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Effect of Ethanol Extract of Temu Giring (*Curcuma heyneana* Val.) Rhizomes in Reducing Blood Glucose Level of Mice after Maltose Loading

Nini Chairani[1], Muhammad Ichwan[2], Tri Widyawati[3]
[123]*Universitas Sumatera Utara, Medan, Indonesia*
Corresponding Author: Nini Chairani

Abstract:
Background*: More than 95% of diabetics are people with type 2 diabetes or often called non-insulin dependent diabetes which is characterized by pancreatic beta cell dysfunction leading to high blood glucose level called hyperglycemia. Hyperglycemia plays critical role in the development and progression of diabetic complication. Postprandial hyperglycemia in diabetes can be controlled by impairing the digestion of dietary carbohydrate by inhibiting α-glucosidase. The α–glucosidase inhibitors such as acarbose, miglitol, voglibose are widely used in the treatment of patients with type 2 diabetes, but the side effects associated with these compounds are a matter of keen concern. Therefore much effort has been directed to search for candidate of the α–glucosidase inhibitors with low side effect and effective from natural sources that can be used as a therapeutic approach in treating postprandial hyperglycemia, including edible plants. Flavonoids can regulate glucose absorbtion and homeostasis, with disaccharides as targets. Many flavonoids have exhibited α–glucosidase inhibitory activities. Temu giring (Curcuma heyneana Val.) is a native plant of Indonesia which rhizomes contains flavonoids, terpenoid, tannin, saponin, curcuminoid.*
Objectives: *The present study was designed to evaluate the effect of ethanol extract of temu giring (Curcuma heyneana Val.) rhizomes in reducing blood glucose level after maltose load.*
Methods*: This research is a laboratory experimental analytic research that uses randomized pre and post test control group design patterns. A total male 30 mice (Mus musculus L.) aged 3-4 months weighing 20-35 grams were fasted 18 hours randomly selected and divided into 5 groups and received the treatment orally. Negative control group received 0.5% Na-CMC, Positive control (Acarbose, 50 mg/kgBW), 0.5% ethanol extract of temu giring (EETG) group (50 mg/kgBW), 1% EETG group (100 mg/kgBW), 2% EETG group (200mg/kgBW). The mice were challenged with maltose ten minutes after treatment. Blood glucose levels were measured at 0, 30, 60 and 120 minutes. Area under the curve (AUC) were calculated to assess the potential of ethanol extract of temu giring (Curcuma heyneana Val.) in reducing blood glucose level in mice. Saphiro-wilk test was used to evaluate the normality data and continued with one-way ANOVA and continued by LSD for normal distributed data or kruskal-wallis for not normal distributed data test and continued by mann-whitney test to assess comparison between treatment groups. The level $p<0.05$ was considered to be statistically significant.*
Results*: The result showed that the 0.5% EETG (50 mg/kgBW) had better effect in reducing hyperglycemia than the other EETG treatment groups by an average 324.08 ± 80.71 minute, mg/dl. Acarbose had better effect in reducing blood glucose level significantly ($p=0.037$) by an average 278.25 ± 8.97 minute, mg/dl.*
Conclusion: *The result of the present study indicated that orally administered ethanol extract of temu giring, had potential effect to reduce the blood glucose level because the AUC_{0-120} level of the three dosages were under the value of negative control with the optimal dosage is 50 mg/kg BW.*
Keywords*: Temu Giring (Curcuma heyneana Val.) Rhizomes, Blood Glucose Level, Diabetes Mellitus, Area Under the Curve (AUC)*

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I. Introduction

Diabetes mellitus (DM) is a chronic metabolic disease with life-threatening complications and is one of the main global health problems that affect around 347 million people worldwide (Eleazu *e.t a.l*, 2013). This number is expected to double by the year 2030, making the diabetes the 7th leading cause of death in the world (Moodley *et. a.l*, 2015). More than 95% of diabetics are people with type 2diabetes or often called *non-insulin dependent diabetes* which is characterized by pancreatic beta cell dysfunction leading to high blood glucose level called hyperglycemia (Ajiboye *et al.*, 2016; Bailey & Day, 2013).

Hyperglycemia plays critical role in the development and progression of diabetic complication such as: renal disorders, neuropathy, retinopathy, ketoacidosis, and cardiovascular disease by numerous mechanism including increased oxidative stress, decrease nitric oxide bioavailability, glucose autoxidation and non-

enzymatic protein glycation (Eleazu *e.t a.l*, 2013; Rahimi *et al.*, 2005). It becomes very important to avoid postprandial hyperglycemia in type 2 diabetes in order to decrease the risk of diabetes complication (Kim, 2019).

