

## Adjuvant Therapy Effect of *Curcuma Longa* Rhizome Extract On TGF- $\beta$ Serum Levels in Leprosy Ulcer Patients

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### ABSTRACT

Leprosy ulcer is one of the worsening manifestations of leprosy that often causes disability if not appropriately handled. Healing of ulcers requires a long enough duration so that a good immunological response is needed to encourage the wound healing process, one of which is transforming growth factor-  $\beta$  (TGF- $\beta$ ), which is necessary of the plants that plays a role in the expression of TGF-  $\beta$  to spur wound healing is *Curcuma longa* rhizome or turmeric rhizome. This study is expected to prove that administering *Curcuma longa* rhizome extract can increase serum TGF- $\beta$  levels in leprosy ulcer patients. This study is an experimental study with a pre and post-randomised single-blind controlled trial design involving 22 subjects with leprosy ulcers. The control group obtained standard therapy for leprosy ulcers, and the treatment group received standard therapy and adjuvant *Curcuma longa* rhizome extract at a dose of 1 g per day for 30 days. TGF- $\beta$  levels were measured by the ELISA method. Data analysis used the Wilcoxon test and the Mann-Whitney test. The results showed no significant difference in TGF- $\beta$  levels after and before the intervention in the control group ( $p=0.79$ ) and the treatment group ( $p=0.14$ ). However, there was a significant difference in TGF- $\beta$  levels after the intervention in the control group and treatment ( $p=0.01$ ). *Curcuma longa* rhizome extract did not show an important role in changes in serum TGF- $\beta$  levels in leprosy ulcer patients. This study showed that administering *Curcuma longa* rhizome extract for 1 month did not show a potential role as an adjuvant therapy.

**Keywords:** *Curcuma longa* rhizome extract, transforming growth factor- $\beta$ , wound healing, leprosy ulcer

### INTRODUCTION

Leprosy is a chronic infection caused by the bacteria *Mycobacterium leprae*. This disease is also known as leprosy or *Morbus Hansen*. This condition generally often raises problems not only in the health sector also in various developing countries due to the limited comprehensive services that can be provided to people infected with leprosy. The recapitulation of leprosy patients in Indonesia as of January 2022, based on data from the Ministry of Health of the Republic of Indonesia, amounted to 12,288 people. Leprosy ulcer is one of the worsening manifestations of leprosy, which often causes disability in leprosy patients, which if not handled properly, will cause further

effects in the form of deformity and even amputation (Mulianto & Fiqnasyani, 2023). Healing ulcers requires a long enough duration so that there is a need for an immunological response that can encourage wound healing, one of which is cytokines transforming growth factor- $\beta$  (TGF- $\beta$ ) that are needed in the process. (Liarte et al., 2020)

Transforming growth factor- $\beta$  has various roles in the wound healing process. Several studies have stated that one of the plants that play a role in wound healing and is expected to increase TGF- $\beta$  expressions. (Morikawa, Derynck, & Miyazono, 2016) (Ashrafizadeh et al., 2020; Mani et al., 2002) Many studies have stated that *Curcuma longa* has various therapeutic effects, one of which is on the wound healing process. *Curcuma longa* is reported to have several ingredients such as curcuminoids, glycosides, terpenes, and flavonoids. A study stated that wounds given curcumin intervention showed more staining results with TGF- $\beta$  than wounds that did not intervene. TGF- $\beta$  plays a role in collagen deposition and angiogenesis in chronic wounds initiated by fibroblast cells, and then TGF- $\beta$  induces collagen production by fibroblast cells. (Fuloria et al., 2022a) (Akbik et al., 2014) (Mani et al., 2002) (Kumari et al., 2022)

Immobilization and proper wound care are the basic principles of leprosy ulcer management. A wide selection of wound care modalities, such as Platelet Rich Plasma, Low-Level Laser Therapy, and so on, have proven to have quite good results, it is just that these various modalities often require high maintenance costs, and the distribution of these facilities is not evenly distributed, so a more affordable option is needed. (Mulianto & Fiqnasyani, 2023) This study is expected to prove that the administration of the *Curcuma longa* rhizome extract can affect serum TGF- $\beta$  levels in leprosy ulcer patients and is expected to be able to give rise to new ideas on leprosy ulcer therapy modalities and increase the effectiveness of wound healing in leprosy ulcers.

