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by Yulia Yusrini

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R Tayeb[1], G Alam[1], E Pakki[1] and Y Y Djabir[1]

[1]Faculty of Pharmacy, Hasanuddin University, Indonesia

E-*mail*: rosanytayeb@yahoo.com

Abstract. The use of fixed-dose combination of antituberculosis drugs (FDC-TB) is used as firstline treatment in tuberculosis. These drugs also have side effects that can damage the liver and kidneys. This study aimed to determine the effect of the paliasa "Tea Bag" hepatoprotector preparation on ALT and AST levels in rats as a supporting therapy for the use of FDC-TB. 20 rats and were divided into 5 groups, Group I was given 1% NaCMC, group II was given FDC-TB suspension, group III was given paliasa tea, group IV was given paliasa tea, and group V was given curcuma suspension, 4 hours later in group III and IV was given FDC-TB suspension, after that 4 hours later again group IV was given paliasa tea. Treatment was given 28 days orally. After the last 24 hours of treatment, blood sampling and measurement using a humanolyzer were carried out. The results showed that the administration of Paliasa Tea Bag can be used as supporting therapy with the use of 2 times a day. It was concluded that the administration of paliasa "tea bag" showed hepatoprotective activity in reducing ALT and AST levels following administration of fixed-dose combination antituberculosis drugs for 28 days.

1. Introduction

Based on the 2015 Global Tuberculosis Report released by World Health Organization (WHO), as many as 58% of new tuberculosis (TB) cases occurred in Southeast Asia and the Western Pacific region in 2014. India, Indonesia and China are the countries with the highest number of TB cases in the world, with 23%, 10% and 10% of the total events in the world, respectively. Indonesia is ranked second alongside China, where 1 million new cases are estimated to occur in Indonesia [1]. WHO reports that as many as 1.5 million people die from TB including 1.1 million HIV negative and 0.4 million HIV positive [1].

The Indonesian Ministry of Health's National TB Management Guidelines for TB treatment in 2008 highly recommends the use of fixed-dose combination of antituberculosis drug (FDC-TB) since it is more profitable [2]. This first line of anti-TB combines 4 anti-TB drugs, namely, Rifampicin, Isoniazid, Ethambutol, and Pyrazinamide [3]. Despite being effective to treat TB, these drugs also have side effects on the kidneys and liver. Rifampicin is a strong inducer of CYP2E1, where this enzyme can regulate the production of hepatotoxic agents and the formation of free radicals by metabolites of rifampicin, while isoniazid will be converted into a reactive metabolite, mono acetyl hydrazine (MAH) which is toxic to tissues with respect to free radical activity. This MAH compound will trigger detrimental effects lead to hepatotoxicity in relation to the mechanism of the cytochrome P450 enzyme [4]

About 10-20% of patients for 4-6 months with isoniazid therapy experience mild liver dysfunction. The high incidence of hepatotoxicity was reported in patients receiving combination of rifampicin with pyrazinamide, from 48 cases reported to be known in the second month of therapy, 37 patients recovered from TB while 11 patients died of liver failure. Rifampicin causes an increase in ALT enzymes in the first 8 weeks of therapy in 10 -15% of patients, with less than 1% of patients showing hepatotoxicity [5]. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) level in the plasma indicate the integrity of the liver cells. The increase in both enzymes may reflect the level of damage of the liver cells. The higher the increase of ALT and AST levels means the more significant the damage to hepatocytes [6].

Paliasa (*Kleinhovia hospita* L.) is a native plant to Indonesia empirically used as a cure for hepatitis. Cycloartane triterpenoid compounds isolated from *Kleinhovia hospita* L. consist of four types, namely kleinhospitines A, B, C, and D, where kleinhospitines C and D show hepatoprotective activity on damaged hepatocyte cell culture induced by H_2O_2 [7]. The eleutherol and kaemferol 3- O-B-D-glucoside compounds have also been isolated from the leaves of *Kleinhovia hospita* L. which has antioxidant activity [8].

In addition, paliasa has also been made in various dosage forms including as conventional tea and "Tea Bag". Previously, it was found that Paliasa tea bag elicits effect as a hepatogenerative agent, shown by a lower level of ALT and AST and increased levels of antioxidant glutathione in paracetamol-induced rats [9]. In addition, has shown that extracts in the tea bag preparation with the doses of 179; 358; 537; 176; 895; 1074 mg/kg BW did not cause toxic effects on the animal model. Based on that, this study aimed to investigate the paliasa “Tea Bag” preparation can be used as supporting therapy to improve hepatocyte function in rats treated with FDC-TB[10].

2. Material and Methods

2.1. Preparation of Study Animals

Twenty healthy Wistar type male rats (*Rattus norvegicus*) weighing 150-200 grams were caged in well-aerated cages. Before the treatment was carried out, rats are adapted first for seven days while given enough food and water.

