

# Topical Epigallocatechin Gallate (EGCG) 1% for Chronic Plantar Ulcers in Leprosy

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## ABSTRACT

**Background:** Chronic plantar ulcers in leprosy (CPUL) increase morbidity, increase medical costs, cause loss of productivity, and decrease quality of life. CPUL is a severe complication of leprosy disease with a 10-20% incidence. In general, CPUL consume a significant amount of time to heal. Green tea extract contains high amount of Epigallocatechin gallate (EGCG). EGCG functions as antiinflammatory, antimicrobial, and immunomodulator. This suggests that EGCG is effective for dermal wound treatment by facilitating reepithelialization. **Purpose:** To investigate the effect of topical EGCG 1% on the CPUL healing process. **Methods:** The topical EGCG 1% were applied every three days for eight weeks. Size of the ulcers, side effects and possible complications were monitored weekly. **Result:** There were significant clinical and statistical differences in the size and depth of the ulcers ( $p=0.000$ ), as observed in the EGCG group. There was no side effect and complication found. **Conclusions:** Topical EGCG 1% was effective for CPUL healing. Sixty three point six percent of the ulcers were clinically healed, 31.8% demonstrated improvement, and 4.6% no effect was observed.

**Keywords:** Epigallocatechin gallate (EGCG), chronic plantar ulcers in leprosy (CPUL), healing process.

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## BACKGROUND

Morbus Hansen (MH) or leprosy is a chronic infectious disease caused by *Mycobacterium leprae* (*M. leprae*), which primarily attacks peripheral nerves. This can damage the peripheral nerve in the form of sensitivity and motor, and autonomic disorders.<sup>1, 2</sup> Trauma, abnormal pressure, and secondary infections can cause tissue loss and worsen nerve damages. About 30% of leprosy patients experience peripheral nerve damage. World Health Organization considers neuropathic ulcers in the case of leprosy as level 2 disability, which can cause deformity and spontaneous limb amputation.<sup>3</sup>

In 2012, 2013 and 2014, the incidences of chronic plantar ulcers in Leprosy Division, Dermatology and Venereology Outpatient Clinic of Dr. Soetomo General Academic Hospital of Surabaya were 10% (3 of 30 leprosy patients with ulcers), 11% (5 of 46 leprosy patients with ulcers) and 17% (8 of 48 leprosy patients with ulcers) respectively; indicating annual increase of CPUL incidence.<sup>4</sup> In Leprosy Division, Dermatology and Venereology Outpatient Clinic of Dr. Soetomo General Academic Hospital of Surabaya, the standard treatments consisted of debridement, dressing (NaCl 0.9% compress, framycetin gauze dressing (FGD), sodium

fusidate 2% ointment application), and oral antibiotics. Patients with chronic plantar ulcers commonly face stubborn wounds on soles. Standard therapies seem less able to give positive results for neuropathic ulcers. Prakoeswa et al. investigated the effectiveness of framycetin gauze dressing and amniotic membrane stem cell metabolic products (PM-AMSC) by comparing two groups of patients. The first group consisted of 22 leprosy patients with chronic plantar pedis ulcers treated with standard FGD, and the second group consisted of 22 leprosy patients with chronic plantar pedis ulcers treated with PM-AMSC. The research concluded that PM-AMSC was more efficient as it speeded up the recovery.<sup>5</sup> Therapeutic modality using PM-AMSC is challenged by the lack of materials for PM-AMSC preparation; therefore, the researchers believe that alternative therapeutic modality is needed. Epigallocatechin gallate (EGCG) is the most abundant beneficial substance contained in green tea, and it is the bio-active source of green tea, which provides stronger antioxidant compared to vitamin C. In addition, EGCG also has antiinflammatory, antimicrobial, and immunomodulatory properties. The findings indicated that EGCG was applicable for dermal wound treatment as it facilitates reepithelialization.<sup>6</sup>

