



Improving Diabetic Foot Ulcer Healing with Adjuvant Bitter Melon Leaf Extract (*Momordica charantia L.*)

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Abstract

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BACKGROUND: Diabetes mellitus is a serious disease that affects more than 340 million people and causes approximately 20% of diabetic ulcer cases worldwide. Wound healing is a complex and dynamic process in restoring cellular structures and tissue layers. It consists of four continuous overlapping phases that are precisely programmed

AIM: This study aims to examine the adjuvant administration of bitter melon leaf extract to increase the healing of diabetic foot ulcers (DFU).

METHODS: This study used a randomized, double-blind, and placebo-controlled trial. A total of 30 DFU patients with a perfusion, extent, depth, infection, and sensation (PEDIS) score of 1–8 who met the criteria were divided into two groups, namely, the treatment group with adjuvant administration of bitter melon leaf extract at a dose of 6 g/day as many as 15 patients and the control group 15 patients with placebo. This intervention was carried out for 4 weeks. DFU cure was measured by PEDIS scores at baseline, weeks 2, 3, and the end of week 4. Data were analyzed using paired t-test and independent t-test.

RESULTS: After 4 weeks of treatment, the PEDIS score in the treatment group decreased at week 2 (0.9 ± 1.8), but not significant ($p = 0.19$), decreased at week 3 (1.9 ± 1.9) and significant ($p = 0.01$), decreased in week IV (2.3 ± 2.1) and significantly ($p = 0.001$). The control group experienced a decrease in week 2 (0.3 ± 2.3), but not significant ($p = 0.71$), decreased in week 3 (1.2 ± 2.5), but not significant ($p = 0.18$), decreased in week 4 (1.9 ± 2.7) and significantly ($p = 0.03$), and there was an effect of adjuvant administration of bitter melon leaf extract on the cure of DFU ($p = 0.004$).

CONCLUSION: Adjuvant administration of bitter melon leaf extract has been shown to increase the healing of DFU.

Introduction

Diabetes mellitus (DM) is a serious disease that affects more than 340 million people and causes approximately 20% of diabetic ulcer cases worldwide [1]. Meanwhile, foot ulcers are the most common wounds in DM patients caused by hyperglycemia, which hinders the healing process. Approximately 2.5–15% of the annual health budget worldwide is attributed to diabetes and diabetic ulcers. Based on the 2014 WHO report, diabetes caused 9% of the 1.5 million adult patients' death in 2012 with over 80% occurring in middle-income countries [2]. Furthermore, about 50–70% of all limb amputations are due to diabetic ulcers with an incidence rate of 1/30 s [3]. Wound healing is a complex and dynamic process in restoring cellular structures and tissue layers. It consists of four continuous overlapping phases that are precisely programmed [4]. Healing of diabetic ulcers can be disrupted due to four factors, namely, persistent hyperglycemia, proinflammatory environment, peripheral arterial disease, and peripheral neuropathy, and impaired neovascularization [5]. Wound healing requires infection

control, inflammation repair, connective tissue matrix regeneration, angiogenesis or vasculogenesis, wound contraction, and reepithelialization [6].

Meanwhile, bitter melon (*Momordica charantia L.*) is a member of the *Cucurbitaceae* family and has been widely cultivated for medicinal purposes due to its various biologically active compounds including momordicin, momorcharin, momordin, charantin, polypeptide-p, and cucurbitacin B, as well as high amounts of vitamin C. The fruits and leaves are rich in minerals and vitamins including iron, calcium, magnesium, phosphorus, and B vitamins as well as β -carotene, potassium, vitamin A, and zinc [7], [8]. Recent studies on the pharmacological properties of the leaf extract showed that this plant has antidiabetic, antilipidemic, antioxidant, antibacterial, anti-inflammatory, antiviral, and anticancer properties [9], [10], [11], [12], [13]. In addition, the bitter melon leaf extract is used to improve the wound healing process [14]. This plant accelerates the production of cell and tissue growth factors, induces fibroblast proliferation, and increases wound oxygenation, thereby accelerating capillary circulation and the wound healing process due to the antioxidant and antimicrobial effects of phytochemicals such as flavonoids and glycosides [15].