2.2. Preparation of Paliasa “Tea Bag”

A total of 5 packets of paliasa "Tea Bag" were weighed and the average weight was calculated. One packet of "tea bag" was brewed with 200 ml of hot water under constant stirring and left for ± 5 minutes. The brewed tea was put in a bottle and ready to be used for animal treatment.

2.3. Preparation of FDC-TB Suspension

The dose of FDC-TB for rats is 133 mg/200g BW. As much as 6.6 grams of FDC-TB was weighed then put into mortar and added little by little of 1% NaCMC colloidal solution while grinded until the drug was evenly dispersed. The suspension was then added with 1% NaCMC colloid suspension in a volumetric flask to reach the volume of 100 mL.

2.4. Preparation of Curcuma® Suspension

Curcuma® is a standardized herb used to improve liver function, in this study Curcuma® is used as a comparison of the hepatoprotector activity of paliasa extract in improving liver function. The dose of Curcuma® as a hepatoprotector for the study animals is 6.17 mg/kg BW = 1.234 mg/200g BW of rats.

0.64 grams of Curcuma® tablets that had been crushed was weighed and then put into mortar and added little by little 1% NaCMC solution while grinded until Curcuma® was evenly dispersed. The suspension was then added with 1% NaCMC in a volumetric flask to reach the volume of 25mL.

2.5. Treatment on Study Animals for Measurement of ALT and AST Levels

The research was carried out using 20 experimental animals of of male rat (*Rattus novergicus*),

which were divided into 5 groups, each group consisted of 4 rats, namely:

- Group I: Treated with 1% NaCMC suspension.
- Group II: Given treatment with FDC-TB with the dosage of 133 mg / kg BW of experimental animals with the volume of 1 mL / 100g BW.
- Group III: Given paliasa "tea bag" with a volume of 4 mL/ 200g BW, 4 hours later FDC-TB was given
- Group IV: Given paliasa "tea bag" with a volume of 4 mL/ 200 g BW rat, 4 hours later FDC- TB was given, 4 hours later paliasa "tea bag" was given again.
- Group V: Given Curcuma® 6.17 mg/kg BW.

All treatments on experimental animals were carried out for 28 consecutive days. In the first week, the second and fourth weeks of the blood samples were taken for ALT and AST measurements after 28 days of treatments.

2.6. Measurement of ALT and AST Level

Initial blood sample was collected prior to treatment (day 0), second week (day 14) and after the treatment completed (day 28). The blood samples were centrifuged at 1500 rpm for 15 minutes. The serum was separated and stored at -20°C. Analysis of serum ALT levels was carried out using reagent kit for ALT and AST (Human®). Blood plasma 100 μL was added with 1000 μL buffer, homogenized and incubated for 5 minutes at 37°C. After incubation, 250 μL of substrate from the kit was added, homogenized and incubated again for 1 minute at 37°C. After that the ALT or AST level was analyzed using humalyzer (Human ®) with 515 nm.

2.7. Data Analysis

The data obtained was analyzed using SPSS 20 software. Data was tested *Kolmogorov-Smirnov* test to check the normal distribution. Analysis was continued with one-way ANOVA followed by the Tukey test to see significant differences between groups (p <0.05).

3. Results and Discussion

3.1 The measurement results of ALT (alanine transaminase)

The measurement of ALT and AST levels in experimental animals treated for 0, 14 and 28 days is depicted in table 1 and table 2, respectively. It is shown that following FDC-TB administration for 14 days increased the ALT level from 76.23 to 87.99 and increased to 117.67 after 28 days (Table 1).This was statistically significant. When given Paliasa tea either once or twice a day, the rat seemed to have normal ALT. This result also similar when rat was given curcuma treatment before FDC-TB administration.

Table 1. Measurement results of ALT Level Before Treatment (day 0), 14 days and 28 days following treatments

Group	Treatment	ALT level (U/L)		
		Day 0	Day 14	Day 28
I	1% NaCMC Suspension	84.34 ± 8.9	76.62 ± 11.3	80.87 ± 0.2
II	FDC-TB suspension	76.23 ± 9.4	87.99 ± 7.3	117.67± 13.3*
III	Paliasa Tea + FDC-TB	70.57 ± 3.1	77.70 ± 16.3	66.51 ± 10.6
IV	Paliasa Tea + FDC-TB + Paliasa Tea	57.72 ± 6.2	62.93 ± 1.0	58.46 ± 21.3
V	Curcuma + FDC-TB suspension	61.9 ± 4.7	65.80 ± 1.1	55.51 ± 7.5

*p<0.05 compared to group I

When measuring AST level, it is shown that in rats treated with 1% NaCMC suspension the level of AST was not changed significantly. However, the treatment with FDC-TB for 28 days was capable to increase the level of AST twice as much before treatment. Even though with Paliasa tea administration, the level of AST in rat blood was still increased, but relatively lower compared to group II that was only treated with FDC-TB.

