

RESEARCH STUDY

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The Effectiveness of Ethanol Extract *Decalobanthus mammosus* (Lour.) A.R.Simões & Staples Tubers Against *Mycobacterium tuberculosis* Induced Lung and Liver Macrophages in Mice

Efektivitas Ekstrak Etanol Umbi *Decalobanthus mammosus* (Lour.) A.R.Simões & Staples Terhadap Makrofag Paru dan Hati Mencit yang Diinduksi *Mycobacterium tuberculosis*

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ABSTRACT

Background: Tuberculosis (TB) cases in Indonesia rank third in the highest number of cases. Incomplete TB treatment causes drug resistance. Ethanol extract of *Decalobanthus mammosus* (Lour.) A.R.Simões & Staples, tubers has the potential as an immunomodulator and antibacterial.

Objectives: This research purpose to decide potency of ethanol essence of *Decalobanthus mammosus* (Lour.) A.R.Simões & Staples tubers on lung and liver macrophage cells in mice induced by *Mycobacterium tuberculosis*.

Methods: Laboratory experimental research using posttest only with control group. The research sample using *Mus mucus* mice was divided into control and experimental groups, with the administration of extract doses of 50 mg/kgBW, 100 mg/kgBW and 150 mg/kgBW, and injection of *Mycobacterium tuberculosis*.

Result: The results showed that *Decalobanthus mammosus* extract dose of 150 mg/kgBW, macrophages were able to overcome *Mycobacterium tuberculosis* infection, with the lowest number of necrotic cells in the lungs. activation of liver macrophages increased at a dose of 50 mg/kgBW extract.

Conclusions: There are differences in macrophages between the liver and lungs. Ethanol Extract of *Decalobanthus mammosus* (Lour.) A.R.Simões & Staples Tubers on lung macrophage cells, the frequency of macrophage activity is much higher compared to the liver.

INTRODUCTION

TB is a communicable disease caused bacteria, usually attacks pulmonary. In 2023, an estimated 10.8 million people worldwide will be infected with TB, including 6.0 million men, 3.6 million women, and 1.3 million children¹. TB exists in all countries and age groups. TB is one of the 10 diseases that cause the largest death in the world. Death was caused in part by resistance to antibiotic therapy to the causative bacteria. Tuberculosis treatment in Indonesia through Anti-Tuberculosis Drug (OAT) is at least 6 months, however, in OAT treatment there is resistance due to incomplete or interrupted treatment². In addition, TB patients undergoing intensive treatment often experience decreased appetite. The effects of treatment with OAT are more pronounced in the first and second weeks³. Some studies report that pulmonary tuberculosis treatment has liver-damaging

side effects, known as Drug-Induced Liver Injury (DILI). Some DILIs are idiosyncratic processes. This mechanism can affect several types of liver cells, such as hepatocytes, and Kupffer⁴. Therefore, prevention and complete treatment are needed by increasing the immune system without damaging the liver organs by using natural ingredients or certain compounds known as immunomodulators⁵. The efforts made by the non-specific immune system are the presence of pathogenic invasion by going through the phagocytosis process of macrophages. *Mycobacterium tuberculosis* (Mtb) infected macrophages respond by secreting pro-inflammatory cytokines such as IL-12 and IFN- γ . Activation of Natural Killer (NK) cells directly or through stimulation by IL-12 produced by macrophages. NK cells activated by IL-12 stimulation produce interferon- γ

cytokines (IFN- γ) that will activate macrophages and increase the eradication of bacteria through phagocytosis activity, so phagocytosis function is important to be optimized in TB patients⁶. Macrophages are responsible for phagocytosis of pathogen-infected cells, so their role in the condition of bacterial infection by TB patients is urgently needed. Activity of macrophage phagocytosis against *Mycobacterium tuberculosis* can be enhanced with immunomodulatory substances⁷, so that the healing process due to infection is faster when the body's immune system functions in optimal conditions. Therefore, it is necessary to discover new treatment alternatives that are effectively able to activate macrophages by utilizing the content of affordable natural ingredients.