## RESEARCH METHODS

This study is an experimental study with a pre and post-randomized single-blinded controlled trial design. The subject of the study involved 22 leprosy ulcer patients undergoing treatment at Kelet Jepara Hospital in the January-April 2024 period. All subjects were divided into two research groups: the control group and the treatment group. The control group subjects received standard therapeutic interventions in the form of Multi Drug Therapy (MDT) for leprosy, NaCl dressings for ulcers, and placebo capsules, while the treatment group subjects received standard therapeutic interventions and 2 x 5 capsules of *Curcuma longa* rhizome extract with a dose of 100 mg per capsule (total: 1000 mg/day). The intervention was carried out for 1 month. *Curcuma longa* rhizome extract capsules were obtained from one of the herbal medicine and pharmaceutical industry companies in Central Java. This research has obtained permission from the Research Ethics Commission of the Faculty of Medicine, Diponegoro University.

All subjects were given a complete explanation of research techniques. The subjects involved in the study have also signed an informed consent sheet. The inclusion criteria in this study were leprosy ulcer patients aged 20-60 years, receiving

standard therapy in the form of MDT and NaCl dressing for ulcers, and agreeing and signing informed consent. The exclusion criteria in this study were subjects who were pregnant or breastfeeding and obtained other treatments other than standard therapy. The dropout criteria are subjects which apply to stop taking medication and develop an allergic or more severe reaction. The measurement of TGF- $\beta$  levels using subjects' blood samples was obtained from the *mediana cubitii* vein as much as 3 ccs each before and after the intervention for 1 month. The measurement of TGF- $\beta$  levels used the Enzyme-linked immunosorbent assay (ELISA) method with the Human TGF- $\beta$  ELISA Kit E3051hu at the GAKI Laboratory, Faculty of Medicine, Diponegoro University. Data analysis used the Wilcoxon test to determine the difference in TGF- $\beta$  levels before and after the intervention in each group. Differences in TGF- $\beta$  levels before and after treatment between groups were observed using the Mann-Whitney test. The data in this study is considered significant if a variable is obtained with a p-value < 0.05. Statistical analysis in this study uses a data analysis application.

## RESULT AND DISCUSSION

Table 1 shows the characteristics of the research subjects, including gender, age, and duration of leprosy.

**Table 1. Characteristics of the Research Subject**

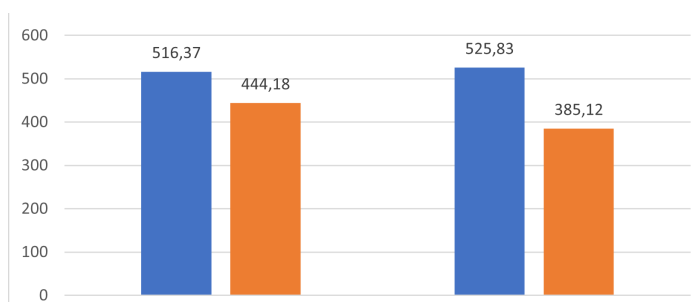
Characteristic	Control (n=11)	Treatment (n=11)
Gender, n(%)		
Male	5(45,5)	8(72,2)
Female	6(54,5)	3(27,3)
Age, n(%)		
21-30 years old	2(18,2)	0
31-40 years old	1(9,1)	6(54,5)
41-50 years old	3(27,3)	1(9,1)
51-60 years old	5(45,5)	4(36,4)
Duration of Leprosy (months), median (min-max)	60(24-120)	60(12-300)

There were more male subjects than female subjects, with 13 people, while female subjects amounted to 9. The characteristics of the study subjects were reviewed, and the age tendency was to be more in the age range of 51-60 years, with a total of 9 people, namely 5 people in the control group and 4 people in the treatment group. The duration of leprosy in the control and treatment groups showed the same duration, namely, having suffered from leprosy for 60 months.