The α-glucosidase, the enzymes found in the brush-border surface membrane of small intestinal cells, plays catalyzing role in the carbohydrate digestion. The breakdown of carbohydrate causes the increasing of postprandial blood glucose level (Murray et al., 2009). Postprandial hyperglycemia in diabetes can be controlled by impairing the digestion of dietary carbohydrate by inhibiting α-glucosidase (Standl *et al.*, 1999). α-glucosidase inhibitors delay breakdown of carbohydrate in small intestine and diminish postprandial blood glucose excursion in diabetic subjects (Husain *et al.*, 2012; Mataputun *et al.*, 2013). Antihyperglycemic exertion of α -glucosidase inhibitor derives from competitive-reversible inhibition to intestinal digestion enzymes (α-amylase, α–glucosidase, such as isomaltase, sucrose and maltase), where this digestion enzyme hydrolyzed carbohydrate (oligosaccharides and disaccharides) in the small intestine to glucose (monosaccharides) (Sugiwa *et al.*, 2010).

The α–glucosidase inhibitors has been recognized as a therapeutic approach for modulation of postprandial hyperglycemia, which is the earliest metabolic defect to occur in type 2 diabetes (Adisakwattana *et al.*, 2012). α–glucosidase inhibitors such as acarbose, miglitol, voglibose are widely used in the treatment of patients with type 2 diabetes (Van de Laar, 2008), but the side effects associated with these compounds are a matter of keen concern (William *et al.*, 2019). Acarbose for example, it has been used as an oral hypoglycemic agent, but it has gastrointestinal side effect include flatulence, abdominal discomfort, bloating, and diarrhea (Kim *et al.*, 2019). Therefore much effort has been directed to search for candidate of the α–glucosidase inhibitors with low side effect and effective from natural sources that can be used as a therapeutic approach in treating postprandial hyperglycemia, including edible plants (Kim *et al.*, 2019).

It is believed that herbal medicine have smaller or fewer severe adverse effects (Riyaphan *et al.*, 2018). Some of plant's secondary metabolites such as flavonoids, alkaloids, terpenoids, anthocyanins, glycosides, curcuminoids, and phenolic compounds have activity as α–glucosidase inhibitors (Kumar *et al.*, 2011; Li *et al.*, 2009) by virtue of their capability to bind with proteins (Ganeshpurkar *et al.*, 2013). Curcumin possess therapeutic agents in lowering blood glucose level better than acarbose (Riyaphan *et al.*, 2018). Flavonoids and phenolics have been reported to exhibit inhibitory effect on α–glucosidase (Limanto *et al.*, 2019). There is a positive correlation between the total polyphenol and flavonoid content and the the ablity to inhibit α–glucosidase (Adisakwattana, 2012).

Flavonoids can regulate glucose absorption and homeostasis, with disaccharides as targets. Many flavonoids such as quercetin and kaemferol, have exhibited α–glucosidase inhibitory activities (He *et al.*, 2019). It has been reported that flavonoids like quercetin and rutin are good inhibitors for α–glucosidase activity, with inhibition activities better than standard compound acarbose, thus can be effective in reducing postprandial hyperglycemia (Limanto *et al.*, 2019). Flavonoids were shown to regulate carbohydrate digestion, insulin secretion, insulin signaling, and glucose uptake in insulin-sensitives tissue through various intracellular signaling pathways (Hanhineva *et al*., 2010)

Temu giring (*Curcuma heyneana* Val.) is a native plant of Indonesia which rhizomes contains flavonoids, terpenoid, tannin, saponin, curcuminoid (Depkes RI, 1989). Some of the previous studies indicate the ability of secondary metabolites of temu giring rhizomes to reduce blood glucose level. Water extract of temu giring rhizomes were proven to reduce blood glucose level and improve beta Langerhan cells defect of streptozotosin (STZ)-induces diabetic rats (Kartini *et al*., 2007). Ethanol extract of temu giring has been reported to reduce the iNOS expression and NO level of pancreatic beta cells in multiple low dose (MLD)-STZ-induced diabetic rats (Lukiati *et al*.,2012). It is also reported that ethanol extract of temu giring was able to increase Superoxide Dismutase (SOD) activity and repair the pancreatic beta cells damage in MLD-STZ-induced diabetic rats, improving hyperglycemia (Lukiati *et al.*, 2012).

