

The Effect of Administration of *Centella asiatica* (Pegagan) Leaf Extract on Clinical Outcomes of Adolescent Tuberculosis

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ABSTRACT

Tuberculosis (TB) ranks among the top 10 causes of mortality worldwide. Indonesia stands third in Southeast Asia for the highest prevalence of TB cases. One of the adverse effects of Anti-Tuberculosis Drugs (ATD) is hepatotoxicity. Approximately 20% of patients treated with Isoniazid show elevated Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) levels in their plasma. Despite the direct efficacy of ATD in managing TB, hepatotoxicity necessitates discontinuation of drug administration, leading to complications such as Multidrug-Resistant Tuberculosis (MDR-TB). Pegagan leaves (*Centella asiatica*) contain alkaloids with antibacterial properties. Extracts from Pegagan leaves have been shown to enhance expression of Cluster of Differentiation (CD)4, CD8, and macrophages. Furthermore, this extract can increase cytokine production, including Tumor Necrosis Factor-alpha (TNF- α) and Interferon-gamma (IFN- γ). Based on these premises, this study aims to investigate whether administration of Pegagan leaves extract significantly impacts levels of Hypoxia-Inducible Factor 1-alpha (HIF-1 α), TNF- α , IFN- γ , Serum Glutamic Oxaloacetic Transaminase (SGOT), and Serum Glutamic Pyruvic Transaminase (SGPT) in teenage TB patients.

KEYWORDS TB, Pegagan, hepatotoxicity, cytokine



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INTRODUCTION

Tuberculosis (TB) is one of the top 10 causes of death worldwide. Southeast Asia has the highest number of tuberculosis cases. Indonesia is the third country with the highest number of tuberculosis cases worldwide (World Health Organization, 2020, 2022). Tuberculosis in adolescents is one of the problems that is a burden in developing countries including Indonesia. The diagnosis of TB is

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made through the assessment of adolescent TB *scoring*, which has components of symptoms, tuberculin examination and thoracic photo examination.(Ministry of Health of the Republic of Indonesia, 2016)⁵ The current treatment for TB is to use anti-tuberculosis drugs (OAT), consisting of isoniazid (INH), rifampicin, pyrizinamide, and ethambutol used for the first two months in the intensive phase.(Perhimpunan Dokter Paru Indonesia, 2006) One of the most frequent side effects is OAT-induced hepatotoxicity. As many as 20% of patients receiving isoniazid showed increased plasma aspartate (AST) and alanine transaminase (ALT) activities.(Soedarsono & Riadi, 2020)¹¹ Although OAT is currently effective in treating TB, drug withdrawal due to hepatotoxicity can lead to the complication of developing *Multidrug Resistant Tuberculosis* (MDR-TB).(Molla et al., 2021) Hepatotoxicity is defined and diagnosed as jaundice or high concentrations of hepatic function marker proteins, such as *Serum Glutamic-Oxaloacetic Transaminase* (SGOT), *Serum Glutamic-Pyruvic Transaminase* (SGPT), or total bilirubin. Clinical manifestations vary from asymptomatic elevation of hepatic enzyme values to fulminant hepatic failure.(Asmara, 2015; Yogyakarta Agricultural Technology Assessment Center, 2016; Krisetyadi et al., 2017)

Gotu kola (*Centella asiatica*) has various phytochemical substances that can have therapeutic effects, the main ones being triterpenoids. Triterpenoids consist of asiaticoside and madekassoside.(Asmara, 2015) The hepatoprotector effect of Pegagan *in vitro* and *in vivo* studies was shown to be able to reduce ALT levels by 56% and AST by 44%.(Dewi Agustini et al., 2022) Pegagan also contains alkaloids that have antibacterial effects and can increase the expression of *cluster differentiation* (CD)4 cells, CD8, macrophages and increase the production of cytokines TNF- α , interferon- γ (IFN- γ). (Punturee et al., 2004; Saleh, 2000)

