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RESEARCH ARTICLE

THE EFFECT OF *Andrographis paniculata* EXTRACT CAPSULES ON BLOOD GLUCOSE LEVEL IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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ABSTRACT

Andrographis paniculata Nees. (AP) leaves, empirically used as an alternative medicine for various diseases including diabetes mellitus, but the scientific evident for treatment in humans were still limited published reports. This study analyzed the effects of hypoglycemic AP capsules (APC) as an additional therapy in patients with type 2 diabetes mellitus. The design of this study was double-blind randomized controlled trial, cross-over design in 34 subjects who were divided into two groups. The first group received two APC 2 times daily for 14 days, and the second group received 2 placebo capsules (PC) 2 times daily for 14 days. Both groups kept taking metformin as standard therapy, then the evaluation of blood glucose levels on day 14. The result showed that showed that administration of APC for 14 days fasting blood glucose levels (13.47 mg/dL) greater compared to PC (-8 mg/dL) but not significantly. The APC significantly reduced blood glucose 2 hours after meal at 34.91mg/dL and significant ($p<0.05$).

INTRODUCTION

Diabetes mellitus (DM) was a chronic metabolic disease which is characterized by the high levels of blood glucose and more than 90% of patients having type 2 diabetes mellitus (T2DM) (Soegondo *et al*., 2009). T2DM was apparently precipitated in environmental factors which are not healthy and lifestyle changes. According to the World Health Organization (WHO), patients with DM in Indonesia were projected to increase from 8.4 million in year 2000 to 21.3 million in the year 2030. Based on the pattern growing of population from the Central Statistics Agency (CSA) in 2003, an estimated population of Indonesia over the age of 20 years was 133 million. The prevalence of DM increased, at 14.7% (8.2 million) in urban areas and 7.2% in rural areas (5.5 million) (Soegondo *et al*., 2009).

Research and Development Department of Health in 2008, has just had a national prevalence of impaired glucose tolerance (pre diabetes) of 10.25% and 5.7% for DM. The data above shows that the number of patients with DM was more numerous and was very difficult to be handled alone and should be done in integrated services (Soegondo *et al*., 2009). The management of DM, could be done through non-pharmacological include education, nutritious meal planning, physical exercise, and pharmacological oral hypoglycemic drug. (Waspadji, 2009). Oral hypoglycemia drug (OHO) must be used for the whole life and thus treatment costs are high and some of these drugs have vary side effects. That was why researcher looks for alternative use of medicinal plants that are effective, safe, cheaper and easy to find the raw material because it was available in nature. Several medicinal plants have been used for lower blood glucose levels, one of them is *Andrographis paniculata* (AP) (3,4). A series of studies has been shown to lower the AP blood glucose and presumably through several mechanisms, namely as: a). Induce insulin secretagogue (Wibudi, 2006) b). Inhibit gluconeogenesis in the liver (Zhang and Tan, 2000; Yulinah *et al*., 2001)c). Inhibiting alpha-glucosidase in the stomach (Subramanian *et al*., 2008; Borhanuddin *et al*., 1994; Yu *et al*., 2003; Husen *et al*., 2004) and d). Improve insulin resistance in the peripheral muscle, fat and liver tissues (Zhang and Tan, 2000; Yulinah, *et al*., 2001; Subramanian *et al*., 2008; Dandu, and Inamdar, 2009). AP believed to have hypoglycemic effects in animals but has not been widely used in medicine as an anti diabetic in Indonesia, because the studies in humans were still limited. Algorithms treatment of T2DM without the complications, generally begins with metformin, either as a single drug or a combination. This study was conducted to analyze the effects AP leaves extract capsules as additional therapy for 14 days to lower blood glucose levels greater than placebo capsules (PC) in patients with T2DM. The uses of traditional medicine in Indonesia not only take place in the village where there was no health facilities, but in a big city where modern health medicines were easily obtainable. Medicinal plants used as an alternative medicine have increased in many countries in the world, mostly because plant-derived drugs and herbal formulation are commonly considered to be less toxic and side effects than synthetic ones. Therefore, traditional Indonesian medicine was a heritage that must be preserved, researched and developed (Dewoto, 2007).

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MATERIALS AND METHODS

The study was performed during April 2012 to September 2012. Each 550 mg *Andrographis paniculata* capsule (APC) containing 70% dry extract of AP leaves and 30% filler of lactose, magnesium stearate and aerosol; and was registered for sale in Indonesia.