Gender distribution in this study is in line with previous studies related to the epidemiology of leprosy in Indonesia which male patients dominate. Various factors, such as differences in habits, lifestyle, and concern for hygiene, also affect why leprosy tends to occur more in men. Male mobility tends to be higher, resulting in men being more susceptible to contact with lepers. The age characteristics of the subjects in this study were dominated by the age range of 51-60. This data differs from a report by the

Ministry of Health of the Republic of Indonesia in 2019, which stated that the incidence of leprosy in Indonesia is highest at a young and productive age. (Liu et al., 2018; Martoreli Júnior et al., 2021; Peraturan Menteri Kesehatan Republik Indonesia Nomor 11 Tahun 2019 Tentang Penanggulangan Kusta, 2019; Rosita et al., 2022) As reported, productive age is a risk factor for leprosy because it tends to have higher activity and mobility at that age. This causes the risk of exposure to be higher. In addition, excessive activity is also related to physical stress and changes in the body's immune system (Rosita et al., 2022).

The average result of pre-intervention serum TGF-β levels in the control group was 516.37 pg/ml, while the post-intervention was 444.18 pg/ml. The average TGF-β of pre-intervention serum in the treatment group was 525.83 pg/ml, while the post-intervention group was 385.12 pg/ml.



**Graphic 1.**  
Average of TGF-β serum levels pre and post-intervention: control (left) and treatment (right)

The analysis of the difference in TGF-β serum levels pre-intervention and post-intervention in each group did not show significantly different results as shown in the table below.

**Table 2. Results of Different Test Results of TGF-β Serum Pre-Intervention and Post-Intervention Levels of Each Group**

Group		Median (min-maks)	p
Control	Pre	346,90 (232,40-1483,60)	0,79
	Post	323,00 (294,40-979,40)	
Treatment	Pre	253,50 (214,50-1917,50)	0,14
	Post	251,40 (95,90-1125,50)	

Description: significant p<0.05

Differential testing of serum TGF- β levels was also carried out between the two groups which showed significant differences in post-intervention between the control group and treatment while in pre-intervention there was no significant difference.

**Table 3. Results of the level difference test TGF-β Pre and Post Intervention Between Groups**

	p

Pre-Intervention (Mann-Whitney)	Treatment Control	0,178
Post-Intervention (Mann-Whitney)	Treatment Control	0,011*

Description: Significant  $p < 0.05$

A number of literature states that *Curcuma longa* rhizome (turmeric rhizome) with the active content of curcumin, has a fairly wide pharmacological effect. Previous studies have shown that turmeric rhizomes have a number of effects, such as anti-inflammatory, antioxidant, anti-cancer, anti diabetic, and promote the wound healing process (Ashrafizadeh et al., 2020; Fuloria et al., 2022b; Jyotirmayee & Mahalik, 2022). One of the mechanisms that is allegedly involved is modulating TGF- $\beta$  good upregulation and downregulation (Ashrafizadeh et al., 2020). A study related to topical administration of curcumin content in experimental animals showed wound repair and an increase in TGF- $\beta$  which was more significant than in the control group. (Abu-Hijleh et al., 2024) In vitro studies on models of human gingival fibroblast showed that administering turmeric extract with curcumin content for 24 hours significantly improved the expression TGF- $\beta$ 1 and its receptors (Rujirachotiawat & Suttamanatwong, 2021). Likewise, topical administration to rats with diabetes lesions showed an increase in TGF- $\beta$  and induced angiogenesis after the intervention for 19 days (Kant et al., 2015).

This study is not in line with a number of literature above, where in this study, there was no significant change in serum TGF- $\beta$  serum levels between control up and the treatment. Some previous studies related to the role of curcumin in wound healing were in vitro and in vivo studies the topical administration of extracts, while this study was a clinical study with the administration of extracts orally. Curcumin has the characteristics of rapid absorption and metabolism in the human body, so it tends to be easily eliminated and its bioavailability is very limited. This condition results in a significantly reduced therapeutic role (Abu-Hijleh et al., 2024). Another study also showed a difference between systemic TGF- $\beta$  levels and TGF- $\beta$  levels obtained from local lesions. An increase in TGF- $\beta$  expression is not necessarily followed by an increase in serum TGF- $\beta$  levels. These results indicate that the systemic immune response does not necessarily describe what occurs in local lesions and vice versa.

## CONCLUSION

There was no significant difference in serum TGF- $\beta$  levels before and after adjuvant therapy of *Curcuma longa* rhizome extract at a dose of 1 gram per day for 1 month, as well as in the control group that only received standard therapy. This study generally shows that the administration of 1 gram of turmeric rhizome extract per day for 1 month has no potential role as an adjuvant therapy for leprosy ulcers

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