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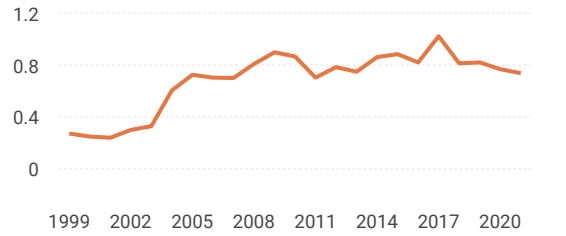

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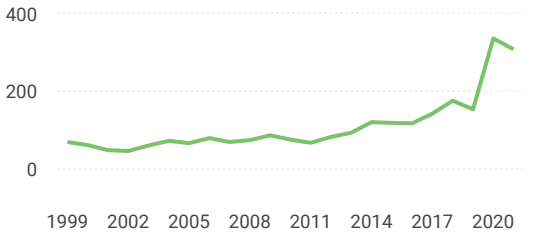

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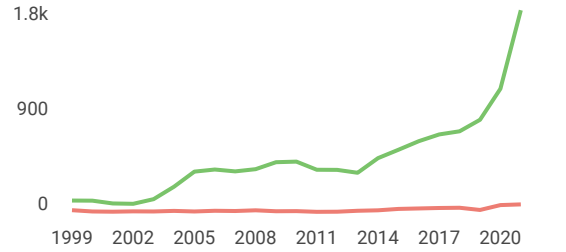

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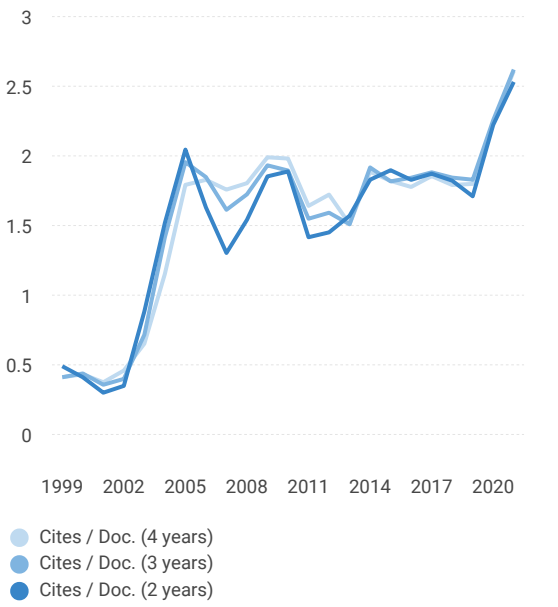

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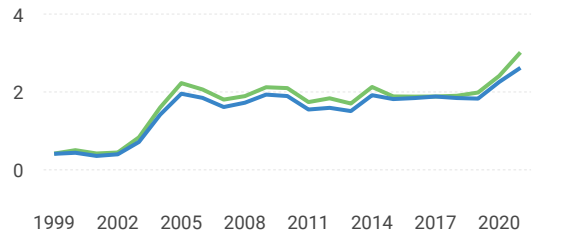

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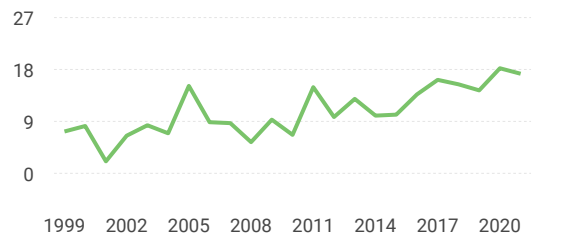

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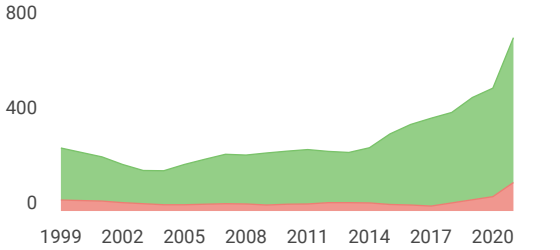