Clinical Study

Design

The study was approved by Ethics Committee of Faculty of Medicine, University of Indonesia - Cipto Mangunkusumo Hospital, Jakarta, Indonesia. A double-blind, crossover design, randomized controlled

clinical trial, conducted at the patients at Gatot Soebroto, Army Central Hospital, Jakarta, Indonesia.

Methods

After obtained informed consent from all subjects, they were randomly assigned to two groups: APC group and the PC group. All subjects received the metformin as standard therapy (ST) for T2DM patients and the diet according to the Standard Operational Procedure (SOP) clinical nutrition. Subjects distinguished in the APC group received additional 2 APC two times daily, while the PC group received additional 2 PC two times daily. The period of study was divided into three phases: the first phase for 2 weeks the patients were given PC or APC; second phase was wash out phase with only ST for one week (Ulbricht and Seamon, 2010; Panossian, *et al*. 2000). And in the third phase for 2 weeks made changes, the group who previously received PC will get APC and group previously received APC now receiving PC. Blood sampling from subject were taken through a vein in the arm fold area (*fossa cubiti*) of 5 ml for examination and fasting glucose levels 2 hours after meal. The day before the blood test, patients were advised to take 10 hours of fasting. The same procedure was carried out to determine the blood glucose levels after 14 days of therapy. The blood sampling performed at the Laboratory of Gatot Soebroto Army Central Hospital, Jakarta, Indonesia.

Subjects

The study protocol was approved by Ethics Committee of Faculty of Medicine, University of Indonesia - Cipto Mangunkusumo Hospital, Jakarta, Indonesia with a study of each subject of 35 days. The informed consent was explained to the patients and they agreed to participate by signing a written consent form. The 34 subjects were selected for the study using the following criteria. Inclusion criteria were: patients with T2DM, aged 40 to 65 who come to the Gatot Soebroto, Army Central Hospital, Jakarta, selected from the medical record and DM diagnosis by a specialist in internal medicine, and was using metformin for the past 2 years. Fasting blood glucose level of the subjects was ≥ 126 – 200 mg/dL and blood glucose 2 hours after eating ≥ 200 – 300 mg/dL declined to sign the informed consent. Exclusion criteria were the tested positive pregnant and lactating women. The results of laboratory tests have impaired renal and liver function. Criteria drop out during the study if the subject was not obedient to undergo laboratory tests that have been established at the beginning of the study, change the type of drug that has been established at the beginning of the study, experienced a side effect of APC and refused to continue the research.

Statistical analysis

The data were presented in terms of mean and standard deviation, analyzed by descriptive and analytical (wilcoxon signed ranks test) statistics, and all analysis was made using the SPSS statistical software package and p value of less than 0.05 was considered, statistically significant.

RESULTS AND DISCUSSIONS

Table 1 summarized the profile of the subjects in this experimental. In the present study, of the 40 subjects, six of them were drop out because they mistakenly taking anti diabetic medication before starting the study, illness and other reasons. These 34 subjects included 22 female (64.7%) and 12 male (35.3%). The majority of female among the subjects, were a picture distribution of persons with diabetes in the community according to the World Health Organization (2006). According to the American Diabetes Association (2008), the incidence of T2DM on women was higher than men.

Age of the patients who participated in the study ranged from 41-65 years, mean age was 54.26 ± 0.89 years, a total of 64.7% of subjects aged between 50-59 years. Studies in humans according to age have no clinical data. Researchers took the reference of the diabetes mellitus study in general. These results are consistent with estimates made by the American Diabetes Association (2006) that people with T2DM spread over the age of 45-64 years. This was due to many changes in the body's organs, especially in the pancreas that produce insulin in blood. Insulin plays an important role in the breakdown of glucose in the body's metabolism (Adhiarta, 2010). T2DM usually appears at age 45 or older and most over 50 years old. The body mass index (BMI) of the subjects was found only in 8.8% subjects that had normal BMI criteria, the majority of subjects were obesity type 1 (44.10%). A total of 76.5% had been suffering from diabetes mellitus for 10 until 19 years. Referring to the Society of Endocrinology branch Surabaya, Indonesia (2011) classify BMI in this study based on the criteria of Indonesia. It was said that a person with T2DM, had BMI criteria for obesity type 2 greater than or equal to 30 (Tjokroprawiro, 2011). In other words, the subjects in this study had a lower BMI, so it could be said that the BMI was not always comparable with T2DM. Inclined to say that lifestyle changes such as being overweight or obesity or lack of exercise as a trigger for T2DM.

