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Full Length Research Paper

Purple sweet potato tuber extract lowers mallondialdehyde and improves glycemic control in subjects with type 2 diabetes mellitus

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Oxidative stress and chronic hyperglycemia are related to progressivity of type 2 diabetes mellitus (T2DM). Purple sweet potato tuber possesses high anthocyanin (ANT) antioxidant. The objective of this study is to prove that supplementation of purple sweet potato tuber extract can lowers mallondialdehyde (MDA) and improves glycemic control in T2DM subjects. A randomized double blinded pre-post tests controlled group design study enrolling 38 T2DM subjects was conducted at Diabetes Outpatients Clinic, Sanglah Hospital for 4 weeks observation. Subjects were divided into 2 groups: the Control Group (placebo) and the group who were given 75 mL purple sweet potato tuber extract containing 11 gram ANT (ANT Group), 3 times a day 30 minutes after meal. All subjects were treated with standard diabetic care. One subject of each group was dropped out from this study, therefore each group finally consisted of 18 subjects; male-female ratio was 9/9 among Control Group and 8/10 among ANT Group; average of age was 51.94±5.01 years and 51.78±4.97 years, respectively. Levels of MDA was found significantly lower in ANT Group than in that of Control Group after administration (0.43±0.08 *vs.* 0.52±0.15 µM, p=0,04). Decreased (the difference between post- and pre-test [Δ]) MDA levels in ANT Group was higher compared to that in Control Group (0.1250.12 *vs.* -0.030.15 µM, p=0.002). Improvement of fasting and 2 hours post-prandial (2hpp) plasma glucose levels in ANT Group started at week 1 and continued till week 4. Improved fasting and 2hpp plasma glucose (Δ) in the ANT Group was better than among Control Group (67.167 *vs.* -1.83 mg/dl, p<0.001; 72.11 *vs.* -15.4 mg/dl, p=<0,001; respectively). Improved glycated albumin (Δ) was also found significantly among subjects in the ANT Group than those in the Control Group (24.13±5.86 *vs.* 26.18±8.1 %, p=0,049). Purple sweet potato tuber extract administration could lower MDA levels and improved glycemic control (decreased fasting and 2hpp plasma glucose levels and glycated albumin) in subjects with T2DM.

Keywords: purple potato tuber extract, malondialdehyde, glycemic control.

INTRODUCTION

Currently diabetes (especially type 2 diabetes mellitus [T2DM]) has become pandemic and it is a serious health problem and a big threat to human life. In 2014, International Diabetes Federation predicted that 387 millions of world population (8.3%) suffered from diabetes, and the prevalence increased year after year, especially among new middle-high or high income countries (IDF, 2014). Diabetes is a progressive

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metabolic disease characterized by hyperglycemia mainly due to insulin resistance and beta cells failure (ADA, 2014).Chronic hyperglycemia is a crucial factor of chronic complication through induction of oxidative stress sensitive signaling (Evans et al., 2002).Increased thiobarbituric acid reactive substances (TBARS), mallondialdehyde (MDA), oxidized glutathione enzyme, and decreased superoxide dismutase (SOD) and catalase are indicators that lipid peroxidation occurs in hyperglycemic state (Roy et al., 2008).

Management strategy for subjects with T2DM are now available world widely as guidelines proposed both by international or local diabetes organisations (PERKENI, 2011; ADA, 2014). Since oxidative stress inducing hyperglycemia has an important role in the progress and course of chronic complication of T2DM, some efforts have been tried to reduce oxidative stress by supplementation of foods or natural resources; one of them is phythochemistry contain antioxidant namely anthocyanin (ANT) (Gosh and Konishi, 2007). Anthocyanin is a flavanoid group antioxidant found in large amount in some kind purple colored plants, such as purple sweet potato (He and Giusti, 2007).Purple sweet potato grown in Bali contains high concentration of ANT, i.e. purple sweet potato tuber extract in water (1 kg purple potato tuber in 1 liter water) contain ANT around 146 mg/mL (Suprapta, 2004). A study on the effect of ANT antioxidant on diabetic rat was conducted by Guo *et al*. (2007), animals fed 0.5% ANT from black rice extract have shown decrease of TBARS levels and improvement of glutathione enzyme. Similar study on steptozotocin induced diabetic rat fed with 146mg/cc ANT in purple sweet potato tuber extract showed reduced MDA, SOD and plasma glucose significantly as compared to control group (Sutirta Yasa, 2012). Purple sweet potato tuber extract has been used in several studies and currently marketed in forms of safe drink and sweet wine in Bali.

