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Hypoglycemic effect of *Phaleria macrocarpa* (Scheff.) Boerl dry extract in healthy adults

Meiyanti*, Eveline Margo**, Pusparini***, Lie Tanu Merijanti†, and Alvina Lesmana***

ABSTRACT

BACKGROUND

The prevalence of diabetes in Indonesia continues to increase and causes many complications. Fruits of *Phaleria macrocarpa* (Scheff.) Boerl. (PM) are used in the traditional health system of the Indonesians, as effective remedy in the management of diabetes mellitus. The aim of this study was to evaluate the effect and magnitude of doses of PM dry fruit extract (PME) on blood glucose levels in healthy adults.

METHODS

This research was of pre-posttest design involving 30 healthy volunteer subjects aged 20-55 years receiving glucose loads. At pre-test the subjects were given orally 75 g glucose, and at post-test they were given PME at doses of 125 mg and 250 mg. Data collection included anthropometric examination and blood glucose level. The area under the curve (AUC) of blood glucose levels was measured at 0, 15, 30, 60, 120, and 180 minutes. Data analysis was performed using paired t-test with $p < 0.05$.

RESULTS

The percentage of reduction in AUC between pre- and post-test after administration of PME 125 mg was 12.1% and significant ($p=0.000$). But the percentage of reduction in AUC between pre- and post-test after administration of PME 250 mg was 4.07% and not significant ($p=0.06$). The reduction in AUC between post-test PME 125 mg vs PME 250 mg showed significant results ($p=0.011$).

CONCLUSION

This study demonstrated that a dose of 125 mg *Phaleria macrocarpa* (Scheff.) Boerl. dry extract has a hypoglycemic effect in healthy adults, and may therefore be suitable for use as traditional anti-diabetic drug.

Keywords: *Phaleria macrocarpa*, extract, blood glucose, healthy adult

*Department of Pharmacology and Medical Pharmacy, Faculty of Medicine, Trisakti University, Jakarta

**Department of Physiology, Faculty of Medicine, Trisakti University, Jakarta

***Department of Clinical Pathology, Faculty of Medicine, Trisakti University, Jakarta

†Department of Occupational Health, Faculty of Medicine, Trisakti University, Jakarta

Correspondence:

dr. Meiyanti, SpFK
Department of Pharmacology and Medical Pharmacy, Faculty of Medicine, Trisakti University
Jalan Kyai Tapa No 260 – Grogol, Jakarta - Indonesia
Phone: +6221-5672731 ext 2805
Email: meiyanti_suhardi@yahoo.com
ORCID ID: orcid.org/0000-0002-1770-5504

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INTRODUCTION

The use of traditional medications of plant origin (herbals or *jamu*) is steadily increasing in Indonesia, as indicated by the increasing number of herbal-producing industries. Some of the reasons for the increasing use of herbals are their ready availability, lower prices and traditional medicinal effects.

On the other hand, the use of traditional herbals in the community is as yet empirical, so that their quality, medicinal effects, and safety are in doubt. To raise the status of herbals to that of phytopharmaceutical or phytotherapeutic medications, it is imperative to test these herbals on humans through clinical trials.

One of the medicinal plants that is widely used in the community is *Phaleria macrocarpa* (Scheff.) Boerl. (PM), locally known as *mahkota dewa*. *Phaleria macrocarpa* belongs to the division of *Spermatophyta*, subdivision *Angiospermae*, class *Dicotyledonae*, order *Celastrales*, family *Thymelaceae* and genus *Phaleria*. This plant originates from Papua and is also known as *Phaleria papuana* Warb. var. *wichannii* (Val.) Back.⁽¹⁾ Four parts of the plant are used in herbal medicine, namely the stem, leaf, seed coat and fruit. The stem is used for bone cancer, while the leaf is for impotence, blood disorders, allergy and diabetes mellitus. The fruit of PM contains alkaloids, saponins, flavonoids, and polyphenols that are frequently used as antioxidants.^(2,3) *Phaleria macrocarpa* extracts prepared from different parts of the plant have a number of medicinal properties, such as anticancer, antidiabetic, antihyperlipidemic, anti-inflammatory, anti-bacterial, anti-fungal, and antioxidant.⁽⁴⁾

In the community PM is frequently used as alternative medication for the treatment of diabetes mellitus, in addition to oral antidiabetics.⁽⁵⁾ Diabetes mellitus (DM) is at present a global health problem. Data from several global studies state that DM is a serious health problem, which is caused by the increasing numbers of patients

with DM from year to year. In 2011 around 366 million adults suffered from DM, a fourfold increase from the 108 million in the 1980s, and it was estimated that in the year 2030 there would be a very large increase of up to 551 million in the number of patients with DM.⁽⁶⁾

