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Original Article

THE EFFECT OF BITTER MELON FRUIT EXTRACT (*MOMORDICA CHARANTIA L.*) SUPPLEMENTED WITH SNAKEHEAD FISH POWDER (*CHANNA STRIATA*) ON CLINICAL IMPROVEMENT OF DIABETIC ULCERS: A RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

Objective: This study aims to examine supplementation of a combination of bitter melon extract with snakehead fish powder for clinical improvement of diabetic foot ulcers (DFU).

Methods: This study used a randomized, double-blinded, placebo-controlled trial. A total of 50 DFU patients who met the criteria were divided into 2 groups, namely: 25 patients as the treatment group were given supplementation of bitter melon extract combination with snakehead fish powder and a control group of 50 patients who received a placebo. This intervention was carried out for 4 w. DFU clinical improvement was measured with perfusion, extent, depth, infection, sensation (PEDIS) scores at baseline, weeks 2, 3, and 4. Data were analyzed using a generalized linear model (GLM) and post hoc.

Results: After 4 w of treatment, the PEDIS score of the treatment group in week 1 decreased in week 2 (6.48±1.19), significantly (p = 0.003), decreased in week 3 (5.64±1.18) and significantly (p = 0.0001), decreased in week 4 (4.28±1.06) and was significant (p = 0.0001), while the control group in week 1 decreased in week 2 (5.68±2.30), but not significant (p=0.574), decreased for week 3 (5.52±2.23), but not significant (p=0.161), decreased for week 4 (5.28±2.13) and not significant (p=0.056), and there was an effect of supplementation with a combination of bitter melon extract and snakehead fish powder on the PEDIS score (p=0.004).

Conclusion: Supplementation of a combination of bitter melon extract with snakehead fish powder significantly reduced PEDIS Score on DFU patient and has an effect on clinical improvement.

Keywords: Bitter melons, *Momordica charantia L.*, Channa striata, Ulcer clinical improvement, Diabetic foot ulcer

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INTRODUCTION

Hyperglycemia is a recurring metabolic disorder called diabetes. This illness is a significant public health issue and is currently ranked as the fourth leading cause of mortality in the majority of developed nations [1-6]. High levels of AGEs can damage tissues and result in a number of unfavorable cellular events, such as an increase in free radical activity that can harm cell membranes and increase cross-linking, disruption of protein breakdown, mutations, changes in enzyme function, etc. Vascular problems associated with diabetes are brought on by these biochemical and cellular abnormalities [7-10]. Angiogenesis, which is defined as the development of new blood vessels instead of old ones, is dysregulated and results in several vascular problems. In patients with diabetes mellitus, the microenvironment has an impact on how the angiogenic response turns out. For instance, DFU, which result from considerable delays and cause acute and chronic wound healing difficulties, are one tissue in which hypervascularization occurs. This is in contrast to diabetic retinopathy, which affects the retina and causes hypervascularization [11-13]. Hemostasis, inflammation, proliferation, and remodeling are the four continuous steps that make up the connective tissue repair process, which is the basic reaction in wound healing. The repair process necessitates the synchronization of many cells, growth factors, and cytokines [9, 14, 15].

Delayed collagen synthesis and decreased epithelial formation coupled with decreased angiogenesis have been observed during the proliferative phase of the healing process [16-18]. Other factors implicated in the delayed healing process include decreased production of growth factors, vascular endothelial growth factor (VEGF), delayed inflammatory response, excessive protease activity, and impaired nitric oxide synthesis [19]. The lack of complementary therapies during treatment results in poor wound healing control, which can lead to diabetic foot ulcers that require amputation. Complementary therapies that can activate cell growth factors that are approved for DFU and other diabetes-related wounds are typically not available. Previous studies found that natural products can work as therapeutic agents to assist in the process of treating a variety of illnesses, including diabetic wounds [20-22]. One of them is Snakehead Fish (Channa striata) and Bitter Gourd (*Momordica charantia L.*).

The fruit extract of the bitter melon (*Momordica charantia L.*), a plant that grows in tropical and subtropical areas of Asia and Africa, is prized for its numerous health advantages. This traditional tropical plant has long been touted for its pharmacological effects and nutritional benefits due to the bioactive chemicals it contains. The fruit and leaves are abundant in zinc, beta-carotene, potassium, vitamin A, calcium, magnesium, phosphorus, iron, and vitamin B [23-25]. This plant is utilized in folk medicine around the world to cure many illnesses due to the presence of numerous bioactive chemicals, some of which have strong biological effects. It has been employed in a variety of medical conditions, including bacterial and viral infections, obesity, diabetes, cancer, hypertension, and even AIDS [24-30]. In order to hasten the healing of wounds, bitter melon fruit extract is also used [31-33]. M. charantia fruit powder's ability to simulate wound healing in rats has been evaluated, and powder ointment showed a substantial response in terms of epithelization time, wound-contracting capacity, and wound closure speed [34-36].