Several EGCG research confirmed the role of EGCG in wound healing. Research experiment by Neves et al. involved male Wistar rats as experimental animals. The control group was treated with plain water ad libitum, whereas the experimental group was treated with green tea. All rats were then surgically operated on their back in the second week. The research concluded that rats in the experimental group tended to experience faster wound recovery compared to the control group. Park et al. found that the antimicrobial properties of green tea inhibited the 95% growth of gram-negative bacteria *Escherichia coli*, *Pseudomonas putida*, and *Salmonella typhimurium* and gram-positive bacteria *Staphylococcus aureus* and *Bacillus subtilis* with green tea 70% (GT70). In addition, green tea microtones inhibited bacterial growth at the wound site and improved the healing process. Kim et al. adsorbed various concentrations of EGCG into a collagen sponge (CS) to observe its effect on the wound healing process in type 2 diabetic rats. On day 14, the researchers observed a significant and faster reduction of wound sizes among rats that had been treated with 10 ppm of EGCG collagen sponge (E-CS). Kim et al. also histologically observed a significant increase of reepithelialization rates, granulation tissue thickness, and capillary density at the wound site treated with 10 ppm of E-CS. Kim et al. found that combination of CS and EGCG at low concentrations could improve wound healing process among diabetic rats by accelerating the reepithelialization and angiogenesis and increasing the cellular reorganization of granulation tissue through by triggering myofibroblast activity.<sup>7</sup>

Topical EGCG treatment was expected to speed up the wound healing process. A faster recovery would reduce costs and improve patients' quality of life. Should the hypothesis be confirmed, this research is expected to contribute to the development of topical herbal medicine for CPUL.

## METHODS

This was an observational cohort study (before and after the treatment evaluation) conducted by observing the clinical improvement of CPUL after topical EGCG therapy. The sample of the study was 22 CPULs (both single and multiple ulcers). The acceptance criteria were adult patients with ulcers > 6 weeks, minimum ulcer size of 9 cm<sup>2</sup> and ≤ 0.5 cm depth, good general conditions, and willing to participate in the study by signing the informed consent. The rejection criteria were systemic corticosteroid medication in the past two weeks, patients with hemophilia/blood clotting disorder/using

anti-platelet, hypersensitivity to adhesive plaster, and diabetes mellitus.

Debridement was performed before treatment. Once the ulcer clean, the size and depth were measured, and it was treated with topical EGCG 1%. The ulcers were covered with transparent film dressings and opened every three days for clinical examination and EGCG treatment. The subjects visited the Dermatology and Venereology Outpatient Clinic in Dr. Soetomo General Academic Hospital Surabaya every week for ulcer treatment with EGCG and examination. The subjects should attend the follow-up treatment and examination for two months maximum. Therefore, should the participant recover in less than two months and no side effect observed, the follow-up was no longer needed. This research has been reviewed and approved by the Ethics Committee at Dr. Soetomo General Academic Hospital.

## RESULT

The basic data of the research subjects are presented in Table 1. The male (45.5%) and female (54.5%) research subjects were evenly distributed. All subjects were older than 21 years old, where the 59.1% of the participants aged 21-50 years old, and the 40.9% aged more than 50 years old with the average age of  $52.82 \pm 10.07$  years. Forty point nine percent of the subjects' occupation requires intensive standing/walking, such as farmers, pedicab pullers, garbage pickers, construction workers, and factory workers. The other 59.1% of the subjects' occupation does not require intensive standing/walking, such as housewives, chicken breeders, and drivers of motorized pedicabs. There were fifteen research subjects suffering from plantar ulcers for 1 to 5 years (68.2%), and the other seven subjects for less than one year (31.8%). The average period of ulcers was  $13.82 \pm 7.95$  months (Table 1).

The average percentage of ulcer recovery has increased every week. At the end of the study (week 8), the average reduction of ulcer size reached  $84.11\% \pm 30.47\%$ , and the average decrease in ulcer depth was  $85.45\% \pm 25.40\%$ . The average size and depth of ulcer per week were obtained by reducing the initial average size and depth with the average size and depth in n-week. It was then divided by the average size and depth of the initial ulcer and multiplied by 100% (Table 2 and Figure 1).

Table 3 shows the clinical ulcer improvement of the research subjects at the end of the treatment, categorized into recovered, improved, permanent, or worsened. "Recovered" means the ulcer closed, and "improved" means that the size and the depth of the ulcers are smaller than the initial size and depth.