Several *in vitro* studies and *in vivo* studies on animals indicate PM's effect as an antidiabetic. In the study by Ali et al.⁽³⁾ on rats it was concluded that a methanol extract of PM fruit pericarp has hypoglycemic effects. The study of Triastuti et al.⁽⁷⁾ concluded that PM has nephroprotective effects through PM's anti-hyperglycemic and antioxidant effects. The study by Ali et al.⁽⁸⁾ concluded that PM fruit pericarp methanol extract is able to decrease hyperglycemia *in vitro* as well as *in vivo* through inhibition of carbohydrate hydrolyzing enzymes. From several studies it is apparent that by using methanol as solvent, a higher content of active compounds may be obtained from PM, but since methanol is known to be toxic, it cannot be used as a commonly recognized safe solvent.⁽⁹⁾ In contrast to the foregoing studies, the study conducted by Hending⁽¹⁰⁾ states that the leaves of PM have antidiabetic effects. The study of Meiyanti⁽¹¹⁾ concluded that PM pericarp powder at a dose of 500 mg can decrease the blood glucose level of healthy persons after a glucose load. Although there are many studies on evaluation of the hypoglycemic effect of PM fruit pericarp extract (PME) in animals, there is scanty information on the hypoglycemic effect of PME in healthy adult humans. In addition, to date the extracts of PM have not yet been sufficiently standardized to yield detailed quantitative information of their phytoconstituents.⁽¹²⁾ The preparation of PM from the grinding and drying, up to the selection of extraction method and solvent to be used, will affect the efficacy and phytochemical contents of PM.^(13,14) Accordingly there is a need to conduct a study for evaluation of the hypoglycemic effect of PME in healthy human adults using a different solvent, with administration of the extract at several doses.

METHODS

Research design

This study was of experimental pre-post test design and was conducted in the *kelurahan* (village) of Angke, *kecamatan* (district) of Tambora, Jembatan Dua, West Jakarta from February until April 2018.

Study subjects

This study used a sample size of 30 subjects, which was calculated using $\alpha=5\%$, $Z\alpha=1.96$, $\beta=20\%$, and $Z\beta=0.842$, with $SD=17.86$ and mean difference (\bar{X})=9.84 mg/dL.⁽¹¹⁾ The minimum number of subjects required was 26, but in anticipation of a drop-out level of 15%, the total number of subjects was increased to 30.

The subjects were selected by consecutive non-random sampling. The inclusion criteria were as follows: i) males and females aged 18-55 years, ii) with body mass index of $\geq 18.5 - 25 \text{ kg/m}^2$, iii) not suffering from chronic diseases such as hypertension and diabetes mellitus, iv) not consuming certain herbal preparations (*jamu*) or vitamin supplements, from 1 week prior to the start of the study up to the completion of the study, v) not consuming caffeine-containing beverages and fruit juice and not smoking within the last 24 hours, vi) agreeing to participate in the study and to sign a declaration of informed consent. The exclusion criteria were: i) being currently pregnant or breast-feeding, ii) consuming other medications, such as corticosteroids, that may affect the blood glucose level, from 1 week prior to the start of the study up to the completion of the study, iii) having participated in other studies in the 3 months prior to the present one.

Plant material collection and preparation of extracts

The preparation used in this study consisted of capsules containing a dry extract of PM pericarp (PME). The PM pericarp (without seed coat and seed) was obtained from plant nurseries in the region of Semarang, Central Java. The harvested pericarp was cut up and oven-dried at

40 p C for 1 day. The dried pericarp was then ground into a powder, from which an extract was prepared with water and ethanol as solvents.⁽¹⁵⁾ The prepared extract was placed in gelatin capsules, with half their number containing 125 mg PME and the remaining capsules containing 250 mg PME, but of identical appearance.

Intervention

The intervention given consisted of the administration of one of the capsules containing PM dry pericarp extract (PME) from Semarang, Central Java. At each visit the subjects received 400 calories (or 75 gram of glucose), in accordance with the glucose oral tolerance test procedure.⁽¹⁶⁾ At the first visit the subjects received a glucose load only, whereas at the following visit on day 4, each subject received 125 mg PME. After a wash-out period of 1 week, at the next visit on day 11 the subjects received 250 mg PME. The doses used in this study were based on a previous study, which found that 500 mg of PM fruit powder has hypoglycemic effects and that one gram of PM fruit powder yields 250 mg of extract, so that the present trial was conducted with the doses of 125 mg and 250 mg PME.⁽¹¹⁾