Meanwhile, extract of Snakehead Fish (Channa striata) is a protein source that has been used empirically in wound healing [37-40]. Channa striata is a freshwater fish that is common in tropical countries like Indonesia [41, 42]. This fish extract has been used extensively to speed up wound healing because of its part in the body's process of producing new cell tissue [40, 43]. It also has the capacity to regulate molecular and immunological mechanisms. Snakehead fish extract (Channa striata) contains substances that have anti-inflammatory properties (such as arachidonic acid), which promote collagen formation and wound epithelialization. It also contains aspartic acid, which aids in the wound healing process, and amino acids (AAs) required for albumin synthesis (such as lysine, arginine, and glutamic acid). Channa striata also possesses antibacterial and anti-nociceptive properties [39-40, 44, 45].

The hypothesized synergistic mechanism of bitter melon fruit extract (*Momordica charantia L.*) supplemented with snakehead fish powder (Channa striata) lies in the complementary bioactive properties of both components [32]. Bitter melon is known for its potent antioxidant and anti-inflammatory activities, primarily due to compounds such as charantin, vicine, and polypeptide-p, which help reduce oxidative stress—a key contributor to delayed wound healing in diabetic ulcers. Meanwhile, snakehead fish powder is rich in essential amino acids, albumin, and omega-3 fatty acids, which promote collagen synthesis, tissue regeneration, and angiogenesis [33]. The combination of these two extracts is believed to create a synergistic effect, where the antioxidant and anti-inflammatory actions of M. charantia protect tissue from further damage while the C. striata component accelerates the healing process through enhanced structural repair and cellular proliferation [34].

Existing therapies for diabetic ulcers, such as topical antibiotics, debridement, and advanced wound dressings, often fall short in addressing the multifactorial nature of chronic wound healing, particularly in diabetic patients with impaired immunity and poor microcirculation [35]. Moreover, these conventional treatments may lead to prolonged healing time, high recurrence rates, and limited cost-effectiveness. This study addresses these limitations by exploring a natural, integrative approach that targets both oxidative damage and tissue regeneration simultaneously. By combining bitter melon extract and snakehead fish powder, this intervention offers a promising adjunct or alternative therapy with potential to improve clinical outcomes, reduce healing time, and enhance patient quality of life in the management of diabetic ulcers [4].

MATERIALS AND METHODS

Making a combination of bitter melon extract with snakehead fish powder

Bitter gourd extract was macerated with ethanol solvent. After being filtered, it is evaporated to evaporate the solvent. Snakehead fish, after removing the head and feces, is steamed, drained and dried. After drying, blended and sifted. Capsule manufacture combination of bitter melon extract with snakehead fish powder carried out at the Universitas Muhammadiyah Surakarta (UMS) Clinical Pharmacy Laboratory. The bitter melon extract was prepared using a solvent extraction method with 70% ethanol, resulting in an extraction yield of 15%. The extract was standardized to contain 5% charantin. The snakehead fish extract was prepared using a similar method, with an extraction yield of 20% and standardization to contain 10% arachidonic acid.

Clinical trials

A randomized, double-blinded, placebo-controlled experiment was employed in the study at the public health centers in Surakarta City's Purwosari, Pajang, Nusukan, and Banyuanyar. The Health Research Ethics Committee of Dr. Moewardi General Hospital/School of Medicine Eleven March University of Surakarta, Indonesia, gave its approval to this research protocol (Number: 904/VI/HREK/2022).

Patients

The inclusion criteria included DFU patients with a PEDIS score of 1–8, 30-65 y old, hemoglobin levels>10 g/dl, BMI 18.5–22.9, albumin levels>3 g/dl, ankle-brachial index (ABI) values>0.6–1.3, and DM duration of 0–15 y. Patients also had to be willing to participate in the study and give their written consent. Patients with co-morbidities (cardiovascular disease, pulmonary disease, and immunology), steroid therapy and chemotherapy, dropout, allergies with the use of bitter melon fruit extract, chronic hypoxia, sepsis, age 30 y or>65 y, stress, obesity, alcohol consumption, smoking, and patients with minor amputations (below knee or above knee) planned from the beginning were excluded from the study. Fig. 1 shows the flow chart that shows the patients that were enrolled and tracked. The sample size was calculated based on a power calculation to ensure statistical robustness. Assuming a mean difference in PEDIS score reduction of 2 points between the treatment groups, with a standard deviation of 3 points, a sample size of 50 participants per group was required to achieve 80% power at a significance level of 0.05.