Decalobanthus mammosus (Lour.) A.R.Simões & Staples tubers one of the potential plants whose applications are used for biomedicine⁸. Empirically, the bioactive compounds of alkaloids, tannins, flavonoids, and polyphenols, are believed to be anti-inflammatory, analgesic, laxative, swelling reliever, poison neutralizer, coolant, stop bleeding, lower blood sugar levels, fever, and inhibit cancer⁹. *Decalobanthus mammosus* tubers also contains resin, resin, starch, bitter substances, and sap. Fresh sap *Decalobanthus mammosus* tubers contains oxidase enzymes. *Decalobanthus mammosus* tuber n-hexane extract contains quinone, phenolics, triterpenes and steroids. Ethyl acetate extract *Decalobanthus mammosus* tubers contains flavonoids, Quinone, Phenolic triterpene and steroids¹⁰. Research on ethyl acetate fraction of methanol extract of *Decalobanthus mammosus* has antiinfluenza A activity of the H1N1 subtype and has the potential to be an antiviral agent against SARS-CoV-2 through virus inhibition tests, RT-PCR, and tests Plate¹¹. Agil et al's research conveyed Phytochemical tests detected several *Decalobanthus mammosus* compounds such as polyphenols, terpenoids, and triterpenoids, which showed inhibiting activity against Mtb in the Middlebrook 7H10 medium¹². Scientifically, the diversity of pharmacological effects of *Decalobanthus mammosus* tubers as immunomodulators has not been widely reported, so research on the role of *Decalobanthus mammosus* tubers extract on phagocytosis of macrophage in the lungs and livers of mice infected with Mtb in vivo is needed.

METHODS

This research method is a laboratory experiment with a posttest-only control group design. The study was divided into a placebo group and an Experimental Group (EG). The clinical trial served as comparison to assess

effectiveness that intervention on the lungs and livers of mice. Data analysis was performed using statistical tests with the Anova One Way SPSS program to determine treatment effect between groups. Ethics approval was obtained from the Research Ethics Committee of the Ministry of Health Polytechnic of Surabaya, number EA/2126/KEPK-Poltekkes_Sby/V/2024, dated March 18, 2024.

Ethanol Extract

Decalobanthus mammosus are dried by drying them in the sun or using an oven at 40°C until dry. Then it is mashed so that simplicia powder is obtained. Simplicia was extracted using 70% ethanol (1:5 ratio) for 1 hour with occasional stirring. The resulting filtrate is taken and the residue is re-extracted using ultrasound 3 times. Filtrate thickening is carried out using Rotary Evaporator until ethanol extract is obtained. The extracts obtained were then thickened by evaporation over the waterbath so that ethanol extract of thick *Decalobanthus mammosus* was obtained and phytochemical tests were carried out by spectrophotometry method¹³.

Test of Ethanol Extract of *Decalobanthus mammosus* (Lour.) A.R. Simões & Staples on Macrophages

The study sample was male *Mus musculus* mice (n=30) with a body weight ranging from 15 to 25 grams, each consisting of six mice. The experimental group consisted of four groups. The normal group (K1) without Mtb, the positive group (K2) was given (Na.CMC 0.5%+Mtb infection), and the extract treatment group was 50 mg/kgBW+Mtb infection (EG1), the extract group was 100 mg/kgBW+Mtb infection (EG2), the extract group was 150 mg/kgBW+Mtb infection (EG3). On the 21st day, the mice were anesthetized and euthanized with ketamine. A surgical procedure is performed to extract the lung and liver tissue of mice, examined under a microscope using Hematoxylin Eosin (HE) staining. The severity of histopathological effects of the lungs and liver is determined by the presence of necrosis in the lungs and liver.

RESULTS AND DISCUSSIONS

Research on the effectiveness of ethanol extract *Decalobanthus mammosus* (Lour.) A.R.Simões & Staples tubers on macrophage in the lungs and liver of mice induced by *Mycobacterium tuberculosis*. Phytochemical test to determine the bioactive potential of tubers using an ethanol extraction process. This research was conducted at the Health Polytechnic, Ministry of Health Surabaya.

Table 1. Phytochemical Analysis of *Decalobanthus mammosus* (Lour.) A.R.Simões & Staples Tubers

Parameter	Mean $\pm$ RPD(%)
Flavonoid	0.002 $\pm$ 1.72
Polifenol	6.0 $\pm$ 1.2
Tanin	4.2 $\pm$ 0.8
Alkaloid	17.78* $\pm$ 1.17*
Saponin	6.45 $\pm$ 3.2

*The largest phytochemical analysis content in alkaloids
RPD= Relative Percent Difference