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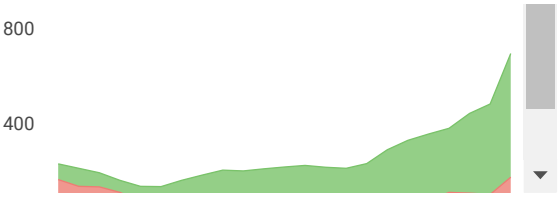

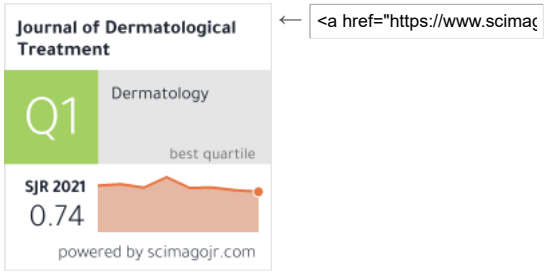

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Efficacy of topical epigallocatechin gallate (EGCG) 1% on the healing of chronic plantar ulcers in leprosy

C. R. S. Prakoeswa, R. N. Oktaviyanti, D. M. Indramaya, E. Hendradri, S. Sawitri, L. Astari, D. Damayanti & M. Y. Listiawan

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To link to this article: https://doi.org/10.1080/09546634.2020.1729333

Accepted author version posted online: 18 Feb 2020.
Published online: 27 Feb 2020.

JOURNAL OF DERMATOLOGICAL TREATMENT
https://doi.org/10.1080/09546634.2020.1729333

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ARTICLE

Efficacy of topical epigallocatechin gallate (EGCG) 1% on the healing of chronic plantar ulcers in leprosy

C. R. S. Prakoeswa[a], R. N. Oktaviyanti[a], D. M. Indramaya[a], E. Hendradri[b], S. Sawitri[a], L. Astari[a], D. Damayanti[a] and M. Y. Listiawan[a]

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ABSTRACT

Background: Chronic plantar ulcers in leprosy (CPUL) occur in areas that have a sensory and an autonomic nerve impairment where the wound healing takes longer. Framycetin gauze dressing (FGD) is best used in the wound healing process during the inflammatory phase because it contains antibiotics. Epigallocatechin gallate (EGCG) is the highest component in the extract of green tea that can accelerate blood vessel formation, has an anti-inflammatory effect, and reepithelialization.
Objective: To investigate the effect of topical EGCG 1% on the healing of CPUL.
Materials and methods: An analytical experimental approach comparing the topical EGCG 1% and FGD applied every 3 days up to 8 weeks on the healing of CPUL. Size of the ulcers, side effects and possible complications from both approaches were monitored weekly.
Results: Ulcer healing in the EGCG group was significantly better than the FGD group with significant clinical and statistical differences ($p < .032$). There were no side effects in both the study groups. Complications, such as an increase in the size of the ulcer, were noted in one subject in the control group. This may have been caused by FGD and claw foot condition.
Conclusions: EGCG 1% is more effective than FGD in accelerating the healing process of CPUL.

ARTICLE HISTORY
Received 26 December 2019
Accepted 8 February 2020

KEYWORDS
Epigallocatechin gallate (EGCG); chronic plantar ulcers in leprosy (CPUL); framycetin gauze dressing (FGD)

Introduction

Chronic plantar ulcers in leprosy (CPUL) occur in areas that have a sensory and an autonomic nerve impairment where the wound healing takes longer because of the lack of growth factors and blood supply due to autonomic nerve impairment and is often accompanied by superinfection (1–3). Standard wound care in daily practice such as debridement, wound care dressing and infection control with oral or topical antibiotics usually give unsatisfactory results because they do not modulate the formation of new blood vessels and the formation of collagen needed in the process of wound healing, that is necessary for wound healing.

Difficult healing in leprosy ulcers has an impact on the social and economic lives of patients and their families (3,4). Epigallocatechin gallate (EGCG) is the most extract in green tea, and is the main source of bioactive green tea, has antioxidants that are far more powerful than vitamin C (5). EGCG is the largest component that covers 65% of the total catechins and is therapeutically active. EGCG is a complex molecule with flavanol as its core, accompanied by gallocatechol and gallate esters. *gallate* (6). EGCG has several health effects. Some of these effects include anti-inflammatory, anti-infective, antioxidant, anti collagenase, angiogenesis, and antifibrosis. This suggests that EGCG can be used for the treatment of dermal wounds by facilitating angiogenesis and reepithelialization (7).

