

***Clitoria ternatea* Extract as Adjuvant Therapy on Reducing IL-6 Levels in Reversal Reaction**

Nadya Audina N. S^{1*}, Muflihatul Muniroh², Novi Kusumaningrum³,
Farmaditya EP M.⁴, Renni Yuniati³

¹Biomedical Science, Faculty of Medicine, Diponegoro University, Indonesia

²Department of Physiology, Faculty of Medicine, Diponegoro University, Indonesia

³Dermatology and Venereology Department, Faculty of Medicine, Diponegoro University, Indonesia

⁴Histology Department, Faculty of Medicine, Diponegoro University, Indonesia

*Corresponding Author: audinadyasadikin@gmail.com

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Abstract. Reversal reaction is a type IV cellular hypersensitivity reaction in leprosy. Interleukin-6 is a mediator with a pleiotropic effect on inflammation and immune response. Steroids are the standard therapy in the treatment of reaction reversal. *C. ternatea* flower extract has anti-inflammatory properties. Long-term use of steroids can cause side effects. Therefore, it is necessary to give adjuvant therapy that can shorten the treatment period. This study aims to analyze the effect of adjuvant therapy of *C. ternatea* extract to reduce IL-6 levels in a reversal reaction. Experimental research design with pre and post-randomized single-blinded controlled trial, involving 22 subjects with reversal reaction. The control group received standard therapy and the treatment group received standard and adjuvant therapy with *C. ternatea* extract. IL-6 levels were measured by ELISA. Data analysis used the Wilcoxon test and Independent T-test. The results showed a significant difference in the treatment group ($p=0.003$) and control group ($p=0.016$). The mean decrease in serum IL-6 levels in the treatment group was 81.35 pg/ml and in the control group was 24.30 pg/ml ($p=0.027$). *C. ternatea* showed a significant IL-6-lowering effect in patients with reversal reactions. This study has demonstrated the potential of *C. ternatea* extracts as adjuvant therapy in patients with leprosy reactions.

Keywords: Leprosy Reaction, Reversal Reaction, *C. ternatea*, IL-6, Anti-inflammatory

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INTRODUCTION

Leprosy is an infectious disease caused by infection with the bacterium *Mycobacterium leprae* (*M. leprae*) that attacks skin tissue, peripheral nerves, and the respiratory tract (Lee et al., 2019). WHO data from 2015 to 2019 Indonesia ranks third with the most leprosy sufferers in the world (WHO, 2020). Ministry of Health of the Republic of Indonesia (2021), shows the prevalence rate of leprosy in Indonesia in 2018 was 0.70 and in 2019 it was 0.74 cases/10,000 population. In 2020 it was reported that there were 11,173 new cases of leprosy and a prevalence rate of 0.49 cases/10,000 population. The highest frequency of leprosy is suffered by the productive age group (35-54 years), men, low education, and workers with heavy physical activity (Kamal & Martini, 2015; Meiningtyas et al., 2018). Leprosy is included in the category of Neglected Tropical Diseases (NTDs) because it is related to poverty, especially in the tropics (Firdaus, 2019; Lastória

& de Abreu, 2014).

Leprosy reactions are an acute episode of leprosy and the biggest cause of nerve damage (Vionni et al., 2016). Leprosy reactions are immunological phenomena that can occur before, during, and after treatment (Darmaputra & Ganeswari, 2018). Clinically, patients with leprosy reactions often complain because physically there are swollen skin lesions, this often causes discontinuation of therapy because patients perceive a reversal reaction as a failure of therapy (Naafs & van Hees, 2016). Study results by (Timu et al., 2021), showed that 80% of leprosy patients in Kupang City did not comply with taking medication because they had a leprosy reaction. Based on this study, some leprosy patients who experienced leprosy reactions did not go to health facilities to ask whether they were still taking medication or not because they were embarrassed by their condition. Based on WHO guidelines, steroids (Prednisolone) are the main therapy for leprosy reactions. Steroid therapy can provide

anti-inflammatory effects by suppressing the activity of the immune system. Side effects of long-term use of steroids can include hyperglycemia, hypertension, hyperpigmentation, diabetes, immunosuppression, osteoporosis, dyspepsia, and growth disorders in children (Aljebab et al., 2017; Negera et al., 2018; Williams, 2018). Therefore, adjuvant therapy is needed to shorten the treatment period with steroids and prevent steroid side effects.

