cell so that it is able to increase insulin secretion[2,16].

Hiperinsulinemia occurs in prediabetic condition or insulin resistance and then the secretion decline due to β-cells exhaustion or overwork[2]. The biological effect of insulin is divided into two major groups, they are metabolic effect and mitogenic. The metabolic effect is glucose transport, lipid metabolism, protein synthesis and glycogen whereas the mitogenic effect among others are the cell growth and mitogenesis[22].

In other part of the study shows also that the supplementations of *U.lobata* extract give a good description of β-cell. It is shown as a normal shape, size and number of β-cell compared to diabetic groups. This conditions support the function of β-cell to produce insulin in order to maintain blood glucose level. But, the diabetic group shows β-cells destruction which is signaled by a decrease number of β-cell. The water extract of *U.lobata* produce more insulin compared to ethanolic. It is caused by the bioavailability of GLP-1 can be preserved so it will increase the insulin secretion. Beside the quality of β-cells in water extract supplementation group are better, it showed by a normal both of size and number cells. The active compounds and their synergistic interaction in *U.lobata* extract are predicted have a role to increase insulin production[4,5,23].

The Effect of U. Lobata Leaf Extract on AUC Glucose of Diabetic Rats

Suplementation of ethanolic and water extract from *U.lobata* significantly decrease AUC glucose of diabetic rats post glucose-induced. It is controlled by *U.lobata* active compounds which has DPP-IV inhibitory activity so that GLP-1 bioavaibility can be retained for insulin biosynthesis when the blood glucose level increase after stimulating of oral nutrition[3,5]. GLP-1 acts outside of metabolism purpose, that is inhibiting of gastric juices secretion, inhibiting of the GIT motility and inhibiting of the rate of gastric-emptying[2,3]. It is beneficial to prevent the increase of blood glucose level post prandial[5,6].

Insulin works to maintain blood glucose level after glucose-induced by metabolic pathway. This hormone transports glucose from blood to tissue and synthesis glycogen from glucose in muscle in order to reduce blood gucose level. In diabetic groups, the insulin secretion is disrupted so that they lose their control to maintain blood glucose level[22]. This is showed by AUC glucose in diabetic group which is bigger than treatment and normal groups.

Water extract of *U.lobata* regulate more blood glucose level post glucose stimulation compared to ethanolic extract of *U.lobata*. It is predicted due to the poor of active compound solubility and absorption in ethanolic extract, so that affect their activities to control blood glucose level. The reducing of active compounds solubility occur due to the formation of complex compounds and the change of active compound conformation so that decrease inhibitory activity on DPP-IV that contribute to maintain blood glucose level on diabetic groups[16,18].

The effect of U. lobata leaf extract on body weight, food consumption and glucose level of diabetic rats

Aqueous extract *U.lobata* reduce food consumption so that affect body weight gain of diabetic rats. It's related to active compound stigmasterol, mangiferin and β-sitosterol in *U.lobata* that maintain bioavailability of GLP-1 trough inhibitory activity on DPP-IV. Their's interaction with GLP-1 receptor in brain could reduce the rate of gastric-emptying, inducing satiety [1,3]. The oral administration of *U.lobata* leaf extract decrease both of fasting blood glucose level and random. GLP-1 activity in pancreas has functions in stimulating the secretion of insulin by cAMP activation, increasing β-cell masses by MAPK pathway, and inhibiting the secretion of glucagon [13]. In liver, it will decrease fatty acid metabolism, increasing glucose utilization and cardioprotection. All of them contribute to maintain blood glucose level in T2DM [1,]

CONCLUSIONS

Water extract of *U. lobata* stronger decrease DPP-IV level and blood glucose AUC and also increase insulin level and GLP-1 compared to ethanolic extract. The conformation change of active substances result a poor solubility and absorption in ethanol extract contribute to decrease their biology activity.

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