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Efficacy of Adjuvant Therapy Curcuma Longa Rhizome Extract and Moringa Oleifera Leaf Extract to Wound Healing in Leprosy Ulcer Patients

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ABSTRACT

Leprosy (Morbus Hansen) is a chronic infectious disease caused by *Mycobacterium leprae*, primarily affecting the peripheral nerves and leading to sensory loss and the formation of chronic ulcers. This study investigates the efficacy of *Curcuma longa* rhizome and *Moringa oleifera* leaf extracts, known for their antibacterial and anti-inflammatory properties, in promoting wound healing in leprosy-related ulcers. Utilizing a pre-post, randomized, single-blinded controlled trial design, the study was conducted at Kelet Regional Hospital, Jepara, from January to April 2024. Participants included leprosy ulcer patients with a mean disease duration of 101.5 months, predominantly male (63.6%), and largely in the 51–60 age group (39.4%). Results indicated significant improvements in PUSH (Pressure Ulcer Scale for Healing) scores from pre-test to post-test within both the intervention and control groups ($p<0.001$). However, intergroup analysis showed no statistically significant difference in PUSH scores between groups (pre-test $p=0.669$; post-test $p=0.198$). These findings suggest that while *C. longa* and *M. oleifera* extracts have promising therapeutic potential in enhancing ulcer healing, their clinical efficacy may be limited by factors such as oral bioavailability. This research contributes to the limited literature on the use of plant-based adjunctive therapies in leprosy ulcer management and underscores the need for further studies with larger samples and improved delivery mechanisms to optimize clinical outcomes.

Keywords: *Leprosy ulcer, Curcuma longa, Moringa oleifera, PUSH scores, wound healing*

INTRODUCTION

Leprosy is classified as one of the neglected tropical diseases (NTDs), with a persistently increasing number of new cases reported annually. According to the World Health Organization (WHO), in 2019, over ten thousand new cases were reported in countries such as Brazil and India (Maymone et al., 2020). Leprosy, also referred to as Morbus Hansen (MH), is a chronic infectious disease caused by Mycobacterium leprae, an acid-fast, gram-positive bacterium (Chen et al., 2022). This bacterium primarily resides in Schwann cells and macrophages (Darmawan & Rusmawardiana, 2020), impairing sensory nerves and causing affected individuals to lose sensitivity to temperature, touch, and pain (Pucca, 2023). In addition to nerve involvement, leprosy can affect the upper respiratory tract, adrenal glands, joints, bones, and eyes (Maymone et al., 2020).

Leprosy diagnosis is primarily clinical and is confirmed by bacteriological examinations such as serological tests, Polymerase Chain Reaction (PCR), skin smears, or biopsies (Bhandari et al., 2023). According to WHO (2018), the diagnosis of leprosy is established by identifying at least one of the following: (a) loss of sensation in hypopigmented or erythematous skin lesions; (b) thickened or enlarged peripheral nerves with sensory loss and/or muscle weakness in the affected area; or (c) the detection of acid-fast bacilli in a skin smear (WHO, 2018). Peripheral nerve damage leads to skin sensory deficits, particularly in the feet, which may result in ulcer formation. If left untreated, these ulcers can progress to bone damage and eventually require amputation (Govindasamy et al., 2023).

Wound healing in leprosy-related ulcers is prolonged and relies heavily on an optimal immune response, including the role of Transforming Growth Factor-β (TGF-β) cytokines

(Liarte et al., 2020). TGF-β, which comprises isoforms such as TGF-β1, TGF-β2, and TGF-β3, is secreted by keratinocytes, macrophages, platelets, and fibroblasts, playing a critical role in tissue regeneration and wound healing, including coagulation, inflammation, proliferation, and remodeling (Pakyari et al., 2013). Moreover, TGF-β signaling through the SMAD3 pathway also regulates energy and glucose homeostasis (Pakyari et al., 2013). Dysregulation of TGF-β activity is associated with impaired wound healing and chronic wounds, including those seen in leprosy ulcers (Gumede et al., 2024; Kiritsi & Nyström, 2018). This impaired healing is linked to suboptimal epidermal differentiation and excessive epidermal proliferation, although the complete mechanisms remain to be fully elucidated (Kiritsi & Nyström, 2018).