"Constant" means that the size and depth of the ulcers are similar to the initial size and depth. The last, "worsen" means that size and the depth of the ulcers are bigger than the initial size and depth.

**Table 1.** Demographic data of research subjects

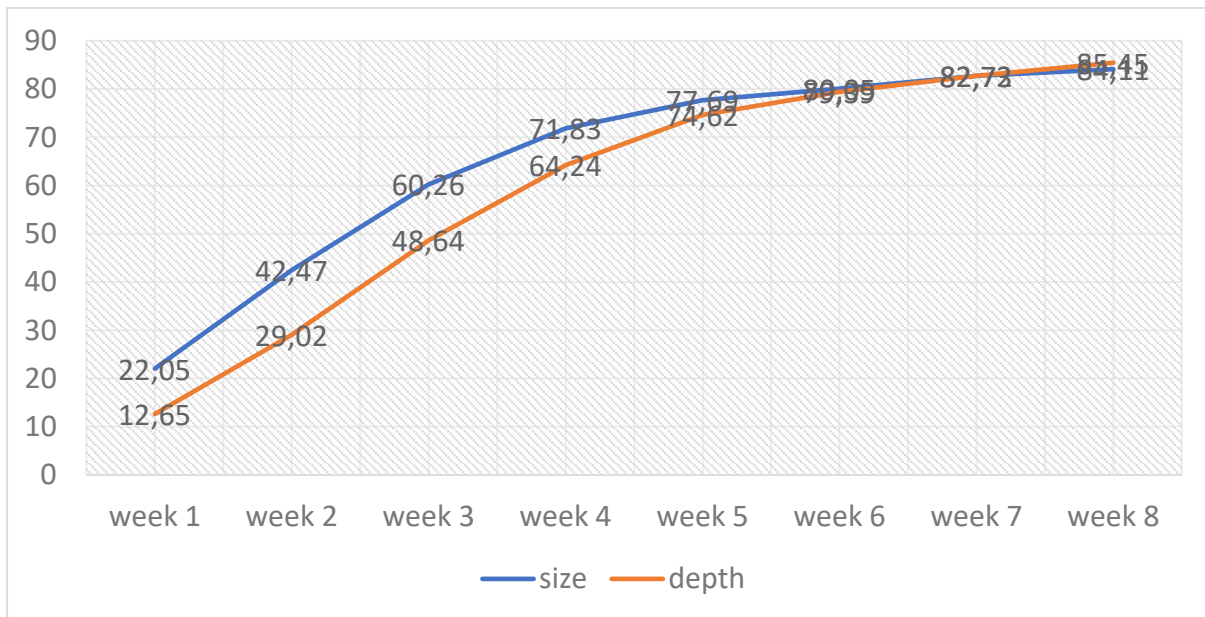
Variable	EGCG (n = 22)	p=0.05
Gender		
Male, n (%)	10 (45.5)	
Female, n (%)	12 (54.5)	
Age (years)		p=0.334
21 – 50 years, n (%)	13 (59.1)	
> 50 years, n (%)	9 (40.9)	
Occupation		p=0.001
A lot of standing/walking for a long time, n (%)	9 (40.9)	
Rarely standing/walking for a long time, n (%)	13 (59.1)	
Period of ulcer (years)		p=0.008
< 1 year, n (%)	7 (31.8)	
1 – 5 years, n (%)	15 (68.2)	
> 5 years, n (%)	0 (0)	
Size of initial ulcer		p=0.000
1 cm <sup>2</sup>	3 (13.6)	
1-4 cm <sup>2</sup>	12 (54.5)	
5-9 cm <sup>2</sup>	7 (31.8)	
Depth of initial ulcer		p=0.000
0.2	7 (31.8)	
0.3	6 (27.3)	
0.4	3 (13.6)	
0.5	6 (27.3)	