Parameter for evaluation of hypoglycemic effect

The parameter used to determine the subjects' responses to glucose loading was the area under the curve (AUC).⁽¹⁷⁾ The hypoglycemic effect of the PME was determined by using the AUC of the serum glucose level of healthy volunteers who did not receive the PME and acted as controls, to be compared to the AUC of the serum glucose level of subjects receiving the PME at doses of 125 mg and 250 mg. The AUCs were calculated with the trapezium formula⁽¹⁸⁾ for each respective intervention:

$$\text{AUC}_{0-n} = t_1 - t_0 / 2 \cdot (C_0 + C_1) + t_2 - t_1 / 2 \cdot (C_2 + C_1) + \dots + t_n - t_{n-1} / 2 \cdot (C_n + C_{n-1})$$

Measurement of blood glucose level

The blood glucose level was determined in accordance with the oral glucose tolerance test standard procedure. Each of the blood samples was drawn from the cubital vein and then tested prior to the oral glucose load and respectively at 15, 30, 60, 120 and 180 minutes⁽¹⁶⁾ after the oral glucose load and administration of the PME-containing capsules. The serum glucose level was measured in duplicate using the glucose oxidase-phenol and 4-aminophenazone (GOD-PAP) enzymatic colorimetric assay that had been validated with a Perkin-Elmer Lambda 3B spectrophotometer. The reagent used was Glucose GOD FS from DiaSys, Germany. Prior to the study, calibration curves were constructed and validation tests were performed on the measurement method, consisting of tests of accuracy, precision, and stability.

Statistical analysis

The AUC of the blood glucose level was calculated using the trapezoidal rule for a period of 3 hours (AUC₀₋₃ hours). The Kolmogorov test of normality of the data distribution showed that the data were normally distributed. The characteristics of the subjects were presented as mean \pm SD. The absorbed amount of the ingested glucose with or without PME was statistically compared with the paired t- test. Differences at $p < 0.05$ were considered significant.

Ethical clearance

This study obtained ethical clearance from the Faculty of Medicine, Trisakti University, under no. 123/KER/FK /XII/2017.

RESULTS

The subjects participating in this study totaled 30 males and females with mean age of 34.2 ± 10.5 years, with 19 (63.33%) female subjects. The subject characteristics may be seen in Table 1.

Tests of accuracy and precision of the daily (within run) glucose level showed that the

Table 1. Distribution of features characteristics of the subject (n=30)

Characteristic	n
Age (years)	34.17 \pm 10.5
Sex	
Female	19 (63.3)
Male	11 (36.7)
Weight (kg)	54.62 \pm 8.17
Height (m)	1.57 \pm 0.09
Body mass index (BMI) kg/m ²	22.06 \pm 2.12

Data were presented as mean \pm SD, except for sex n (%)

coefficient of variation (CV) for the normal controls (Merck Qualitrol® HSN) was 0.95% with accuracy (recovery) of 98.21%, whereas for the high controls (Merck Qualitrol® HSP) the CV was 1.5 % and accuracy 97.12%. The tests of accuracy and precision of the day-to-day glucose level showed that for HSN the CV was 2.16% with accuracy of 98.35% whereas for HSP the CV was 3.05% with accuracy of 95.23%.

The mean blood glucose levels of the study subjects at 0, 15, 30, 60, 120 and 180 minutes after glucose loading, without administration of PME (pre-test), as compared with post-test administration of PME at doses of 125 and 250 mg, may be seen in Figure 1. Peak blood glucose level with or without administration of PME was reached within 30 minutes after glucose loading, whereas the lowest level was reached within 180 minutes (3 hours) after glucose loading.

Pre-test glucose level within the first 30 minutes (glucose peak) was 122.45 ± 20.98 mg/dL, while for post-test PME doses of 125 mg and 250 mg the results were $107.09 \pm 20/98$ mg/dL and 117.6 ± 21.80 mg/dL, respectively. The decrease in glucose level at the glucose peak was 12.5% and 3.96% for post-test PME doses of 125 mg and 250 mg, respectively, as compared with pre-test levels. The area under the curve for blood glucose level up to 3 hours (AUC₀₋₃ hours) was calculated using the trapezoidal rule. For the post-test PME dose of 125 mg there was a decrease in blood glucose level, with mean decrease in AUC₀₋₃ hours of 12.1%, which was

