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Effect of *Curcuma longa* Extract as Adjuvant Therapy on IL-6 Serum Levels in Leprosy Type 1 Reaction Patients

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ABSTRACT
Type 1 leprosy reaction / Reversal reaction (RR) is an inflammatory episode in existing leprosy lesions and aggravates the pain rate. Long-term therapy with steroids causes a variety of side effects, so an adjuvant therapy alternative is needed to alleviate steroid use. *Curcuma longa* rhizome extract has become an anti-inflammatory therapy choice in various previous inflammatory diseases. This study aims to determine the anti-inflammatory effect of *Curcuma longa* rhizome extract as an adjuvant therapy for reversal reaction patients by analyzing serum levels of IL-6 as a marker of inflammation. The pre and post-test randomized single-blinded controlled trial was conducted on two groups, namely control (RR patients with steroid therapy & placebo) and treatment (steroid therapy & *Curcuma longa* rhizome extract 1 gram/day). IL-6 serum levels were analyzed from sampling before and after the intervention for one month. The serum levels of IL-6 post-test in the control group were significantly higher than those of the pre-test. The treatment group showed lower serum levels of IL-6 post-test compared to pre-test, although there was no significant difference. *Curcuma longa* rhizome extract 1 gram/day for one month as adjuvant therapy for patients with type 1 leprosy reaction did not significantly reduce serum IL-6 levels.

Keywords: *Curcuma longa,* Leprosy, Reversal reaction, IL-6

INTRODUCTION

Leprosy, also known as *Morbus Hansen*, is a disease classified as a Neglected Tropical disease (NTD) due to infection with the bacterium *Mycobacterium leprae* (*M. leprae*) (WHO, 2019). Leprosy cases are still widely found in various tropical countries such as Indonesia, India, and Brazil which contribute 79% of the total new cases in the world. One of the complications of leprosy that can arise is a leprosy reaction, which is an inflammatory/inflammatory reaction due to the presence of bacteria or parts of bacteria that have died and remain in body tissues (Walker, 2020; WHO, 2019, 2021). Leprosy reactions are categorized based on the immunological mechanism that triggers inflammation, namely leprosy type 1 reaction reversal reaction/RR) and leprosy type 2 reaction (Erythema Nodusum Lepromatous/ENL) (Walker, 2020). The clinics that can appear differ according to the category. Type 1 leprosy reactions are characterized by acute inflammation around skin lesions, such as edema and ulcers,

and are often accompanied by nerve damage. The leprosy type 2 reaction leads to systemic symptoms that affect various organs, causing a high level of pain. (Minister of Health of the Republic of Indonesia, 2019; Walker, 2020)

The immunological mechanism that mediates the type 1 leprosy reaction is dominated by the cellular immune response, while the type 2 leprosy reaction is by the humoral immune response. The cellular immune response to type 1 leprosy reaction is mediated by T-helper-1 (Th-1) cells that produce various inflammatory mediators such as Interleukin-1β (IL-1β), IL-2, IL-6, Tumor necrotizing factor-α (TNF-α), and Interferon-γ (IFN-γ). (Walker, 2020; WHO, 2020) In contrast to the leprosy type 2 reaction which tends to produce antibodies to attack the *M. Leprae* bacterial antigen. (Walker, 2020) Inflammatory mediators are widely used as markers of diagnosis and development of therapy. For example, IL-6 is significantly higher in patients with type 1 leprosy reactions than in patients without leprosy reactions. (Luo et al., 2021; Walker, 2020; Yuniati & Agusni, 2018) IL-6 is an important marker in the type 1 leprosy reaction because of its role in activating various inflammatory pathways such as Mitogen-activated pathway kinase (MAPK), Nuclear factor-kappa *B* (NF-kB), and Janus kinase-signal transducer and activator of transcriptor (JAK-STAT) (Ashrafizadeh et al., 2020; Zhang et al., 2019)

Leprosy reactions can be treated with steroids for 12-20 weeks of tapering-off doses combined with anti-leprosy multi-drug therapy (MDT). Long-term steroids have side effects in the form of damage to various organs, such as peptic ulcers, osteoarthritis, hyperglycemia, and Cushing's syndrome (Menteri Kesehatan Republik Indonesia, 2019; Yasir et al., 2023). Alternative leprosy reaction therapy needs to be developed to optimize the anti-inflammatory process against leprosy reactions and minimize long-term steroid use. An alternative therapy that has the potential to be an anti-inflammatory is turmeric rhizome or *Curcuma longa* rhizome. This plant has been widely known as a spice ingredient. It has been researched to treat various diseases, including as adjuvant therapy in inflammatory diseases such as osteoarthritis, rheumatoid arthritis, and ulcerative colitis (Jamil et al., 2023; Pinsornsak P & Niempoog S., 2012; Simadibrata M et al., 2017). *Curcuma longa* rhizome extract also plays a role in lowering IL-6 levels by inhibiting the inflammatory signaling pathways MAPK, JAK-STAT, and NF-kB. These various pieces of evidence are the basis for researchers to determine the anti-inflammatory effects of turmeric herbal plants by analyzing serum IL-6 levels of leprosy patients with type 1 reaction before and after the intervention (Jamil et al., 2023; Zhang et al., 2019).