However, no direct *in vivo* evidence available for its effect on postprandial hyperglycemia after disaccharides load. The present study was designed to evaluate the effect of ethanol extract of temu giring (*Curcuma heyneana* Val.) rhizomes in reducing blood glucose level after maltose load.

II. Material and Methods

This research is a laboratory experimental analytic research that uses randomized pre and post test control group design patterns. The location and sampling maintenance of experimental animals was carried out in the Pharmacology and Toxicology Laboratory and Biology Laboratory, Faculty of Pharmacy, Universitas Sumatera Utara. This study was conducted after obtaining an ethical clearance from the Ethnic Commission of the Faculty of Mathematics and Natural Sciences, Universitas Sumatera Utara with license number 0770/KEPH-FMIPA/2019.

The population in this study were all male mice (*Mus musculus* L.) weighing 20-35 grams, aged 3-4 months, active, healthy and no physics disability obtained from the Animal House of Pharmacology and

Toxicology Laboratory, Faculty of Pharmacy, Universitas Sumatera Utara. The sample of this study were 30 male mice (*Mus musculus* L.) from affordable population that met the inclusion criteria. All the animals had *ad libitum* access to water and food (standard laboratoty chow) a 12h light-12h dark cycle in room temperature (25 ± 5^0C).

The research tools used in this study consisted of electric scales, spatulas, measuring cylinder, volumetric flask, mortars, beaker glass, glucometer and glucometers test strips (Easy touch®GCU), 1cc syringe, handscoon, scissors, cotton, oral sonde, stop watch, refrigerator, and jam bottle.

The research materials used in this study were 96% ethanol extract of temu giring (*Curcuma heyneana* Val.) rhizome (EETG) obtained from Biology Laboratory, Faculty of Pharmacy, Universitas Sumatera Utara, 100 mg acarbose (PT. Dexa Medica) as positive control, 0,5% Na-CMC, and maltose powder (technical).

2.1 Procedure Methodology

Thirty male mice (*Mus musculus* L.) previously fasted for 18 hours before treatment and randomly divided into 5 groups of six, and treated as follows:

Group I : 0.5% Na-CMC as negative control
Group II: 50 mg/kg body weight Acarbose as positive control
Group III : 50 mg/kg body weight EETG as 0.5% EETG
Group IV : 100 mg/kg body weight EETG as 1% EETG
Group V: 200 mg/kg body weight EETG as 2% EETG

The mice were treated with maltose (4g/kg body weight; p.o.) ten minutes after giving the above treatments. Blood specimens were obtained by pricking the mice tail vein and place a drop of blood on the glucometer strips. The blood glucose level (BGL) were measured at 0 (before treatment) and 30, 60 and 120 minutes after the maltose loading respectively using a glucometer (Easy touch®GCU). The change in blood glucose from the basal level after the maltose load was analyzed and represented as delta blood glucose level. The blood glucose area under the curve (AUC) were calculated by trapezoidal approximation of blood glucose levels. Blood glucose level at x minute were defined as BGL(x) and the $AUC_{0\text{-}120}$ was determined using the formula as follows:

$$AUC_{0\text{-}120}\ (\text{minute.mg /dl}) = \frac{BGL\ (0) + BGL\ (30)x\ 2 + BGL\ (60)x3 + BGL\ (120)x\ 2}{4}$$

where BGL 0', BGL 30', BGL 60', BGL 120' represent BGL at 0, 30, 60, and 120 minutes (Sakaguchi *et al.*, 2015).

2.2 Statistical Analysis

Data was analyzed using SPSS version 25 (SPSS Inc.). Saphiro-wilk test was used to evaluate the normality data and continued with one-way ANOVA for normal distributed data or kruskal-wallis for not normal distributed data test to ascertain the significance of differences between mean values of two continuous variables and confirmed by post-hoc test using least significance differences (LSD) for ANOVA and by nonparametric mann-whitney test for kruskal-wallis test to assess comparison between treatment groups. The level $p<0.05$ was considered to be statistically significant.

III. Result and Discussion

3.1 Result

Postprandial blood glucose variation was measured after loading maltose to the normal mice with and without coadministration of ethanol extracts of temu giring (*Curcuma heyneana* Val.) rhizomes (EETG). Compared to negative control, there was no significant difference on the 30 minutes post-load blood glucose level in the group that received 50 mg/kg BW EETG, 100 mg/kg BW EETG and 200 mg/kg BW EETG along with maltose (Figure 1). It showed that the average of the 30 minutes post-load blood glucose increased in almost the same number. Acarbose, as positive control, had lowest blood glucose level compared to other groups by average 96.83 ± 6.01, while the others had high blood glucose level by an average $103.00 \pm 10{,}90$ mg/dl in the group that received 50 mg/kg BW EETG, 104.17 ± 23.11 mg/dl in the group that received 100 mg/kg BW EETG and 106.50 ± 17.48 mg/dl in the group that received 200 mg/kg BW EETG along with maltose (Table 1).

