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Effect of Karamunting Fruit Juice (*Melastoma malabathricum* L.) to Advanced Glycation End-Products (AGEs) and Lipid Profile as Advanced Complications of Diabetes Mellitus

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Abstract: Hyperglycemia as a result of Diabetes Mellitus (DM) could lead to an increase in free radicals that lead to oxidative stress, it will end with the formation of Advanced Glycation Ends Products (AGEs) and dyslipidemia which contributed in the complications of diabetes. Karamunting is believed and consumed by local society for treat DM, unfortunately currently there is no scientific data to support it. The purpose of this study was to determined the potential Karamunting fruit plants that are typical South Kalimantan by calculating the levels of methyl glyoxal, carbonyl, LDL, HDL, total cholesterol and triglycerides. This study is consists of six groups each of six male rats. Then do the induction streptozosin in Groups 2-5 mice at a dose of 40 mg kg^{-1} intraperitoneally, followed by treatment in the form of: Group 1 and 2 are given distilled water; Group 3 was given metformin (anti-hyperglycemic medications) 10 mg kg^{-1}; Group 4-6 granted Karamunting fruit juice with successive doses 0:01 mg g^{-1}; 0.1 mg g^{-1}; 1 mg g^{-1}. AGEs results showed that there were a significant reduction of carbonyl levels in fruit juices Karamunting within three doses (0.01, 0.1 and 1 mg g^{-1}), i.e., from 3.273 into 2.598; 2.485; 2.470 ($p<0.005$) and a significant decrease methyl glyoxal levels, i.e., from 0.039 into 0.021; 0.018; 0.016 ($p<0.005$). On result of the levels of LDL, HDL, triglycerides and total cholesterol showed a non-significant results ($p>0.05$). It can be concluded that it could lower the level of AGEs compound but not lipid profile significantly. There were no significant differences between the three different doses of metformin and Karamunting ($p>0.05$) indicating that the Karamunting has the same efficacy with metformin.

Key words: Diabetes mellitus, advanced glycation ends products, lipid profile, *Melastoma malabathricum* L., doses

INTRODUCTION

Diabetes Mellitus (DM) is a non-communicable disease which increased steadily from year to year. WHO predicts increase in the number of patients with Non Insulin Dependent Diabetes Mellitus (NIDDM) from 8.4 mln. in 2000 to about 21.3 mln. in 2030 (Soegondo, 2006). Indoensian Health Research (Riskesdas) in 2007, obtained that the proportion causes of death due to DM in the age Group 45-54 year take place in 2nd ranks (14.7% in urban areas and 5.8% for rural areas). While the South Kalimantan Health Research (Riskesdas) in 2011, the prevalence of DM in South Kalimantan reached 1.0% (range 0.3-1.7%) which 6 districts/cities with exceeding province prevalence are Banjarmasin, Banjarbaru, Barito Kuala, Tapin, Banjar and Hulu Sungai Selatan (Agency for Health Research and Development, 2011).

Hyperglycemia as a result of Diabetes Mellitus (DM) could lead to an increase in free radicals that lead to oxidative stress, it will end with the formation of Advanced Glycation Ends Products (AGEs) and dyslipidemia which contributed in the complications of diabetes (Soegondo, 2006). Diabetes Commission of World Health Organization (WHO) recommends the traditional methods for the treatment of diabetes mellitus in order to be further investigated. Plants with neutralizing AGEs and dyslipidemia effects and may provide a useful source of new components oral antidiabetic. (Ogundipe *et al*., 2003). Karamunting is one of the option. Karamunting (*Melastoma malabathricum* L.) is a typical plant growing in South Borneo, easy to be got, rich of commodity and contains flavonoid that can act as an antioxidant (Faravani, 2008). Karamunting is believed and consumed by local society for treat DM, unfortunately currently there is no scientific data to support it as anti-AGEs and anti-dyslipidemia.

