EFFECT OF SEA CUCUMBER ON REDUCING PERIWOUND MACERATION AND INFLAMMATION-RELATED INDICATORS IN PATIENTS WITH DIABETIC FOOT ULCERS INDONESIA

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Abstract

Introduction: *Maceration is one of the problems affecting the healing process of diabetic foot ulcers (DFUs). In complementary therapies, sea cucumber is known to have higher absorbency. However, there are few studies on the reducing of periwound maceration and inflammation-related indicators in DFU.*

Methods: *This was an observational study at a wound care clinic in Indonesia. Thirty-one DFU patients received treatment with sea cucumber were enrolled in the study. As control samples, 35 DFU patients treated with honey were also included. All were new occurrence DFU and had maceration at the baseline. The maceration area and inflammation-relate indicators including TNF-□, MMP-2, and MMP were measured on baseline and week 4.*

Results: *There were no significant differences between two groups at the baseline. In the multiple linear regression model, sea cucumber significantly associated with the proportion of maceration reduction than honey at week 4 (β =0.520, p=0.001). There were no significant differences between two groups in levels on TNF-α, MMP-2, and MMP at week 4.*

Conclusions: *Our results demonstrated that sea cucumber might be appropriate for reducing DFU periwound maceration.*

Keywords: *complementary therapy, diabetic foot ulcer, honey, maceration, sea cucumber*

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INTRODUCTION

Diabetes mellitus (DM) represents one of the public health issues in Indonesia with an increasing number of patients estimated at 10.7 million people for 2019 (Saeedi et al., 2019). This number of patients rivals the top ten countries for number of people with DM (Saeedi et al., 2019). Moreover, diabetic foot ulcers (DFUs) are chronic wounds and among the most common complications of diabetes mellitus (DM), often resulting in lower-extremity amputation and impaired quality of life (Bakker et al., 2016; Prompers et al., 2008). Prevalence of DFU in a regional hospital in Eastern Indonesia was 12.0% (Yusuf et al., 2016). Therefore, proper treatment of DFU patients is also an important healthcare issue in Indonesia.

The DFU-healing process is influenced by several factors, both local and systemic. One of the local factors is maceration. Our previous study found that non-macerated DFUs healed significantly faster than DFUs with maceration (Haryanto et al., 2017a). Maceration is defined as the softening and breaking down of skin as a result of prolonged exposure to moisture (Gray & Weir, 2007; Voegeli, 2012). Maceration occurs due to excessive exudation and might be caused by increasing proteolytic activity, especially that of matrix metalloproteinase (MMP) activity resulted in persistent inflammation in chronic wounds. Maceration has been implicated in damage to the wound bed, degradation of the extracellular matrix and considered as the origin of periwound skin problems (White & Cutting, 2003). Therefore, reducing DFU maceration is critical to promoting wound healing and toward faster wound closure.

In complementary therapies, sea cucumber is known to have higher absorbency (Dong et al., 2019). This higher absorbency may be expected to reduce lateral tracking of fluid and the risk of periwound maceration. Moreover, sea cucumber is a marine animal that contains various bioactive compounds including triterpene glycosides (saponin), sulfated polysaccharides, phenolics, and fatty acids (FAs) (Bordbar, Anwar, & Saari, 2011; Pangestuti & Arifin, 2018).

These have anti-inflammatory and antimicrobial activities. In Indonesia wound care clinic, sea cucumber has been used for local wound care. However, so far, no study has been performed evaluating the effect of sea cucumber on maceration in DFU patients. Therefore, this study aimed to explore the specific efficacy of sea cucumber on DFU with maceration to provide new local treatment of DFU with excessive exudate.

METHODS

Study design

An observational and prospective study was performed at the Kitamura Clinic, a private wound care clinic in rural Indonesia, between September 2017 and August 2018.

