Original Article

The Effect of Bitter Melon (*Momordica charantia L.)* Leaves Extractonon Glycated Albumin in Diabetic Foot Ulcers: Randomized Controlled Trial

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Abstract

Objective: This study aims to prove the effect of supplementation of bitter melon leaves extract on glycemic status in diabetic foot ulcer (DFU). **Materials and Methods:** This study used a randomized, double-blinded, and placebo-controlled trial. Thirty DFU patients based on PEDIS 1-8 scores who met the criteria were divided into 2 groups consisting of 15 patients as a treatment group with the administration of bitter melon leaves extract at a dose of 6 g/day and 15 patients as a control group of with placebo. This intervention was conducted in 4 weeks. Glycemic status was measured by the value of glycated albumin and examined at baseline and at the end of treatment. Data were analyzed using paired t-test and independent t-test. **Results:** After 4 weeks of treatment, there was an increase in the baseline value of glycated albumin in the treatment group from 24.5 ± 11.7% to 25.8 ± 12.7% or an increase of 1.3 ± 6.3% and a decrease in the control group from 27.5 ± 13.1% to 25.8 ± 8.5% or a decrease of 1.7 ± 12.4%. The results of the analysis of the effect of supplementation of bitter melon leaves extract on the value of glycated albumin were not significant (p = 0.99). **Conclusion:** The supplementation of bitter melon leaf extract with a dose of 6 g / day did not significantly affect the value of glycated albumin.

Keywords: Bitter melon, Momordica charantia L., glycated albumin levels, diabetes mellitus, diabetic foot ulcer

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Introduction

Diabetes mellitus (DM) has increased the prevalence in the world, especially in developing countries[1,2]. The prevalence numbers in patients with diabetes mellitus were growing rapidly in the world that might generally correlated lead as with living in the urban area, increasing older adult population, and lifestyle alteration[3]. Diabetes is a metabolic disease characterized by hyperglycemia and impaired carbohydrate metabolism, fat, and insulin resistance, and it becomes one of the causes of death in the world[4]. Hyperglycaemia convinced the characterize depressed oxidative aim to assist the development of organ failure and lead in to complication of DM[5]. Foot ulcers Diabetic (DFU) is the most serious complication of DM and the main cause of non-traumatic leg amputation[6]. Patients with DM have a risk for 15-20 times more likely to be amputated

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than those without DM[6-7]. Of patients with diabetes, 15-25% will experience DFU in their lifetime[8]. However, if patients get amputated, patients with DM will have a 5-year mortality ratecount around 50%[9-10]. Thosecomplications may lead to a decrease in the quality of life of diabetic patients[11].

Diagnostic criteria for DM can be established by examining blood glucose levels, HbA1c, and glycated albumin (GA)[12-13]. Several previous studies have explained that GA is more reliable in monitoring DM and is a better marker in glycemic control than HbA1c in the hemodialysis patients, the glucose levels that have to fluctuate related to DM type 2 with poor control[14]. The management of DFU focused on normalizing blood glucose at the first level. This intervention was set as a consideration to use bitter melon leaves. Bitter melon (*Momordica charantia L.*, MC) has been used in the tropical region as traditional medicine, especially with hypoglycemic condition[15-16]. In vitro and experimental studies on animals report the hypoglycemic activities with the mechanism of alpha-glycosidase inhibition, insulin-like properties, an insulin secretagogue, the improvement of pancreatic beta-cell function, the increase in GLUT-4 in skeletal muscle cells and the decrease in hepatic gluconeogenesis[15,17-19]. The aim of this study is to prove the effect of Bitter melon leaves extract on glycemic status in the DFU.