Turmeric (Curcuma longa) and moringa (Moringa oleifera) are commonly used as spices and herbal medicines, particularly in Asia (Pareek et al., 2023; Fuloria et al., 2022). Turmeric, belonging to the ginger family, is recognized for its antibacterial, anti-inflammatory, and antioxidant properties due to its high curcumin content, which has potential benefits for wound healing. Dehghani et al. (2020) demonstrated that a 1% curcumin cream promoted neoangiogenesis in diabetic wound models. Similarly, Kant et al. (2015) found that curcumin enhanced the expression of TGF-β and Vascular Endothelial Growth Factor (VEGF), stimulating angiogenesis and accelerating wound healing. Comparable wound healing benefits were observed with M. oleifera leaf extract, which contains phenolic compounds that exhibit antioxidant properties, inhibit pro-inflammatory cytokine production, suppress nuclear factor kappa β (NF-κB) activation, and increase TGF-β expression (Bhattacharya et al., 2018).

Despite these promising findings, limited research has been conducted on the effects of C. longa and M. oleifera extracts in the treatment of leprosy ulcers. Therefore, this study aims to investigate the potential of these extracts to enhance wound healing in leprosy ulcers. The findings are expected to contribute to the development of more effective therapeutic strategies for managing chronic wounds in leprosy patients.

Leprosy, or Morbus Hansen, is a chronic infectious disease caused by *Mycobacterium leprae*, leading to significant peripheral nerve damage, sensory loss, and the development of chronic ulcers (Govindasamy et al., 2023). These ulcers, primarily on the lower extremities, pose a persistent clinical challenge due to their propensity for secondary infections and delayed wound healing, which can progress to severe complications such as osteomyelitis and amputation (Bhandari et al., 2023; Maymone et al., 2020). Chronic wounds in leprosy are associated with impaired immune responses and sustained inflammation that hinder the normal tissue repair processes (Liarte et al., 2020).

The biological basis of wound healing encompasses four key stages: hemostasis, inflammation, proliferation, and remodeling (Pakyari et al., 2013). Central to this process is Transforming Growth Factor-β (TGF-β), a multifunctional cytokine known to regulate immune responses, fibroblast activity, angiogenesis, and extracellular matrix production (Kiritsi & Nyström, 2018). TGF-β, particularly the TGF-β1 isoform, plays a critical role in the modulation of fibroblast-to-myofibroblast differentiation, promoting granulation tissue formation and collagen synthesis (Pakyari et al., 2013). However, in chronic wounds such as leprosy ulcers, the dysregulation of TGF-β signaling has been observed, leading to excessive inflammation, impaired keratinocyte migration, and poor tissue remodeling (Liarte et al., 2020; Gumede et al., 2024). Additionally, chronic inflammation in leprosy ulcers may perpetuate oxidative stress, further inhibiting effective wound healing (Bhattacharya et al., 2018).

Phytotherapy, or plant-based therapy, has emerged as a complementary approach in wound management due to the anti-inflammatory, antioxidant, and antimicrobial properties of certain medicinal plants. Among these, *Curcuma longa* (turmeric) and *Moringa oleifera* (moringa) have been widely studied in both *in vitro* and *in vivo* models (Shedoeva et al., 2019; Fuloria et al., 2022). Curcumin, the principal bioactive component of turmeric, has been shown to facilitate wound healing by promoting angiogenesis via upregulation of VEGF, stimulating

fibroblast proliferation, enhancing collagen synthesis, and modulating TGF-β expression (Kant et al., 2015; Dehghani et al., 2020). It also exhibits antimicrobial properties against *Staphylococcus aureus* and *Pseudomonas aeruginosa*, which are commonly associated with chronic wound infections (Adeliana et al., 2021).

Similarly, *Moringa oleifera* leaves are rich in polyphenols and flavonoids, which possess anti-inflammatory and antioxidant properties that can mitigate oxidative stress and modulate immune responses in chronic wounds (Bhattacharya et al., 2018). M. oleifera has also been shown to inhibit the activation of NF-κB and increase endogenous antioxidant enzymes such as superoxide dismutase and catalase, contributing to tissue regeneration (Al-Ghanayem et al., 2022). Despite this, the clinical application of these plant extracts in leprosy ulcer management remains underexplored, with most studies focusing on diabetic wounds or experimental models (Shedoeva et al., 2019; Al-Ghanayem et al., 2022).