Objective of the study: The purpose of this study was to determined the potential Karamunting fruit plants that are

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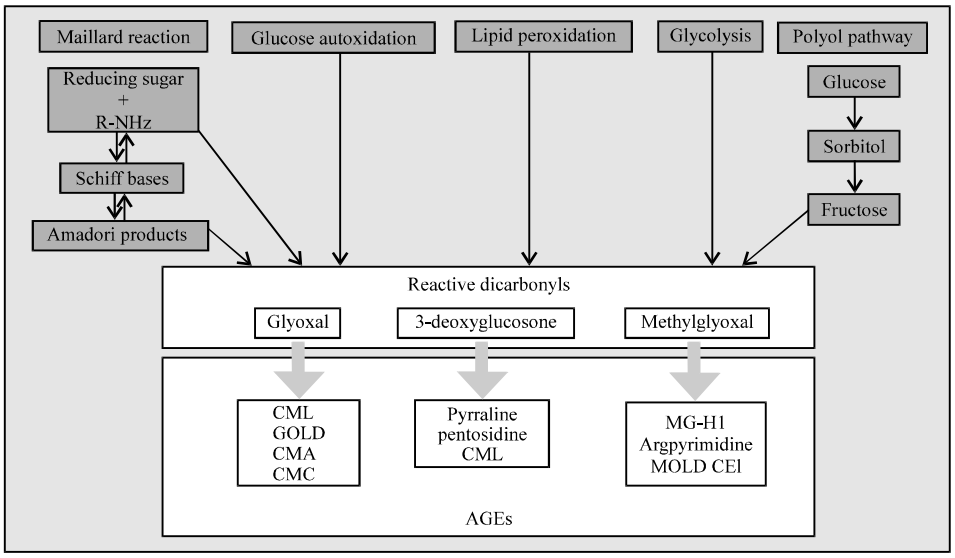

Fig. 1: Formation of AGEs (Nowotny *et al*., 2015)

typical South Kalimantan by calculating the level of 6 parameters: methyl glyoxal, carbonyl, LDL, HDL, total cholesterol and triglycerides.

Literature review

AGEs and dyslipidemia in diabetes mellitus: Diabetes Mellitus is a chronic metabolic disease characterized by hyperglycaemia due to lack of insulin secretion, inefficacy of insulin or both of the cause (Abbas and Maitra, 2005). Various complications can be caused by poor control of diabetes. These complications include vascular disease such as systemic (accelerated atherosclerosis) heart disease, microvascular disease of the eye as a cause of blindness and retinal degeneration (diabetic retinopathy) cataracts, kidney damage as a cause of kidney failure and peripheral nerve damage (diabetic neuropathy). Usually when diabetes is detected, this syndrome has been developed and there are one or 2 complications (Suhartono *et al*., 2005, 2010).

High level of blood glucose in chronic hyperglycaemic state will form AGEs because glucose which binds to proteins (glycated protein) can be oxidized and produce Reactive Oxygen Species (ROS). The combination of glycation and glucose oxidation result in the formation of AGEs (advanced glycogen end-products). The process of formation of AGEs is an irreversible process that lasts a long time and can cause tissue damage and lead to various complications as above (Halliwell and Gutteridge, 1998; Kariadi, 2001). Low insulin intake, increased ROS and pancreatic cell damage will induce another metabolic disorder called dyslipidemia which is marked by increased level of total cholesterol, Low-Density Lipoprotein (LDL) and triglyceride. This condition can pose a risk of coronary artery disease or cardiovascular disease (Fridlyand and Philipson, 2005). Improved blood lipid levels may pose a risk of coronary artery disease or cardiovascular disease. Increased cholesterol levels (hypercholesterolemia) causing arteriosclerosis and the risk of heart disease (myocardial infarction). High serum cholesterol levels may be associated with a genetic predisposition (hereditary) biliary obstruction and dietary intake. Increased triglycerides in a long time will cause obesity. High LDL cholesterol and low HDL cholesterol is a risk for atherosclerotic disease. Conversely, low LDL cholesterol and high HDL cholesterol may reduce the risk of coronary artery disease (Fridlyand and Philipson, 2005) (Fig. 1).

Antioxidant and flavanoid: In order to curb the occurrence of oxidative damage due to the accumulation of AGEs we need a defense system capable of removing, cleaning (scavenger) resist formation or negate the effects of AGEs. The system is known as an antioxidant. Animal studies proved that antioxidants can inhibit the early stages of retinopathy, nephropathy and neuropathy in diabetes mellitus. Similarly to human studies, an antioxidant shown to inhibit the microvascular complications, decrease the incidence of coronary heart disease, improvement of cardiac autonomic nervous system and vascular vasodilatation (Suhartono, 2008; Oleg *et al*., 2015).