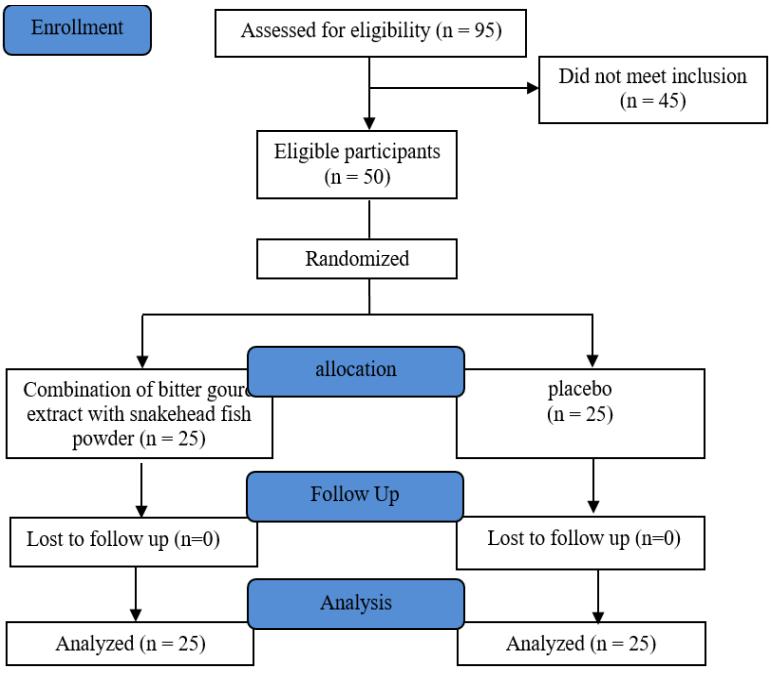

Fig. 1: The flow of participants through the trial

Study procedure

Patients were given both an oral and written explanation before the trial began, and they all provided informed consent. The patient was assessed for study eligibility at the initial appointment. Then, the eligible patients were randomly using block randomization process and divided into the treatment group and the control group. The study employed a computer-generated block randomization method to allocate participants into treatment groups. This method ensures that the treatment groups are balanced in terms of participant characteristics. For four weeks, the treatment group consumes a mixture of bitter melon extract and snakehead fish powder, while the control group receives a placebo. Both participants and outcome assessors were blinded to the treatment allocation. The blinding was maintained by using identical capsules for both treatment groups, and the contents were only known to the study pharmacist. Medication adherence was assessed at the conclusion of the trial by counting the number of medications taken and speaking with each control patient. The dosage regimen was 500 mg/kg/day of the combination extract, administered in capsule form. Each capsule contained 250 mg of the extract and 250 mg of excipients.

Ethics approval and consent to participate

Prospective Participants are invited to participate in this research. All participants received an explanation regarding the purpose of this study, namely to examine the supplementation of a combination of bitter melon extract with snakehead fish powder in patients with DFU. Informed consent was obtained from each participant before the study. Participants are allowed to withdraw from this study at any time. The ethical clearance for this research was obtained from the Commission of Health Research Ethics at RSUD Dr. Moewardi/FK UNS Surakarta (Number: 904/VI/HREK/2022).

Outcome measurements

The PEDIS score was used to quantify the DFU clinical improvement, which was the main efficacy outcome. Both groups had their DFU clinical progress evaluated at weeks 1, 2, 3, and 4.

Statistical analysis

The number of participants (n), mean, and standard deviation are shown as the study results. Data were examined with SPSS; statistical significance was determined if $P<0.05$. If the variables being analyzed are not normally distributed, non-parametric statistical techniques are applied. Generalized linear model (GLM) and Post hoc analysis of the mean difference between the findings of the PEDIS score measurement. Generalized linear models (GLM) were used to analyze the longitudinal data, as it allows for the analysis of non-normal data and accounts for the correlation between repeated measurements. GLM was chosen over repeated-measures ANOVA due to its flexibility and ability to handle non-normal data.