Phytochemical compounds had been an important function in protection and therapy from bacteria infections included tuberculosis. Specifically, bioactive compounds medicines, like secondary products and antioxidants, were recorded to have anti-tubercular activity. The overview have abridged profit of extracted compounds and review ability process involved in precaution and medicine of tuberculosis¹⁴. Based on the results of phytochemical studies (Table 1), the ethanol extract of *Decalobanthus mammosus* (Lour.) A.R. Simões & Staples contains flavonoids, quinones, phenolic compounds, terpenoids, and steroids, most of the plants contain alkaloids¹⁵. Extensive research indicates that bioactive plant compounds such as flavonoids, alkaloids, terpenoids, and phenolic exhibit significant antibacterial properties against *Mycobacterium* species, inhibiting the bacteria's growth and replication, and sometimes, causing cell death. Phytocompounds act by disrupting bacterial cell walls and membranes, reducing enzyme activity, and interfering with essential metabolic processes. The combination of these processes reduces the overall survivability of the bacteria. Beyond their direct antibacterial effects, certain phytochemicals demonstrate synergy with standard tuberculosis antibiotics, thereby enhancing therapeutic efficacy and mitigating the risk of drug resistance. Notably, these compounds also offer hepatoprotective benefits by reducing inflammation and necrosis caused by isoniazid and ethambutol. Consequently, phytochemicals represent a promising field of research for the

development of new TB medicines¹⁴. In addition, *Decalobanthus mammosus* also has anti-inflammatory properties which are important for surviving severe cytokine storms, inflammation caused by respiratory microbial infections⁸. The development of new, more effective and safer therapies is a priority in TB treatment⁴. The extract can serve as an immunomodulatory agent that increases the activity of macrophages, which plays an important role in combating *Mycobacterium tuberculosis*¹². This research is a complementary therapy for TB. As a traditional medicinal plant with antibacterial potential, get used as therapy to increase the effectiveness of TB treatment¹⁶.

Effect of Ethanol Extract of *Decalobanthus mammosus* (Lour.) A.R. Simões & Staples on Lung Macrophages

Macrophages function as innate immunity, the initial defense against infection. Macrophage cells has an essential role in the phagocytosis and play as Antigen Presenting Cells (APC) which initiate and direct immunity towards the cellular immunity system mediated by T cells in infections by intracellular bacteria such as *Mycobacterium tuberculosis*¹⁷. Increasing macrophage phagocytic activity in vivo in mice model of TB infection aims to reveal the role of ethanol extract of *Decalobanthus mammosus* tubers. Immunomodulatory activity testing in this study was carried out with three dose variations, treatment levels of 50 mg/kgBW, 100 mg/kgBW, and 150 mg/kgBW.

Table 2. Test Results of Ethanol Extract of *Decalobanthus mammosus* Tubers on Lung Macrophages Necrosis in Mice

Group	n	Mean	SD
K1	6	1.4	2.93
K2	6	2.1	3.39
EG1	6	4.7	5.88
EG2	6	2.4	2.82
EG3	6	0.8*	1.06*

*The smallest mean and standard deviation of necrotic lung macrophage cells
SD: Standart Deviation

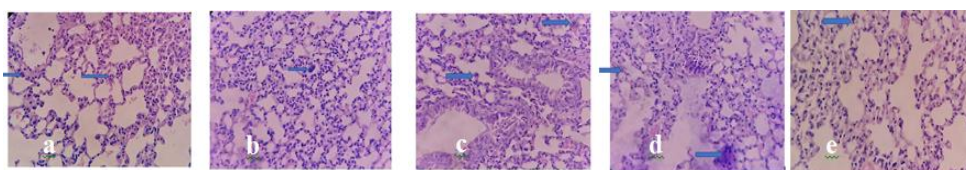


Figure 1. Blue Arrows Show Necrotic Lung Macrophages, with Purplish-Blue Macrophages. (a) Negative group (K1), (b) Positive group (K2), (c) 50 mg/kgBW (EG1), (d) 100 mg/kgBW (EG2), (e) 150 mg/kgBW (EG3)

Based on the ANOVA test, the sig value shows p-value 0.08, the results show that there is no significant difference between groups. This means that all EGs did not have significantly different activities with the positive control. However, the highest dose showed an increase in activity compared with other doses.