The mechanism of exogenous antioxidant activity in reducing the effects of free radicals (free redicals scavenging) is through ionic metal chelating so that the

metal ions sequestered and prooxidant effect of metal can be inhibited. For example, through the chain termination propagation of free radicals (free redical chains breaking) by acting as a hydrogen donor or hydrogen acceptor resulting in the blockade against free radicals purge and trap the carbonyl group (carbonyl group traps) (Suhartono, 2008). One of the proven antioxidant is flavonoid. Flavonoids are natural phenolic compounds that act as an antioxidant by capturing free radicals, reducing oxidative stress by scavenging the ROS and decreasing the expression of TNF-α (Rais *et al*., 2015; Tiwari and Rao, 2002).

Flavonoids can reduce blood cholesterol levels in mice who have hyperlipidaemia and reduce the oxidation of LDL cholesterol which has an important role in the process atherogenesis. Flavonoids reduce cholesterol synthesis by inhibiting the activity of the enzyme acyl-CoA cholesterol Acyl Transferase (ACAT) in cells HepG2 that play a role in the decline of esterification of cholesterol in the intestine and liver as well as inhibit the activity of the enzyme 3-hydroxy-3-methylglutaryl-CoA which causes inhibition of cholesterol synthesis. Saponins can bind to bile acids and cholesterol (from food) to form micelles which cannot be absorbed by the intestine. While the tannin in the body will bind to body proteins and will coat the walls of the intestine, so that absorption of fat is inhibited. Additionally, tannins protect the gut against unsaturated fatty acids. Tannin protection process performed in the form of compaction the mucosal lining of the gastrointestinal tract that inhibits the absorption of nutrients (including fats and cholesterol) by the digestive tract. Based on this, allegedly Karamunting fruit which contained flavonoids, saponins and tannins can lower blood cholesterol levels (Metwally *et al*., 2009; Terao *et al*., 2008).

Karamunting (*Melastoma malabathricum* L.): Karamunting is one of the plants that often grow on wetlands in South Kalimantan. a wild plant, growing in a place that gets enough sunlight such as on the slopes, shrubs and a field that is not too dry. The stem is erect, 0.5-4 m high has many branches, scaly and hairy. The leaves are single, round or oblong leaves, sharp edges, base rounded and flat edges. Karamunting flowers are numerous, out at the end of branches, reddish purple color flowers. Karamunting fruit when ripped will split and divided into several sections, reddish dark purple and small brown seeds (Koay, 2008).

Based on empirical studies, plant Karamunting used daily by the people of South Kalimantan to treat treat diarrhea, dysentery, lekorea, hemorrhoids, infections and toothache. Karamunting plant parts that are often used are the leaves and flowers Karamunting. This plant contains many antioxidant flavonoids, saponins and tannins (Faravani, 2008).

MATERIALS AND METHODS

Research model: This study is an experimental research with posttest-only control group design as a method. Mice were used as subjects in the form of a male rat (*Rattus norvegicus*) Sprague-Dawley. Mice as many as 36 subject were divided into 6 groups and each group consisted of 6 rats (replication) were chosen randomly (randomization). Control group is consisted of 3 group (normal, positive control, negative control) and treatment group is also consisted of 3 group (three different doses: 0.01, 0.1 and 1 mg g^{-1} BW). Independent variable is Karamunting fruit juice at a dose of (0.01, 1 mg g^{-1} BW) and dependent variable is methylglyoxal, carbonyl, LDL, HDL, total cholesterol and triglycerides which are calculated by spectrophotometry and colorimetric chemical method. The Research has done as the following step.

Preparation and acclimatization: The preparation stage includes the preparation of tools and materials as well as the adaptation of rats before being given treatment for 7 days.

Operations: In this step, the production of Karamunting (*Melastoma malabathricum* L.) fruit juices with aquadest results in the form of liquid juice is done; inducing streptozosin in group 2-5 at a dose of 40 mg kg^{-1} BW intraperitoneally. measurement of blood sugar levels after induction streptozosin, giving treatment in all groups for 28 day namely: the 1st group was given aqudest and 20 g of feed; 2nd group was given metformin 10 mg kg^{-1} body weight and feed 20 g; Group 4 was given 0.01 mg g^{-1} of Karamunting fruit juice and 20 g of feed; Group 5 was given 0.1 mg g^{-1} of Karamunting fruit juice and 20 g of feed; and Group 6 was given 1 mg g^{-1} of Karamunting fruit juice and 20 g of feed; last step is termination of subject to take a blood from the heart of white mice and measured the levels of methyl glyoxal, carbonyl, LDL, HDL, total cholesterol and triglycerides by spectrophotometry (λ = 576 nm) and colorimetric chemical method.