Moreover, a key issue identified in the literature is the delivery method of these compounds. The majority of existing research demonstrates significant wound-healing benefits through topical applications of turmeric and moringa extracts, while systemic (oral) administration studies remain limited (Abu-Hijleh et al., 2024; Fuloria et al., 2022). This creates a scientific gap regarding the effectiveness of oral supplementation in the clinical management of chronic wounds, such as those associated with leprosy.

METHOD

a) Research Design

This research is an experimental study with a pre-post-randomized single-blinded controlled trial design. The research sample was leprosy ulcer patients who underwent treatment at the polyclinic and hospitalization at Kelet Regional Hospital Jepara in January-April 2024. Before the intervention for four weeks, an examination of *C. longa* rhizome extract and *M. oleifera* leaf extract was carried out at the Integrated Laboratory of Diponegoro University, Semarang. The research permit was obtained from the Health Research Ethics Commission of the Faculty of Medicine, Diponegoro University with number 598/EC/KEPK/FK-UNDIP/XII/2023.

b) Inclusion and Exclusion Criteria

The inclusion criteria are 1) patients with leprosy ulcers who are 20-60 years old; 2) are receiving Multidrug Therapy (MDT) therapy and NaCl dressing; and 3) approve and sign the informed consent form. Meanwhile, patients who are pregnant or breastfeeding, receiving treatment other than MDT, and have signs of acute inflammation will be excluded. If the patient shows signs of an allergic reaction, the reaction becomes more severe or proposes to stop taking the medication while the study is ongoing, the patient will be dropped out.

c) Instruments

The tools needed in the process of making and analyzing the extract of *C. longa* and *M. oleifera* include analytical scales, blenders, ovens, ultrasonic bath extraction equipment, rotary evaporators, glass tools, cuvettes, and spectrophotometers. A ruler is used to measure the Pressure Ulcer Scale for Healing (PUSH) Score. There are 3 components of the Pressure Ulcer Scale for Healing (PUSH) score—wound area, amount of exudate, and kind of wound—were used to evaluate the healing process. The formula for calculating wound area was length x width. After the bandage was removed from the wound, the amount of exudate was measured visually. The tissue in the wound region was used to determine the type of tissue. Necrotic tissue is characterized by black, brown, or tan tissue that clings tenaciously to the borders of the wound or ulcer. Necrotic tissue might appear stiffer or softer than the surrounding skin. Mucinous, yellow-or white-colored tissue that adheres to the ulcer in strings or clumps is what defines slough. Tissue that

appears granular, wet, and pink or meaty red. Granulation tissue is a pink or meaty red tissue that has a glossy, wet, granular appearance. Epithelial tissue is the new pink tissue that forms the islands or borders on the surface of the ulcer. Resurfacing occurs when the wound is entirely covered in epithelium. The current sub-scoring was used to evaluate the three factors, and the results were summed up to create a PUSH score with a maximum value of 17 and a minimum value of 0. The better the wound healing, the lower the PUSH score.

LENGTH X WIDTH (in cm²)	0 0	1 < 0.3	2 0.3 – 0.6	3 0.7 – 1.0	4 1.1 – 2.0	5 2.1 – 3.0	Sub-score
		6 3.1 – 4.0	7 4.1 – 8.0	8 8.1 – 12.0	9 12.1 – 24.0	10 > 24.0	
EXUDATE AMOUNT	0 None	1 Light	2 Moderate	3 Heavy			Sub-score
TISSUE TYPE	0 Closed	1 Epithelial Tissue	2 Granulation Tissue	3 Slough	4 Necrotic Tissue		Sub-score
							TOTAL SCORE

Figure 1. Pressure Ulcer Scale for Healing Score

The ingredients used are turmeric rhizome extract prepared by the brand capsule "Sari Kunyit Sido Muncul" with a content of 100 mg/capsule (registration no. POM TR 192333771) and moringa leaf extract prepared by the brand capsule "Sari Daun Kelor Sido Muncul" with a content of 300 mg/capsule (registration no. POM TR 132371791.

