

Hepatoprotective Activity of the Combined Leaf Extracts of Syzygium Polyanthum and Moringa oleifera Against Antituberculosis Drug-Induced Hepatotoxicity in Rats

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Abstract

Oral antituberculosis drugs (OAT) used repeatedly can negatively impact the liver. Natural compounds with high antioxidant potential could be used as hepatoprotective agents. This study aims to determine the hepatoprotective activity of the combination ethanolic leaf extract of *Syzygium polyanthum* (SPEE) and *Moringa oleifera* (MOEE) in rats administered with OAT. The hepatoprotective activity of the combination of SPE and MOE was determined by calculating the SGOT and SGPT levels of rats administered rifampicin (RMP), pyrazinamide (PZA), and isoniazid (INH) for 14 days. An experimental study using eight groups: standard control (CMCM-Na), negative control treatment with OAT (RMP 100 mg/kg BW; PZA: 252 mg/kg BW INH 50 mg/kg BW), positive control (OAT + Curcumin 100 mg/kg BW), OAT+SPEE 150 mg/kg BW group, OAT+MOEE 400 mg/kg BW group, and 3 group OAT + combination SPEE and MOEE (25%: 75%; 50%:50%; 75%:25%). SGPT & SGOT levels were determined using spectrophotometry with analytical methods using specific SGPT & SGOT reagent kits at 340 nm. After 14 days of OAT administration, SGOT levels increased by 1.3-fold, and SGPT levels increased by 1.8-fold compared to baseline levels. This considerable increase is still considered mild hepatotoxicity. The combination of SPEE: MOEE (25%:75%) was most effective in decreasing SGOT levels by 23.5%, or 1.3-fold, whereas the combination treatment of SPEE: MOEE (75%: 25%) was most effective in reducing SGPT levels by 51.56%, or 2-fold. The ratio value of the decrease in SGOT and SGPT levels from single SPEE and MOEE and the combination of both ($p>0.05$). The combination treatment of SPEE and MOEE in rats administered OAT showed an additive effect and could evolve as a hepatoprotective substance.

Keywords: Hepatoprotective, OAT, *Syzygium polyanthum*, *Moringa Oleifera*

1. INTRODUCTION

Tuberculosis (TB) is an infectious illness that remains a serious global health issue. According to the Global Tuberculosis Report, there will be 10.6 million TB cases worldwide in 2021, with 1.2 million deaths (World Health Organization, 2022). Based on the health profile, tuberculosis cases in Indonesia climbed by 17%, propelling it to second place in the world behind India. The frequency of tuberculosis cases in Indonesia reached 354 per 1,000 people [1]. According to the health profile, tuberculosis cases in Indonesia climbed by 17%, making it the second highest in the world behind India. Indonesia has 354 tuberculosis cases per 1,000 people [2].

First-line TB treatments include rifampicin (RIF), isoniazid (INH), and pyrazinamide (PZA), all of which have been linked to liver damage. Hepatotoxic cases vary greatly; in one study, [3] the prevalence of hepatotoxicity due to Anti-Tuberculosis Drugs (OAT) was 22.5%, with an average patient suffering from mild degrees, while Ardiani & Azmi, (2021) 43.2% of samples exhibited hepatotoxicity due to OAT [4]. Serum SGPT and SGOT levels can indicate liver impairment [5]. Natural substances with significant antioxidant activity could serve as hepatoprotective agents.

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The green plants with high antioxidant activity, including bay leaves and moringa leaves, can reduce hepatotoxicity caused by the medication doxorubicin [6], [7]. Meanwhile, moringa leaves (*Moringa oleifera*) contain antioxidant compounds such as phenolic acids and complex flavonoids such as quercetin, isorhamnetin, and kaempferol [8]. Moringa leaf extract given to CCl₄-induced mice can accelerate the regeneration of liver cells damaged by CCl₄ exposure. Bay leaves (*Syzygium polyanthum*) and moringa leaves (*Moringa oleifera*) are widely available in the community and have been demonstrated to have antioxidants and chemicals that promote liver function. This study aims to determine the hepatoprotective activity of the combination ethanolic leaf extract of *Syzygium polyanthum* (SPEE) and *Moringa oleifera* (MOEE) in rats administered with OAT.

2. MATERIALS AND METHODS

Materials

This study utilised leaf samples of *Syzygium polyanthum* and *Moringa oleifera* collected from Cilongok District, Banyumas Regency, approved by the pharmacognosy and phytochemistry laboratory at the UMP Faculty of Pharmacy. It also employed curcuminoid standards (CAS-No: 458-37-7), Na CMC, SGOT, and SGPT reagents (Glory Kemenkes RI AKL), as well as tablets containing isoniazid, rifampicin, and pyrazinamide. The test subjects were male Wistar rats (aged 2-3 months) from the UMP Faculty of Pharmacy Pharmacology Laboratory.