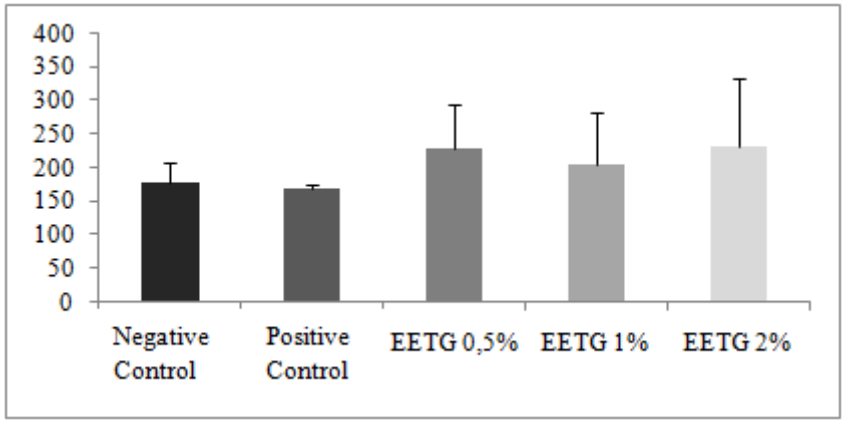

Figure 1. Histogram of Blood Glucose Level Comparison Among Groups That Received 50 mg/kg BW EETG, 100 mg/kg BW EETG and 200 mg/kg BW EETG Along with Maltose 30 Minutes after Maltose Load

Table 1. Effect of 0.5% Na-CMC, 0.5% Acarbose (50 mg/kg BW), 0.5% EETG (50 mg/kg BW), 1% EETG (100 mg/kg BW), 2% EETG (200 mg/kg BW) on The Blood Glucose Level of Normal Mice after Maltose Loading (4g/kg BW)

Groups of Treatments	Blood Glucose Level (mg/dl)			
	0'	30'	60'	120'
Negative Control	92.33 ± 8.62	177.83 ± 30.57	201.50 ± 45.40	228.33 ± 54.96
Positive Control	96.83 ± 6.01	169.67 ± 5.16	142.17 ± 8.82	125.17 ± 1.94
0.5% EETG	103.00 ± 10,90	229.67 ± 64.89	160.67 ± 68.35	126.00 ± 40.56
1% EETG	104.17 ± 23.11	206.17 ± 77.73	206.67 ± 144.36	119.00 ± 46.26
2% EETG	106.50 ± 17.48	231.67 ± 102.76	186.00 ± 74.00	127.67 ± 23.59

In the negative control group blood glucose level increase by an average 85.5 mg/dl at 30 minutes after the maltose load, while the standard comparator, acarbose produces 72.83 mg/dl increase at the same time but lower than the negative control. In the groups that received 50 mg/kg BW EETG along with maltose, the 30 minutes post-load blood glucose level increased by 122.98 mg/dl on an average (Figure 1). Similar kind of effect was observed in the group that received 100 mg/kg BW EETG and 200 mg/kg BW EETG. The blood glucose level was increased by 102 mg/dl and 125.17 mg/dl respectively 30 minutes after maltose load. But the highest peak of the 30 minutes post-load blood glucose level was observed in the group that received 200 mg/kg BW EETG along with maltose by 206.17 ± 77.73, increase significantly ($p<0.05$) by 125.17 mg/dl or about 117.53%.

The blood glucose level started to decrease at 60 minutes and continue to 120 minutes after maltose load. The lowest blood glucose level was at 120 minutes after maltose load (Figure 2). Compared to negative group that had 228.33 ± 54.96 mg/dl on the blood glucose level , the three dosage of temu giring extract decreased blood glucose level significantly ($p<0.05$) by average 126.00 ± 40.56 mg/dl in the 0.5% EETG group, 119.00 ± 46.26 mg/dl in the 1% EETG group, and 127.67 ± 23.59 mg/dl in the 2% EETG group. The three dosage reduced glycemic by 21.58% in the 0.5% EETG group, 42.42% in the 1% EETG group, and 31.36% in the 2% EETG group. While the positive control, acarbose, had better significantly affect ($p<0.05$) in reducing blood glucose level by 125.17 ± 1.94 mg/dl on an average.

