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Effect of *Rhizophora apiculata bark* Extract on SGOT Levels in Rattus norvegicus Induced by Dexamethasone

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Abstract

Background: The liver's presence of fat has a histological picture with lipids >5%, and no secondary cause is called NAFLD. *Rhizophora apiculata* can serve as a therapeutic or prophylactic agent in NAFLD due to its flavonoid content. Objective: The study aimed to determine the effect *of Rhizophora apiculata* extract administration on SGOT levels in white rats subjected to dexamethasone induction. **Methods:** The experimental animals were categorized into four groups, each comprising 8 rats: the negative control group (K-), no treatment; the positive control group (K+), which was administered dexamethasone at a dosage of 5 mg/kg BW from the 15th to the 21st day; prophylaxis group 1 (KP1), which received *Rhizophora apiculata* ethanol extract at a dosage of 56 mg/kg BW from the 8th to the 21st day, along with dexamethasone at 5 mg/kg BW from the 15th to the 21st day; and treatment group 2 (KP2), which was given *Rhizophora apiculata* ethanol extract at 56 mg/kg BW and dexamethasone at 5 mg/kg BW from the 15th to the 21st day. KP1 received the *Rhizophora apiculata* ethanol extract 7 days earlier than KP2. **Result:** The data were not normally distributed ($p < 0.05$), so the Kruskal-Wallis test was carried out, which yielded $p < 0.05$. Consequently, the post hoc test was continued, namely the Mann-Whitney U test. The Mann-Whitney test comparing the K- group and K+ yielded $p < 0.05$, indicating that the increase in SGOT level was caused by dexamethasone-induced effects. The K+ group and KP1 and KP2 showed $P > 0.05$, indicating no significant difference in SGOT level. **Conclusion:** The study concludes that the *Rhizophora apiculata* extract at a dose of 56 mg/kg BW for 7 days can not reduce SGOT levels in male Rattus norvegicus induced by dexamethasone

Keywords: Antioxidants, Dexamethasone, Flavonoids, Rhizophora apiculata

Original Research Article

INTRODUCTION

There is fat in the liver (steatosis) and has a histological picture with lipid >5% and does not have secondary causes (alcohol consumption, viruses, genetics, and other causes) called Non-Alcoholic Fatty Liver Disease (NAFLD). NAFLD has symptoms and signs such as fatigue, pain or dullness in the right upper quadrant, hepatomegaly, but sometimes has no symptoms (Guney-Coskun & Basaranoglu, 2024; Topal et al., 2021). In the general population in Indonesia, the incidence of NAFLD is 51% and in

patients with diabetes mellitus, it is as much as 45.2%. Male, type 2 diabetes mellitus, triglycerides ≥150mg/dl, HDL <40 mg/dl, and SGPT ≥35 U/L are some of the risk factors for NAFLD (Sulaiman, 2023).

The pathogenesis of NAFLD can be the basis for dividing the type of NAFLD into primary and secondary types, where metabolic syndrome and insulin resistance are associated with primary NAFLD. A collection of symptoms associated with metabolic disorders, such as insulin resistance, dyslipidemia, hyperglycemia, and hypertension, is called metabolic syndrome. Long-term use of high-dose corticosteroids can induce metabolic syndrome. Insulin resistance can cause increased triglycerides and release of free fatty acids due to decreased inhibition of hormone-sensitive lipase (HSL) then the release of free fatty acids, which will be taken up by the liver (Di Pasqua et al., 2022).