Several studies have shown the function of green tea in accelerating the wound healing process by accelerating the inflammatory phase, helping the proliferation phase and making collagen deposition take place faster. This acceleration is thought to be an effect of EGCG in accelerating the formation of new blood vessels and their anti-inflammatory effects. In addition, the antimicrobial effect of EGCG can accelerate healing by preventing infection. Several experiments on the effect of green tea on the wound healing process have been carried out by Karimi and friends in mice by giving burns with a hot iron after the rats were anesthetized. After that, for 21 days the mice were given a vaseline cream treatment containing green tea extracts, while in another group of mice were given vaseline cream and normal saline. After that, every day, measurements of the size of the wound with a caliper, and several rats examined histopathological skin samples. Histopathological examination performed to get a picture of inflammatory cells, epithelial regeneration and angiogenesis. After checking every day, it was found that mice given vaseline with green tea extracts had a decreased surface area of the skin that had burns faster than other groups of mice. From the results of histopathological examination, it was found that mice given vaseline with green tea extract experienced an increase in the process of epithelialization, angiogenesis and reduction of inflammatory cells which gave the most significant results. EGCG research on wound healing has also been done on human subjects, namely research conducted by Shahrahmani and friends who used EGCG in wounds after episiotomy, and in that study obtained significant results on wound healing in research subjects (8).

In this study, the efficacy of EGCG 1% ointment on the wound healing of CPUL was compared with the standard treatment with FGD. The FGD is a sterile wound care product

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containing a broad-spectrum antibiotic from the aminoglycosides class namely Framycetin sulfate B.P. 1%.

Materials and methods

Study design and participants

An 8-week prospective-controlled clinical trial was conducted at the Dermatology and Venereology out-patient clinic of Dr. Soetomo Teaching Hospital Surabaya between July 2019 and September 2019. This clinical study was approved by the Ethical Committee Board of Dr. Soetomo Teaching Hospital Surabaya and registered at www.ina-registry.org. All patients signed informed consent prior to participation.

Forty-four patients with a plantar ulcer due to leprosy, persisting for more than 6 months, were released from leprosy treatment fulfilling the inclusion and the exclusion criteria. Patients were divided into two groups: EGCG (intervention) group and FGD (control) group with matching pair selection based on the type of occupation and the size of ulcer described below:

- The type of occupation:
  - Requires long-standing or walking
  - Does not require long-standing or walking
- The size of ulcer:
  - $<1\,cm^2$
  - $1–4\,cm^2$
  - $4–9\,cm^2$

The ointments were prepared at the Farmasetika Airlangga University. The green tea ointment was prepared using the hydro-alcoholic extract of green tea. The yielded extract was dissolved in some distilled water and mixed with hydrocarbon bases for ointment and Eucerin to give a 1% green tea ointment.

Treatment procedures

All ulcers were surgically debrided and cleaned with sterile normal saline. The width and depth of the ulcer at baseline were then measured and photographed. The width of the ulcer was measured using OPSITE-FLEXIGRID film, while the depth of the ulcer was measured using a sterile cotton stick and a ruler.

The EGCG 1% topical and the FGD were applied to the ulcer by a researcher every third day. In the patients in the EGCG group, the ulcer was covered with a transparent film dressing and then covered with adhesive plaster dressing after the EGCG 1% topical had been put on the ulcer. In the patients in the FGD group, the ulcer was covered with sterile gauze and then covered with adhesive plaster dressing after FGD had been put on the ulcer.

All the ulcers were evaluated every week for a maximum of 8 weeks. The weekly evaluation included measurement of the size and the depth of the ulcer and an assessment of any side effects or complications arising either directly or indirectly from the treatment. A photograph was also taken.

A side effect that may have occurred was allergic contact dermatitis. This could have been caused by a hypersensitivity reaction to substances in the EGCG 1% topical or the FGD. A complication that could have occurred was the worsening of the condition of the ulcer that could have been caused directly or indirectly by the application of the EGCG 1% topical or the FGD.