Population, Samples, and Sampling

The study populations were patients with DFU treated with sea cucumber, those who met the following criteria; i) patients who were ≥ 21 years old, ii) ankle brachial index (ABI) of 0.7–1.2, iii) patients presenting with a new wound, iv) wound exhibiting maceration as determined using the subscale (maceration) of diabetic foot ulcer assessment scale (DFUAS) (Arisandi et al., 2016) with a score ≥ 1 (maceration at the wound edge), and v) willingness and ability to give informed consent to participate in this study. Patients with systemic signs of infection and/or gangrenous ulcer were excluded from the study. DFUAS is a validated wound assessment tool specifically developed for DFU to evaluate wound severity and monitor the wound healing process, using 11 domains (depth, size, size score, inflammation/infection, proportion of granulation tissue, type of necrotic tissue, proportion of necrotic tissue, proportion of slough, maceration, type of wound edge, and tunneling). The minimum and maximum scores on this scale are 0 and 98, respectively; scores increase with wound severity (Arisandi et al., 2016).

As control dressing samples, DFU patients treated with honey were also enrolled in this study during the same study period. The inclusion and exclusion criteria were the same as the DFU patients treated with sea cucumber. In this clinic, honey was used as routine local wound dressing agent in the management of DFU because honey has antibacterial and anti-inflammatory properties (Astrada et al., 2019; Haryanto et al., 2012; Vandamme et al., 2013).

Materials

The sea cucumber (Sthicopus hermanii) extract gel base used here was similar to that used in a previous study (Haryanto et al., 2017). More specifically, sea cucumber was dried at room temperature for two weeks and pulverized and mixed with ethanol 96% for 48 hours. After 48 hours, the mixture was filtered and the extract concentrated using a rotary evaporator set a 40oC and eventually stored at 4–8oC. The gel was prepared by dissolving Carbopol 940 in distilled water 100 mL, and triethanolamine was added. Next, methyl paraben was added to the mixture until a clear consistent gel base was obtained. Hence, the gel formulation was prepared using sea cucumber extract in ethanol (2.5%), the Carbopol 940 gel base (1.75%), methyl paraben (0.18%) and triethanolamine (1.75%) (Harynato et al., 2017). Similar to our previous studies, commercially available honey (by Apis dorsata) was used (Harynato et al., 2017b). The honey was sterilized and stored in a sterile container until being used for treatments.

Procedure

Local wound care procedure

Dressings were removed and exudate or scabs were removed from the wound bed and periwound by cleansing with normal saline. If necrotic tissue was present, the wound care specialist nurse conducted surgical debridement. And wound bed and periwound were wiped by gauzes. Then the gauzes soaked in sea cucumber gel or honey were applied to the wound bed. Other dry gauzes were piled up to prevent runoff and absorb exudate that leaked from the wound bed. The gauzes were secured to the skin with medical tape. All wound care procedures were performed based on the clinic routines by one of the wound care specialist nurses in this clinic. The frequency of dressing change was determined by the amount of exudate.

Collecting variables

Demographic data included age, gender, body mass index (BMI), duration of DM, DM treatment, fasting blood sugar (FBS), HbA1c, ankle brachial index (ABI), smoking status, and neuropathy (assessed by the 5.07 Semmes Weinstein monofilament test). Wound characteristics included data pertaining to wound onset, trigger of the wound, wound location, Wagner classification (Oyibo et al., 2001), and DFUAS (Arisandi et al., 2016).