Table 1. Demographic characteristics subjects at the beginning of the study

No	Characteristics	Frequency (n = 34)	Percent (%)
1		Ages (years)	
	40- 49	7	20.6
	50-59	22	64.7
	60-65	5	14.7
2		Sex	
	Male	12	35.3
	Female	22	64.7
3		Body Mass Index (BMI)	
	Normal	3	8.8
	Over Weight	9	26.5
	Obesity type 1	15	44.1
	Obesity type 2	7	20.6
4		Duration of T2DM (years)	
	0-4	5	14.7
	5-9	3	8.8
	10-14	12	35.3
	15-19	14	41.2

Description: Distribution of subjects according to age, sex, body mass index, duration of T2DM

Table 2.The blood glucose levels of baseline and after 14 days After Therapy on PC-APC Group.

Laboratory test	PC Group (mg/dL)		APCGroup (mg/dL)	
Blood Glucose Levels	*Baseline*	14 Days	*Baseline*	14 Days
Fasting	186,38	193,97	179,71	166,24
2 hours AM	242,12	234,12	248,12	213,21

Description: The blood glucose levels fasting and 2 hours After Meal, baseline and 14 days after therapy on PC – APC group.

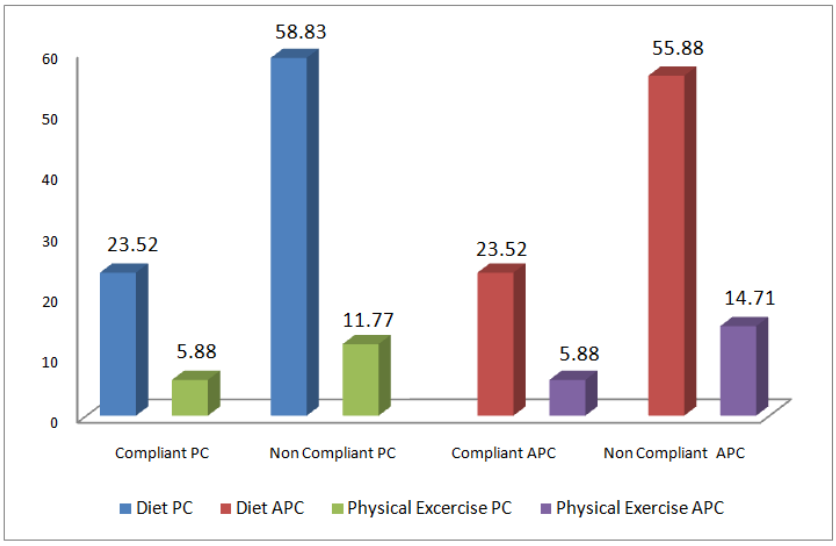
Table 3. Statistical test results 14 days After Therapy APC Group

Blood Glucose Levels	APC Groups after 14 days After Therapy	P-value
Fasting	13,47mg/dL	0,163
2 hours AM	34,91mg/dL	0,001*

Description: Changes in blood glucose levels and the APC group, statistical test results: blood glucose levels 2 hours After Meal significant

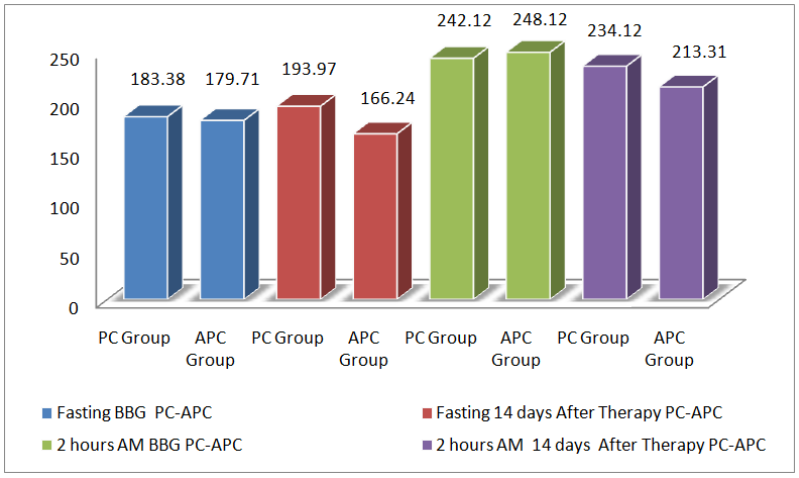
When someone was diagnosed with T2DM showed that pancreatic beta cell function was only 50% (Del Prato, S. 2004). It was important to know how long a person had T2DM, so it could estimate how much the ability of beta cells to maintain the blood glucose levels remain normal. Compliance was determined based on an assessment of 3 programs, including a schedule, the amount and type of dietary foods and beverages, as well as physical exercise / sport. Compliance 3 programs in the PC and APC group had the same scores (23.52%) and no compliance of the same program was very small (5,88%). Disobedience in diet foods and drinks slight more prominent in the PC group (58,83%) compared to the APC (55,88%) and for physical exercise / sport in the PC group (11,77%) rather smaller than the APC (14,71%) (Figure 1)