Dexamethasone is a glucocorticoid drug that has the chemical formula $C_{22}H_{29}FO_5$. Dexamethasone is a drug that is anti-inflammatory, immunosuppressive, and vasoconstrictive. Dexamethasone has a genomic and non-genomic mechanism of action. The genomic mechanism involves interaction with DNA sites and activation of specific protein transcription, while the non-genomic mechanism involves activation of receptors mediated by factor kappa beta. Dexamethasone can be indicated for short-term and long-term use. There are various routes for the use of dexamethasone, such as oral, injection, parenteral, and rectal. Long-term use of high doses of dexamethasone can cause NAFLD and result in impaired liver function, which can be detected through examination of SGPT and SGOT markers. In this study, subcutaneous dexamethasone induction for seven days resulted in increased appetite and weight gain. This condition also triggered dyslipidemia and increased liver deposits.(Di Pasqua et al., 2022; Hasona et al., 2017; Razzaq et al., n.d.; Sawy et al., 2018)

SGOT is an isoenzyme produced in the cytosol and mitochondria and can be found in various organs such as the heart muscle, liver, skeletal muscle, and other organs. If there is damage or injury to the liver, the liver will release the SGOT and SGPT enzymes. Enzymes also function as markers in examinations to determine abnormalities in the liver.(Beyoğlu et al., 2024; Majeed et al., 2019)

Indonesia is a maritime country that has many types of mangrove plants that have various functions, one of which can be used in the health sector as medicine. Mangrove plants can be a prevention or prophylaxis for NAFLD because of the flavonoid content, which can be antioxidants and anti-inflammatories. According to research, flavonoid compounds can regulate MDA, superoxide dismutase, and calatase, which play a role in inhibiting the formation of oxidative stress, which can reduce NAFLD (Banjarnahor & Artanti, 2014; Vittaya et al., 2022)

MATERIALS AND METHODS

This study employed an experimental methodology by comparing two groups after therapy administration. To provide adequate population representation, the sample was chosen at random. 24 male Rattus norvegicus, weighing 150–250 grams and aged 9–12 weeks, were employed in this study. The study, which was authorized by the medical faculty's ethics committee under the number I/076/UHT.KEPK.03.VIII/2024, was carried out in September 2024 at Hang Tuah University's Faculty of Medicine's Hyperbaric Laboratory.

Making *Rhizophora apiculata bark* extract

Rhizophora apiculata bark is washed with clean water, then cut into smaller pieces. These pieces are dried in an oven and then crushed into powder. After that, 600 grams of this powder is put into a jar containing 1.5 liters of 95% ethanol, where it is stirred occasionally for the first 6 hours and left for the next 18 hours. After 24 hours, the results are filtered to obtain the filtrate. After that, the ethanol solvent mixed with the filtrate is evaporated so that it disappears with a rotary vacuum evaporator to obtain a liquid extract.

Treatment stage

Division of experimental animal groups

Animals were acclimatized for 7 days before treatment began. A 60cm X 40cm X 30cm cage containing 5-6 mice was placed in a room with a room temperature between 22 and 24°C, humidity between 50 and 60%, light and dark every 12 hours, and daily evaluations were conducted.

The male Rattus norvegicus were randomized into 4 groups. The negative control group (K-) is the untreated group. Positive control group (K+) is the group of experimental animals induced with dexamethasone for seven days, from the 15th to 21st day. The profilaxis group 1 (KP1) is which received *Rhizophora apiculata bark* ethanol extract at a dosage of 56 mg/kg BW for seven days from the 8th to the 21st day, along with dexamethasone at 5 mg/kg BW for seven days from the 15th to the 21st day. KP1 received the *Rhizophora apiculata bark* ethanol extract 7 days earlier than KP2. Treatment group 2 (KP2) is the experimental group given *Rhizophora apiculata bark* extract as therapy for seven days, from the 15th to 21st day, simultaneously with induced dexamethasone at 5 mg/kg BW(Handajani, 2021).