Administration of *Decalobanthus mammosus* ethanol extract at a dose of 150 mg/kgBW to the treatment group showed an increase in the number of lung macrophages and fewer lung cells experienced necrosis compared to other treatments (Table2). The extract of lung cells from mice infected with *Mycobacterium tuberculosis* at a dose of 150 mg was

effective in activating lung macrophages, with an average of 0.8 necrotic cells. In vivo testing of increased phagocytosis activity of macrophages in TB infection model mice purposed to determine the effectiveness of ethanol concentrate of *Decalobanthus mammosus* tuber. The test was carried out by performing a histopathological examination of the lungs of mice with necrosis cells (Figure1). Based on the appearance of necrosis cells, it was obtained that the 150 mg/kgBW dose test showed the least number of necrosis cells than EG1 and EG2. This is possible because there are bioactive compounds that are able to activate lung macrophages and cells that have undergone little damage (necrosis).

The phytochemical results (table 1) show that *Decalobanthus mammosus* tubers ethanol extract contains including alkaloid, polyphenols, saponin, bioflavonoids, tannins. Characteristic Alkaloids soluble in acidic conditions and permeable to lipid membrane make as a candidate Treatment. Alkaloids have inherently appear chemical substances of small molecular comprised nitrogen in the heterocyclic, Potency includes anti-proliferative, growth suppression, antidepressant, analgesic, spasmolytic, anticancer, anti-inflammatory, antimicrobial, Pesticide, and oxidation inhibitor¹⁸. The numerous biological activities, beneficial alkaloids as adjuvant therapy to develop drug-sensitive TB, relieve drug reactions, and antimicrobial resistance. In recent times, alkaloids demonstrated potent antimycobacterial activity against strains of *Mycobacterium*¹⁴. Secondary metabolites of the alkaloid compound group are thought to have similar role of the cytokine IFN- γ in maintaining the immune response and enhancing the nonspecific immune response in the form of increased specific immune responses to activate macrophages to perform phagocytosis of infectious agents entering the body⁶. Saponins are chemical compounds that can increase the activity of the body's immune system, and have anti-bacterial and anti-viral properties¹³. Some of the compounds of *Decalobanthus mammosus* tuber are polyphenols, terpenoids, and triterpenoids, which exhibit inhibitory activity against *Mycobacterium tuberculosis*. Several plants with terpenoid content and showing antituberculosis activity have been identified, including *Byrsonima crassa*, and *Juniperus communis* L. (*Cupressaceae*)¹². Flavonoid play a role by increasing IL-2 activity and lymphocyte proliferation. The proliferation of lymphocytes will affect the CD4 cells, then the Th1 cells are activated. flavonoids are also likely to trigger the

proliferation and differentiation of suspected T cells and B cells through the production of cytokines IL-2, IL-4, and IL-1. Tannins can act as immunostimulators by helping to optimize immune system function, by increasing the phagocytosis activity of macrophages in destroying microbes⁶.

Lung tissue necrosis due to *Mycobacterium tuberculosis* infection usually occurs in the form of granulomas, which are typical structures that form as part of the immune response. Early in the study, lesions were detected but in low amounts, and their expression increased significantly only after the lesions began to undergo necrosis. There is an image of necrosis that is associated with the onset of cellular hypersensitivity (delayed hypersensitivity) against *Mycobacterium tuberculosis*. Based on the study, necrosis was found in the seventh week in the form of caseous necrosis appearing in the center of the granuloma. The emergence of this necrosis is related to dysregulation of host lipid metabolism due to interaction with Mtb and inflammatory mediators such as TNF- α which stimulates granuloma formation, as a form of good body immune response¹⁹.

Effect of Ethanol Extract of *Decalobanthus mammosus* (Lour.) A.R. Simões & Staples on Liver Macrophages

In this study, the number of necrosis epithelial cells was measured for each mice sample infected with MTb. Evaluation was conducted in a group of mice treated with ethanol extract of *Decalobanthus mammosus* and a control group that did not receive treatment. The following table presents the total number of necrosis cells and the average number of necrosis cells for each sample:

Table 3. Test Results of Ethanol Extract of *Decalobanthus mammosus* Tubers on Liver Macrophage Cell Necrosis in Mice

Group	n	Mean	SD
K1	6	7.5	14.3
K2	6	41.7	41.9
EG1	6	6.3*	6.4*
EG2	6	33.3	30.3
EG3	6	60.2	58.2