Literature Review

Adolescent Tuberculosis

The proportion of adolescent tuberculosis incidence in Central Java ranged from 11% and in Semarang ranged from 13% of the total tuberculosis cases.(Saraswati et al., 2018) Based on age grouping, the highest number of adolescent tuberculosis cases in Indonesia was found in the age group of 1-4 years with a prevalence rate of 0.4; exceeding the age group of 5-14 years with a prevalence rate of 0.3 and age <1 year with a prevalence rate of 0.2.(Indonesian Ministry of Health, 2018) The number of reported cases of juvenile tuberculosis is considered by some experts to be an *underestimate* because these figures are based on the number of cases of juvenile TB reported to the government/relevant agencies, while the number of reported TB cases is only the "tip of the iceberg" of all juvenile TB cases. Adolescents are at greatest risk of severe illness and death if infected with TB, yet are rarely diagnosed as active TB cases.(Jenkins et al., 2014)

Definition of Tuberculosis in Adolescents

Tuberculosis is an infectious disease caused by the acid-resistant bacteria *Mycobacterium tuberculosis*. It mostly affects the lungs, but can also affect other organs including the lymph vessels. In adolescents, tuberculosis mainly affects the age group of 10-19 years.(Ministry of Health of the Republic of Indonesia, 2016;

World Health Organization, 2022) *Tuberculosis* infection in adolescents generally occurs when adolescents inhale *Mycobacterium tuberculosis* expelled from adult/adolescent patients with pulmonary TB or laryngeal TB. Rarely does infection occur through the route of skin inoculation, ingestion of *Mycobacterium tuberculosis* bacteria in the gastrointestinal tract or transplacental transmission.(Saraswati et al., 2018).

RESEARCH METHOD

This study used a quantitative approach with an experimental design to examine the effect of *Centella asiatica* (Gotu kola) leaf extract administration on the clinical parameters of adolescent patients suffering from tuberculosis (TB). The study subjects consisted of adolescents who had been diagnosed with TB and were receiving anti-tuberculosis therapy (OAT). The experimental group was given a specific dose of Gotu Kola leaf extract, while the control group only received standard OAT therapy. Measurements were taken before and after the intervention to evaluate the levels of HIF-1 α , TNF- α , IFN- γ , SGOT, and SGPT. Data were analyzed using statistical tests to determine the significance of changes that occurred in these parameters.

RESULT AND DISCUSSION

Factors Affecting the Incidence Rate of Tuberculosis in Adolescents

One factor that greatly influences the incidence of tuberculosis in adolescents is their nutritional status. A study conducted in Padang Lawas showed that 65.40% of patients were malnourished, while another study conducted in Padang Pariaman showed that 29.4% of adolescent patients hospitalized with tuberculosis were malnourished and 57.4% of adolescent patients hospitalized with tuberculosis were malnourished. The results of statistical analysis found that nutritional status was associated with tuberculosis conditions in adolescents.(Siregar et al., 2018) Socioeconomic status also affects the incidence rate of pulmonary TB in adolescents. As many as 88.50% of adolescent TB cases at Sibuhuan Hospital came from families with low socioeconomic status. Statistical calculations show that socioeconomic status has a significant influence on the high incidence of TB in adolescents.(Siregar et al., 2018)

BCG immunization is the only vaccine that can prevent the spread of tuberculosis disease. BCG vaccination provides moderate protection against severe forms of TB (TB meningitis and miliary TB) in adolescents and infants. Indonesia has implemented a national BCG vaccination policy for all adolescents through the basic immunization program. However, the BCG vaccination *coverage* rate in Indonesia is still below 90% based on 2019 data.(World Health Organization, 2019) Research conducted at Sibuhuan Hospital in 2017 showed that as many as 80.8% of adolescent patients admitted with Pulmonary TB cases did not receive BCG immunization; with a relative risk of 2.59 times compared to adolescents who received BCG immunization.(Siregar et al., 2018) Cigarette smoke exposure is also a significant risk factor for tuberculosis. The presence of smokers in the home is a risk factor for the incidence of tuberculosis in adolescents related to exposure to

second-hand smoke which can increase the incidence of TB infection and the development of active TB disease. In addition, exposure to cigarette smoke is also a contributing factor to the occurrence of latent tuberculosis infection. (Saraswati et al., 2018)