Data analysis: ANOVA statistical test α = 95% followed by a post-hoc test to determine the differences between the results of methyl glyoxal, carbonyl, LDL, HDL, total cholesterol and triglycerides in the positive control group vs. treatment group (Fig. 2).

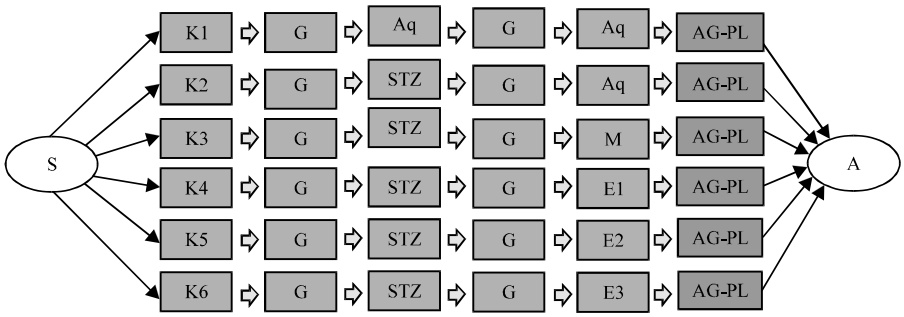

Fig. 2: Research scheme; K1 = Normal group; K2 = Negative control group; S = Sample; K3 = Positive control group; M = Metformin of administration; K4 = Treatment group (dose 1); AG-PL = AGEs and Profile Lipid; K5 = Treatment group (dose 2); G = Glucose measurement; K6 = Treatment group (dose 3); A = Analysis of Data; Aq = Aquadest administration; STZ = Streptozosin intraperitoneal administration; E1 = Karamunting juice administration (dose 1); E2 = Karamunting juice administration (dose 2); E3 = Karamunting juice administration (dose 3)

RESULTS AND DISCUSSION

Data analysis: Total 36 rats are examined and the results are shown Table 1 and Fig. 3. The ANOVA concluded there is a significant result for carbonyl level ($p = 0.002$). Post hoc also explained, there is a significant results for Group 1 and 2 ($p = 0.001$). It means there is a significant increase in the level of AGEs within hyperglycemic state in DM. Group 2 vs 3 showed unsignificant results ($p = 0.201$) it explained that metformin could not reduce the level of methylglioxal. Group 2 vs. 4 showed no signifancy ($p = 0.091$) means at 0.01 dose is not significantly enough to reduce the methylglyoxal but the result in the Group 2 vs. 5 and Group 2 vs. 5 are signifant ($p = 0.031$; $p = 0.027$) mean at 0.1 dose and 1 mg dose can reduce the level of methylglyoxal in the blood significantly (Table 2 and Fig. 4).

ANOVA concluded there is a significant result for carbonyl level ($p \leq 0.001$). Moreover, there is a significant results for group 1 and 2 ($p \leq 0.001$). It means there is a significant increase in the level of carbonyl within hyperglycemic state in DM. Moreover, Group 2 vs. 3, Group 2 vs. 4, Group 2 vs. 5, Group 2 vs. 6 results are signifant consequtively ($p \leq 0.001$) mean at 0.01; 0.1 and 1 mg dose can reduce the level of carbonyl in the blood significantly (Table 3 and Fig. 5).

As seen above, 3 doses of Karamuntung, respectively could decrease cholesterol, the higher the dose given, less cholesterol level will be achieved. The efficacy of metformin could be achieved also by Karamunting. Unfortunately, in cholesterol analysis, ANOVA's result showed unsignificant value ($p = 0.430$) but bivariate analysis used to compared between metformin vs. Group 4-6, the results are unsignificant ($p = 0.458$; 0.868; and 0.706). It means Karamunting's efficacy are same as metformin (Table 4 and Fig. 6).

As well as Cholesterol, in HDL's result, three doses of Karamuntung respectively could decrease HDL level, the higher the dose given, less HDL level will be achieved. Unfortunately, in HDL analysis, ANOVA result showed unsignificant value ($p = 0.313$). As the chart show, the metformin's results are similar with 1 mg g^{-1} BW dose of karamunting and there is no signifant value ($p = 0.0863$) that indicating 1 mg g^{-1} BW dose of karamunting has same efficacy as metformin (Table 5 and Fig. 7). For LDL, the result is quiet diverse. Moreover, in LDL statistic analysis, ANOVA result showed unsignificant value ($p = 0.603$) (Table 6 and Fig. 8).