EGCG: Epigallocatechin gallate

**Table 2.** The recovery percentage of chronic plantar ulcer of leprosy

The recovery percentage of chronic plantar ulcer in leprosy	EGCG (n =22)
The average percentage of ulcer size reduction (%)	
Week I ± SD	22.05 ± 17.21
Week II ± SD	42.47 ± 25.19
Week III ± SD	60.26 ± 32.15
Week IV ± SD	71.83 ± 32.71
Week V ± SD	77.69 ± 32.04
Week VI ± SD	80.05 ± 31.30
Week VII ± SD	82.72 ± 30.72
Week VIII ± SD	84.11 ± 30.47
Average percentage of ulcer depth reduction (%)	
Week I ± SD	12.65 ± 18.19
Week II ± SD	29.02 ± 48.64
Week III ± SD	48.64 ± 29.70
Week IV ± SD	64.24 ± 29.80
Week V ± SD	74.62 ± 31.29
Week VI ± SD	79.39 ± 28.26
Week VII ± SD	82.73 ± 26.94
Week VIII ± SD	85.45 ± 25.40

EGCG: Epigallocatechin gallate, SD: Standard deviation

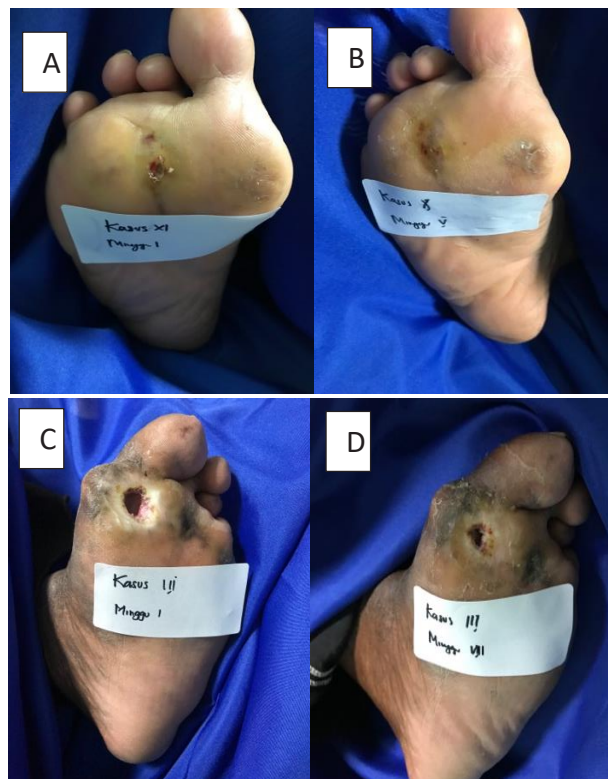


**Figure 1.** The average percentage of ulcer recovery per week.

**Table 3.** Clinical improvement of ulcer at the end of the research

Clinical improvement of ulcer at the end of the research	EGCG (n = 22)
Recovered, n (%)	14 (63.6)
Improved, n (%)	7 (31.8)
Constant, n (%)	1 (4.6)
Worsen, n (%)	0 (0)

EGCG: Epigallocatechin gallate



**Figure 2.** (A) Chronic plantar ulcer on patients with leprosy before topical Epigallocatechin gallate (EGCG) 1% therapy, (B) The ulcer is recovered in the fifth week after the topical EGCG 1% therapy, (C) Chronic plantar ulcer on patients with leprosy before topical EGCG 1% therapy, (D) The size and depth of ulcer get smaller in the eighth week after the topical EGCG 1% therapy.

**Table 4.** The comparative test for the size of ulcer before and after the treatment

Size of ulcer		EGCG (n=22) Means $\pm$ SD	Values p = 0.05
Size	Before	3.77 $\pm$ 2.89	P=0.000
	After	3.49 $\pm$ 3.29	
Depth	Before	0.34 $\pm$ 0.16	P=0.000
	After	0.12 $\pm$ 0.14	

\*Significant differences ( $p < 0.05$ ), SD: Standard deviation

EGCG: Epigallocatechin gallate

Shapiro Wilk test confirmed that the data were not normally distributed ( $p < 0.05$ ); therefore, nonparametric statistical tests, the Wilcoxon test, was performed. Table 4 shows the comparative test results of ulcer sizes before and after treatment. The statistical test confirmed that there were significant differences in ulcer size ( $p = 0.000$ ) and ulcer depth ( $p = 0.000$ ) before and after treatment.