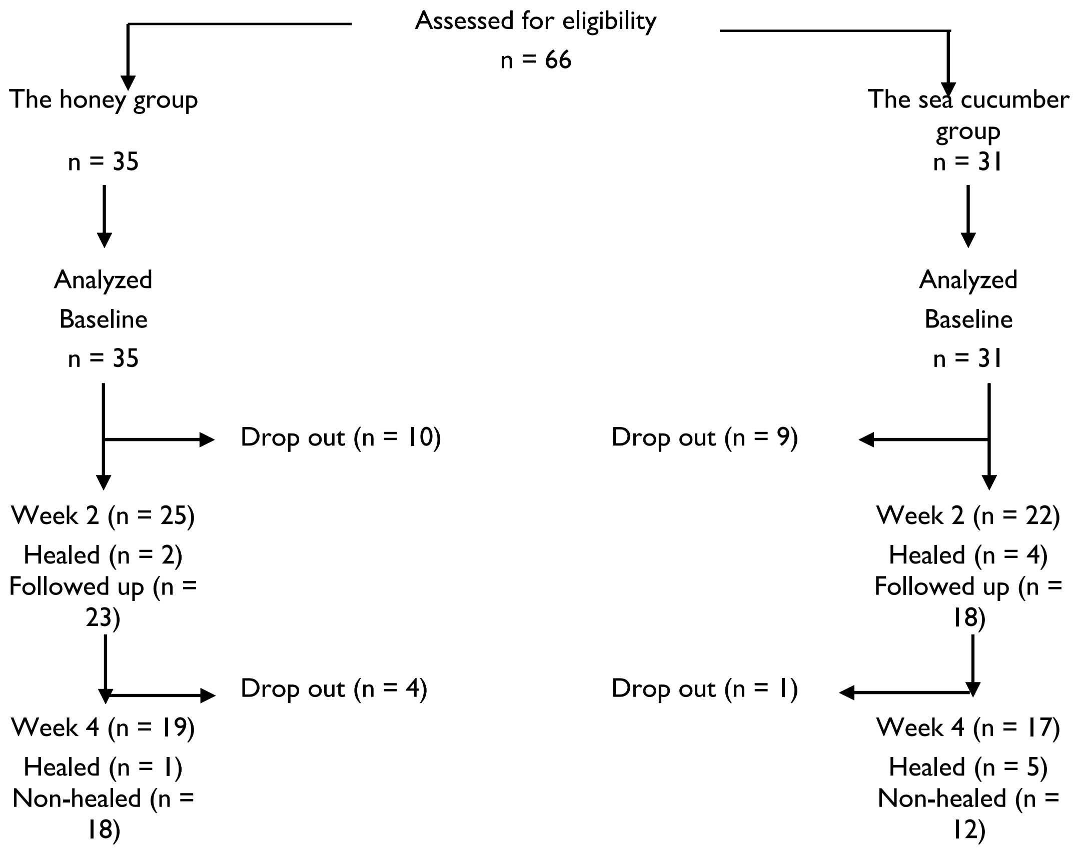


Figure 1. Patients flow diagram

Outcomes measures

The primary outcome was the macerated area, which was defined as pale skin color and a wrinkling, swollen appearance of the exposed skin surface (Bryant, 2012). Photographs of each patient's wound including DFU surrounding skin were taken at the baseline, weeks 2 and 4 by one of the wound care specialist nurses at this clinic. The photo shows the patient's ID and the information of the local wound care. After all the data collecting at the clinic was over, the researcher who didn't work at the clinic measured the maceration area by using ImageJ software (Wayne Rasband, National Institute of Health, Bethesda, MD) in the laboratory.

The secondary outcomes were inflammation-related indicators, such as expression levels of TNF-α, MMP-2, and MMP-9 (Patel et al., 2016). Wound blotting method was employed. Wound blotting is a non-invasive assessment tool for biochemical analysis of exudate and is performed by attaching a nitrocellulose membrane onto the wound surface

In particular, the DFU and surrounding skin were cleaned with normal saline and wiped with gauze, and fresh exudate was collected by attaching nitrocellulose membranes (Supported Nitrocellulose Membrane, Bio-Rad, Hercules, CA) covering the entire wound surface for 10 sec. The collected membranes were stored at 4°C until use.