RESEARCH METHODS

This study is a pre and post-test randomized single-blinded controlled trial. The study was conducted on type 1 leprosy reaction patients undergoing treatment at Kelet Jepara Hospital and was carried out from January to April 2024. The inclusion criteria of this study were type 1 leprosy reaction patients aged 20-60 years, not pregnant, only undergoing anti-leprosy MDT treatment and steroids without other treatment, and agreeing to informed consent of the study. The dropout criteria of the subjects of this study are patients who experience worsening leprosy reactions to ENL type or undergo other treatments during the study. A total of 22 research subjects

were then randomly grouped into each control and treatment group. Eleven people in the control group received anti-leprosy MDT therapy, steroids, and placebo capsules for one month. Eleven people in the treatment group received MDT therapy, steroids, and *Curcuma longa* rhizome extract capsules 1 gram/day for 1 month. *Curcuma longa* rhizome extract capsules were obtained from the product of one of the herbal medicine and pharmaceutical industry companies in Central Java, Indonesia which is registered with the Food and Drug Control Agency (BPOM) with a dosage of 100 mg per capsule and the drinking rule in this study is 2x500 mg. The content of *Curcuma longa* rhizome extract capsules was re-analyzed for its phytochemical content in the form of levels of flavonoids, tannins, saponins, and steroids in the integrated laboratory of Gadjah Mada University. Blood samples of patients from the *mediana cubitii* vein as much as 3 cc were taken before and after the intervention for one month. The blood sample was used for the analysis of serum IL-6 levels using Enzyme-linked immunosorbent assay (ELISA) at the GAKI laboratory, Faculty of Medicine, Diponegoro University.

The statistical analysis used was a test of the difference in serum IL-6 levels before the intervention compared to after the intervention in each group using the Wilcoxon test because the data distribution was abnormal. The analysis of the difference in serum IL-6 levels between the control group and the treatment was carried out by the Mann-Whitney test. The statistical analysis of this study uses a computer analysis program.

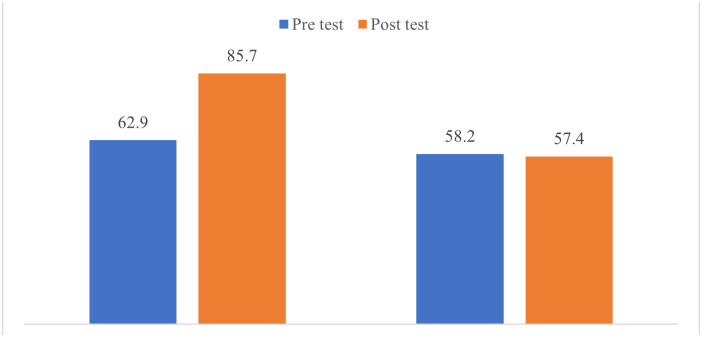
RESULT AND DISCUSSION

Table 1. Characteristics of the Research Subject

Characteristic	Control	Treatment
Gender, n(%)		
Male	7(63,6)	6(54,5)
Female	4(36,4)	5(45,5)
Age, n(%)		
21-30 years old	1(9,1)	6(54,5)
31-40 years old	1(9,1)	1(9,1)
41-50 years old	6(54,5)	3(27,3)
51-60 years old	3(27,3)	1(9,1)
Length of illness in months, median (min-max)	12(12 – 48)	24(2 – 120)

The researcher analyzed the characteristics of the research subjects from gender, age, and duration of leprosy. A total of 13 (59.1%) male patients and 9 (40.9%) female patients participated in this study. This is in accordance with the epidemiology of leprosy patients from one meta-analysis study which was dominated by men as much as 63% compared to 37% women. and data on leprosy patients in Indonesia in 2020 with 62.9% males and 37.1% females. Higher activity for men than women such as work leads to a higher risk of leprosy infection. The age distribution of leprosy patients in this study is in line with epidemiological studies that show that leprosy cases occur

more in the adult age group than children because the symptoms are not typical so they do not go to health facilities immediately. Other research states that patients of productive age are more at risk of being infected with leprosy due to high social and occupational activities. The median length of leprosy in the subjects of this study was 12 to 24 months. An observational study stated that the duration of patients suffering from leprosy was on average above 12 months (Kementerian Kesehatan Republik Indonesia, 2023; N. S et al., 2023; Nazli et al., 2021; Ramasamy et al., 2018; Yang et al., 2022, 2022, 2022). Another study mentioned episodes of leprosy reactions more than four times in 48 subjects with a period of more than 12 months (Putri et al., 2022).