The treatment would have been discontinued if the patient experienced side effects or complications. The patient would then receive the standard treatment for these events. No supportive treatment other than the study drug was given and .the participants were asked to reduce prolonged standing or walking.

Table 1. Demographics of the patients and baseline characteristics.

Variable	FGD ($n=22$)	EGCG ($n=22$)
Sex		
Male, *n* (%)	13 (59.1)	10 (45.5)
Female, *n* (%)	9 (40.9)	12 (54.5)
Age (years)		
21–50 years, *n* (%)	12 (54.5)	13 (59.1)
>50 years, *n* (%)	10 (45.5)	9 (40.9)
Occupation		
Requires long standing/walking, *n* (%)	11 (50.0)	9 (40.9)
Does not require long standing/walking, *n* (%)	11 (50.0)	13 (59.1)
Duration of ulcer (years)		
<1 year, *n* (%)	6 (27.3)	7 (31.8)
1–5 years, *n* (%)	15 (63.6)	15 (68.2)
>5 years, *n* (%)	1 (9.1)	0 (0)

Table 2. Clinical improvement of the ulcers at the end of the study.

Improvement of the ulcers at the end of the study	EGCG ($n=22$)	FGD ($n=22$)
Healed, *n* (%)	14 (63.6)	8 (36.6)
Improved, *n* (%)	7 (31.8)	8 (36.6)
Persisted, *n* (%)	1 (4.6)	5 (27.7)
Worsened, *n* (%)	0 (0)	1 (4.6)

Statistical analysis

All the enrolled patients were evaluated. The nonparametric Wilcoxon and Mann–Whitney U tests were used to determine significant differences between samples before and after treatment within the same group and between the two groups. A p-Value $< .05$ was taken as an indication of significance. All statistical analyses were performed using SPSS version 22.0 software (SPSS Inc., Chicago, IL).

Result

The sex ratio of the patients, between male and female, was almost equal and the mean age of both groups was 53.36 ± 9.38 years, the mean duration of the ulcers was 13.89 ± 6.93 months and the mean size of the ulcers at the baseline was $2.89 \pm 2.04\,cm^2$. There were no dropouts in the study. All the included patients completed the study protocol. The demographics of the patients and baseline characteristics are shown in Table 1.

The mean percentage of ulcer healing per week in both the study groups are shown in Figure 1. The healing percentage increased each week in both groups. The healing percentage of the EGCG group was 2–3 times higher than the healing rate in the FGD group. At the end of the study, the FGD group had a mean percentage of size reduction of the ulcers of $52.65 \pm 53.16\%$ and the mean percentage of depth reduction of $50.91 \pm 42.72\%$, whereas the EGCG group had a mean percentage of size reduction of the ulcers of $84.11 \pm 30.47\%$

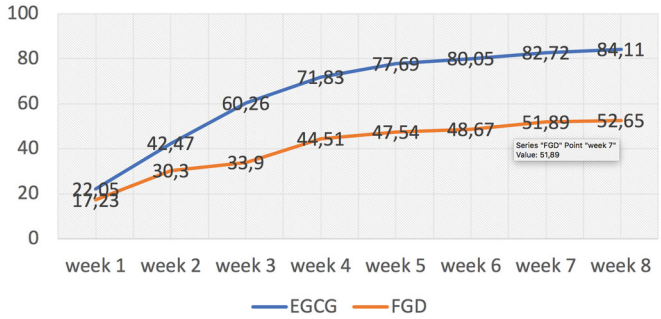

Figure 1. The mean percentage of size reduction of ulcers every week between three groups.

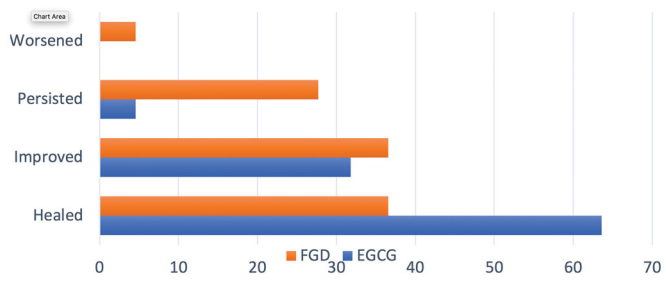

Figure 2. Clinical improvement of the ulcers at the end of the study.

and a mean percentage of depth reduction of the ulcers of 85.45 ± 25.40%.