TNF-α was detected indirectly using a goat polyclonal antibody for TNF-α (dilution 1:250; sc-1350, Santa Cruz Biotechnology, Dallas, TX) as the primary antibody and Alexa Fluor 488-conjugated donkey anti-goat IgG antibody (dilution 1:1500, ab150133, Abcam plc, Cambridge,

Table 1. Demographic and baseline wound characteristics of the enrolled subjects

	Honey (n = 35)	Sea cucumber (n = 31)	p
Age, years (mean [SD])	55.1 ± 10.3	56.9 ± 8.8	0.460
Gender (*n* [%] female)	12 (57.1)	12 (57.1)	0.548
BMI, kg/m^2 (mean [SD])	23.1 ± 4.3	23.6 ± 2.5	0.536
Duration of DM (years)	5.7 ± 5.5	9.1 ± 6.2	0.021
Treatment of DM (*n* [%])			0.603
Oral	18 (85.7)	19 (90.5)	
Insulin	3 (14.3)	2 (9.5)	
Fasting blood sugar, mg/dl (mean [SD])	250.1 ± 103.9	245.1 ± 99.2	0.841
HbA1c, % (mean [SD])	10.4 ± 2.0	10.8 ± 2.3	0.250
Ankle-brachial index (mean [SD])	0.9 ± 0.1	0.9 ± 0.1	0.276
Smoking (*n* [%])			0.426
None	19 (90.5)	20 (95.2)	
Smoker	2 (9.5)	1 (4.8)	
Neuropathy[a] (*n* [%] yes)	15 (42.9)	12 (38.7)	0.805
Wound onset, days (mean [SD])	28.1 ± 28.9	19.7 ± 19.5	0.175
Trigger (*n* [%])			0.415
Footwear	2 (5.7)	3 (9.7)	
Trauma	14 (40.0)	8 (25.8)	
Needle	3 (8.6)	1 (3.2)	
Unknown	16 (45.7)	19 (61.3)	
Location (*n* [%])			0.830
Toe	11 (31.4)	13 (41.9)	
Dorsal	5 (14.3)	4 (12.9)	
Plantar	9 (25.7)	6 (19.4)	
Lateral	3 (8.6)	4 (12.9)	
Heel	7 (20.0)	4 (12.9)	
Wagner (*n* [%])			0.073
1	5 (14.3)	12 (38.7)	
2	21 (60.0)	10 (32.3)	
3	8 (22.9)	8 (25.8)	
4	1 (2.9)	1 (3.2)	
DFUAS (mean [SD])			
Total score	27.7 ± 6.7	26.8 ± 7.9	0.651
Depth	3.0 ± 0.9	2.5 ± 1.2	0.074
Size	3.4 ± 1.9	2.7 ± 1.3	0.111
Size score	3.3 ± 2.2	2.5 ± 1.5	0.114
Inflammation/ Infection	1.5 ± 0.6	1.4 ± 0.6	0.497
Proportion of granulation tissue	3.4 ± 1.4	3.7 ± 1.5	0.406
Necrotic tissue			
Type of necrotic tissue	1.3 ± 0.6	1.4 ± 0.5	0.762
Proportion of necrotic tissue	3.3 ± 1.5	3.6 ± 1.5	0.422
Proportion of slough	3.3 ± 1.5	3.6 ± 1.5	0.422
Maceration	1.7 ± 0.7	1.7 ± 0.7	0.979
Type of wound edge	3.4 ± 0.1	3.6 ± 1.1	0.426
Tunneling	0.0±0.0	0.0 ± 0.0	1.000
Maceration area, cm^2 (mean [SD])	10.3 ± 8.3	8.3 ± 8.6	0.333

[a]Determined only by 5.07 Semmes Weinstein monofilament test.
BMI, body mass index; DM, diabetes mellitus; SD, standard deviation; DFUAS, diabetic foot ulcer assessment scale.

Table 2. Factors related to proportion of maceration removal at week 4

	B	β	p value
Group	173.759	0.52	0.001
Maceration area at baseline	6.259	0.30	0.051
$R2$	0.302		
Adjusted $R2$	0.26		
Group: 0=honey,1=sea cucumber			

β: standardized partial regression coefficients; R2: coefficients of determination

was detected indirectly using rabbit polyclonal antibody for MMP-2 (dilution 1:250, sc-10736, Santa Cruz Biotechnology, Dallas, TX) as primary the antibody and Alexa Fluor 555-conjucated donkey anti-mouse IgG antibody (dilution 1:500, ab150062, Abcam plc) as the secondary antibody. MMP-9 was detected indirectly using mouse monoclonal antibody for MMP-9 (dilution 1:250, sc-21733, Santa Cruz Biotechnology, Dallas, TX, USA) as the primary antibody and Alexa Fluor 647-conjugated donkey anti-mouse IgG antibody (dilution 1:750, ab150111, Abcam plc) as the secondary antibody.