Methods

Preparation of the bitter melon leaf extract

Bitter melon leaf was obtained from agricultural land in Boyolali Regency, Central Java Province, Indonesia. It was selected with good quality, as indicated by the fresh, flat, and green leaves. The leaf was washed, dried in a drying cabinet, made into a coarse powder, and then macerated for 3–5 days with 50% ethanol. The maceration results were filtered with a vacuum cleaner and evaporated with an evaporator until the mixture is slightly thick. This extract was re-evaporated in a water bath until it became thick with water content below 20%. The mixture was then added with corn starch in a ratio of 1:2 and stirred until homogeneous. Furthermore, the mixed extract was dried in an oven at a temperature of 40°C, mashed with a blender, and then placed into capsules. The manufacture of bitter melon leaf extract capsules was carried out at the UMS Clinical Pharmacy Laboratory, Surakarta, Central Java, Indonesia.

Clinical trial

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

Patients

The inclusion criteria include DFU patients with a perfusion, extent, depth, infection, and sensation (PEDIS) score of 1–8, aged 30–65 years, had hemoglobin levels >10 g/dl, BMI ranges from 18.5 to 22.9, had albumin levels >3 g/dl, and ankle-brachial index (ABI) values >0.6–1.3, DM persistent for 0–15 years, willing to participate in the study, and signed informed consent. Meanwhile, the exclusion criteria include patients initially scheduled for minor amputation (Below Knee or Above Knee), has chronic hypoxia, sepsis, aged <30 years or >65 years, stress, obese, alcoholics, smokers, patients with comorbidities such as cardiovascular and lung disease, as well as immunology, steroid therapy and chemotherapy, and allergic to the use of bitter melon leaf extract. The flow chart depicting the recruited and followed-up patients is shown in Figure 1.

Study procedure

Patients first received an explanation both orally as well as in writing and then submitted informed consent. At the first visit, the patients were examined for eligibility in this study and randomized into the treatment

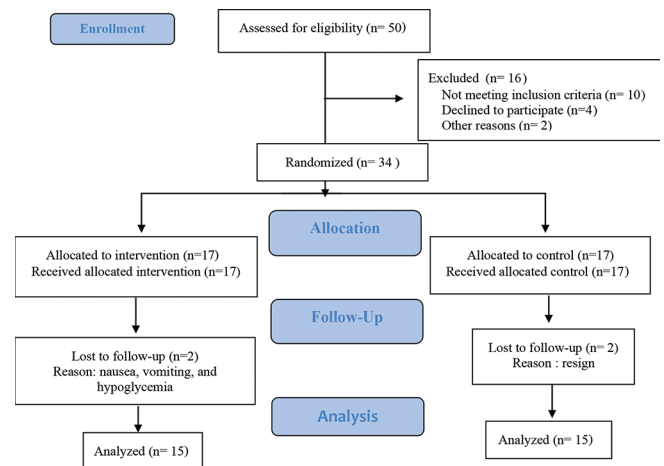


Figure 1: Flow of participants through the trial

and control groups. The treatment group received bitter melon leaf extract orally at a dose of 6 g for 4 weeks while the control received a placebo. Furthermore, medication adherence was determined by counting the number of drugs taken and interviewing each control patient.

Outcome measurement

The primary efficacy outcome was measured using the PEDIS score. The DFU healing was assessed at baseline, followed by the second, third, and the end of the 4th week in both treatment groups.

Statistical analysis

The results of the analysis were presented as the number of patients (n), mean, and SD. The data were analyzed using SPSS, and $p < 0.05$ indicate a significant difference. Meanwhile, non-parametric statistical methods were used when the variables are not normally distributed. The mean difference analysis between the PEDIS score measurement used the paired sample t-test, Wilcoxon Signed Ranks Test, and ANOVA.