The purpose of this study was to prove that purple sweet potato tuber extract containing high ANT reduces oxidative stress (expressed by MDA) and improves glycemic control (indicated by lowering fasting and 2 hour post-prandial plasma glucose [FPG and 2hppPG] and glycated albumin [GA]) in subjects with T2DM.

METHODS

This study was an experimental study with double blinded pre-post test control group design. Subjects were patients with T2DM who visited Diabetes Outpatient Clinic, Sanglah Hospital, Denpasar, Indonesia. Allocated samples were those matching with inclusion criteria such as age 30-59 years who got standard care for their diabetes. The subjects were excluded as samples if they had one or more of the following: chronic kidney disease stage 3 or higher, severe anemia, malignancies, hepatic cirrhosis, on corticosteroid treatment, and smoking. A sample was considered drop out if there was loss of contact, not any more stayed at the address, and if suffering from acute severe illness. Thirty-eight subjects were eligible as samples, whom subsequently divided into 2 groups by random permuted block within strata method (Pocock et al., 2008). One group was given juice purple sweet potato tuber extract containing 146 mg ANT/cc aqueous extract (ANT Group), and the other group (Control Group)was given juice with the same color and form as the juice given to the ANT group, but without active ingredient (placebo). Two subjects (one subject in each groups) were dropped out during the study due to some reasons. Finally, 18 subjects of each group were involved and analyzed in the study till the end of study. Subjects in both groups got the standard care for their diabetes during study for 4 weeks of observation. The dose of the aqueous extract was 75 mL, 3 times a day, taken 30 minutes after meal for 4 weeks. The dose was adopted from previous trial in mice or rat and human (Paget and Barnes, 1964; Ludvik et al., 2002; Sutirta Yasa et al., 2012).

The main dependent variables measured in the study were: levels of MDA, FPG, 2hppPG, and GA. Other variables were measured were age, sex, duration of diabetes, kind of medications (oral anti diabetic or insulin or combination), anthropometric parameters, blood pressure, routine blood, liver function (serum glutamic oxaloacetic transaminase [SGOT] and serum glutamic pyruvit transaminase [SGPT], albumin serum), renal function (blood ureum nitrogen [BUN]and serum creatinine [SC]), and plasma lipid. Mallondialdehyde, a lipid peroxidation end-product was measured by spectrophotometric assay technic with Bioxytech® MDA-586 kit (Oxis Research Inc, USA), expressed in unit µM. Plasma glucose was measured by standard hexokinase method, expressed in unit mg/dL. Glycated albumin was measured with GA-L reagent produced by Asahi Kasei Pharma Corporation, Japan, and expressed in percentile. Levels of MDA and GA were measured twice, first as base line (pre-test or week 0) and the second at the end of observation (post-test or week 4), while FPG and 2hppPG were measured weekly.

Data was expressed descriptively and statistically analyzed to differentiate some variables among ANT group and control group both at based line and post-test. Student's t- independent test was used to differentiate the variables in two groups. Q-square test was used to differentiate only for the type of medication in two groups. Repeated Anova and pairwise were used to compare the changes of plasma glucose levels every week. Significant value was confirmed if $p<0.05$. The study was approved by Ethical Clearance Committee, Research and Development Unit, Faculty of Medicine Udayana University/Sanglah Hospital, Denpasar, No: 86/UN.14.2/Litbang/2014.