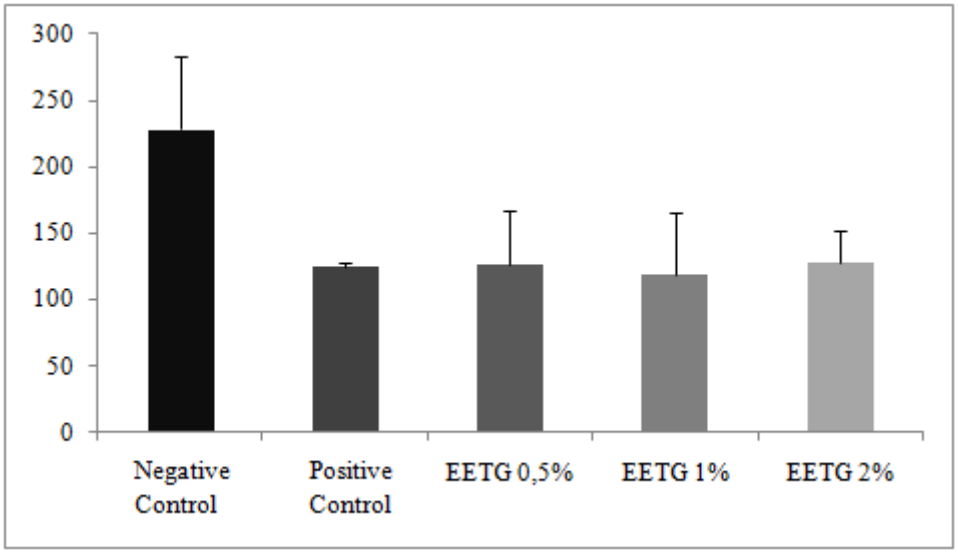

Figure 1. Histogram of Blood Glucose Level Comparison Among Groups That Received 50 mg/kg BW EETG, 100 mg/kg BW EETG and 200 mg/kg BW EETG Along with Maltose 120 Minutes after Maltose Load

The average of blood glucose level was used to calculate the area under the curve (AUC) of each treatment group to the observation time, that showed the changing on the blood glucose level in 120 minutes due to the effect of treatment in each group. The AUC_{0-120} described the hypoglycemic effect of temu giring extract. The lowest AUC_{0-120} level the highest hypoglycemic effect. Compared to negative control, the highest AUC_{0-120} level was observed in the group 2% EETG by an average 345.79 ± 112.72 minute, mg/dl, while the lowest level was observed in the group 0.5% EETG by an average 324.08 ± 80.71 minute, mg/dl. It showed that the 0.5% EETG group had better effect to reduce hyperglycemia than the other EETG treatment groups. While the positive control showed the best effect compare to the three EETG treatment groups, it can reduce hyperglycemia effect significantly ($p = 0.037$) by an average 278.25 ± 8.97 minute, mg/dl.

Tabel 2. Effect of 0.5% Na-CMC, 0.5% Acarbose (50 mg/kg BW), 0.5% EETG (50 mg/kg BW), 1% EETG (100 mg/kg BW), 2% EETG (200 mg/kg BW) on the Area Under The Curve (AUC_{0-120}) of Blood Glucose Level of Normal Mice after Maltose Loading (4g/kg BW)

Mice	AUC_{0-120} (minute, mg/dl)				
	Negative Control	Positive Control	0.5% EETG	1% EETG	2% EETG
1	274.5	272.75	258.75	350	556.75
2	423.75	286.75	270.25	255.25	332
3	429.75	290.75	245.25	301.25	375.25
4	281	279.5	453	612.25	294
5	417.5	270.75	368.25	150.5	257.75
6	437.25	269	349	392.5	259
Average ± SD	**377.29± 77.41**	**278.25 ± 8.97**	**324.08 ± 80.71**	**343.63 ± 155.88**	**345.79 ± 112.72**

3.2 Discussion

Diabetes mellitus is characterized by postprandial hyperglycemia over prolonged period (Kumar *et al.*, 2011). Inhibition of α–glucosidase that hydrolyze dietary polysaccharide into glucose is pivotal in controlling blood glucose level. Hence, inhibitors that targert α–glucosidase serve as a key strategy in the treatment of diabetes mellitus (Limanto *et al.*, 2009). Agents based on natural products are particularly attractive as side effects are minimal and therapies are well-tolerated compared to other oral hypoglygemic agents currently available (Gulati *et al.*, 2012).In the present study, the potential inhibition of the ethanol extract of temu giring on α–glucosidase was evaluated.