Subcutaneous administration of dexamethasone

The rat's tail is lifted with the right hand, then the skin of the rat's nape is pinched with the thumb of the left hand, the rat's body position is rotated so that the surface of the stomach is facing the tail holder, the position of the rat's head must be lower than the abdomen, inject the syringe parallel from the front through the skin until a click is heard, the position of the needle is injected slightly to the side of the center line so as not to pierce the rat's organs. (Handajani, 2021)

Administration of *Rhizophora apiculata bark* extract with a probe

Rhizophora apiculata bark extract is mixed with 1% CMC-Na until homogeneous; the results of this mixture must be made into a suspension or solution. Prepare the probe tube and syringe, hold the mouse using the left hand to maintain the position of the mouse by pulling the skin of the neck so that it is pinched with the thumb. Hook the mouse's tail on the little finger of the left hand, the probe tube is inserted through the mouse's mouth slowly and liver-liver into the mouse's stomach, if it has reached the mouse's stomach, then the *Rhizophora apiculata bark* extract is pumped out of the syringe.

SGOT level examination

SGOT examination uses the enzymatic reaction kinetic method according to IFCC recommendations using a spectrometry tool. Before measuring, the blood sample is centrifuged for 10 minutes at a speed of 3000 rpm. Measurement using Clonicon 4010 spectrometry with a wavelength of 310 nm (Handajani & Nabil, 2023)

RESULTS

SGOT level data in the experimental animal groups are shown in the following table:

Table 1. Descriptive data of SGOT Level in Each Experimental Animal Group

	(K-)	(K+)	(KP1)	(KP2)
1	178	172	222	126
2	179	220	269	197
3	181	255	292	224
4	185	291	316	251
5	208	324	689	252
6	208	431	757	277
7	235	619	802	315
8	285	644	995	471
Average	204,69	365,22	535,44	260,31
Standard deviation	37,137	178,91	300,27	100,75
Minimum	178	172	222	126
Maximum	285	644	995	471

Table 1 shows that the highest SGOT levels were found in prophylaxis group 1 (KP1) and the lowest SGOT levels were found in the negative control group (K-), the average SGOT levels in each group of experimental animals were highest in prophylaxis group 1 (KP1), which was 535.44, the positive control group (K+) was 365.22, treatment group 2 (KP2) was 260.31, and the lowest in the negative control group was 204.69.

Shapiro-Wilk was used for the normality test because the data amounted to <50. This normality test obtained the positive control group ($p = 0.195$), treatment 1 ($p = 0.134$), and treatment ($p = 0.413$) were not normally distributed because they had a value of ($p = 0.037$) ($p < \alpha$). The Kruskal-Wallis test

was then used for the next test because there was data that was not normally distributed. The result of the Kruskal-Wallis test is shown in Table 2

Table 2. Kruskal-Wallis test results for SGPT levels between groups

Group		SGPT Level (p)
K(-)	K(+)	0.027*
	KP1	0.002*
	KP2	0.115
K(+)	KP1	0.172
	KP2	0.208
KP1	KP2	0.036*

Note : * =p<0.05 significant
Group K(-) : without treatment
Group K(+) : induced dexamethazone
Group KP1: prophylaxis with Rhizophora apiculata and induced dexamethasone
Group KP2: treatment with Rhizophora apiculata and induced dexamethasone

Interpretation of the Mann-Whitney U test results from table 2 in the K- group with the K+ group showed a significant difference with significance (p=0.027) (p<α), meaning that the K+ group induced by dexamethasone was able to increase the average SGOT levels significantly. The Mann-Whitney U test on the positive control group (K+) with KP1 and Kp2 with prophylaxis and therapy was not able to reduce the average SGOT levels. The Mann-Whitney U test on prophylaxis group 1 (KP1) with treatment group 2 (KP2) showed a significant difference with a significance of (0.036) (p<α), meaning that treatment group 2 (KP2) with therapy was able to reduce the average SGOT levels better than prophylaxis group 1 (KP1)