In triglysceride analysis, ANOVA result showed significant value ($p = 0.006$). Post hoc revealed that Group 1 vs. 5 has a significant value ($p = 0.039$) therefore means at 1 mg dose, it could decrease triglyceride level.

Methylglioxal and carbonyl: Based on the analysis test above obtained significant results. Post hoc also explained, there is a significant results for Group 1 and 2. It means there is a significant increase in the level of methylglyoxal and carbonyl within hyperglycaemic state in DM. As seen also, the levels in normal mice (Group 1) are low but high in negative control group (Group 2) it can be concluded that the increase in blood sugar levels (hyperglycaemia) in experimental animals is directly proportional to the increase in the levels of methylglyoxal and carbonyl.

In Groups 2 and 3 also showed a significant result, this means that administration of metformin in group 3 generate a significant decrease in the levels

Table 1: Methylglyoxal level each group

Replication	Group 1 normal (mg dL^{-1})	Group 2 negative (mg dL^{-1})	Group 3 metformin (mg dL^{-1})	Group 4 0.01 (mg dL^{-1})	Group 5 0.1 (mg dL^{-1})	Group 6 1 (mg dL^{-1})
1	1.820	3.500	2.140	3.050	2.860	2.140
2	2.180	3.450	3.360	2.090	2.410	2.730
3	1.680	2.090	2.230	2.270	2.450	2.270
4	2.270	3.770	2.860	3.090	2.320	3.000
5	2.140	3.360	2.910	2.820	2.180	2.320
6	2.730	3.450	2.680	2.270	2.680	2.360
Mean	2.136	3.273	2.697	2.598	2.485	2.470
SD	0.368	0.595	0.459	0.438	0.248	0.326

Table 2: Carbonyl level each group

Replication	Group 1 normal (mg dL^{-1})	Group 2 negative (mg dL^{-1})	Group 3 metformin (mg dL^{-1})	Group 4 0.01 (mg dL^{-1})	Group 5 0.1 (mg dL^{-1})	Group 6 1 (mg dL^{-1})
1	0.025	0.031	0.018	0.020	0.015	0.023
2	0.023	0.043	0.022	0.029	0.024	0.021
3	0.020	0.042	0.022	0.026	0.017	0.020
4	0.025	0.044	0.021	0.016	0.017	0.018
5	0.013	0.041	0.028	0.015	0.010	0.010
6	0.023	0.030	0.027	0.019	0.022	0.004
Mean	0.022	0.039	0.023	0.021	0.018	0.016
SD	0.005	0.006	0.004	0.006	0.005	0.007

Table 3: Cholesterol level each group

Replication	Group 1 normal (mg dL^{-1})	Group 2 negative (mg dL^{-1})	Group 3 metformin (mg dL^{-1})	Group 4 0.01 (mg dL^{-1})	Group 5 0.1 (mg dL^{-1})	Group 6 1 (mg dL^{-1})
1	120.0	108.0	129.0	123.0	108	100.0
2	103.0	121.0	112.0	115.0	122	136.0
3	150.0	112.0	086.0	130.0	106	107.0
4	121.0	139.0	127.0	115.0	110	112.0
5	118.0	111.0	115.0	107.0	103	094.0
6	127.0	081.0	093.0	109.0	105	090.0
Mean	123.2	112.0	110.3	116.5	109	106.5
SD	015.3	018.9	017.5	008.6	6.8	16.50

Table 4: HDL level each group

Replication	Group 1 normal (mg dL^{-1})	Group 2 negative (mg dL^{-1})	Group 3 metformin (mg dL^{-1})	Group 4 0.01 (mg dL^{-1})	Group 5 0.1 (mg dL^{-1})	Group 6 1 (mg dL^{-1})
1	53.0	57.0	58.0	56.0	57.0	53.0
2	56.0	56.0	58.0	59.0	54.0	54.0
3	52.0	56.0	43.0	53.0	58.0	59.0
4	51.0	51.0	55.0	55.0	50.0	54.0
5	53.0	57.0	51.0	58.0	56.0	42.0
6	58.0	39.0	34.0	51.0	46.0	30.0
Mean	53.8	52.7	47.7	55.2	54.3	48.7
SD	02.6	07.0	08.8	02.7	05.1	10.7