Method

Ethanol extract of *Syzygium polyanthum* and *Moringa oleifera* leaves is obtained from basic pharmaceuticals using the maceration method. The Indonesian Herbal Pharmacopoeia, edition II, published in 2017, describes the manufacturing process. To produce a standardised ethanol extract, the solvent is evaporated at 50°C with a speed of 90 rpm and a pressure ranging from 180 to 200. The hepatoprotective activity of the combination of SPE and MOE was assessed by measuring SGOT and SGPT levels in rats administered rifampicin (RMP), pyrazinamide (PZA), and isoniazid (INH) over 14 days. An experimental study involving eight groups was conducted:

1. Normal control (CMCM-Na)
2. Negative control treatment with OAT (RMP 100 mg/kg BW; PZA: 252 mg/kg BW; INH 50 mg/kg BW),
3. Positive control (OAT + Curcumin 100 mg/kg BW),
4. Treatment groups: OAT+SPEE 150 mg/kg BW group, OAT+MOEE 400 mg/kg BW group, and 3 group OAT + combination SPEE and MOEE (25%: 75%; 50%:50%; 75%:25%).

SGPT and SGOT levels were determined using spectrophotometry and analytical methods, using specific SGPT and SGOT reagent kits at 340 nm. According to BPOM guidelines (2020), the standard value parameters for SGOT and SGPT in mice are 45 U/L-100U/L and 10 U/L-50 U/L. Statistical tests with One-Way ANOVA using the GraphPad Prism 9 for Windows tool revealed that the data was normally distributed according to the normality test, with a p-value > 0.05.

Results

The study found that the ethanol extracts of *Syzygium polyanthum* (SPEE) and *Moringa oleifera* (MOEE) yielded 18.20% and 16.44%, respectively, in accordance with the Indonesian Herbal Pharmacopoeia. The phytochemical screening test showed that SPEE and MOEE contained flavonoids, phenol alkaloids, and terpenoids. A hepatoprotective activity test was conducted to assess the effectiveness of combining bay leaf and moringa leaf extracts in reducing SGOT and SGPT levels in mice. This test was performed on male white Wistar mice that had experienced hepatotoxicity due to the oral administration of Anti-Tuberculosis Drugs (OAT) for 14 days, which caused a significant increase in SGOT and SGPT levels [9]. After 14 days of OAT administration, SGOT levels increased by 1.3-fold, and SGPT levels increased by 1.8-fold compared to baseline levels. This significant increase is still considered mild hepatotoxicity.

The administration of curcumin to the positive control group at a dose of 100 mg/KgBW on the 14th day reduced SGOT and SGPT levels, indicating that curcumin at that dose acts as a hepatoprotector [10]. There were no significant changes in levels in the normal group after 14 days of therapy. The negative group, which received oral combination OAT therapy, showed a steady increase in SGOT and SGPT levels on the 7th and 14th days. In the positive group, single SPEE and MOEE leaves, as well as a combination of both extracts, increased SGOT and

SGPT levels on the seventh day, indicating that curcumin and the contents of both extracts were not yet effective in hepatoprotective action. The decrease in SGOT and SGPT levels on the 14th day suggests that curcumin, SPEE, MOEE, and their combination are effective hepatoprotectants. The combination of SPEE: MOEE (25%:75%) was most effective in reducing SGOT levels by 23.5%, or 1.3-fold, whereas the combination of SPEE: MOEE (75%:25%) was most effective in decreasing SGPT levels by 51.56%, or 2-fold (Table 1). The ratio of decrease in SGOT and SGPT levels from single SPE and MOEE, as well as their combination, showed no significant difference ($p>0.05$). The combination treatment of SPEE and MOEE in rats administered OAT exhibited an additive effect and could develop as a hepatoprotective agent.

Table 1. Percentage difference in average SGOT and SGPT levels for each group

Treatment	SGOT				SGPT			
	0-7		7-14		0-7		7-14	
Normal control	0,34%	↓	0,75%	↓	1,85%	↓	0%	↑
Negative control (OAT)	34,56%	↑	39,25%	↑	193,69%	↑	36,50%	↑
OAT + Curcumin	47,52%	↑	28%	↓	102,94%	↑	46,86%	↓
OAT+SPE	27,87%	↑	17,75%	↓	59,84%	↑	40,51%	↓
OAT+MOE	29,13%	↑	22%	↓	88,71%	↑	51,71%	↓
OAT + combination (25%: 75%;)	21,09%	↑	23,5%	↓	45,86%	↑	40,21%	↓
OAT + combination (50%: 50%;)	17,75%	↑	13%	↓	54,46%	↑	49,13%	↓
OAT + combination (75%: 25%;)	13,19%	↑	16%	↓	65,52%	↑	51,56%	↓