Hyperglycemia responded due to maltose loading in male mice increased rapidly at 30 minutes after maltose loading. It showed that the three dosage of EETG and acarbose itself, as positive control, had not shown hypoglycemic effects. Maltose is still hydrolyzed by the α–glucosidase enzyme into monosaccharide then the

blood glucose level increasing rapidly. Phytochemical compounds of temu giring extract probably started to work at the 60 minutes after maltose loading that is shown by the blood glucose level (Table 1). The compounds in temu giring extract work better at the 120 minutes after maltose loading. It showed that the compound of the extract demand much time to decrease the blood glucose level in mice. While acarbose had better effect of work.

The glucose area under the curve (AUC), which is an index of whole glucose after glucose loading, has been widely used for calculating the glycemic index and for evaluating the efficacy of medications for postprandial hyperglycemia (Sakaguchi *et al*., 2016). Based on the AUC_{0-120} results suggest that the phytochemical compounds of temu giring extract possessed potential effect in reducing blood glucose level although it's not as fine as acarbose. The phytochemicals analysis qualitative data that obtained from the Biological Laboratory of Faculty of Pharmacy USU, ethanol extract of temu giring contains metabolic secondary compound such as alkaloid, flavonoid, glycoside, saponin , tannin, triterpen/steroid. This metabolic secondary compound may affect the blood glucose level in mice. According to Arif *et al.* (2013), alkaloids, fenols, terpenoids, xanthones, and other compounds have been known to have antidiabetic activity. Steroid compounds are known to have antidiabetic activity by reducing blood glucose levels. Higher concentration of both phenolics and flavonoids trigger the pharmaceutical and biological attributes of a particular plant (William *et al.*, 2019). These results suggest that the phytochemical compound of temu giring extract possessed promising α–glucosidase inhibition activity.

Flavonoids are known to have hypoglycemic effects with several mechanism such as: avoid glucose absorbtion, act as insulin secretagogues or insulin mimetics, stimulate glucose uptake in peripheral tissues and regulate the activity and/or expression of the rate limiting enzyme involved in carbohydrate metabolism pathway (Brahmachari, 2011). Thus, the presence of flavonoids in temu giring rhizome extract induce blood glucose level in mice decrease. Flavonoids exert their α–glucosidase inhibitory activities by forming complexes with enzymes through non-covalent interactions (Zhang *et al.*, 2017). During this process, the enzyme molecules undergo structural changes and energy transfer that can be detected by common experimental methods, such as: fluorescent, spectrometry, isothermal titration calorimetry, etc (He *et al.*, 2019).

Curcumin is one of the constituent in *Curcuma heyneana* Val. (Depkes RI, 1989). The antidiabetic effect of curcumin are exerted by activating the peroxisome proliferator-activated receptors γ (PPAR γ) signaliing pathway and upregulating GLUT 4 translocation, increasing insulin secretion and sensitivity, regulating glucagon synthase kinase 3 (GSK-3) and inhibiting DPP-4 activity. Previously, curcumin and it derivatives (curcuminoids) had been proved as α–glucosidase inhibitors in an enzymatic manner (Riyaphan *et al.*, 2018).

The polyphenolic compounds in plants inhibit the activities of carbohydrate hydrolyzing enzymes, such as α–glucosidase and α–amylase, because of their ability to bind with protein (Mai *et al*., 2007). Tannins, one of the major groups of polyphenols found in plant, have been observed to enhance the glucose uptake through mediators of the insulin-signaling pathaways, such as PI3K (Phosphoinositide 3-Kinase) and p38 MAPK (Mitogen-Activated Protein Kinase) activation and GLUT 4 translocation (Kumari, 2012).

Besides, based on phytochemicals analysis qualitative data, temu giring extract has demonstrated to have alkaloid. It is has been previously demonstrated that alkaloids can exert higher inhibitory activity than flavonoids against α–glucosidase, aldose reductase, and α–amylase, and lipase (Chang *et al*., 2015). This findings enhance the potential of temu giring to overvome hypeglicemia.

IV. Conclusion

The result of the present study indicated that orally administered ethanol extract of temu giring, had potential effect to reduce the blood glucose level because the AUC_{0-120} level of the three dosages were under the value of negative control with the optimal dosage is 50 mg/kg BW.

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