Table 5: LDL level each group

Replication	Group 1 normal (mg dL^{-1})	Group 2 negative (mg dL^{-1})	Group 3 metformin (mg dL^{-1})	Group 4 0.01 (mg dL^{-1})	Group 5 0.1 (mg dL^{-1})	Group 6 1 (mg dL^{-1})
1	48.0	35.0	53.0	50.0	35.0	32.0
2	29.0	43.0	50.0	40.0	47.0	59.0
3	72.0	29.0	29.0	61.0	30.0	33.0
4	49.0	67.0	47.0	46.0	43.0	41.0
5	45.0	33.0	49.0	35.0	32.0	37.0
6	42.0	22.0	44.0	42.0	43.0	52.0
Mean	47.5	38.2	45.3	45.7	38.3	42.3
SD	14.0	15.7	08.5	09.0	06.9	10.9

Table 6: Triglysceride level each group

Replication	Group 1 normal (mg dL^{-1})	Group 2 negative (mg dL^{-1})	Group 3 metformin (mg dL^{-1})	Group 4 0.01 (mg dL^{-1})	Group 5 0.1 (mg dL^{-1})	Group 6 1 (mg dL^{-1})
1	094.0	081.0	091.0	84.0	81.0	075.0
2	091.0	109.0	086.0	85.0	82.0	117.0
3	131.0	133.0	069.0	82.0	91.0	077.0
4	105.0	107.0	0126.0	72.0	83.0	084.0
5	100.0	103.0	075.0	69.0	73.0	074.0
6	133.0	102.0	073.0	78.0	81.0	042.0
Mean	109.0	105.8	086.7	78.3	81.8	078.2
SD	018.4	016.6	020.9	06.5	05.7	023.9