## DISCUSSION

The basic characteristics of the research subjects are presented in Table 1, showing that there were more female subjects than male (54.5% and 45.5%). The research subjects were at least 21 years old or married, pursuant to the Regulation of the Ministry of Health of the Republic of Indonesia Number 290/Menkes/Per/III/2008 concerning Informed Consent, and the Indonesian Civil Code Article 330 concerning minors. All subjects participating in this study have signed informed consent for surgical debridement.<sup>8</sup>

Most research subjects were aged 21-50 years old (59.1%), followed by subjects aged more than 50 years old (40.9%) with a mean of age of  $52.8 \pm 10.1$  years. This was in line with research conducted by Desanchara et al., concluding that the average age of ulcer patients was 45 years.<sup>9</sup> Research by Reynolds et al. on the topical distribution of wheatgrass extract for ulcer healing concluded the patients' average age of  $57.8 \pm 8.8$  years.<sup>1</sup> Age is one of the systemic factors that influence wound healing, suggesting that an older person has a greater possibility of wound healing disorders. Research conducted by Gosain et al. and Keylock et al. claimed that aging caused delayed wound healing in healthy adults. Swift et al. found that aged rats experienced a delay in reepithelialization, collagen synthesis, and angiogenesis in comparison to the younger rats. Aging negatively affects wound healing by increasing platelet aggregation, increasing secretion of inflammatory mediators, late macrophage and lymphocyte infiltration, impaired macrophage function, decreasing growth factor secretion, late

reepithelialization, angiogenesis, and late collagen deposition, decreasing turnover and collagen remodeling, as well as a decreasing in wound strength.<sup>10</sup> Aging is often associated with lower levels of antioxidants. Mitochondria provides energy and produces reactive oxygen species (ROS) to stimulate mitosis and activities needed for wound healing. Aging promotes mitochondrial DNA mutations indicated by increasing of dysfunctional mitochondria and decreasing ability to eliminate; therefore, it increases the ROS levels, which delays the wound healing process.<sup>11</sup> Kruskal Wallis test on age resulted in  $p=0.334$ , indicating that there was no correlation between age and EGCG treatment. EGCG products can reduce ROS by inhibiting ROS enzyme formation (xanthine oxidase, cyclooxygenase, and lipoxygenase) and affect nitric oxide production through nitric oxide synthase (NOS) interaction. In addition, EGCG can also activate superoxide dismutase (SOD), which is a free radical detoxification enzyme that can accelerate wound healing process.<sup>7,12</sup> EGCG also functions as an antioxidant by inhibiting nitric oxide formation, thereby reducing the level of free radicals and the production of toxic products. Epigallocatechin gallate also protects the vascular system, especially the endothelial cells. The antioxidant and antiinflammatory properties of EGCG prevent atherosclerosis by reducing Vascular Cell Adhesion Protein-1 (VCAM-1) formation. EGCG decreases neutrophil aggregation and IL-6 and TNF- $\alpha$  formation so as to minimize ROS-stimulated endothelial cell damage.<sup>13</sup>

Most of the research subjects, about 59.1%, had standing or walking intensive occupation, and the other 40.9% did not. This was in accordance with other studies, suggesting that standing or running intensive occupation affects the occurrence of ulcers. Most research subjects were housewives. In theory, job factors significantly influence plantar ulcer healing process because plantar ulcer management requires sole resting (immobilization). Patients with intensive standing or walking occupations are