d) Research Procedure

Leprosy patients who meet the inclusion and exclusion criteria will be divided into three research groups (**Figure 2.**). The intervention group that receives standard and adjuvant therapy of *C. longa* rhizome extract at a dose of 2x500 mg/day for 30 days, the intervention group that receives standard therapy and adjuvant *M. oleifera* leaf extract with a dose of 2000 mg/day for 30 days, and the control group. The patient's wound healing was assessed before and after the intervention was carried out using the PUSH Score. This score assesses the area of the wound, the number of exudates, together with the type of wound. The sub-score is then totaled to produce a PUSH Score where the minimum value is 0 and the maximum score is 17. The smaller the value, the better the healing.(17)

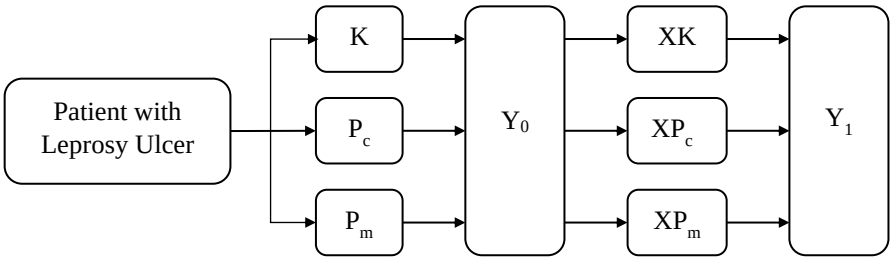

Figure 2. Research Procedure

Description

K : Control group
P_c : *C. longa* intervention group
P_m : *M. oleifera* intervention group
XK : Standard therapy
XP_c : Standard therapy and adjuvant treatment of *C. longa* rhizome extract
XP_m : Standard therapy and adjuvant treatment of *M. oleifera* leaf extract

Y_0 : Pre-test *PUSH Score*
Y_1 : Post-test *PUSH Score*

e) Data Analysis

After the research data has been obtained, it is continued with normality and homogeneity tests with Shapiro-Wilk to assess the distribution. If the data were normally distributed, the data analysis to test the difference in PUSH Score before and after the administration of therapy in each intervention group used a paired t-test, while if the data was not normally distributed, the data analysis used the Wilcoxon test. Furthermore, a multivariate test was carried out to determine the difference in PUSH scores between groups using the Kruskal-Wallis test. This study is considered significant if the p-value is < 0.05.

RESULTS AND DISCUSSIONS

This randomized controlled trial research involved 33 leprosy ulcer patients who were divided into three groups. The characteristics of the sample in each group can be seen in Table 1. The leprosy ulcer patients in this study were predominantly male, with 21 patients (63.6%), with an average leprosy duration of 101.5 months (SD, ±78 months; range 1-25 years). When viewed by age, the sample tended to be more in the age range of 51-60 years (39.4%). After testing the normality of the data, it was found that the data distribution was not homogeneous with $p<0.05$. The results of the pre-test and post-test PUSH Score data analysis in each group with the Wilcoxon test showed a significant difference ($p<0.001$). However, when multivariate tests were conducted to determine the relationship between pre-test and post-test PUSH Scores between groups, the results were not significant (pre-test, $p=0.669$; post-test, $p=0.198$).

Table 1. Study sample characteristic

Characteristic	*C. longa* (n=11)	*M. oleifera* (n=11)	Controls (n=11)	p
Sex, n(%)				
Male	8(72.7)	8(72.7)	5(45.5)	0.308
Female	3(27.3)	3(27.3)	6(54.5)	
Age, years, n(%)				
21-30	0	0	2(18.2)	
31-40	6(54.5)	1(9.1)	1(9.1)	0.027
41-50	1(9.1)	6(54.5)	3(27.3)	
51-60	4(36.4)	4(36.4)	5(45.5)	
Duration of Leprosy, months, mean±SD	65.45±32.36	134.18±79.20	104.73±98.53	0.117
PUSH Score				
Pre, mean±SD	9.36±2.42	10±2.05	9.36±1.63	0.669
Post, mean±SD	8±2.65	9.82±2.09	8.64±1.57	0.198

Patients with leprosy ulcers are predominantly men, with a male-to-female ratio of approximately 2:1. This disparity is attributed to the generally higher mobility of men, which increases their exposure to infection. Furthermore, lifestyle differences, including lower hygiene awareness among men, contribute to this trend (Rosita et al., 2022). The study characteristics also revealed that most patients with leprosy ulcers were older adults. Increasing age is associated with longer disease duration, which raises the risk of developing leprosy ulcers (Govindasamy et al., 2023; Barreto & Salgado, 2010).