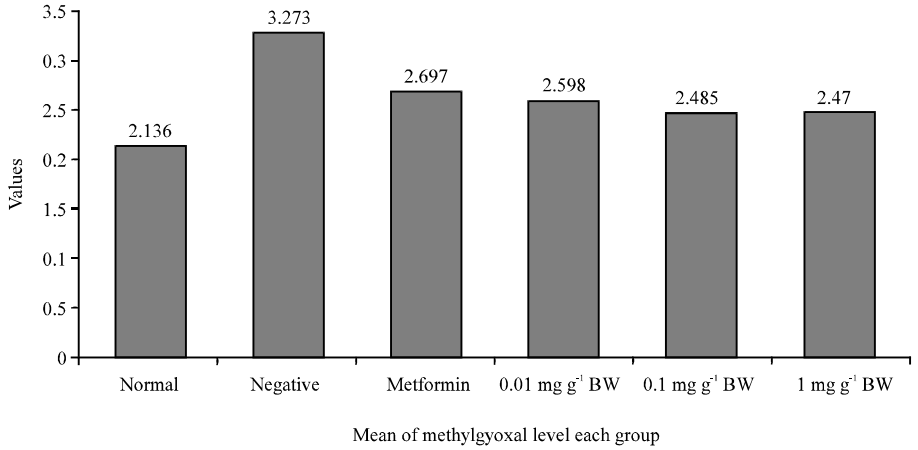

Fig. 3: Mean of Methylglyoxal level each group

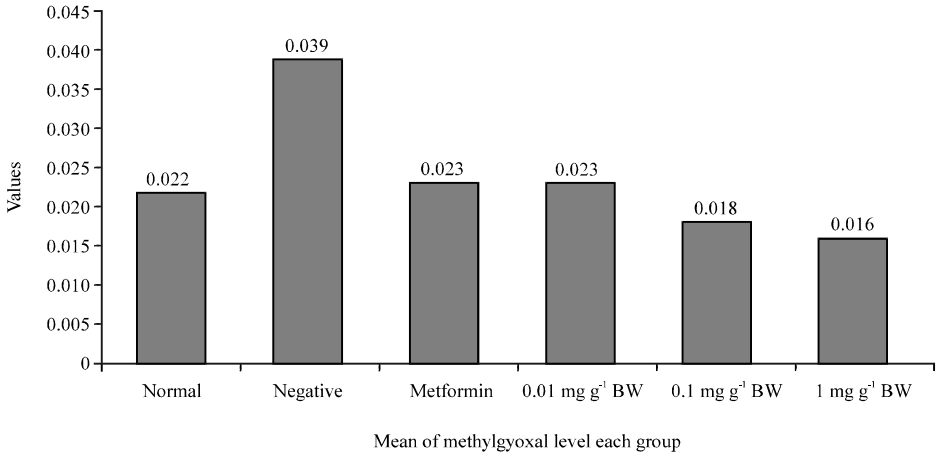

Fig. 4: Mean of carbonyl level each group

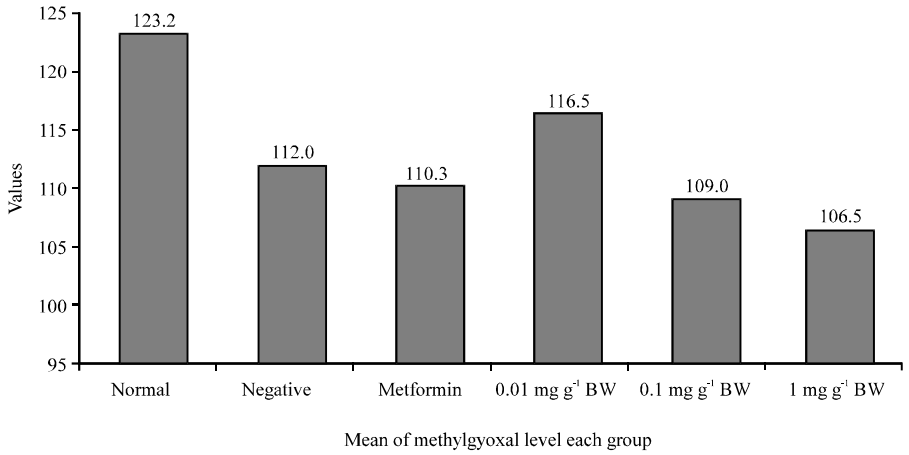

Fig. 5: Mean of cholesterol level each group

of methylglyoxal and carbonyl. This proves that metformin which is the standard treatment of diabetes disease which aims to lower glucose may also reduce levels of methylglyoxal and carbonyl in the blood. In