expected to experience extended wound healing process. During the study, the subjects were not suggested to immobilize but reduce standing or walking.<sup>14</sup> Goa et al. found the relationship between the incidence of ulcers and the amount of pressure in the leg area. The research found that higher pressure increases the risk of having ulcers. The pressure correlates with bodyweight, leg surface, joint and big toe, amputation, degree of anesthesia, the severity of neuropathy, deformity, and hypomobility. Prolonged standing or walking and heavier bodyweight results in greater leg pressure. Healthy people would rest or change position if they feel greater pressure. However, people with leprosy and neuropathy disorders do not change positions, allowing great pressure continues. In addition, autonomic disturbances promote veni-vasomotor reflex disorder, increasing venous pressure, and precapillary resistance to normalize blood flow. The loss of reflexes increases venous pressure, resulting in tissue edema that can inhibit wound healing. Leprosy with distal neuropathy weakens intrinsic muscles and external peroneal muscles, resulting in foot deformity. Such deformity will cause abnormal weight-bearing distribution in the legs. Ulcers will occur in the highly pressured region. In this case, occupation can contribute to ulcers. Persons with intensive standing/walking activity have a greater possibility to suffer from plantar ulcers.<sup>10</sup> The Mann-Whitney test found  $p=0.001$  for the region with ulcer and  $p=0.003$  for the ulcer. Thus, there was a relationship between occupation and ulcer healing with EGCG 1%.

Most research subjects have been suffering from plantar ulcer for more than one year. There were 15 subjects who have been suffering from plantar ulcers for 1-5 years (68.2%) and seven subjects for less than one year (31.8%). The average ulcer incidence was  $13.82 \pm 7.95$  months. Kruskal Wallis test on ulcer duration obtained  $p=0.008$ . Thus, there was a relationship between ulcer duration and ulcer healing with EGCG treatment. Research on CPUL showed that ulcers usually lasted for a very long time. Reynolds CL et al. found that the average duration of the ulcer was 10.4 years. In chronic wounds, a high concentration of pro-inflammatory cytokines and proteases causes sores in a continuous inflammatory phase. The antiinflammatory properties of EGCG inhibit the activation of NF- $\kappa$ B 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, suppressing the inflammatory response.<sup>13</sup>

The percentage of healed ulcers was 63.6%, improved ulcers was 31.8%, persistent ulcers was 4.6%, and no worsened ulcers. The mean of ulcer healing was  $84.11\% \pm 30.47\%$  (size) and  $85.45\% \pm 25.40\%$  (depth). The results of this study were similar to the study of Shahrahmani et al. on the efficacy of EGCG on healing episiotomy wounds and pain reduction after episiotomy. The 99 subjects were randomly divided into three groups, which were green tea ointment group, placebo, and routine care groups. An ointment was carried out for ten days, and the evaluation results showed that there was significant improvement in wound healing and reduction in analgesic use in the EGCG group compared to placebo and standard care group.<sup>16</sup>

In our study, significant results were obtained both in wound size ( $p=0.000$ ) and wound depth ( $p=0.000$ ) after topical EGCG 1% therapy. Prolonged wound healing is usually associated with the inflammatory process. The presence of ongoing inflammation produces ROS, such as superoxide and hydrogen peroxide. Several studies confirmed EGCG roles in the wound healing process by accelerating the inflammatory phase, helping the proliferation phase, and inducing faster collagen deposition. This acceleration is thought to be the effect of EGCG in accelerating new blood vessels formation and its antiinflammatory effect.<sup>17</sup>

EGCG helps wound healing through collagen fibers and angiogenesis formation. It can also manage the expression of vascular endothelial growth factors. This factor is recognized as the strongest angiogenesis. Research by Kim et al. found that membranes containing EGCG can accelerate wound healing by proliferating epithelial cells and forming new capillaries. Shahmarani et al. stated that EGCG has strong antioxidant properties. Antioxidants play an overall important role in wound healing. At higher concentrations, reactive oxygen species can cause tissue damage and slow the healing process by damaging cell membranes.<sup>18</sup> Given the high levels of polyphenols in EGCG and polyphenols antioxidant properties, EGCG has ROS inhibitory mechanism in inducing wound healing.<sup>16,19</sup> Makvandi, Mo, and Aminfar et al. also found that controlling the infection in wounds could accelerate wound healing. EGCG contains antimicrobial properties proven in several studies.

This study concluded that there was a significant difference between wound size and depth before and after topical EGCG 1% therapy.<sup>20</sup> EGCG promotes wound healing process both during inflammatory, the proliferative, and the remodeling phase.<sup>21</sup>

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