The wound blotting membranes were hydrated with PBS and blocked with Blocking One solution (Nacalai Tesque Inc., Kyoto, Japan) for 20 min. The membranes were then incubated with the mixture of primary antibodies (TNF-α, MMP-2 and MMP-9) at room temperature for 1 h. After washing, the membranes were incubated with the mixture of secondary antibodies at room temperature for 1 h. Next, the stained membranes were scanned using a Typhoon 9400TM scanner (GE Healthcare, Piscataway, NJ) and the following setup: for TNF-α, 526 SP filter, laser blue 488, normal sensitivity, PMT: 550 V; for MMP-2, 580 BP 30 filter, laser green 532, normal sensitivity, PMT: 600 V; and for MMP-9, 670 BP 30 filter, laser red 633, normal sensitivity, PMT: 600 V.

Analyzing software (ImageJ, National Institute of Health, Bethesda, MD) was used to process membrane images and analyze the intensity of each protein (TNF-α, MMP-2, and MMP-9). The wound edge was identified based on all protein staining images, using two criteria: 1) when the wound edge could be determined clearly, protein signals were quantified within the wound edge (i.e., wound area); and (2) when the wound edge was unclear, the protein signals were quantified for the entire membrane region. The integrated signal intensity was normalized by dividing it by the wound area. The membranes for protein analysis were obtained at baseline and week 4.

Data Analysis

Descriptive data were expressed as mean (standard deviation) or n (%) for categorical variables. Baseline characteristics were compared using the t-test for continuous and the chi-square or Fisher's exact tests for categorical variables. To compare the change of maceration area of sea cucumber and those of honey over four weeks, a linear mixed-effects model was conducted.

Correlation analysis was performed to investigate the confounding factors of the proportion of maceration reduction at week 4 and the baseline patients' and DFUs' characteristics. Finally, we ran a multiple linear regression model to examine the association between local wound care and rate maceration area at week 4.

The secondary outcome analysis comparing the impact of honey and sea cucumber on the maceration area was determined by a linear mixed-effects model. Levels of TNF-α, MMP-2, and MMP-9 expression were compared by a two-way ANOVA test. All analyses were conducted using SPSS ver.25 (IBM Corp., Armonk, NY, USA).

Ethical Clearance

The study protocol was approved by the ethical committee of the Graduate School of Medicine, Kanazawa University (ref. no. 643-1) and Kitamura Wound Care Clinic (Number: 001/KTMR/1/16). All patients gave informed consent in written.