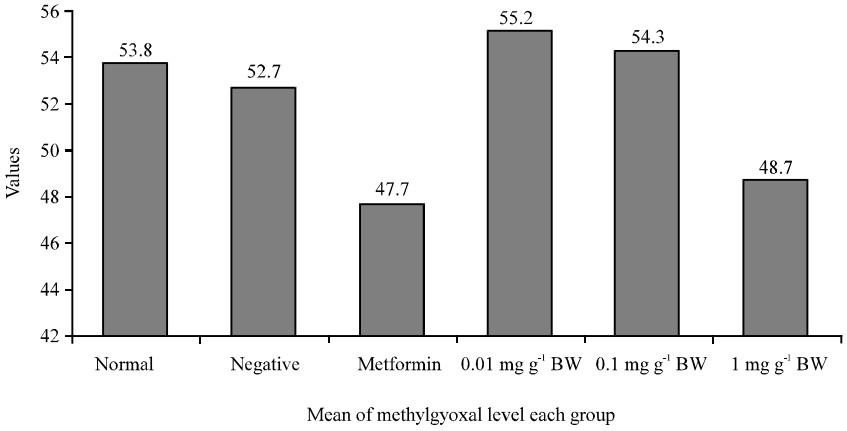

Fig. 6: Mean of HDL level each group

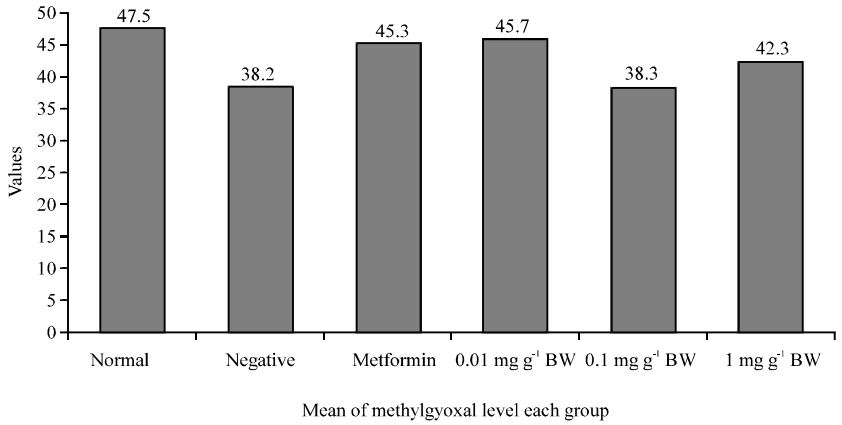

Fig. 7: Mean of LDL level each group

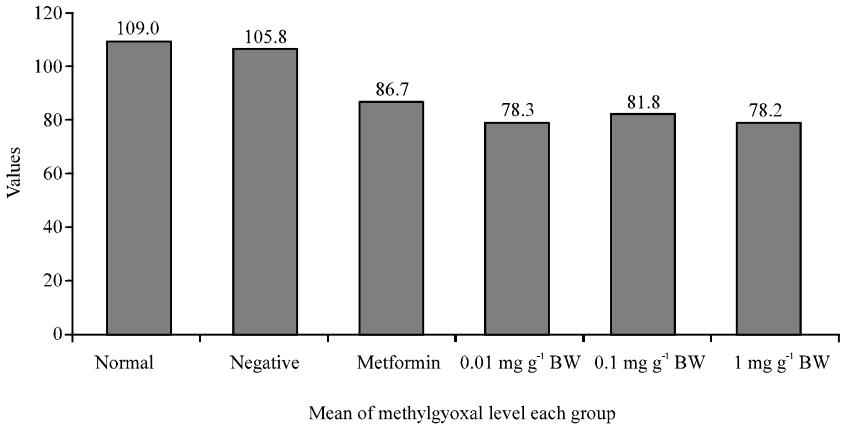

Fig. 8: Mean of Triglysceride level each group

addition, Karamunting at any doses could also reduce their levels in the blood were significantly as the expectations of the research goal. There is no difference between metformin and Karamungting levels of methylglioxal and carbonyl ($p>0.05$) proved that administration of Karamuning fruit juice has an efficacy as metformin (even better) for lowering their levels.

Metformin is one of the standard drugs are often used for DM disease, this drug works to improve insulin sensitivity, thereby improving glucose uptake into tissues.

Administration of Karamunting juice on 3 different doses reduce the level of methylglyoxal and carbonyl in the blood significantly because Karamunting has flavonoid as an antioxidant. The reaction mechanism of flavonoids as antioxidants occur through the process of scavenging reactive oxygen species.

Based on research, the provision of antioxidants could capture free radicals, reduce oxidative stress and decrease the expression of TNF-α. Phytochemical compounds such as flavonoids was able to reduce the complications of diabetes by reducing oxidative stress, ROS and TNF-α (Tiwari and Rao, 2002). Flavonoid also act as potential inhibitors in the uptake of glucose by blocking glucose transport is influenced by the structure of the flavonoid itself (Park, 1999). Flavonoids are also expected to inhibit oxidative damage to pancreatic β cells. In the study Okamoto (1996) reported that streptozosin pancreatic β cell damage by inducing the formation of hydroxyl free radicals. Hydroxyl free radicals attack the pancreatic β cells essential substances (such as cell plasma membrane, lysosomes, mitochondria and DNA) and initiate pancreatic β cell damage (Okamoto, 1996). Flavonoids are thought to have hypoglycemic mechanism through inactivation of hydroxyl free radicals that attack the pancreatic β cells, so the cells can secrete insulin β better (Fahri and Listyawati, 2005).

Lipid profile: The results for lipid profile was respectively insignificant. There are several statement regarding this result). The duration for created dyslipidemia is a long term result. As this research has interfere the condition for 28 days, condition for dyslipidemia couldn't occurred, therefore future research have to be done for extend the duration of intervention for >28 day). Since, there is no disorder and diverse result in this experiment in term of LDL, HDL, Triglyceride and Cholesterol. More parameter needed to be researched to prove the relationship between dylipidemia and chronic DM such as: VLDL, Apo B-100 and histologic imaging of blood vessel to looking for atherosclerotic lesion). Karamuting at 1 mg g^{-1} BW dose are able to reduce LDL, HDL, Triglyceride and Cholesterol and has same efficacy as metformin.

In the other hand, hyperlipidaemia is a secondary condition due to inactivation of insulin. In a physiologic condition, insulin will hold back the synthesis and secretion of hepatic Very Low-Density Lipoprotein (VLDL) by inducing apoprotein B-100 to degradate. Apoprotein B-100 is a major apoprotein needed to synthesize VLDL. In patient with insulin resistance, an increase on non-esterificate lipid acid flux and lack of insulin binding to its receptor will lead to overproduction of VLDL.

CONCLUSION

Karamunting could decrease methylglyoxal and carbony level. It could also decrease the level of triglyceride significantly but not significant for LDL, HDL and Cholesterol. Moreover, its efficacy are in the same level as metformin to recude methylglyoxal, carbonyl, triglyceride, LDL, HDL and Cholesterol.

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