Table 1. Baseline data of several variables in ANT Group and Control Group

Variables	ANT Group (n=18)	Control Group (n=18)	p-value
Gender (Male/Female)	8/10	9/9	0.738
Age (years)	51.78±4.97	51.94±5.01	0.921
Duration of diabetes (years)	6.06±4.77	5.44±7.26	0.767
Type of medications			
Oral antidiabetic(s)	5	5	1.000
Oral antidiabetic(s) +Insulin	2	2	
Insulin	11	11	
Height (cm)	161.28±8.23	167.78±26.40	0.330
Weight (kg)	65.17±12.01	67.78±13.16	0.538
Body mass index (kg/m^2)	25.12±4.97	24.83±5.34	0.867
Waist circumference (cm)	86.61±12.98	90.28±11.43	0.375
Systolic blood pressure (mmHg)	126.11±14.2	126.11±13.3	1,000
Diastolic blood pressure (mmHg)	78.89±6.76	79.44±7.25	0.814
White blood cells (10^3/μL)	8.04±1.79	8.74±2.11	0.293
Hemoglobin (g/dL)	13.37±1.33	12.96±2.23	0.503
Blood ureum nitrogen (mg/dL)	17.58±7.911	20.11±8.34	0.357
Serum creatinine (mg/dL)	0.92±0.22	1.05±0.28	0.154
SGOT (U/L)	25.33±9.18	26.46±15.43	0.792
SGPT (U/L)	27.23±10.66	25.54±12.89	0.671
Albumin (g/dL)	4.03±0.42	3.97±0.44	0.657
Total cholesterol (mg/dL)	170.02±48.49	166.72±36.11	0.818
Triglyceride (mg/dL)	119.05±60.24	190.33±154.53	0.082
LDL choelsterol (mg/dL)	108.9±37.27	102.72±23.33	0.556
HDL cholesterol (mg/dL)	47.23±10.19	41.44±9.3	0.084
FPG (mg/dL)	186.33±77.18	154.17±44.29	0.137
2hppPG (mg/dL)	247.56±83.82	226.22±64.25	0.398
A1C (%)	9.12±2.72	8.33±1.57	0.299
Glycated albumin (%)	26.42±7.91	24.12±5.86	0.330
Mallondialdehyde (μM)	0.56±0.15	0.49±0.11	0.153

Data in mean±SD or frequency. SGOT: *serum glutamic-oxalacetic transaminase*; SGPT: *serum glutamic-pyruvic transaminase*; LDL:*low density lipoprotein*; HDL:*high density lipoprotein*; FPG: fasting plasma glucose; 2hppPG: 2 hours post prandial plasma glucose; A1C, glycosylated hemoglobin.

RESULTS

Data of characteristic of subjects in both groups is seen in Table 1. No significant difference was seen of all variables among the two groups at based line (pre-test). Levels of MDA at the end of observation (week 4) was lower significantly in ANT Group compared to Control Group (0.44±0.84*vs.* 0.52±0.15 μM, p=0.04) and the difference between pre- and post-test (Δ) of ANT Group was found higher significantly than that in Control Group (0.12±0.12 vs. -0.03±0.15 μM, p=0.002).Levels of FPG and 2hppPG at the end of observation (week 4) was lower significantly in ANT Group compared to Control Group (119.17±19.38 *vs.* 166±54.97 mg/dL, p=0.02; 175.44±19.38 *vs.* 241.67±62.88 mg/dL, p=0.001; respectively) and the difference between pre- and post-test (Δ) of ANT Group was found higher significantly than that in Control Group (67.17 *vs.* -11.83 mg/dL, p<0.001; 72.11 *vs.* -15.4 mg/dL, p<0.001; respectively) (Table 2).

Improvement of plasma glucose in ANT Group was seen at week 1, and the difference widened until the end of week 4. On repeated anova test to analyze the difference of plasma glucose every week in both groups, it was found that there was significant decreased FPG in ANT Group compared to that in Control Group (F=5.967, p=0.005; F=1.323, p=0.139; respectively). On pairwise comparison, decreased FPG every week (Δ) showed significant value (186.33 *vs.* 157.94 mg/dL, □28.38 mg/dL, p=0.01 [week 0 and week 1]; 157.94 *vs.* 140.33 mg/dL, □17.61 mg/dL, p=0.015 [week 1 and week 2]; 140.33 *vs.* 129.94 mg/dL, □10.39 mg/dL, p=0.005 [week 2 and week 3]; 129.94 *vs.* 119.17 mg/dL, □10.78 mg/dL, p=0.001 [week 3 and week 4], respectively) in ANT Group, while in Control Group no significant difference

Table 2. Levels of MDA, 2hppPG and GA at pre-test, post-test and the difference (□)

	ANT Group			Control Group			p-value	
	Pre-test	Post-test*	Δ**	Pre	Post*	Δ**	*	**
MDA (μM)	0.56±0.16	0.44±0.84	0.12±0.12	0.49±0.12	0.52±0.15	-0.03±0.15	0.04	0.002
FPG (mg/dL)	186.33±77.18	119.17±19.38	67.17	154.17±42.29	166±54.97	-11.83	0.002	<0.001
2hppPG (mg/dL)	247.56±83.82	175.44±19.38	72.11	226.22±64.24	241.67±62.88	-15.4	0.001	<0.001
GA (%)	26.42±7.91	21.53±5.18	4.89±5.57	24.13±5.86	26.18±8.1	-2.05±6.11	0.049	0.001

MDA: mallondialdehyde; FPG: fasting plasma glucose; 2hppPG: 2 hours post prandial plasma glucose; GA: glycated albumin.
*p-value of the mean difference of post-tests between ANT Group and Control Group; **p value of the mean difference among Δ, analyzed with student's t-independent test.