RESULTS

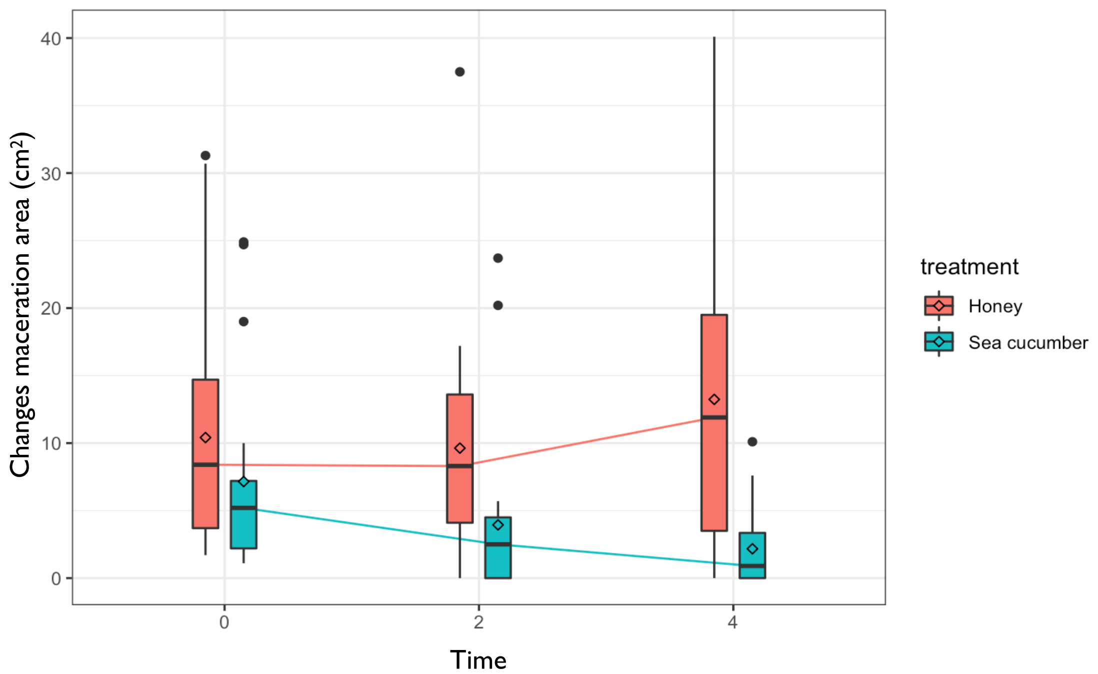
Baseline Characteristics of The Patients And DFUs

Thirty-one patients treated with sea cucumber, and 35 patients treated with honey were enrolled in this study. Twenty-four patients (10 patients in the sea cucumber groups, 14 patients in the honey group, respectively) dropped out the study. After four weeks, nine wounds (9/31; 29.0%) healed in the sea cucumber group, and three wounds (3/35; 8.6%) healed in the honey group (Fig.1).

There were no significant differences between two groups in respect to age, gender, BMI, treatment of DM, FBS, HbA1c, ABI, smoking status, and neuropathy at the baseline. On the contrary, the duration of DM in the sea cucumber group was significantly longer than that of the honey group ($p = 0.021$) (Table 1). There were no significant differences between two groups in respect to wound onset, trigger, location, Wagner, DFUAS total score and maceration area at the baseline (Table 1).

Outcomes

The effect of sea cucumber vs. honey to the changes of maceration area was significantly different ($p = <0.001$). Moreover, sea cucumber significantly