The results of the pre- and post-test analysis showed significant improvements in the PUSH Score in all groups, indicating enhanced wound healing following therapy. Multidrug

therapy (MDT), which includes rifampicin, dapsone, and clofazimine, is known to treat the disease, reduce transmission, and lower relapse rates (Maymone et al., 2020). Additionally, improvements in the PUSH Score were also observed in the group receiving adjuvant therapy with *Curcuma longa* and *Moringa oleifera* extracts. Several in vivo and in vitro studies have demonstrated that *C. longa*, which is rich in curcumin, can promote fibroblast proliferation, collagen deposition, and granulation tissue formation, accelerating wound healing (Shedoeva et al., 2019). Furthermore, a preclinical study in rabbits showed that turmeric extract gel significantly reduced wound size (Adeliana et al., 2021). A similar study using *M. oleifera* leaf extract in wounds infected with *Pseudomonas aeruginosa* in rabbits showed significant wound-healing activity without any signs of irritation (Al-Ghanayem et al., 2022).

However, multivariate tests revealed no statistically significant differences in PUSH Scores between groups before and after treatment. This could be due to the fact that the extract was administered orally, whereas previous studies mostly applied the extracts topically. Curcumin has low oral bioavailability, as it is rapidly metabolized and eliminated from the body (Abu-Hijleh et al., 2024). The same applies to *M. oleifera* extract, where the bioavailability of its phenolic compounds is uncertain due to variability in chemical composition and reductions in concentration after processing (Azlan et al., 2023). These factors may indirectly affect the wound healing process. Although the intervention group receiving adjuvant therapy showed no statistically significant improvement between groups, significant pre- and post-test improvements in PUSH Scores were still noted within each group.

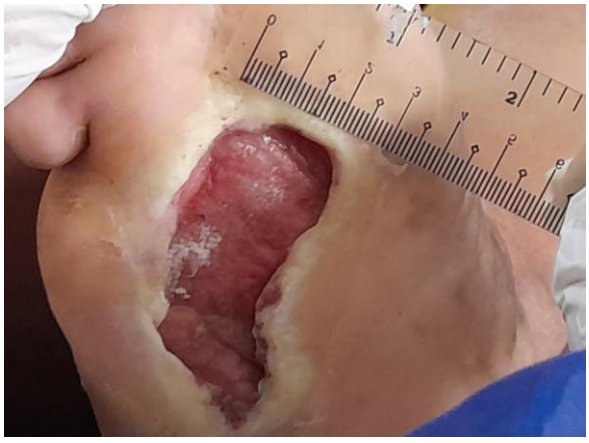

Figure 3. Leprosy ulcer in one of the patients

Limitations of this study include the small sample size due to the stigma surrounding leprosy and the long incubation period of leprosy. The duration of the intervention was short, lasting only four weeks. In addition, the study sample had been suffering from leprosy for different durations and therefore the course of the disease was different. Most of the samples had also been undergoing leprosy treatment for many years along with good therapeutic response. These circumstances can make the immune condition of each sample different. In the future, researchers hope that similar studies will be conducted with a larger and broader sample coverage, as well as a longer duration of intervention.

CONCLUSION

This research investigated the effect of turmeric (*Curcuma longa*) and moringa (*Moringa oleifera*) extracts as adjuvants in treating leprosy ulcers. The results showed significant improvements in PUSH Score for all groups after therapy, indicating improved wound healing. However, multivariate tests did not reveal significant differences between groups. This may be due to the oral administration of the extract, which has low bioavailability

and the influence of the manufacturing process. Further research is needed with a larger sample size to better understand the effects of these herbal extracts on wound healing.

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