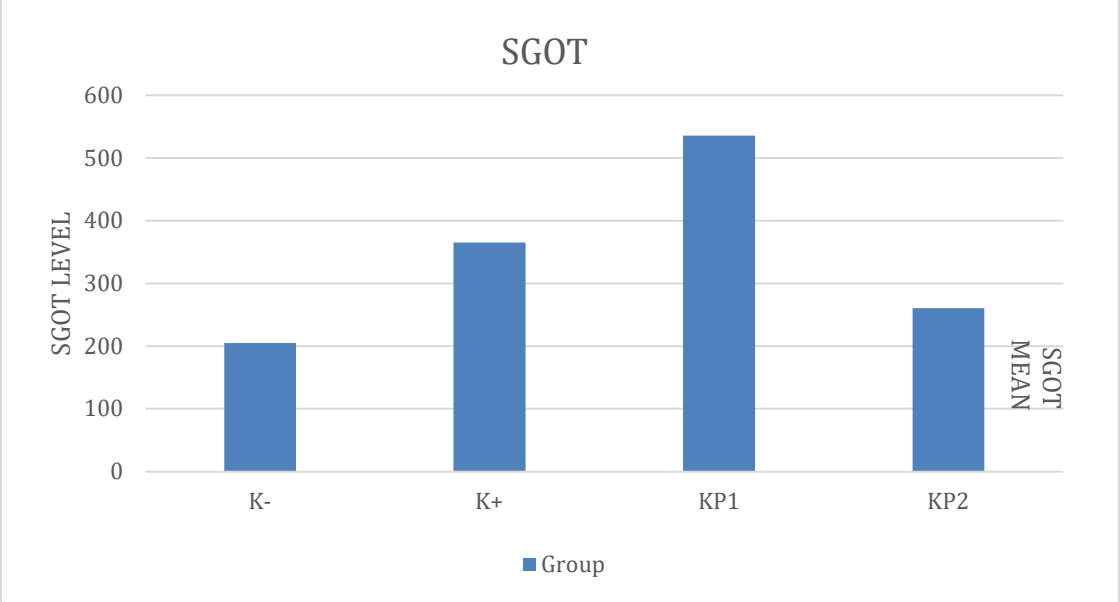

Figure 1. SGOT

DISCUSSION

The study showed that in the positive group, there was an average rise compared to the K- group. According to the research that Batista et al. (2024), which used a dose of dexamethasone 1 mg/kg BW for 7 days, can increase SGOT levels. In addition, dexamethasone with a dose of 10 mg/kg BW for 7 days can increase SGOT levels in line with the study conducted by Mohammed (2021), so that in the range of dexamethasone doses between 1 mg/kg BW to a dose of 10 mg/kgBW, SGOT levels can increase. Therefore, in the K+ group, namely the group given dexamethasone 5 mg/kg BW for 7 days,

in line with the literature that there was an increase in AST or SGOT levels. (Batista et al., 2024; El-Helbawy et al., 2020; Hasona et al., 2017; Liu et al., 2018)

Dexamethasone can cause insulin resistance because dexamethasone can increase glucose levels. The main role of insulin in the liver is to inhibit gluconeogenesis and glycogenolysis. Insulin increases the re-esterification of fatty acids into triglycerides in the liver and adipocytes. On the other hand, insulin stimulates the production of triglycerides and hepatic cholesterol and glucose uptake in muscle and fat. In addition, intracellular glucocorticoids directly control the expression of glucokinase, an enzyme that is important for the use and storage of glucose by the liver. This enzyme in the liver can increase hepatic de novo lipogenesis and facilitate glucose disposal by the liver. Triglycerides will accumulate in hepatocytes due to hepatic lipogenesis that exceeds the secretion capacity of very low-density lipoprotein (VLDL), which will then cause inflammation and liver steatosis. The presence of inflammation in the liver causes the secretion of liver enzymes such as SGPT and SGOT, so that the levels of these liver enzymes will increase.(Rajendran et al., 2014; Suleman, 2018)