RESULTS AND DISCUSSION

Fifty patients with DFU participated in this study. All DFU patients were randomized to 2 groups and supplemented with a mixture of snakehead fish powder and bitter melon extract in the treatment group (n = 25), while the control group (n = 25) received a placebo. There was no difference between the two groups' baseline characteristics (table 1). Age, sex, education, occupation, body weight, body mass index (BMI), length of diabetes mellitus, plasma glucose levels, HbA1C, duration of diabetic ulcers, PEDIS score, use of antidiabetic medications, and ankle bracial index did not differ between the treatment and control groups at baseline Ankle Brachial Index (ABI).

After 4 w of treatment, the PEDIS score of the treatment group in week 1 (6.80±1.25) decreased in week 2 (6.48±1.19), significantly ($p = 0.003$), decreased in week 3 (5.64±1.18) and significantly ($p = 0.0001$), decreased in week 4 (4.28±1.06) and was significant ($p = 0.0001$), while the control group in week 1 decreased in week 2 (5.68±2.30), but not significant (p=0.574), decreased for week 3 (5.52±2.23), but not significant (p=0.161), decreased for week 4 (5.28±2.13) and not significant (p=0.56), and there was an effect of adjuvant administration of bitter melon fruit extract (*Momordica charantia L.*) on the PEDIS score (p=0.041) (table 2 and fig. 2).

Table 1: The characteristics of the participants

Variable	Treatment group (n = 25)	Control group (n = 25)	P-values
Age (years)	57.76±7.97	57.44±10.26	0.903
Gender			0.580
Man(%)	11 (44%)	13 (%)	
Woman(%)	14 (56%)	12 (%)	
Education			0.762
SD(%)	6 (24%)	6 (24%)	
junior high school(%)	5 (20%)	6 (24%)	
high school(%)	12 (48%)	12 (48%)	
PT(%)	2 (8%)	1 (4%)	
Work	11(44%)	9 (36%)	0.570
Housewife(%)	10(40%)	11 (44%)	
Self-employed(%)	0	0	
civil servant(%)	0	0	
Retired(%)	4 (16%)	5 (20%)	
body weight (kg)	62.56±10.34	66.56±13.54	0.246
Body Mass Index (kg/m2)	21.63±1.26	21.46±1.56	0.671
Suffering from diabetes for a long time (years)	6.08±4.66	7.00±3.64	0.441
Plasma glucose level (mg/dL)	219.16±87.16	238.92±71.23	0.385
HbA1C (%)	10.17±1.97	10.49±1.94	0.561
Length of time with ulcer (weeks)	40.28±38.33	64.16±56.33	0.086
PEDIS score	6.80±1.25	5.72±2.31	0.051
Antidiabetic Drugs (OAD)			1.00
Yes (%)	25 (100%)	25 (100%)	
Not (%)	0 (0%)	0 (0%)	
Ankle Brachial Index (ABI)	0.96±0.12	1.06±0.26	0.088

*There is no difference (comparable) p>0.05

Table 2: Effect of supplementation with a combination of bitter melon extract and snakehead fish powder on clinical improvement of DFU

Variable	Treatment group	Δ	P	Control group	Δ	P	P between groups
PEDIS Week I score	6.80±1.25	2.52±1.06		5.72±2.31	0.44±2.13		0.041[b]
PEDISWeekII score	6.48±1.19		0.003[a]	5.68±2.30		0.574[a]	
PEDIS Week III score	5.64±1.18		0.0001[a]	5.52±2.23		0.161[a]	
PEDIS score Week IV	4.28±1.06		0.0001[a]	5.28±2.13		0.056[a]	