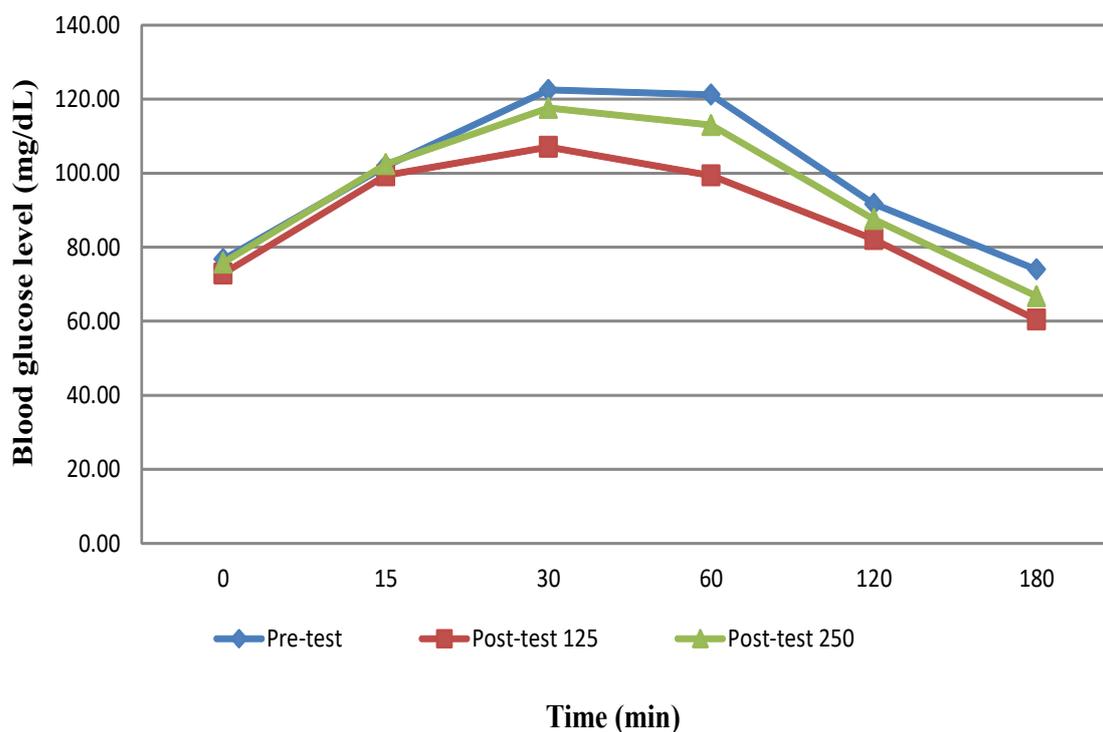


Figure 1. The effect of *Phaleria macrocarpa* extract on blood glucose level (mg/dL) of subjects
Data were expressed as mean \pm SD

higher than the decrease for the post-test PME dose of 250 mg. The post-test PME dose of 125 mg resulted in a significant decrease in AUC ($p=0.000$), whereas the pre-test AUC and the post-test PME dose of 250 mg did not differ significantly ($p=0.06$) (Table 2). A significant difference in AUC was also obtained for the post-test PME dose of 125 mg as compared with the dose of 250 mg ($p=0.011$).

Prior to ingesting the PME, each of the subjects underwent physical examinations with respect to blood pressure, pulse rate, and clinical condition of the heart, lungs and abdomen. These examinations were also performed at each subsequent visit to obtain a continuous picture

of the effect of PM on the vital functions and on complaints emerging during the administration of PME.

There were 2 subjects who complained of a bloated stomach after receiving PME at 250 mg, whereas after administration of 125 mg of PME there were no subjects who had complaints during the course of the study. A number of subjects who received PME showed a reduction in blood pressure. After administration of 125 mg PME there was a reduction in blood pressure of 5-7% in 4 out of the 30 subjects, whereas after administration of 250 mg PME there were 10 out of the 30 subjects who had a blood pressure reduction of 10-12%.

Table 2. Effect of *Phaleria macrocarpa* extract on blood glucose level and area under the curve

Variable	Pre-test	Post-test PME 125 mg	% diff	P	Post-test PME 250 mg	% diff	P
Blood glucose* (mg/dL)	122.45 \pm 20.98	107.09 \pm 20.98	12.5	0.04**	117.6 \pm 21.80	3.96	0.384
AUC (mg.min/dL)	18034.83 \pm 2688.97	15660.18 \pm 2707.28	12.1	0.000**	17092.9 \pm 2444.57	4.07	0.06

*Blood glucose at 30 minutes; * % difference between pre-test and post-test; ** $p < 0.05$ significant difference (paired t-test)

DISCUSSION

Our study results show that within 30 minutes after administration of the PME dose of 125 mg there was a higher mean reduction in blood glucose level as compared with administration of 250 mg PME. Differing results were obtained in the study of Ali et al.⁽³⁾ on rats, showing that administration of PMEs in petroleum ether, methanol, or water did not have an effect in the acute dose hypoglycemic test, but that the methanol and aqueous extracts showed a nonsignificant decrease in blood glucose between 30 and 120 minutes in the intra-peritoneal glucose test.