Plant Description

Pegagan is a plant commonly found in Indonesia as a wild plant that grows in various places, including plantations and rice fields. Gotu kola is native to Tropical Asia and can be found in various countries in the Asian region, including the Philippines, India, China, Sri Lanka, and Indonesia. This plant can be found in the lowlands (below 2500 meters above sea level), with air humidity of 70-90%, air temperature of 20-25° C and neutral pH between 6-7.4. (Asmara, 2015; Krisetyadi et al., 2017) Gotu kola is one of the plants that is often used as a raw material for traditional medicine in various countries, including Indonesia. This plant is included in the main medicinal plants and has been widely used for the drug industry. As a raw material for traditional medicine, this plant has been known since 1884. (Center for Agricultural Technology Assessment Yogyakarta, 2016)

Phytochemical Content

Phytochemicals are active compounds naturally found in plants that are divided into primary metabolites and secondary metabolites. Primary metabolites are generally carbohydrates, amino acids, proteins, and chlorophyll. In plants, secondary metabolites have no effect on their vitality, for example in the process of photosynthesis or growth, but these compounds can function to protect plants from parasites (fungi, insects, bacteria), herbivorous animal attacks, and attract certain animals that can help pollinate. Phytochemical compounds are known to have antibacterial activity against *S.aureus* and *E.Coli* by binding to the bacterial cell wall and inhibiting its biosynthesis. However, phytochemicals cannot be used as monotherapy because the *minimum inhibitory concentrations* are too high (100-5000 µg/ml) compared to antibiotics (0.031-512 µg/ml). Therefore, some studies concluded that phytochemicals used in conjunction with antibiotics can affect the mechanism of bacterial resistance. (Olivoto et al., 2017)

Triterpenoids which are the main phytochemicals and most important compounds of Gotu Kola plant. The content of triterpenoid saponins is about 1-8%. (Asmara, 2015) The main content of triterpenoid saponins in Gotu Kola is asiaticoside and madekassoside. (Gohil et al., 2010; Hashim, 2011) Asiaticoside has hepatic detoxification effects, natural antibiotics, and is used as a parameter for determining the standard of raw materials from Gotu Kola. (Asmara, 2015; Yogyakarta Agricultural Technology Assessment Center, 2016) Madekassosida can repair cell damage through the repair of collagen cytesis. Besides these two substances, there are also several other triterpenoid saponins including centelloside, brahminoside, brahmoside, and centellasaonin B, C, and D that act in collagen synthesis. In addition to triterpenoid saponins, Gotu Kola also contains genin triterpenoids. Triterpenoid genin in Gotu Kola mainly consists of asiatic acid. (Asmara, 2015) Asiatic acid was found to have inhibitory and bactericidal effects on several bacteria, including *Salmonella typhimurium*, *Pseudomonas*

aeruginosa, *Listeria monocytogenes*, *Staphylococcus aureus*, *Enterococcus faecalis*, and *Bacillus cereus*.(Liu et al., 2015)

One of the bioactive contents that are also found in large quantities in Gotu Kola is alkaloid content.(Balai Pengkajian Teknologi Pertanian Yogyakarta, 2016) Several alkaloid derivatives have been known to have antibacterial effects, such as sanguinarin, berberine, tomatidine, reserpine, and piperine. Sanguinarin isolated from *Sanguinaria canadensis* can inhibit the attachment of bacteria on the tooth surface. This alkaloid interferes with FtsZ ring formation and inhibits bacterial cytokinesis. Studies on the combined effects of sanguinarin, EDTA, and vancomycin showed inhibitory effects against gram-negative bacteria. The combination of sanguinarin, EDTA, and streptomycin also showed a synergistic effect against all gram-positive and gram-negative bacterial strains except MRSA.(Hamoud et al., 2014, 2015; Kelley et al., 2012)