3. DISCUSSION

Secondary metabolites such as alkaloids, flavonoids, and terpenoids contribute to the hepatoprotective effects of APEE and MOEE. Flavonoids can inhibit hydrogen ionisation with basal radicals and elevate tubular antioxidative protein levels such as glutathione (GSH). Glutathione combines with basal radicals to form non-toxic compounds, helping to stabilise cells and enhance natural antioxidant retention in the tubules. By increasing the levels of superoxide dismutase, glutathione S-transferase, and glutathione peroxidase, flavonoids can improve insulin sensitivity and prevent the activation of hepatic stellate cells. They can also reduce inflammation by limiting the expression of tumour necrosis factor- α , interferon- γ , and interleukin-6. Furthermore, they can mediate apoptosis and autophagy by modulating the pathways of genes p53, nuclear factor κ B, and phosphatidylinositol 3-kinase/protein kinase B signalling. These flavonoids may offer an alternative approach to treating liver injury [11], [12].

Alkaloids in this substance can enhance mood by effectively preventing the onset of weakened radical reactions. Terpenoid compounds, in addition to potent antioxidant properties, can stimulate hepatocyte regeneration by reducing cell proliferation and promoting liver cell recovery [13], [14].

The combination of SPEE and MOEE in providing hepatoprotective activity is believed to be due to their flavonoid compound content, which is reported to produce a synergistic antioxidant enhancement effect. This aligns with other studies indicating that flavonoids and their derivatives have potential as hepatoprotective agents due to their high antioxidant and anti-inflammatory activities. However, further review of studies related to bioavailability and effectiveness in vivo in living organisms is necessary [18].

Curcumin, a positive control, exhibits hepatoprotective effects because it contains polyphenols that enhance the body's natural antioxidant activity, stabilise cell membranes, and promote cell regeneration. Other studies suggest that flavonoid molecules act as antioxidants in SPEE and MOEE by trapping free radicals and reducing oxidative stress, which has been proven to be hepatoprotective. Increased SGPT levels, particularly in the cytoplasm of liver cells, indicate hepatotoxicity, while SGOT is found in both the cytoplasm and mitochondria [4]. Although the

combination of SPEE and MOEE has a positive hepatoprotective effect, curcumin's effectiveness is significantly superior. This is consistent with the high antioxidant activity reported in several previous studies of curcumin. Furthermore, curcumin's hepatoprotective activity has been demonstrated in several *in vivo* studies with chemotherapy agents. [21], [22]

The reagent in the SGOT examination catalyses the conversion of the amino group of L-aspartate to 2-oxoglutarate, producing L-glutamate and oxaloacetate. These are then reduced to L-malate by the enzyme Malate Dehydrogenase (MDH) in conjunction with Nicotinamide Adenine Dinucleotide (NADH), and subsequently oxidised to NAD⁺. The amount of NADH oxidised correlates with the SGOT activity as measured by absorbance. The reagent used for the SGPT examination catalyses the transfer of an amino group from L-alanine to 2-oxoglutarate, forming pyruvate and L-glutamate. The pyruvate is reduced by Lactate Dehydrogenase (LDH), generating lactate and oxidising NADH to NAD⁺. The activity of SGPT, indicated by a decrease in absorbance proportional to NADH, reflects the conversion from pyruvate to lactate.

Examining liver injury using enzymatic reactions with high-accuracy SGOT and SGPT markers can detect damage based on the levels of SGOT and SGPT in plasma. Elevated SGOT and SGPT levels may indicate liver conditions such as hepatitis virus infection, fatty liver, or adverse drug effects. In this study, the induction of hepatotoxic medicines, specifically a combination of OAT in the form of INH, RIF, and PZA, administered alongside plant extracts, demonstrated potential as a supplementary therapy for hepatoprotection by reducing SGOT and SGPT levels after 14 days of treatment. This finding aligns with several studies that provide strong evidence and can explain the hepatoprotective properties of various plants examined *in vivo*. SGPT and SGOT as indicators of hepatoprotective activity are also limited because, in addition to liver damage, elevated SGOT levels can also be caused by issues with the heart, kidneys, pancreas, and lifestyle choices like heavy exercise or drug use. Furthermore, low SGPT/SGOT levels can sometimes occur without any health issues, such as a vitamin B6 deficiency, and high SGOT/SGPT levels alone do not always indicate a serious liver illness. However, in hepatoprotective research, these two parameters are highly relevant in suggesting a decrease in liver function due to the induction of antituberculosis drugs [26].

4. CONCLUSION

The combination of SPE and MOE shows additive hepatoprotective effects and is not statistically different from each treatment alone. The combined treatment group of SPE and MOE (25%:75%) resulted in a decrease in SGOT levels. Conversely, the most significant reduction in SGPT was observed with the 75%:25% combination dose, which demonstrated the greatest percentage decrease.

CONFLICT OF INTEREST

The author declares there were no conflicts of interest during the research or writing of this article.

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