Materials and Methods

a. The production of bitter melon leaves extract

Bitter melon was obtained from agricultural areas located in Surakarta, Central Java, Indonesia. Bitter melon (Momordica charantiaL, MC) leaves were selected from the best quality leaves. The leaves were characterized by flat leaves and fresh green color; more over, the leaves continued to be washed and dried in the dryer cupboard. The dried bitter melon leaves changed into a coarse powder then they were macerated in 3 to 5 days using 50% ethanol until it submerged. Afterward, these processes continued to the maceration process in which the results of leaves powders were filtered using a vacuum Buchner. The filter/maceration results are generally evaporated with the evaporator observed until them wereslightly thick. The thick extracts continued to be evaporated again on the water bath until they were very thick, and the level of moisture content was below 20%. The result of the thick extract was added by amprotab/corn starch in a ratio of 1:2, andthen it was stirred until homogeneous. This process continued to the micturition process of extract that was dried in an oven at 40°C until dry; then, it was mashed with a blender. The powder was inserted into the capsule. Moreover, the making of bitter melon leaves extract capsules was conducted at UMS Pharmacy Laboratory.

b. Clinical trial

The study design used a randomized, double-blinded, placebo-controlled trial conducted in Dr. Moewardi General Hospital Surakarta, Indonesia. The study protocol was approved by the Health Research Ethics Committee of Dr. Moewardi General Hospital/School of Medicine University of Sebelas Maret, Indonesia.

c. Patients The inclusion patient's criteria were diabetic foot ulcer patients with PEDISscores met of 1-8, aged 30-65 years old, hemoglobin levels of > 10 g/dl, BMI of 18.5 - 22.9, albumin levels of > 3 g / dl, ankle-brachial value index (ABI)> 0.6 - 1.3, Length of DM: 0-15 years, willing to participate in this research and consider to sign the informed consent. Exclusion patient's criteria were: those who had been planned for minor amputations (below knee or above knee), those having a chronic hypoxia, sepsis, aged<30 years or> 65 years, stress, obesity, having record of alcohol consumption or currently consuming alcohol, smoking, those being with co-morbidities (cardiovascular disease, lung, and immunology), steroid therapy and chemotherapy, drop out, allergies with the use of bitter melon leaves extract. The flow chart that describes patients who are recruited and acted upon can be shown in Figure 1.

d. The procedure of the study

The data will be collected from patients, the researcher explained the research project, and those agreed to participate got informed consent to be signed. The informed consent consisted of information about the research purpose, ethical principles including beneficence and non-maleficence, participants' right to withdraw anytime from this study, and confidentiality of participants' data. The patients got explanations both verbally and in writing. At the first visit, patients were examined for eligibility in this study. The eligible patients were divided

randomly into two groups, namely the control group and treatment group. The control group specified a placebo with a dose of 6 grams orally for 4 weeks, and the treatment group specified bitter melon leaves extract at a dose of 6 grams orally for 4 weeks. At the end of this study, medication adherence was determined by calculating the number of drugs taken and interviewing each patient's control.

e. The outcome measurement

The primary efficacy result is a change in the value of glycated albumin measured using a colorimetric enzymatic method. Measurement of glycated albumin values at baseline and end of week 4 in both groups.

f. Data analysis

The results of the study are presented as follows: a number of patients (n), mean, and SD. Data were analyzed using SPSS by which the data are statistically significant if $P \leq 0.05$. Non-parametric statistical methods are used if the variables studied are not normally distributed. Analysis of mean is different between the results of measurements of glycated albumin levels with paired t-test and independent t-test.

Results

Thirty patients with diabetic foot ulcers participated in this study. All patients were randomized and then given 6 g/day of bitter melon leaves extract in the treatment group (n = 15) and placebo (n = 15) in the control group. All baseline characteristics between the 2 groups did not show differences (Table 1). All baseline parameters in the treatment and control group have no differences. Age, gender, education, occupation, body weight, Body Mass Index (BMI), duration of diabetes, duration of ulcer, PEDIS score, antidiabetic medicine, ankle-brachial index (ABI), and serum TNF-α levels have no differences between groups and no changes after the experiment. After 4 weeks of treatment, there was an increase from baseline levels of GA in the treatment group, an increase from 24.5 ± 11.7% to 25.8 ± 12.7% or an increase of 1.3 ± 6.3% and the control group decreased from 27.5 ± 13.1% to 25.8 ± 8.5% or a decrease of 1.7 ± 12.4%. The results of the analysis show that supplementation of bitter melon leaf extract to the levels of glycated albumin was not significant (p = 0.99)