The evaluated parameter was the area AUC because the effect to be evaluated was the response of the blood glucose level on administration of PME. In our study there was a better hypoglycemic effect at a PM dose of 125 mg as compared with a dose of 250 mg. This shows that the methods of pre-extraction and extraction, as well as the solvent used in the extraction process, will influence the concentration and phytochemical constituents of PM. In addition, the point to be considered is the region from which the PM fruits come. The active constituents contained depend very much on the plant parts used (leaf, stem, or fruit) and on the type of solvent used in the preparation of the extract.^(12,19) Region of origin, type of soil, growing medium, and fertilizers used will affect the mineral content of the fruit.⁽²⁰⁾

The four parts of the PM plant that are frequently used in the community are the stem, leaf, pericarp, and fruit. Previous studies on the chemical composition of the pericarp and pericarp of PM found alkaloids, saponins, flavonoids, and polyphenols.⁽²¹⁻²³⁾ The decrease in blood glucose is effected by the action of saponins and flavonoids. The effect of saponin on the cell membrane inhibits the absorption of the smaller nutrient molecules that should be absorbed, such as glucose. Abnormalities in cell structure are thought to cause disturbances in the glucose transporter system, leading to inhibition

of glucose absorption.⁽¹⁵⁾ The study of Sabina et al.⁽²⁴⁾ concluded that the decrease in blood glucose level after administration of PME is presumably due to inhibition of α -glucosidase, which is an intestinal enzyme that converts disaccharides into glucose. This enzyme acts to inhibit glucose absorption in the small intestine. The antidiabetic activity of PM through inhibition of α -glucosidase was also concluded by Elya et al.⁽⁵⁾

The fruit of PM is thought to contain flavonoids that can increase insulin secretion, alter the metabolism of Ca^{2+} ⁽²⁵⁾ and regenerate the pancreatic islets of Langerhans, particularly the β -cells.⁽²⁶⁾ Similar findings were obtained in the study that was conducted by Arjadi and Mustafa⁽²⁷⁾ who concluded that PME can decrease the blood glucose level in diabetic rats, and regenerate the cells of the pancreatic islets of Langerhans of diabetic rats.

The decrease in blood glucose level as a result of PME administration is presumably effected through 2 main mechanisms, i.e. intra-pancreatic by repairing the β -cells of the islets of Langerhans and by stimulating insulin release. The increased insulin secretion is due to sympathomimetic stimulation by the alkaloid, causing increases in insulin secretion. The flavonoids contained in PME have antioxidant effects that protect against damage to the cells of the pancreas from free radicals. The second mechanism is extra-pancreatic, through inhibition of intestinal glucose absorption by the alkaloids.⁽²⁸⁾

The complaint found among the subjects was a sense of bloating in the stomach after administration of the PME dose of 250 mg, which may be caused by the rather high saponin content (20.4%)⁽¹¹⁾ in PM fruits that causes gastric irritation. In addition, there was also a decrease in blood pressure of the subjects after administration of both the PME doses of 125 mg and 250 mg. This decrease in blood pressure is the result of the action of PM fruit as ACE inhibitor.⁽²⁹⁾

The main limitation of this study is its design as a pre-post test experimental study without controls, so that further studies should be

conducted in accordance with the standards of a good clinical trial (randomized, using controls, and conducted on patients with diabetes). The clinical implication of this study is that dry PM fruit extract has antidiabetic effects, so that it can be used both as medication for the prevention of diabetes and as additional medication in patients with diabetes. The recommendation for further studies is to conduct a clinical trial in patients with diabetes comparing the extract to standard antidiabetics, so as to find more on the efficacy of PM as an antidiabetic. Biologically active plant extracts may be further exploited in the future by pharmaceutical and nutraceutical industries.

CONCLUSIONS

Phaleria macrocarpa extract has hypoglycemic effects on blood glucose level in healthy adult humans. The PME dose of 125 mg has better hypoglycemic efficacy than the dose of 250 mg.

CONFLICT OF INTEREST

The investigators state that there is no conflict of interest in this study.

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CONTRIBUTORS

M contributed to study concept, design and drafting manuscript. EM and P contributed to acquisition of data and critical revision of manuscript for intellectual content. AL and LTM contributed to data analysis and critical revision of manuscript for intellectual content. All authors have read and approved the final manuscript.✚

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