* The smallest mean and standard deviation of necrotic liver macrophage cells

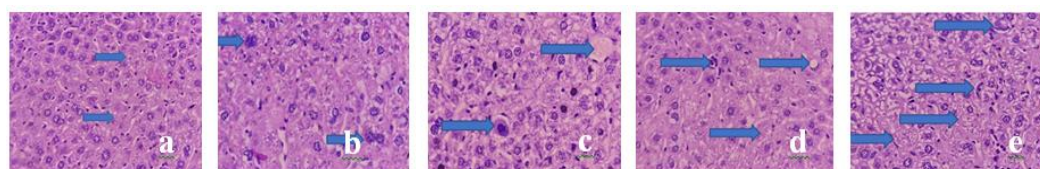


Figure 2. Blue Arrows Show Necrotic Liver Macrophages. (a) Negative group (K1), (b) Positive group (K2), (c) 50 mg/kgBW (EG1), (d) 100 mg/kgBW (EG2) (e) 150 mg/kgBW (EG3)

Based on the ANOVA test, the shows p-value 0.24 the results show that there is no significant difference between groups. This means that a dose of 50 mg/kgBW showed better liver cell activity in mice stimulated by *Mycobacterium tuberculosis*. The EG1 treatment group was given ethanol extract of *Decalobanthus mammosus* tubers, showing the lowest number of macrophages compared to groups. These results show that the smallest dose of ethanol extract of *Decalobanthus mammosus*

tubers is able to provide a therapeutic effect in reducing liver tissue damage in mice infected with *Mycobacterium tuberculosis*. Experimental groups 2 and 3 showed a high number of necrotic cells compared to positive control group. This shows significant damage. *Decalobanthus mammosus* ethanol extract has not been maximized in fighting infection so that necrosis occurs. In addition to the lungs, *Mycobacterium tuberculosis* can also spread to other body part, like the liver. Liver TB is predicted to

occur in about 1% of active tuberculosis cases, with 79% due to micronodular and 21% macronodular native liver tuberculosis²⁰. These TB bacteria reach the liver via hematogenous or lymphatic spread, more commonly via hematogenous. Hematogenous spread in military TB occurs due to pulmonary TB infection (active or inactive) via the hepatic artery, whereas via the portal vein in focal hepatic TB or complex primary TB. The occurrence of primary TB in the liver itself is pretty rare. Furthermore, the liver will respond with the formation of both caseous and non-caseous granulomas. In miliary TB, multiple small TB shows central caseation and fibroid necrosis²¹. The characteristic features of tuberculosis are chronic granulomatosis accompanied by caseous necrosis. Regarding its architecture, the liver constitutes a massive organ with relatively dense tissue and Unlike pulmonary tissue, this structure lacks internal cavitation. However, once the accumulation of necrotic debris surpasses a critical limit, after the proliferation of *Mycobacterium tuberculosis* in the liver, macrophages may not be enough to remove it, and for then, the *Decalobanthus mammosus* tubers extract cannot penetrate to destroy the *mycobacteria* interior, which causes the healing of liver tissue to be significantly impaired. Inhibited transcription factors lead to the lack of regulation of T-cell expansion and function, that greatly donate to continuing immune tolerance and liver macrophages within recognizing MTb²². The dissimilar immunity and corporate form might lead to significant difference disease among of hepatic and pulmonary tuberculosis. Presently, several review that center on the pathology differences between pulmonary and hepatic tuberculosis are available.

From the explanation above, administration of Ethanol Extract of *Decalobanthus mammosus* allows the development of more phagocytic liver macrophages in mice infected with *Mycobacterium tuberculosis*. Further research is needed regarding the appropriate dosage and preparation of *Decalobanthus mammosus* tubers. Study of inflammatory cytokine expression as a phagocytic activity of macrophage cells.

CONCLUSIONS

In conclusion, we found that there are differences in macrophages between the liver and lungs. Ethanol Extract of *Decalobanthus mammosus* (Lour.) A.R.Simões & Staples Tubers on lung macrophage cells, the frequency of macrophage activity is much higher compared to the liver, which is induced by *Mycobacterium tuberculosis*. Immunity and structural characteristics may be important influencing factors.

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CONFLICT OF INTEREST AND FUNDING DISCLOSURE

The authors declare no conflict of interest related to article. This study was funded by the authors.

AUTHOR CONTRIBUTIONS

EDW: conceived the study and statistical analysis; WD and FRPD: supervision the experimental procedures and data collection; K: writing initial draft, histopathological analysis, analysis to data. All authors critically reviewed and revised the manuscript for intellectual content, approved the final version, and agreed to be accountable for all aspects of the work.

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