Discussion

Glycated albumin demonstrates a shorter blood glucose status than HbA1c, which is 2-4 weeks[20]. Glycated albumins can capture the fluctuations and the change in glycemic status more quickly and significantly than HbA1c[21]. It showed that the results of this study indicate that the differences in GA values between treatment and control groups have no meaning. The results of this study indicate an increase in the value of GA in the treatment group. This condition may occur in patients with chronic liver disease; moreover, GA value is higher in these patients. This phenomenon may due to the prolonged half-life of serum albumin due to decreased albumin synthesis. The control group has a decreased GA values. This condition may occur in patients with nephrotic syndrome, hyperthyroidism, and steroid treatments such as glucocorticoids related with increasing the metabolism of albumin. The decrease in GA value in these conditions is related to the shortening of the half-life of serum albumin[20].

Bittermelon (*Momordica charantia L.,* MC) has generally been maximized in the tropical area as traditional medicine, especially with hypoglycemic

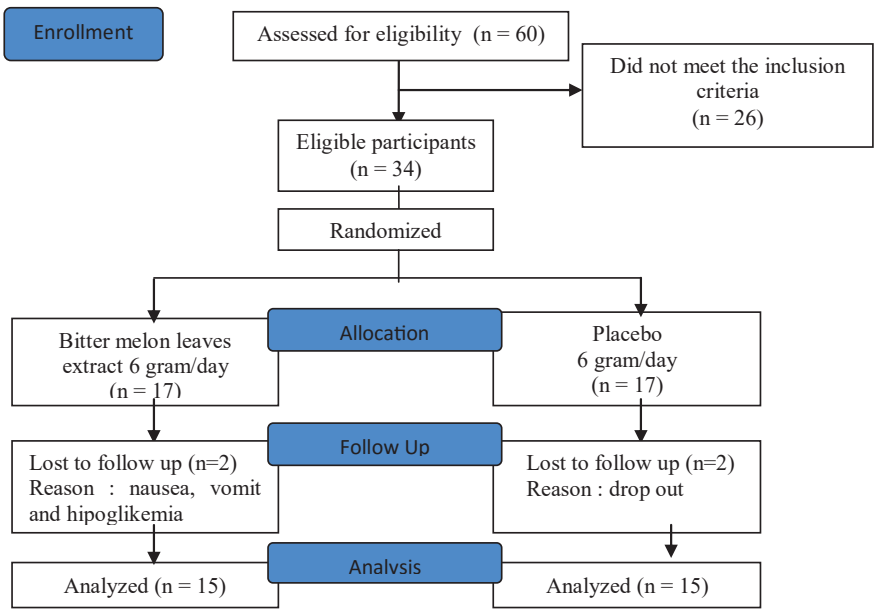

Figure 1. The flow of participants through the trial.