Table 2. Measurement results of AST Level Before Treatment (day 0), 14 days and 28 days following treatments

Group	Treatment	AST level (U/L)		
		Day 0	Day 14	Day 28
I	1% NaCMC Suspension	98,06	88.85	88.01
II	FDC-TB suspension	110.75	171.5	228.13*
III	Paliasa Tea + FDC-TB	113.30	110.23	153.97*
IV	Paliasa Tea + FDC-TB + Paliasa Tea	98.03	106.08	126.20*
V	Curcuma + FDC-TB suspension	105.25	102.63	106.53

*p<0.05 compared to group I

Comparison of ALT levels in plasma between groups has showed that rats in group II has the highest ALT and the elevation was significant (Figure 1). Compared to group I that serves as placebo, the ALT level in group II was around 30% higher (p<0.05). This indicates that FDC-TB for 28 days has caused an alteration in hepatic function or even damage the cell. Rats treated with paliasa tea bags and curcuma did not experienced a significant increase in ALT and was significantly lower than ALT levels in rats given FDC-TB.

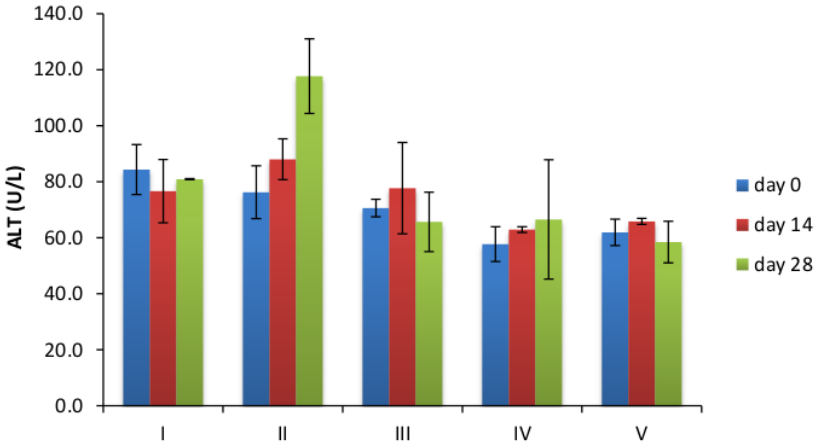

Figure 1. The comparison between ALT level of rat plasma initially prior to treatment, day 14 and day 28 following treatments. *p<0.05 compared to controls (group I) and other treatment groups

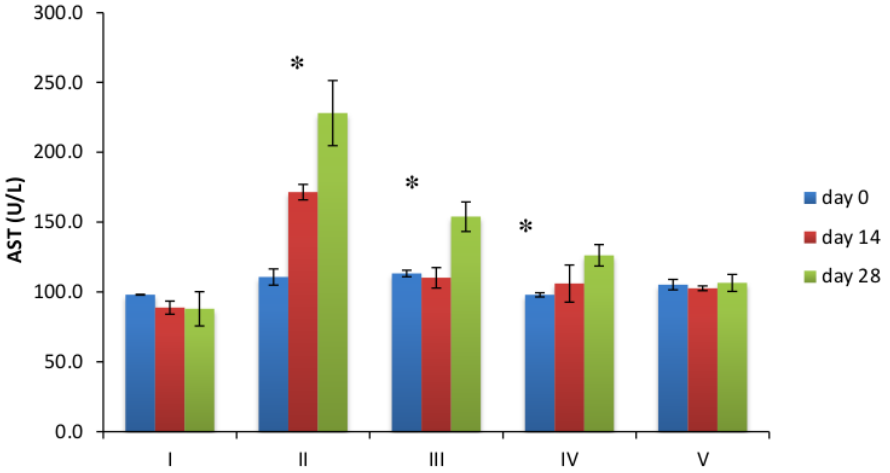

Figure 2. The comparison between AST level of rat plasma initially prior to treatment, day 14 and day 28 following treatments. *p<0.05 compared to normal control(group I)

The elevation of AST level of rats in group II was more than 100% compared to placebo group (group I). What interesting is that the AST level in group III and IV could not be maintained b y paliasa tea administration. Different from ALT level, AST may also indicate organ function other than the liver as it also found in many other organs including the heart. However, the AST level of the rats treated with paliasa tea was still significantly lower than those given FDC-TB only. This may indicate there is alleviation of liver damage in rats treated with paliasa tea. In contrast, with curcuma treatment, the level of AST was still maintained in rats treated with FDC-TB, showing a potent hepatoprotective effect of curcuma. Previously, another study has also shown hepatoprotective activity of Paliasa in the form of ethanolic extract against doxorubicin-induced toxicity [11]. It is assumed that the antioxidant activity of Paliasa was the main mechanism of its protective effect.

4. Conclusion

Based on this study, paliasa tea obtained from "tea bag" preparation may improve the hepatic dysfunction in experimental animals shown by reduced ALT and AST levels following FDC-TB treatment for 28 days.

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