There are 2 types of leprosy reactions, type 1 or reversal reaction (RR) and type 2 or erythema nodosum leprosum (ENL). The clinical manifestation of the reversal reaction is the leprosy lesions are more and more active suddenly with or without ulceration, edema, and neuritis can occur to cause permanent nerve damage (Yuniati, 2017). Reversal reactions are caused by increased cellular immune responses in the form of delayed-type hypersensitivity reactions to *M. leprae* antigens on nerves and skin (Pratamasari, 2015). The reversal reaction causes inflammation of the skin or nerves in patients with borderline type (BT, BB, and BL) (Yuniati, 2017).

Skin lesions become more erythematous and new lesions appear. Skin lesions may be accompanied by mild to severe neuritis which can lead to more severe nerve damage (Khadge et al., 2015). Type 1 reactions often occur during the MDT treatment period because of an excessive increase in cell-mediated immunity (CMI) to phagocytize germ fragments that have died due to MDT administration. If there is an increase in the CMI response to the *M. leprae* antigen, it leads to the clinical form of tuberculoid, or upgrading. However, similar symptoms may also occur before starting treatment, or during inadequate therapy. In this case, there is a decrease in the CMI response to the *M. leprae* antigen, similar to the clinical form of lepromatous, or downgrading (Fischer, 2017; Khadge et al., 2015).

M. leprae infection triggers MHC class II expression which will activate CD4⁺ lymphocytes to release TNF- α and IFN- γ , as well as an increase in cytotoxic T cells that selectively kill infected cells (Mungroo et al., 2020; Ramaswamy et al., 2011). Th1 response in the reverse reaction is also related to the expression of IL-12, IL-1b, and IL-2 cytokines (Froes et al., 2020). The pro-inflammatory effect of IL-6 is characterized by an increase in mast cell activity through the ongoing inflammatory process and can exacerbate the lesion. Up-regulation of Th17/Treg balance is thought to be responsible for impaired immunological tolerance that can lead to the

development of autoimmune and chronic inflammatory diseases (Kimura & Kishimoto, 2010). Several studies have described proinflammatory mediators in dental infection and leprosy reactions, particularly IL-6 and TNF- α (Cortela et al., 2015). Excessive levels of TNF- α , IL-6, and IL-8 which are increased in the serum of patients with a reversal reaction indicate that the cellular immune response plays an important role in the mechanism of the reversal reaction (Yuniati, 2017; Yuniati & Agusni, 2018). Other studies have also reported increased levels of IL-4, IL-6, and IL-8, which are chemotactic for neutrophils in reversal reaction lesions (Lockwood et al., 2011). A study (Yuniati & Agusni, 2018) showed that IL-6 levels were significantly increased in the group of leprosy patients with reversal reactions compared to the group of patients without reversal reactions.

C. ternatea has a high level of availability and is easy to cultivate. *C. ternatea* flowers contain alkaloids, saponins, terpenoids, phenols, flavonoids, and glycosides (Cahyaningsih et al., 2019; Escher et al., 2020; Nair et al., 2015). Several studies reported that the content of *C. ternatea* flower extract, especially flavonoids, was effective as an anti-inflammatory (Al-Snafi, 2016; Cahyaningsih et al., 2019). In vitro, inflammatory activity of the ethanol extract of *C. ternatea* showed that the extract's performance was equivalent to aspirin (Suganya et al., 2014). The anti-inflammatory effect of *C. ternatea* flower extract was influenced by its flavonoid content. Flavonoid compounds have anti-inflammatory effects by inhibiting the release of pro-inflammatory cytokines (Ginwala et al., 2019). The potential of *C. ternatea* flower as a nutraceutical material for protection against chronic inflammatory diseases by suppressing the excessive production of pro-inflammatory mediators from macrophage cells (Nair et al., 2015). Research by (Thilavech et al., 2021), reported that oral administration of a 2 g daily dose of *C. ternatea* flower extract reduced levels of proinflammatory cytokines (IL-6 and TNF- α) in obese male patients after consuming a high-fat diet. The study aimed to analyze the effect of adjuvant therapy of *C. ternatea* extract for reducing IL-6 levels in leprosy patients with a reversal reaction.

This research is expected to prove the benefits of *C. ternatea* extract as an anti-inflammatory by reducing IL-6 levels so that it can be applied for adjuvant therapy of leprosy with a reversal reaction. In addition, this research is expected to

be used as a basis for further research and development of phytopharmaca for improving public health.