The clinical features of ulcers in patients can be seen in Figures 3 and 4. The clinical improvement in the ulcers at the end of the study is shown in Figure 2. It shows the number of patients that were completely healed, improved, persisted and worsened. The definitions are as follows: 'completely healed' if the ulcer closed, 'improved' if the size of ulcer was reduced at the end of study as compared with that at the baseline, 'persisted' if the size of ulcer at the end of study was still the same and 'worsened' if the size of ulcer was larger at the end of study as compared with that at the baseline. In this study, the percentage of completely healed ulcers was higher in the EGCG group (63.6%) than that in the FGD group (36.6%) is shown in Table 2.

No adverse events were encountered in either of the study groups, but a complication occurred in 1 patient (4.5%) in the FGD group when the size of the ulcer became wider. During the clinical examination of this patient, neither any clinical signs of allergic contact dermatitis nor any clinical signs of infection (no erythema on the skin around the ulcer, no swelling, no warmth on palpation, odorless and no exudation) were found. The ulcer had enlarged in the 3rd week of treatment. Consequently, the FGD treatment was discontinued in the 3rd week and the wound care was replaced with normal saline. Follow-up was continued until the 8th week. In the 4th and the 5th week, the size and the depth of the ulcer remained the same. In the 6th, the 7th and the 8th week, the size of the ulcer increased, but the depth remained the same. This patient had a clawfoot and the ulcer was positioned at the head of the first metatarsal. The worsening of the ulcer in this patient was not caused directly by the treatment with FGD but was caused by the clawfoot. This patient required a pressure reducing measure such as an appropriate shoe or sandal for reducing the pressure on the ulcer.

A comparison test for the difference in the size of the ulcers before and after treatment between the two groups was tested using the Mann–Whitney U test. The results showed a significant difference between the EGCG group and the FGD group, as well as the difference in the size of the ulcers ($p < .032$) and the difference in the depth of the ulcers ($p < .032$).

Discussion

The results of this study demonstrated that EGCG 1% ointment improved healing rates of CPUL better than FGD. In this study, the age of most subjects was 21–50 years. The age of the subject of this study is in accordance with the age of the research subjects in various studies of ulcers in MH patients including research by Desancha et al. who examined the health quality of MH ulcers that have an average age of 45 years. Aging decreases the inflammatory response in wound healing, which may be due to the slowdown of the infiltration of T cells in the wound area. This also leads to prolonged inflammatory response and decreases the angiogenesis all of which are essential in the process of cell proliferation. The collagen formation that is required on the remodeling is also decreased in older patients (8). Old age is also often associated with low levels of antioxidants. Mitochondria function to provide energy and produce reactive oxygen species (ROS) to stimulate the occurrence of mitosis and the activities needed for wound healing. As we age, an increase in mitochondrial DNA mutations is indicated by an increase in the number of dysfunctional mitochondria accompanied by a decreased ability to eliminate them so that an increase in ROS levels can delay the wound healing process (9). In theory, age influences the wound healing process, but in this study, age is not significantly related to ulcer healing, this indicates that the administration of EGCG can overcome the risk factors for age, where EGCG which functions as an antioxidant can eliminate ROS that increase due to the influence of age, so age does not affect in healing ulcers.

All the participants in this study underwent surgical debridement and were asked to reduce prolonged standing and walking. Surgical debridement is important in wound care in order to remove callus and necrotic tissue because these may be a source of focal pressure (callus) or focal infection (necrotic tissue) that inhibit the wound healing process (10). Surgical debridement also brings all the ulcers in the same phase of wound healing (coagulation and inflammation phase) at the baseline of the study (11,12).