Results

This study involved 30 DFU patients selected at random and divided into two groups (Figure 1), namely, treatment ($n = 15$) and administered with 6 g/day bitter melon leaves extract orally as well as control ($n = 15$) treated with a placebo. Baseline characteristics data between the two groups showed no difference, as presented in Table 1. There were no differences in all baseline parameters including age, gender, education, occupation, weight, body mass index (BMI), length of DM, duration of ulcer, PEDIS score, antidiabetic medicine, and ABI. After 4 weeks of treatment, the PEDIS score in the 2nd week for the treatment group decreased insignificantly

Table 1: Demographics and characteristics of subjects

Variable	Treatment Group (n = 15)	Control Group (n = 15)	p-value ^a
Age (years)	55 ± 7.3	53.1 ± 8.6	0.30
Gender			0.56
Male (%)	9 (60)	11 (73.3)	
Female (%)	6 (40)	4 (26.7)	
Education			0.54
Elementary School (%)	1 (6.7)	1 (6.7)	
Junior high school (%)	8 (53.3)	10 (66.7)	
Senior high school (%)	4 (26.7)	2 (13.3)	
University (%)	2 (13.3)	2 (13.3)	
Work			0.31
Housewife (%)	6 (40)	9 (60)	
Entrepreneur (%)	8 (53.3)	4 (26.6)	
Civil servants (%)	0	1 (6.7)	
Retired (%)	1 (6.7)	1 (6.7)	
Body weight (kg)	56.9 ± 8.9	56 ± 7.5	0.45
Body mass index (kg/m ²)	21.6 ± 1.3	21.7 ± 1.3	0.64
Length of suffering from DM (years)	8.5 ± 5.9	8.47 ± 6.6	0.38
Length of ulcer (weeks)	23.1 ± 34.8	24.40 ± 33	0.69
PEDIS Score	4.5 ± 1.4	5.3 ± 2.1	0.23
Antidiabetic drugs (OAD)			1.00
Yes (%)	15 (100)	15 (100)	
No (%)	0	0	
Ankle Brachial Index (ABI)	0.9 ± 0.1	1 ± 0.1	0.23

^aNo difference (comparable) $P > 0.05$. PEDIS: Perfusion, extent, depth, infection and sensation.

by 0.9 ± 1.8 , with $p = 0.19$, but decreased significantly by 1.9 ± 1.9 in weeks 3 as indicated by $p = 0.01$, and 2.3 ± 2.1 in week 4 with $p = 0.001$. Meanwhile, the control group experienced an insignificant decrease in week 2 by 0.3 ± 2.3 with $p = 0.71$, and week 3 by 1.2 ± 2.5 , with $p = 0.18$, but decreased significantly in week 4 of 1.9 ± 2.7 as indicated by $p = 0.03$, which implies that the adjuvant administration of extract bitter melon leaves (*M. charantia L.*) affects the PEDIS score with $p = 0.004$ (Table 2 and Figure 2).

Table 2: Effect of bitter melon extract on PEDIS Score

Variable	Treatment Group	Δ	p	Control Group	Δ	p	p between groups
PEDIS score of week 1	4.5 ± 1.4	2.3 ± 2.1		5.3 ± 2.1	1.9 ± 2.7		0.004 ^c
PEDIS score of week 2	3.7 ± 1.8		0.003 ^a	5 ± 2.3		0.05 ^a	
PEDIS score of week 3	2.7 ± 1.9		0.00001 ^a	4.1 ± 2.5		0.01 ^a	
PEDIS score of week 4	2.2 ± 2.1		0.02 ^b	3.4 ± 2.7		0.04 ^b	

^a Paired sample t-test; ^b Wilcoxon Signed Ranks Test; ^c ANOVA. PEDIS: Perfusion, extent, depth, infection, and sensation.