METHODS

This research is an experimental study with pre and post randomized controlled trial design. This research was conducted using a single-blind method, in which the research subjects did not know they would be placed in the treatment or control group. The research subjects were leprosy patients with reversal reactions who were treated at the Donorejo Hospital, Jepara. 22 subjects were divided into two groups (control and treatment groups). In the treatment group, *C. ternatea* flower extract capsules were given at a dose of 2000 mg/day and Prednisolon. While the control group was given a placebo capsule and Prednisolone. The treatment was carried out for one month. The research was started after ethical approval was obtained from the Research Ethics Commission of the Faculty of Medicine, Diponegoro University No.110/EC/KEPK/FK-UNDIP/IV/2022.

Before starting the research, the research subjects were given detailed information and explanations about what would be done during the research. Subjects who were willing to participate in the study were asked to sign the consent form provided. Inclusion criteria were leprosy patients with reversal reactions aged 20-60 years, receiving prednisolone therapy, agreeing and signing the informed consent form. Exclusion criteria were pregnancy or breastfeeding, presence of other acute inflammatory disease, receiving treatment other than Prednisolone and MDT. Drop out criteria are that a more severe reaction occurs or leads to ENL, proposes to stop taking medication. Blood samples were taken from the median cubital vein as much as 3 cc in pretreatment and posttreatment (after 1 month) to measure serum IL-6 levels. Measurement of IL-6 levels using the ELISA method using the EliKine Human IL-6 ELISA Kit. The examination uses a wavelength of 450 nm.

Data were analyzed using Fisher's exact and Mann Whitney tests for gender, age, and length of illness. Wilcoxon test to determine the difference in mean serum levels of IL-6 pre and post in the

control and treatment groups. Meanwhile, the Independent T test was used to determine the difference in the mean decrease in IL-6 levels in the two groups. The significance value in this study is if the analyzed variable has a p value <0.05.

RESULTS AND DISCUSSION

The characteristics of the subjects in this study are shown in table 1. This study shows that most of the research subjects were male with a percentage of 81.1% in the control group and 90% in the treatment group with a value of ($p = 1.000$). Characteristics of research subjects based on age showed that the control group was more in the age range of 31-40 years with a percentage of 36.4%. In the treatment group showed more research subjects aged 20-30 years with a percentage of 45.5%. The distribution of age groups between the control and treatment groups was relatively similar in value ($p = 0.861$). Distribution of subjects based on length of illness in the control group had a median of 15 months, while in the treatment group had a median of 8 months. Based on the median length of illness, it did not show a significant difference with the value ($p = 0.510$). Based on the results of the study, it can be said that this study has good internal validity. This study was controlled by using a research methodology design through randomization, restriction through inclusion and exclusion criteria, and the data analysis process, so it was assumed to be evenly distributed in this study.



Figure 1. Leprosy patient with a reversal reaction characterized by inflamed and swollen patches on the skin lesions.

Table 1. Characteristics of research subjects

Characteristics	Control (n = 11)	Treatment (n = 11)	p
Gender, n (%)			
- Men	9 (81.8)	10 (90.9)	1.000*
- Female	2 (18.2)	1 (9.1)	
Age, n (%)			0.861*
- 20-30 year	3 (27.3)	5 (45.5)	
- 30-40 year	4 (36.4)	3 (27.3)	
- 40-50 year	1 (9.1)	1 (9.1)	
- 50-60 year	3 (27.3)	2 (18.2)	
Length of illness (months), median (min-max)	15 (1 – 67)	8 (1 – 31)	0.510^

Note: * = fisher exact, $p > 0.05$ i.e. there is no relationship between gender and age with reversal reaction. ^ = mann whitney > 0.05 i.e. there is no difference between length of illness with reversal reaction.

The total research subjects were 19 male (62.9%), while 3 subject were female (37.1%). Previous studies reported the incidence of leprosy in men was more than women (Ayudianti et al., 2014; Primasanti et al., 2016; Rosdiana et al., 2021). The more incidence of leprosy in men is related to the greater mobility of men so that the opportunity for contact with leprosy patients is greater. The age of the most research subjects is in the age range of 20-40 years. Leprosy patients with reversal reactions mostly occur in the productive age range (Rosdiana et al., 2021; Sari & Darmada, 2018). Age is an independent risk

factor for the incidence of reversal reactions that are more likely to be experienced by patients of productive age because they are associated with high activities outside the home, so they have a greater risk of being exposed to sources of leprosy transmission (Rosdiana et al., 2021). Characteristics of the subject based on the length of illness, the results obtained were approximately one year. Another study also stated that the longest patient suffering from leprosy was in the range of 6-12 months (Antonius et al., 2018; Ayudianti et al., 2014; Nazli et al., 2021).