Table1. The Baseline characteristics of patients

Variable	Intervention Group (n = 15)	Control Group (n = 15)	p-value[a]
Age (years)	55±8.4	53.1±7.5	0.25
Gender			0.46
Male(%)	4 (26,7)	6 (40)	
Female(%)	11 (73.3)	9 (60)	
Education level			0.64
Elementary(%)	1 (6.7)	1 (6.7)	
Junior High School(%)	3 (20)	5 (33.3)	
Senior High School(%)	9 (60)	7 (46.7)	
University/ College(%)	2 (13.3)	2 (13.3)	
Employment			0.61
Housewife(%)	3 (20)	5 (33.3)	
Industrial(%)	10 (66.6)	8 (53.3)	
Governmentstaff(%)	1 (6.7)	1 (6,7)	
Retirement(%)	1 (6.7)	1 (6,7)	
Body Weight (kg)	55.9±7.8	56±8.6	0.33
Body Mass Index (kg/ m^2)	21.6±1.2	21,7±1.2	0.53
Duration of Illness DM (Years)	8.5±6.9	8.47±5.6	0.37
Duration of Illnessulcers (Weeks)	23.1±34.7	24.4±33	0.78
Scoreof PEDIS	4.5±1.4	5.3±2.1	0.23
antidiabetic Medicine			1.00
Yes (%)	15 (100)	15 (100)	
No (%)	0	0	
Ankle Brachial Index (ABI)	1±0.1	0.9±0.1	0.22

[a]There is no significant difference between the group (compare) p > 0,05

Table2 Theeffect of Bitter Melon (Momordica charantia L.) Leaves Extract on GA

Variable	Baseline	ΔWeeks 4	p within-group	p between-group [b]
Values of GA (%)				
Intervention Group	24,5±11,7	1,3±6,3	0,44	0,99
Control Group	27,5±13,1	-1,7±12,4	0,61	

[a]paired sample t-test

[b]t independent sample test

activity[15-16]. The previous studies in animals in vitro and experimental have explained their hypoglycemic activity with the mechanism of inhibiting alpha-glycosidase, insulin secretagogues, insulin-like properties, improved function of pancreatic beta cells, increased GLUT-4 in skeletal muscle cells and decreased hepatic gluconeogenesis[15,17-19]. This research is in line with the study conducted by Yin et al. (2014), reporting that supplementation of bitter melon fruit does not show a significant glycemic increase in either A1c or FPG[22]. Rahman et al. (2015) find that bitter melon fruit has a weaker hypoglycemic effect, but it is more effective than glibenclamide in preventing cardiovascular risk due to diabetes[23], Boone et al.(2017) also find that the consumption of bitter melons can reduce 50% postprandial glucose, but it does not affect insulin response. Those might explain that bitter melon does not affect the level of glucose tolerance. Bitter melon can be used to control blood sugar levels in diabetic patients; however, in this study, only a portion of people with diabetes have decreased blood glucose levels[24].

Conversely, from several studies, Dans et al. (2007) report that bitter melon leaves extract capsules may reduce fasting glucose levels[25], Lim et al. (2010) find that bitter melon leaves extract tablets may stimulate insulin secretion in Type 2 DM patients which results a decrease in glucose after eating[26], Sani et al. (2015) reveal that bitter melon leaves extract has a hypoglycemic effect on diabetic rats[27], Xu et al. (2015) state that bitter melon significantly has ant diabetic activity in diabetic rats induced by alloxan[28], Aljohi et al. (2016) find that bitter melon not only has a hypoglycemic effect but also is able to prevent the formation of AGE in vitro[29], Mahmoud et al. (2017) bitter melon has an excellent ant diabetic and antioxidant activity and has great potential for the treatment of diabetes, whether used for prophylaxis of treatment[30].

Conclusion

The supplementation of bitter melon leaf extract with a dose of 6 g/day does not significantly affect the value of glycated albumin. This study recommends further examination of albumin levels, liver function test (LFT), proteinuria, levels of T3, T4, and TSH because it affects the value of glycated albumin.

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Conflicts of interest

All authors report no conflict of interest

Ethics approval and consent to participate

The eligible prospective participants were invited to participate in this study. All participants got an explanation of the purpose of this study thatis to examine the effect of bitter melon leaves extract on levels of glycated albumin. Informed consent was obtained from each participant before the study. Participants are allowed to withdraw from this research at any time. Ethical clearance of this study was obtained from the Commission of Health Research Ethics Hospital Dr. Moewardi/FK UNS Surakarta (Number: 902/XI/HREK/ 2016).

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