Table 3. Safety monitoring on liver and renal functions

	ANT Group			Control Group		
	Pre-test	Post-test	p-value*	Pre-test	Post-test	p-value*
BUN (mg/dl)	17.58±7.91	16.44±0.66	0.13	20.11±8.34	21.50±10.30	0.58
SC (mg/dl)	0.92±0.22	0.84±0.24	***0.004***	1.05±0.28	0.96±0.28	***0.01***
SGOT (U/L)	25.33±9.18	25.85±8.63	0.27	26.46±15.43	26.76±16.19	0.55
SGPT (U/L)	27.23±10.66	27.24±10.32	0.98	25.54±12.89	25.16±11.55	0.57

BUN: blood urea nitrogen; SC=*serum creatinine*; SGOT: *serum glutamic-oxalacetic transaminase*; SGPT: *serum glutamic-pyruvic transaminase*. *p value of the mean difference pre-test and post-tes intra groups, analyzed by paired t-tes

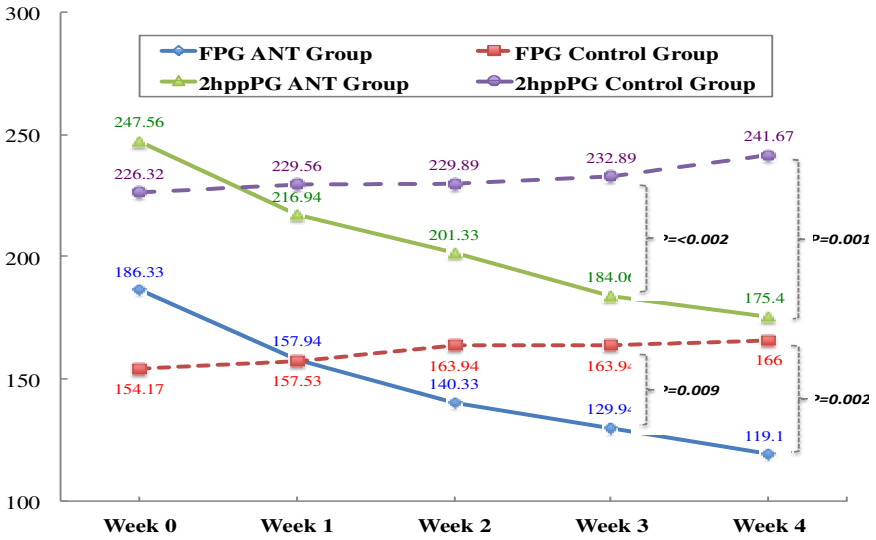

Figure 1. Weekly levels of fasting and 2hpp plasma glucose (FPG and 2hppPG) in ANT Group and Control Group.

value was found at each week. Similar result was also noted on 2hppPG. Weekly levels of 2hppPG decreased significantly in ANT Group as compared to Control Group (F=8.806, p=0.001; F=0.838, p=0.524, respectively). On pairwise comparison, decreased 2hppPG every week (Δ) revealed significant value (247.56 vs. 216.94 mg/dL *vs.*□30.61 mg/dL, p=0.001 [week 0 and week 1]; 216.94 *vs.* 201.33 mg/dL, 15.61 mg/dL, p=0.002 [□ week 1 and week 2]; 201.33 *vs.* 184.06 mg/dL, □17.27 mg/dL, p=0.013 [week 2 and week 3]; 184.06 *vs.* 175.44 mg/dL, □10.78 mg/dL, p=0.001 [week 3 and week 4], respectively) in ANT Group; while in Control Group there were no significant difference value seen at each week (Figure 1).

Glycated albumin recently is used as indicator for glycemic control for 2-4 weeks. In this study it was noted that GA at the end of observation (post-test) was lower in ANT Group than in Control Group (21.53±5.18*vs.* 26.18±8.1 %, p=0,049).Improvement of GA (□) was better in ANT Group compared to that in Control Group (4.89±5.57 *vs.* -2.05±6.11, p=0.001) (Table 2).