Blood glucose levels, criteria for subjects who participated in this study had levels of fasting blood glucose ≥ 126-200 mg/dL and 2 hours after meal ≥ 200-300 mg/dL. The baseline was initial blood glucose levels, the screening when recruiting subjects. At the beginning of this study, subjects no longer carried out checks of blood glucose levels because they had not received additional therapy on PC or APC. The mean fasting blood glucose levels on PC group was 186.3 ± 56.50 mg/dL and on APC group was 179.71 ± 58.79 mg/dL. The mean blood glucose 2 hours after meal for PC group is 242.12 ± 60.47 mg /dL and for APC group was 248.12 ± 41.00 mg/dL. Median of fasting blood glucose level in the PC group was 181.50, minimum



Description: Compliance Diet and Physical Exercise PC and APC Group

Figure 1. Compliance with the 3 programs on PC and APC Group



Description: The blood glucose levels fasting and 2 hours After Meal on PC-APC group
BBG means Baseline Blood Glucose 2 hours AM means 2 hours After Meal

Figure 2. The blood glucose levels, Baseline and 14 days after Therapy on PC-APC Group

value and maximum of PC are 103-341 mg/dL, and in the APC group was 166.00 mg/dL with minimum values and maximum are 102-422 mg/dL. After 14 days of therapy, the mean fasting blood glucose levels in the PC group was 193.97 ± 67.36 mg/dL and 166.24 ± 55.82 mg/dL for APC group (Figure 2). Blood glucose levels 2 hours after meal 14 days after therapy in the PC group was 234.12 ± 71.53 mg/dL and APC group had a mean blood glucose levels 2 hours after meals of 213.21 ± 71.53 mg/dL. Median of fasting blood glucose levels in PC group was 179.00 mg/dL with minimum values and maximum was 89-340 mg/dL, and in APC group is 154.50 mg/dL with minimum values and maximum are 69-323 mg/dL. Median of 2 hours after meals for the PC group was 224.50 mg/dL with minimum values and maximum were 118-382 mg/dL and for the APC group was 198.50 mg/dL with minimum values and maximum were 143-469 mg/dL. Baseline fasting blood glucose levels, the PC and the APC group of 6.67 mg/dL (186.38 to 179.71) and blood glucose levels two hours after meal was – 6 mg/dL (242.12 to 248.12). No significant differences in fasting blood glucose levels and glucose levels 2 hours after meal. Fasting blood glucose levels in the PC group: 14 days after therapy can be increased by 8 mg/dL (186.38 to 193.97). Blood glucose levels 2 hours after meal seemed a decrease of 8 mg/dL (242.12 to 234.12) but not significantly (Table 2). In the protocol, researchers had been determined that the differences between blood glucose levels was the average of two groups, base on the clinical judgement was 10 mg /dL. The results of this study through statistical tests on the APC group is blood glucose level, 2 hours after meal 14 days after therapy (34.91 mg/dL) was decreased significantly ($p < 0.05$). On the PC group, the blood glucose levels 2 hours after meal 14 days after therapy (8mg/dL), was smaller than determined by the researcher (10mg/dL), but is not significant (Table 3).

Conclusion

APC Clinical trials showed the significant differences, in the APC group for blood sugar 2 hours after meal 14 days of treatment ($p = 0.001$), while the PC, there was an increased in fasting glucose and 2 hours after meals was decreased 14 days after therapy, but not significant. Further research was needed 12 weeks as clinical trials in general and also to determine the effectiveness of therapeutic doses of APC.

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