In a chronic wound, one may detect a prolonged inflammatory response, elevated protease activity, and pro-inflammatory cytokines. These findings may account for the delayed wound healing process (13,14). The prolonged inflammatory response may be caused by infection or just inflammation. The FGD is an antibiotic wound dressing that works in the inflammatory phase of wound healing by treating the infection and contra-acting colonization. It is not effective in an inflammatory phase of wound healing that is not caused by infection. It is also not effective in the proliferative phase of wound healing.

The role of EGCG as an anti-inflammatory is by inhibiting the activation of NF-κB transcription factors and protein activators thereby reducing the production of inflammatory factors. In addition, EGCG can also inhibit the production of IL-8 which can reduce neutrophil aggregation so that it can suppress the inflammatory response. Thirteen EGCG products can help reduce ROS by inhibiting the formation of ROS enzymes (xanthine oxidase, cyclooxygenase, and lipoxygenase) and affect the

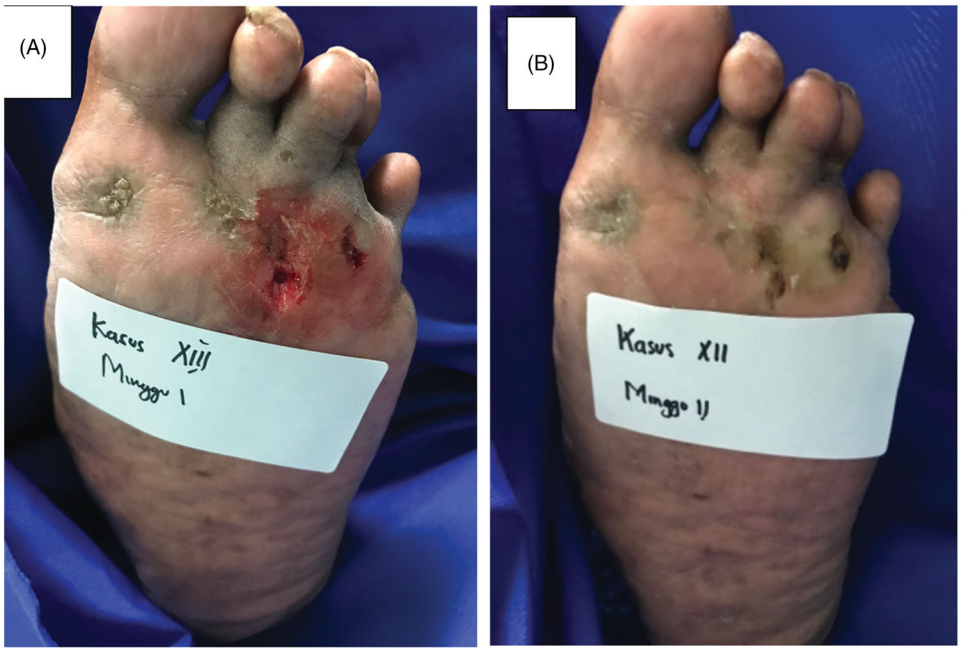

Figure 3. (A) Chronic ulcer before the application of EGCG 1% ointment, (B) completely healed ulcers on week 2 after the application of EGCG 1% ointment.