Table 2. The Average IL-6 Levels Pre and Post Treatment

Group	N	Mean $\pm$ SD	Median (min-max)	p
Control	Pre	11	70.67 $\pm$ 35.39	0.016
	Post	11	46.36 $\pm$ 34.76	
Treatment	Pre	11	97.96 $\pm$ 76.50	0.003
	Post	11	16.61 $\pm$ 17.80	

Note: Wilcoxon, $p < 0.05$ is significant i.e. there were differences in IL-6 levels between patients with reversal reactions before and after being given adjuvant therapy with *C. ternatea* flower extract.

The average posttest IL-6 level in the control group was 46.36 pg/ml lower than the pretest 70.67 pg/ml and in the posttest's treatment group, it was 16.61 pg/ml lower than the pretest was 97.96 pg/ml (Table 2). Based on the results of statistical tests in Table 3, the p-value < 0.05 showed a significant difference in the decrease in

IL-6 levels. The results of this study showed that the standard therapy and adjuvant *C. ternatea* extract had more effect on decreasing IL-6 levels compared to the control group which was only given standard therapy. This is shown in table 3, that the decrease in IL-6 in the treatment group was higher than in the control group.

Table 3. The Average Decrease in IL-6 levels

Group	N	Mean $\pm$ SD	Mean Difference	Median (min – max)	p
Control	11	24.31 $\pm$ 33.90	-57.04	7.7 (4 – 73.5)	0.027
Treatment	11	81.35 $\pm$ 71.44		80.4 (0.1 – 187.3)	

Note: Independent *T* test, $p < 0.05$ is significant i.e. there was a difference in the average decrease in IL-6 levels between patients with a reversal reaction before and after being given adjuvant therapy with *C. ternatea* flower extract.

Under normal conditions, IL-6 is regulated and expressed in very small amounts except in chronic infectious conditions such as leprosy reactions or trauma. Increased IL-6 can facilitate the recruitment of inflammatory cells and the formation of immune complexes indirectly that contribute to the pathomechanism of leprosy reactions. IL-6 increases the risk of leprosy reactions by disrupting the balance between T reg cells and Th17 cells. IL-6 migrates to the bone marrow through the bloodstream and triggers the differentiation of naive CD4⁺ T cells into Th17 cells and suppresses the differentiation of naive

**Figure 2.** *Clitoria ternatea* flower.

The flavonoid and phenolic content of *C. ternatea* has an anti-inflammatory effect by inhibiting the release of pro-inflammatory cytokines (Ginwala et al., 2019). Research conducted by (Thilavech et al., 2021), reported that the anti-inflammatory effect of *C. ternatea* flower in this study could be through changes in the signaling pathways of mitogen-activated protein kinase (MAPK) and nuclear factor- κ B (NF- κ B) indicating a cytoprotective and anti-inflammatory role in the pathology of obesity. Meanwhile, in this study, the mechanism used to suppress inflammation, the effect of flavonoid and phenolic content in *C. ternatea* flower inhibits the cyclooxygenation enzyme so that arachidonic acid

CD4⁺ T cells into reg T cells (Siswati et al., 2021).

Several studies have shown that adjuvant administration can affect the levels of pro-inflammatory cytokines and anti-inflammatory cytokines in leprosy patients receiving MDT-WHO therapy. The adjuvant administration of *Nigella sativa* seed supplements in MB type leprosy patients has an effect on decreasing IL-10 levels and increasing IFN- γ levels. Based on these studies, *Nigella sativa* has an inhibitory effect on Th2 cells and their cytokines, as well as a stimulating effect on Th1 and its cytokines (Retno et al., 2017; Primasanti et al., 2016).

metabolism can be inhibited thereby preventing the inflammatory process (Nair et al., 2015). By inhibiting the metabolism of arachidonic acid and the scavenging of free radicals that play a role, the process of prostaglandin formation will be inhibited so that the inflammatory process in the tissue is reduced.

In this study, it was shown that the adjuvant administration of *C. ternatea* flower extract at a dose of 2 grams/day for 30 days was proven to affect reducing IL-6 levels so that it could be used as adjuvant therapy in patients with leprosy reactions. It is hoped that further research will be carried out using stratified doses of *C. ternatea* extract, to determine the optimal dose as adjuvant therapy.

CONCLUSION

There was a significant difference in the mean decrease in IL-6 levels in the control and treatment groups. This study generally proves that adjuvant therapy with *C. ternatea* flower extract affect reducing IL-6 levels in leprosy patients with reversal reactions. This research, it is expected to develop the anti-inflammatory potential of *C. ternatea* as an adjuvant therapy ingredient.

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