Group (n)			
Honey	35	25	19
Sea cucumber	31	22	15

Figure 2. Changes in maceration area by two groups

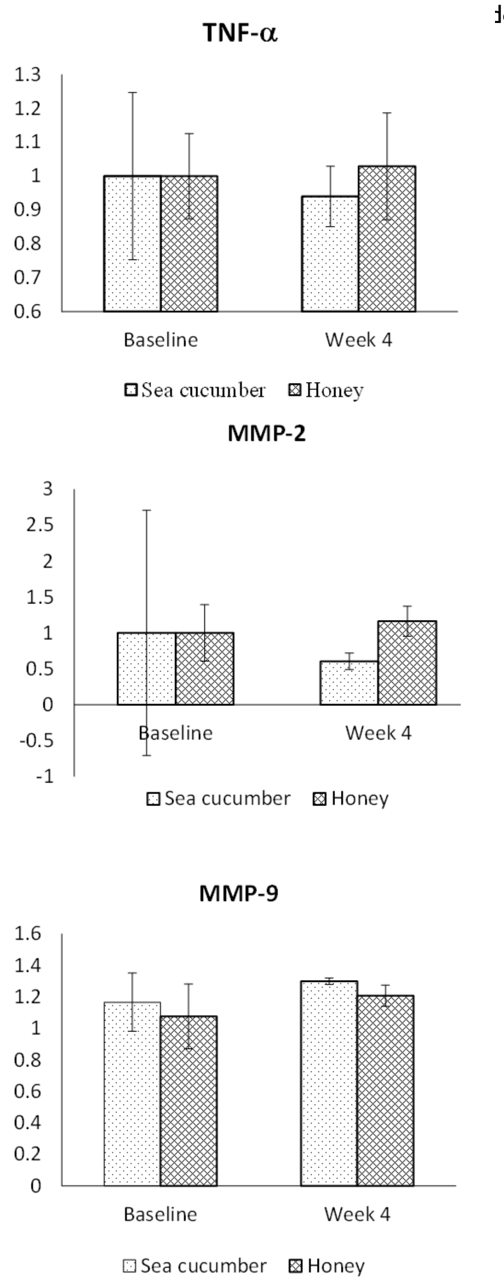


Figure 3. Two-way ANOVA for TNF-α, MMP-2 and MMP-9 with follow-up and the local treatment.

drove changes in the maceration, with decreasing area of maceration (p = 0.001), meanwhile, honey had no significant effect to changes in the maceration area (p = 0.166) (Fig.2).

There was no significant correlation between the mean proportion of the maceration reduction at week 4 and the duration of DM (r=0.287, p=0.090). In the multiple regression analysis, sea cucumber showed a significant association with the proportion of maceration reduction than honey at week 4 (β= 0.520, p=0.001) (Table 2).

There were no significant differences between the two groups in levels of TNF-α, MMP-2 and MMP-9 at baseline and week 4 (Fig.3).

DISCUSSION

Effectiveness exudate management, i.e., achieving a moist wound bed but not macerated periwound skin, is essential for promoting DFU healing (Haryanto, 2016). In the present study, we found that sea cucumber was more effective in reducing skin maceration in periwound skin of DFU than honey over four weeks. According to previous studies, effectiveness of wound healing of sea cucumber was reported in rats' burn wounds (Zohdi et al., 2011), DFU mice wounds intragastrically administered (Li et al., 2018), and human skin graft donor sites wound (Poh Yuen Wen et al., 2018). To these evidences, our study could add the new evidence for the clinical use in DFU wound care.

There was a significant difference between two groups in the DM duration; however, this had low association with the proportion of reducing maceration area at week 4. Moreover, multiple regression analysis revealed the effectiveness of sea cucumber on maceration reduction. These results suggested that sea cucumber could be truly influencing the maceration reduction.

The effectiveness of sea cucumber on reducing maceration might be inferred from the structure and functional materials with biological activities. Sea cucumber contains protein, including collagen fibers, 47% (Pangestuti & Arifin, 2018). The collagen fibers in sea cucumber have water absorption capacity (Dong et al., 2019). Exudate is absorbed into the sea cucumber and resides in these gaps and pores between collagen fibers. Moreover, the sea cucumber contains significant amount of glycosaminoglycan, which can have high absorbency (Dong et al., 2019). Regarding to biological activities,many ingredients in sea cucumber have biological activities such as anti-inflammatory, immunomodulatory, angiogenesis-increasing (Bordbar, Anwar & Saari, 2011; Pangestuti & Arifin, 2018).

Unexpectedly, TNF-α, MMP-2, and MMP-9 expression didn't significantly decrease at week 4. Thus, we assumed the structure of collagen fibers might have more association with maceration reduction than the biological activities over four weeks. Periwound skin maceration was reduced as the results of promoting effect of sea cucumber on wound healing. Further study is needed related to the wound healing.

In the honey group, the maceration area tended to increase over four weeks. Honey contains sugar (75-79%) and water (20%) (Vandamme et al., 2013). This sugar content of honey draws exudate from the wound by osmosis (Vandamme et al., 2013). However, according to our result as shown in Fig.3, sugar in honey could not control the amount of exudate wound, resulting in periwound skin maceration area expanded.

This study has some limitations. The proportion of dropout from this study was high (32.2% in sea cucumber group, 30.0% in honey group), and observation period was four weeks. These facts might have association with the outcomes. There might be detection bias in evaluating the outcomes by using DFU photos.

CONCLUSIONS

The result of this study demonstrated that sea cucumber (Sthicopus hermanii) might effectively reduce maceration in DFU periwound skin. Further study is needed to investigate the wound healing.

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CONFLICT OF INTEREST

All the authors have no conflict.

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