The aqueous extract is consumed safely and has been

marketed as safe drink and has been studied in animal and human. Safety report on liver function and renal function has been observed in this study. Levels of serum transaminases (SGOT and SGPT)did not change in ANT group as well as in control group from base line to the end of observation. The same observation also was done on renal function (BUN and SC) (Table 3). In general, there were no specific complains expressed by patients during observation.

DISCUSSION

This study showed that subjects to whom ANT was administrated for 4 weeks had lowered MDA than those in control subjects. The result is similar to that of another study conducted by Basu et al. (2009) in their study on women with metabolic syndrome they noted decrease of lipid peroxidation, levels of MDA and plasma 4-hydroxinoneal after supplementation of ANT for 4 weeks. A study on STZ induced diabetic rats also demonstrated efficacy of anthocyanin rich extract in reducing levels of MDA and increasing SOD and total antioxidant capacity (Sugimoto et al., 2003; Sutirta Yasa, 2012). Improvement of MDA levels was also observed in rats after feeding with anthocyanin rich extract from black rice and ANT extract from black soya been skin (Guo et al., 2007; Nizamutdinova et al., 2009). Anthocyanin used in this study was extracted from purple sweet potato tuber which containied high anthocyanidin compared to other potato variants (Montilla et al., 2010). The antioxidant capacity of ANT in terms of lowering levels of MDA was mediated by its capacity to bind ABTS+ radical, DPPH, peroxyl radical and oxygen peroxide (Heinonen et al., 1998; Gosh and Konichi, 2007)Previous two studies using the same extract by Jawi et al. in hypertensive patients showed that the extract did not only lower blood pressure and MDA comparable to captopril, but it also possessed better effect on increasing SOD levels (Jawi et al., 2014; Jawi et al., 2015). Therefore, the extract from purple sweet potato grown in Bali consistently possesses antioxidant property.

In this study, administration of ANT from purple sweet potato tuber extract obviously improved glycemic control both short-termly (expressed by improved FPG and 2hppPG) and intermediately (indicated by decreased GA). Glycated albumin is recently used as indicator for glycemic control for 2-4 weeks. It is more stable for the purpose of evaluating glycemic control compared to plasma glucose, and expresses glycemic control within intermediate duration, meanwhile,HbA1c reflects long-term glycemic control. The effect of ANT in improving glycemic control was consistently confirmed in several studies on animals as well as on humans. A trial by Ludvik et al. (2002) showed that administration of sweet potato extract (Caipo) in subjects with diabetes could lower plasma glucose and HbA1c more significantly than with placebo. In animal study using STZ induced diabetic mice fed with purple sweet potato tuber extract for 60 days, improvement plasma glucose was noted at week 4. Pathologically, the extract also could prevent islet cells necrosis better than without extract (Sutirta Yasa et al., 2012). Several studies both *in vivo* and *in vitro* have shown that ANT lowered plasma glucose in hyperglycemic state (Jurgonski et al., 2008; Nizamutdinova et al., 2009; Zhang et al., 2011). Protective property of ANT on oxidative stress is understood to relate with the provision of appropriate environment for islet cell proliferation and increase insulin production. A *in vitro* study has demonstrated increased proliferation and decreased apoptosis of beta cells exposed with high concentrate of glucose that was observed after being added with ANT from blueberry extract (*Vaccinium angustifolium*) (Martineau et al., 2006).The role of ANT in lowering plasma glucose might be mediated by effect of ANT as anti-inflammation. As widely known, inflammation is related to insulin resistance and glucose metabolism disorder. Several study have shown that ANT is able to lower the expression of TNF-alpha, MCP-1, IL-6and improves insulin receptor autophosphorylation (Sasaki et al., 2007; DeFuria et al., 2009; Nizamutdinova et al., 2009). Related to improvement of glucose levels, ANT has activity as competitive inhibitor of alpha-glucosidase enzyme (McDougall et al., 2005; Adisakwattana et al., 2009). In a study by Gharib et al. (2013) administration of cyanidin, an active form of ANT, in mice could lower GA. Administration of delphinidine and cyanidin chloride with a dose of 100 mg/mL per day for 8 weeks in mice proved to lower GA up to 8.5-14.6%.Glycated albumin itself can stimulate stress oxidative in endothelial cells via up regulation of main subunit Nox4 NADPH oxidase (Janeiro et al., 2010).

This study supports previous studies carried out on the effect of ANT as antioxidant and in improvement of glucose metabolism. Based on results of this study and several other studies, it can be concluded that ANT has antioxidant property and improves plasma glucose through several mechanisms, and that the extract was safe for the liver and kidney functions.

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