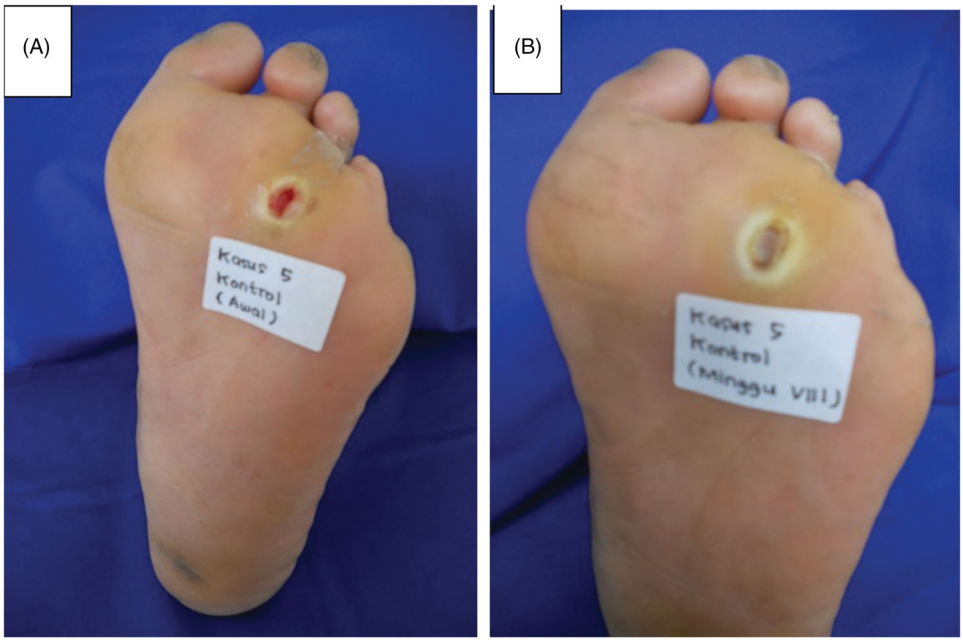

Figure 4. (A) Chronic ulcer before the application of FGD, (B) recovered ulcer on week 8 after the application of FGD.

production of nitric oxide through the interaction of nitric oxide synthase (NOS). In addition, EGCG can also activate SOD, which is a free radical detoxification enzyme (7). So that it can accelerate the process of wound healing. In addition, the function of EGCG as an antioxidant is by inhibiting the formation of nitric oxide thereby reducing levels of free radicals which can increase the production of toxic products. EGCG also plays a role in the protection of the vascular system, especially endothelial cells (6).

The prolonged healing of wounds is solved by an inflammatory process. The presence of ongoing inflammation produces ROS such as superoxide and hydrogen peroxide. Several studies have shown the function of EGCG in accelerating the healing process by accelerating the inflammatory phase, helping the proliferation phase and making collagen deposition faster. This acceleration forms the effect of EGCG in accelerating blood vessel formation and its anti-inflammatory effect. The use of EGCG helps wound healing through the formation of collagen fibers and angiogenesis and can also regulate the expression of vascular endothelial growth factors. This factor is recognized as the strongest angiogenesis.

In several other studies that state the risk of work which is standing/walking long affects the occurrence of ulcers. In theory, the factor has a big influence on the healing process of plantar ulcers, because one of the management of plantar ulcers is resting the soles of the feet from pressure (immobilization). Patients with plantar ulcers who have jobs that require a lot of

standing/walking for a long time are expected to experience a larger wound healing than patients with plantar ulcers who have jobs that do not require standing/walking for long periods. Other research by Goa and his colleagues regarding trophic ulcers on MH is that there is a relationship between the incidence of ulcers and the amount of pressure on the foot area contained in these ulcers, the higher the pressure in certain areas of the foot, the more the risk of ulcers. The amount of pressure on the feet is affected by body weight, leg surface, movement of the joints and big toe, amputation, degree of anesthesia, the severity of neuropathy, deformity and hypomobility. The longer a person stands/walks and the greater his weight is, the greater is the pressure on the legs. In addition, MH patients, due to autonomic disturbances, experience venivasomotor reflex disorder that controls increased venous pressure when standing by increasing precapillary resistance so that blood flow can be normal. The loss of reflexes results in increased venous pressure resulting in tissue edema that can inhibit wound healing.

In order to be near to the actual situation in this study, immobilization and pressure relief footwear were not advised. The study participants were only asked to reduce prolonged standing or walking. Immobilization of study participants was difficult because they were in a good general condition and had to work. Further studies using appropriate footwear to relieve pressure on ulcers should be undertaken.

There were no complications or side effects due to EGCG 15 in the subjects of the study. The results of this research still have limitations, so it is expected to be developed in the further studies, that is, the experimental analytic research by applying design of randomized controlled clinical trials to compare the gel on ulcer healing CPUL with the treatment *offloading* in the form of board feet designed specifically to help reduce stress and repetitive mechanical stress that can affect the healing process. In addition, applying additional criteria in selecting a good match between the groups *(matching)* based on the location of the ulcer and the anatomical structure to reduce bias.

Acknowledgments

This study was supported by the RSUD Dr. Soetomo Teaching Hospital/Medical Faculty of Airlangga University.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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