[a]Generalized linear model (GLM); [b]Post hoc

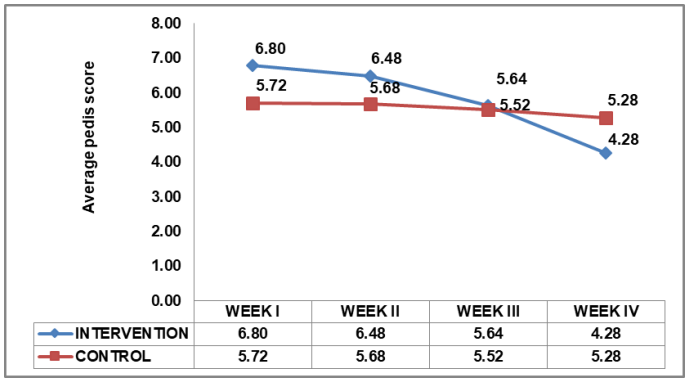

Fig. 2: DFU clinical improvement data at weeks 1, 2, 3 and 4

DISCUSSION

As evidenced by a decline in weeks 1, 2, 3, and 4, the findings revealed a significant difference in the PEDIS scores between the treatment and control groups (fig. 2). These findings are consistent with earlier research that showed administering bitter gourd extract enhanced and sped up the healing of wounds [4, 31-33, 46]. Diabetic ulcer patients who receive treatment with bitter melon fruit extract can speed up the healing of diabetic wounds by accelerating wound contraction, decreasing closing time [32, 47-51], epithelialization, and tissue [32, 52]. In diabetic patients, the use of this plant's fruit extract in topical ointments and powder form greatly accelerates tissue regeneration and epithelialization during wound healing [44, 48], with the mechanism of antioxidant and anti-inflammatory [53, 54]. A component of collagen, hydroxyproline, is made more frequently in injured skin as a result of vitamin C, so the higher the level of hydroxyproline, the more frequently collagen is produced. Collagen fibers are tough proteins that reinforce wounds and hasten the healing process [55, 56]. According to Pullar *et al.* (2018), and DePhillipo *et al.* (2018), vitamin C supplementation enhanced fibroblast activity and number, which may have caused an increase in the quantity of collagen [57, 58]. Vitamin A also promotes the growth of fibroblast cells, slows down cell division and proliferation, and boosts the production of collagen [48, 59].

Research conducted by Apriasari *et al.* (2022) stated that the use of Channa extracts at a concentration of 20% in rats with diabetic wounds can reduce NF-κB expression, and the anti-inflammatory effect of Channa micropeltes can increase VEGF expression and the number of neovascular cells in the process of angiogenesis in diabetic wound healing [42]. It was discovered that snakehead fish tissue and mucus extracts had significant levels of amino acids, particularly glycine and arachidonic acid. Both are said to speed up wound healing by re-epithelializing injured tissue and starting the manufacture of collagen [44]. According to a study by Yuliana (2022), albumin plays a critical role in wound healing because it can activate the expression of the epidermal growth factor receptor (EGFR) and increase the NF-B signal. The high concentration of essential amino acids and albumin in snakehead fish plays a significant role in wound healing. Tyrosine kinase activity, which activates gene transcription, DNA synthesis, and cell proliferation, can be stimulated by activating EGFR [38]. The combination of bitter melon and snakehead fish extracts demonstrates promising wound healing properties, potentially attributed to their anti-inflammatory and angiogenic effects. Charantin, a bioactive compound in bitter melon, has been shown to exhibit anti-inflammatory properties by inhibiting pro-inflammatory cytokines [42]. Similarly, arachidonic acid in snakehead fish may contribute to wound healing by promoting angiogenesis and tissue repair [25]. Our findings are consistent with previous studies on individual extracts. Singh *et al.* (2018) reported that bitter melon extract accelerated wound healing in diabetic rats by reducing inflammation and oxidative stress [42]. Kwan *et al.* (2020) found that snakehead fish extract enhanced wound healing by promoting angiogenesis and collagen synthesis [25]. Additionally, snakehead fish extract is suggested for postoperative wound healing and post-pregnancy rehabilitation, and it is also known to create polyunsaturated fatty acids, which control prostaglandin production and wound healing [60]. Limitation of this study are the short follow-up period (4 w) may not be sufficient to assess complete wound healing, as the healing process can take longer in diabetic patients. Additionally, the lack of biomarker data (e. g., VEGF, collagen levels) limits our understanding of the underlying mechanisms.

CONCLUSION

Supplementation of a combination of bitter melon extract with snakehead fish powder significantly reduced PEDIS Score on DFU patient and has an effect on clinical improvement. However further studies are needed to determine the optimal dosage of the combination extract, and then patients with DFU without severe comorbidities may benefit from this treatment and regular monitoring of wound healing progress and biomarkers (e. g., VEGF, collagen levels) may help optimize treatment outcomes.

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AUTHORS CONTRIBUTIONS

Concept and design (Fahrun Nur Rosyid, Muhtadi, Andi Suhendi), data collection and ethical clearance (Fahrun Nur Rosyid, Sh Sugiharto, Ahmad Fadhlur Rahman), analysis and interpretation of data (Fahrun Nur Rosyid, Muhtadi, Andi Suhendi, Sh Sugiharto), manuscript draft and translation (Fahrun Nur Rosyid, Sh Sugiharto, Dwi Linna Suswardany, Dwi Rosella Komala Sari).

CONFLICT OF INTERESTS

Declared none

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