Accumulation of liver fat in more than 5% of hepatocytes without additional causes of liver steatosis is known as non-alcoholic fatty liver disease. This includes a range of conditions that can start with benign steatosis and progress to fibrosis, non-alcoholic steatohepatitis, and eventually hepatocellular cancer. Oxidative stress caused by the oxidation of cytotoxic free fatty acids increases cytokine levels while decreasing hepatic antioxidant levels. In addition, it has been shown that by-products such as MDA, produced by increased lipid peroxidation, further stimulate cytokine synthesis. Reactive oxygen species (ROS) and other free radicals can be released when fats stored in the liver are oxidized. ROS damages the liver by lowering endogenous antioxidants and causing lipid peroxidation by damaging unsaturated fatty acids in cell membranes. This liver damage then leads to the release of liver enzymes such as SGPT and SGOT. (Handajani, 2019; Jairaman et al., 2021; Massart et al., 2022; Mustofa et al., 2024)

Rhizophora apiculata contains various compounds such as flavonoids, tannins, and alkaloids. The use of Rhizophora apiculata bark is because the extract of the bark has a higher content of phenolic compounds than other parts, which is in line with research conducted. Flavonoids reduce the formation of reactive species, such as radicals. Pro-oxidant enzymes such as xanthine oxidase are inhibited by flavonoids. Furthermore, the formation of reactive species is reduced by inhibiting lipoxygenase and cyclooxygenase, which are enzymes that can oxidize molecules other than their typical substrates. In addition, Flavonoids can strengthen or maintain the body's natural antioxidant defenses. Many flavonoids cause glutathione S-transferase, Heme-oxygenase 1 (HO-1), and other antioxidants (Rahayuningsih et al., 2021)

The most common substance found in plants that contains nitrogen is alkaloids. We can find these alkaloids in various parts of plants, from beautiful flowers to roots hidden in the soil. This is corroborated by studies carried out by Maisarah et. Al., 2023. CYP450 first breaks down alkaloids to produce DHPAs and/or DHR, which then cause mitochondrial dysfunction and hepatic GSH depletion, which causes excess ROS. ROS results in the activation of signaling pathways, such as Nrf2-mediated activation of antioxidant response element genes. The Nrf2-mediated antioxidant defense system and Nrf2 nuclear translocation help keep excessive ROS levels from accumulating in cells and tissues. An imbalance between the generation of Reactive Oxygen Species (ROS) and the antioxidant system can trigger hepatocyte damage, a condition known as hepatotoxic, which is in line with research. Alkaloids work by reducing the amount of Bcl-x protein, an anti-apoptotic protein, which inhibits hepatocyte proliferation and causes cell death and increases the amount of Bax, a pro-apoptotic protein that promotes the release of mitochondrial cytochrome c for cell death. In addition, an inflammatory response occurs due to the presence of alkaloids, namely monocytes release cytokines in response to PA, including endothelin-I (ET-1), IL-1β, and TNF-α. The cytokine called TNF-α causes normal endothelial cells to die immediately(Maisarah et al., 2023.)

The availability of nutrients in the soil is very important for mangrove growth. If mangroves grow in an environment that lacks nutrients, the nutrient content in the mangrove body itself will decrease in line with research conducted by. The growth of *Rhizophora apiculata bark* mangroves can vary from region to region. In this study, the administration *of Rhizophora apiculata bark* mangroves to the

prophylaxis group (KP1) and the therapy group (KP2) was unable to inhibit liver damage due to dexamethasone induction, which can be proven in statistical tests that did not show a decrease in SGPT levels compared to the positive control group (K+). The prophylaxis group (KP 1) had an average higher SGPT level than the treatment group (KP2) but this was not statistically significant. This may happen because the duration of administration period of Rhizophora apiculata bark was longer compared to the treatment group. This may be due to insufficient antioxidant levels in *Rhizophora apiculata bark* mangroves used as an extract, or it may also be that the extraction process can affect their composition. In addition, environmental factors as a medium for mangrove growth can also affect the content of mangrove.(Alsareii et al., 2022; Jairaman et al., 2021; Latompai et al., 2020)

CONCLUSION

Rhizophora apiculata bark extract cannot reduce SGOT levels in male Rattus norvegicus induced by dexamethasone. However, this study also found that the duration of *Rhizophora apiculata bark* extract administration also affected SGOT levels.

CONFLICT OF INTEREST

No conflict of interest

REFFERENCE

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