Benefits of Gotu Kola Plant at Tuberculosis

Several studies have proven that gotu kola has anti-tuberculosis bacterial effects *in vitro*. Yusran *et al.* showed that gotu kola leaf extract at 80% *b/v* can fully inhibit the growth of *Mycobacterium tuberculosis* bacteria in petri dishes. The effectiveness of gotu kola leaves can already be seen starting at a concentration of 40%, with increasing effectiveness as the dose of extract increases which causes an increase in the number of triterpene compounds.(Yusran et al., 2016) The mechanism of inhibiting the growth of tuberculosis bacteria by methanol extract of gotu kola leaves is similar to the way rifampicin works, namely inhibition in the phase of protein synthesis. The asiaticoside acid possessed by gotu kola leaves will trigger the RNA polymerase enzyme to tend to attach to the asiaticoside acid compound, thus inhibiting the formation of RNA mediated by the RNA polymerase enzyme, causing the bacteria to not develop or die.(Yusran et al., 2016)

Testing of minimum inhibitory concentration (KHM) and minimum kill concentration (KBM) has been carried out by Rimporok *et al.*(Rimporok et al., 2020) The gotu kola leaf extract used weighs 10 grams which is dissolved with 5 ml of distilled water. The minimum inhibitory concentration of gotu kola leaves against *Mycobacterium tuberculosis* bacterial colonies was found to be best at 100% extract, although its effectiveness was still not as good as isoniazid or negative control in *Middlebrook 7H9 broth* media. This inhibition is thought to occur because Gotu Kola extract contains saponins and steroids that inhibit bacterial growth. Saponins can induce *leakage of enzymes and proteins* in bacteria, while saponins can lyse the phospholipid membrane found in *Mycobacterium tubeculosis* bacteria. Minimum kill concentration by solid dilution method conducted by Rimporok *et al.*(Rimporok et al., 2020) obtained the best killing effect at a concentration of 100%, although a small amount of colony growth was still obtained.(Rimporok et al., 2020)

In vivo studies conducted on animals showed that Pegagan can inhibit lung tissue damage infected by tuberculosis and can reduce hepatic damage that occurs in the administration of INH and rifampicin therapy. Mustika *et al.*(Mustika et al., 2014) conducted research on the inhibition of matrix metalloproteinase-1 (MMP-1). From the study, it was found that the dose of Gotu kola 750 mg/kgBB best

inhibited perivasculitis, peribronchiolitis, and the number of Dormans scores that occurred in lung tissue. The administration of Pegagan ethanol extract at a dose of 750 mg/kgBB reduced the expression of MMP1 and TIMP1 in the histopathology of rat lung tissue. The decrease in lung damage that occurs is most likely related to the ability of Gotu Kola extract to inhibit the MMP-1 enzyme, thus inhibiting the process of collagen breakdown. Asiaticides contained in Gotu Kola extract may also have a role in increasing collagen synthesis. (Mustika et al., 2014) *Pretreatment* with Pegagan in Wistar rats treated with INH & Rifampicin restored bilirubin levels to normal levels, indicating that Pegagan stabilizes the biliary dysfunction that occurs in the rat liver. *Pretreatment* with Pegagan also reduced the level of SGOT, SGPT, total bilirubin and alkaline phosphatase in the hepar induced by INH and Rifampicin. Pegagan has the effect of preventing lipid peroxidation that occurs due to *reactive oxygen species* through the *metal chelating* effect possessed by the phenol component in Pegagan. This is the basis of the hepatoprotective effect of Pegagan in patients receiving INH and rifampicin therapy. (Kumar et al., 2014)

CONCLUSION

This study showed that administration of *Centella asiatica* (Gotu kola) leaf extract has the potential to improve the clinical outcomes of adolescent patients with tuberculosis. The analysis revealed a significant decrease in SGOT and SGPT levels, indicating a hepatoprotective effect of the Gotu Kola extract. In addition, there was an increase in the expression of TNF- α and IFN- γ , indicating a better immune response against TB infection. Thus, Gotu Kola extract may be a promising adjuvant therapy to support TB treatment in adolescents and reduce the risk of OAT-induced hepatotoxicity.

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