Discussion

Effect of the administration of bitter melon leaf extract on ulcer repair

The results showed that there was a significant difference in PEDIS scores between the treatment and control groups as indicated by the decrease in weeks 1, 2, 3, and 4 (Figure 2). These results are consistent with previous studies which reported that administration of bitter melon extract improves and accelerates the wound healing process in rabbits [14], [16], [17]. Furthermore, Liu *et al.* (2021) stated that the treatment with bitter melon leaf extract tends to improve blood glucose control in patients with type 2 DM [18]. It also increases wound contraction, closure time, epithelialization, tissue regeneration [19], and hastens the wound healing process in diabetic

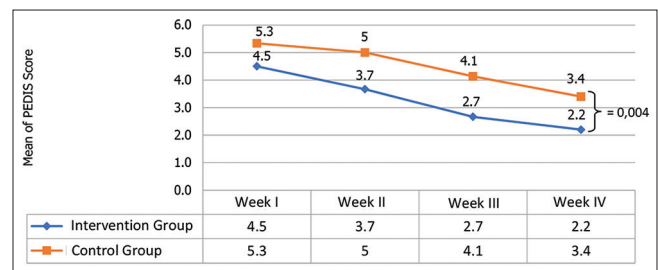


Figure 2: Ulcer repair data as measured by the perfusion, extent, depth, infection, and sensation score in the treatment group and the control group weeks 1, 2, 3, and 4

animals [20], [21]. The powdered leaf extract of this plant significantly increases tissue regeneration and epithelialization of wound contraction in a mouse ulcer model [22]. Moreover, topical administration improves and enhances the wound healing process in patients with diabetes [23], [24]. It also decreases inflammation, increases granulation tissue formation and angiogenesis, thereby accelerating healing [4], [25], [26], [27].

Vitamins A and C contained in the bitter melon leaf have antioxidants and anti-inflammatory properties [4], [28]. In damaged skin, vitamin C increases the formation of hydroxyproline, which is a component of collagen, hence, the higher the hydroxyproline, the greater the collagen formed. Collagen fibers are fibrous proteins which strengthen wounds, thereby accelerating the closure process [16].

Rembe *et al.* (2018) reported that the administration of vitamin C increases the activity and number of fibroblasts. This stimulates an increase in the number of collagen, elastin, and glycosaminoglycan fibers [29]. Furthermore, vitamin A has antioxidant activity, increases fibroblast cell proliferation, modulates cell proliferation and differentiation, increases collagen and hyaluronic synthesis, and decreases MMP [30]. It also plays an important physiological role in the growth of skin epithelium, protects mucous membranes and epithelial cells from cornification processes, and increases the resistance of mucous membranes to infection by covering the epithelium [28]. This study is limited due to the low number of DFU patients used. Besides, the examination was not carried out on other variables that might affect DFU healing, including albumin levels, oxygen tension, leukocyte, estrogen, and cortisol levels, as well as fibroblast and collagen count.

Conclusion

The administration of adjuvant from bitter melon leaf extract improves Diabetic Foot Ulcers (DFU) healing. Further studies need to increase the number of DFU patients as samples, examine albumin, oxygen tension, leukocyte, estrogen, and cortisol levels, as well as fibroblast and collagen counts.

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Authors' Contributions

Concept and design (Fahrur Nur Rosyid, Muhtadi), data collection and ethical clearance (Fahrur Nur Rosyid, Dian Hudiawati, Sugiyarti), analysis and interpretation of data (Fahrur Nur Rosyid, Muhtadi), manuscript draft and translation (Fahrur Nur Rosyid, Muhtadi, Ahmad Fadhlur Rahman).

Ethics Approval and Consent to Participate

Prospective participants were invited and oriented on the purpose of this study, namely to examine the administration of the adjuvant of bitter melon leaf extract to improve DFU healing. Informed consent was obtained before the study and the participants were allowed to withdraw at any time. The ethical clearance was obtained from the Commission of Health Research Ethics at RSUD Dr. Moewardi/FK UNS Surakarta (Number: 780/VIII/HREK/2021).

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