Graph 1.
Overview of IL-6 Serum Levels in Each Group: Control group (Left), Treatment group (Right)

Table 2. Results of differential test of serum IL-6 levels

Group		Median (Min-Max)	*P*
Control	*Pre*	62,9 (1,9-611)	*0,026a
	Post	85,7 (3,5-608,1)	
Treatment	*Post*	58,2 (1,9-76,7)	0,477a
	Post	57,4 (1,2-73,8)	
Pre-test	Control group - Treatment group		0,189b
Post-test	Control group - Treatment group		*0,005b

Description: *Significant *p<0.05;* a: Wilcoxon Test; b: Mann Whitney test.

The results of this study showed that the serum levels of IL-6 post-test in the control group were significantly higher than those of the pre-test. This is not in line with previous research by Moreno et al., who stated that the serum level of IL-6 in leprosy reaction patients at the beginning of the study was higher than one month after the study with standard therapy (Vilani-Moreno et al., 2021). However, in another study by Saini *et al,* it was stated that IL-6 levels of leprosy reaction patients remained high during the first 8-180 days of treatment (Saini et al., 2016).

Some previous studies have focused more on the clinical improvement of leprosy reaction patients in monitoring and evaluation of therapy than on the analysis of serum IL-6 levels. Clinical guidelines and leprosy management by the Indonesian Association of Dermatologists and Venereologists suggest that treating leprosy reactions with steroids for 20 weeks will show better clinical improvement than 12 weeks of therapy. (Van Veen et al., 2016; Wagenaar et al., 2017)(Indonesian

Association of Dermatologists and Venereologists, 2017)A randomized controlled trial study showed that steroid therapy in patients with nerve functional impairment (NFI) for 20 weeks or 32 weeks showed the same clinical improvement, and the longer the steroid was given, the more delayed the immune response in some patients. (Wagenaar et al., 2017) This is one of the factors that monitoring leprosy reaction patients in the first month has not shown significant clinical improvement.

Previous in vitro studies have shown that corticosteroids can lower IL-6. In contrast to one observational study that showed corticosteroid therapy failure in 23 out of 79 children with severe ulcerative colitis with elevated serum levels of IL-6 after corticosteroid therapy. Corticosteroid therapy failure can be caused because pro-inflammatory cytokines such as IL-6, IL-2, and IL-4 can induce phosphorylation (Quante et al., 2008; Strandberg et al., 2008; Wine et al., 2013). Glucocorticoid receptor-α (GRα) through the p38-MAPK pathway, thereby affecting GRα's affinity for steroids. Glucocorticoids reduce the response of T cell receptors through Lck inhibition which acts as a regulator of inositol 1,4,5 triphosphate and plays a role in suppressing the immune response, but this process must occur over a long period of time, not just in a matter of hours or days (Harr et al., 2009; Irusen et al., 2002). High serum levels of IL-6 also indicate an active inflammatory process occurring in leprosy patients. Leprosy reactions can occur due to an immune response to *M. leprae* microorganisms either in whole form or fragments in the patient's body. Compliance with taking standard leprosy therapy drugs, namely MDT, leprosy, and steroids in leprosy reaction patients is an important point in the development of therapy. In some studies, it is mentioned that patients who have stopped taking steroids have been proven to experience relapses and recurrent leprosy reactions even more than four times (Pinheiro RO et al., 2018; Putri et al., 2022; Wagenaar et al., 2017; Walker, 2020).

In contrast to the treatment group, post-test serum IL-6 levels were lower, although not as significant than the pre-test. A total of 8 study subjects showed a decrease in serum IL-6 levels post-test compared to pre-test. The decrease in IL-6 levels in the treatment group can be affected by the administration of steroid therapy and adjuvant *Curcuma longa* extract, which contains curcuminoids *and* has been proven to have an anti-inflammatory role by inhibiting inflammatory pathway mechanisms such as MAPK, JAK-STAT, and NF-κB (Chen et al., 2018). Curcumin can also inhibit gene expression signaling from TNF-α by inhibiting p300/CREB-specific acetyltransferase, thereby inhibiting cell transcription and the formation of inflammatory products. (Aggarwal BB et al., 2013; Derosa et al., 2016)

Curcuma longa extract in this study also contains flavonoids, tannins, and saponins. The three active ingredients have been widely proven to have an anti-inflammatory effect. Flavonoids can inhibit the Th17 regulatory mechanism, which is a determining factor in the reaction mechanism of leprosy. Like flavonoids, tannins also play a role in Th1, Th2, and Th17 regulatory barriers in reducing IL-6 products. Another active ingredient, saponins, play a role in inhibiting the mechanism of the NF-κB inflammatory pathway so that its by-products, such as IL-6 and advanced inflammatory processes, can be inhibited (Gandhi GR et al., 2018; Khan et al., 2022; Piazza et al., 2022).

CONCLUSION

This study showed that the administration of *Curcuma longa* rhizome extract at a dose of 1 gram/day for one month as adjuvant therapy for patients with type 1 leprosy reaction did not significantly reduce serum IL-6 levels.

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