Trad. Med. J., September-December 2023
Vol. 28(3), p 189-196
ISSN-p : 1410-5918 ISSN-e : 2406-9086

Submitted : 26-05-2023
Revised : 07-07-2023
Accepted : 26-10-2023

# Hepatoprotective Activity of Ethanol Extract of Notika Leaves (*Archboldiodendron calosericeum* (kobuski)) on Liver Function in Carbon Tetrachloride-induced Mice

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## ABSTRACT

Notika leaves are traditional medicinal plants used as antimalarial medications by the Papuans. Notika leaf is an endemic plant with many benefits but has not been scientifically proven. Plasmodium falciparum is a species of malaria that damages up to 50% of red blood cells, and its schizogony process mainly occurs in the liver. This study aims to confirm the activity of the ethanolic extract of notika leaf in improving liver function by using an experimental pre and post-test-only control group design with five treatment groups of Wistar strain mice. The normal group was treated with 0.5% NaCMC, the negative group was treated with 0.5% NaCMC and Carbon Tetrachloride (CCl4), and the third, fourth, and fifth groups received extract with doses of 125 mg/kgBW, 250 mg/kgBW, and 500 mg/kgBW, respectively. The extract was administered for seven days and, on the eighth day, was induced with CCl4 intraperitoneally. The SGOT and SGPT levels in mice were measured using a 5010v5+ photometer, and liver histopathology was examined using HE (Hematoxylin-Eosin) dye. The SGPT levels in the normal, negative, third, fourth, and fifth groups were 20.6 U/L, 52.08 U/L, 32.8 U/L, 19.8 U/L, and 7.8 U/L, respectively. Meanwhile, the SGOT levels were 18 U/L, 54.2 U/L, 28.2 U/L, 17.8 U/L, and 7.4 U/L in the normal, negative, third, fourth, and fifth groups, respectively. Based on ANOVA analysis, the SGPT and SGOT levels of the mice liver-treated group with notika leaf extract show significant values of < 0.05. The extract exhibits hepatoprotective activity and liver histological characteristics that do not induce necrosis at a dose of 500 mg/kgBW.
**Keywords:** Notika leaf; *Archboldiodendron Calosercium*; Hepatoprotector; SGPT; SGOT

## INTRODUCTION

Indonesians have long used traditional medicinal herbs to maintain health, prevent disease, and treat health. The increase in the use of herbal medicines in Indonesia is influenced by the increased use of Indonesia's rich natural resources. The embodiment of the movement back to nature is very beneficial in the field of medicine as an alternative to medical treatment. Notika leaf (*Archboldiodendron calosercium* (Kobuski)) is one of the traditional medicinal plants empirically used by the Papuan people for the treatment of malaria which contains secondary metabolites including alkaloids, flavonoids, tannins, saponins, and terpenoids (Nuralifah et al., 2018).

Polyphenol secondary metabolites such as flavonoids can inhibit and neutralize the occurrence of oxidation reactions involving free radicals. Free radicals *OH can damage hepatocyte cell membranes, causing the release of various enzymes from hepatocytes, including SGOT (Serum Glutamic Oxaloacetic Transaminase), and SGPT (Serum Glutamic Pyruvic Transaminase) (Ike Yulia Wiendarlina, Min Rahminiwati, 2018), which are the commonly used as a biomarker of liver damage (Santosa et al., 2020). Liver function disorders can be caused by various factors such as viral and parasitic infections, alcohol abuse, side effects of drugs and herbal products, genetic factors, autoimmune diseases, liver cancer, and obesity. Liver disease is one of the diseases in Indonesia that has a fairly high prevalence. Based on the 2018 Riskesdas data, in July the number of hepatitis patients in Indonesia reached 30 million people, making the disease ranked 11th (Apriliani et al., 2015). Hepatitis prevalence in 2018 (1.2%) is twice as high as in 2007 (Kemenkes RI, 2018).

Liver disorders are characterized by increased activity of serum transaminases in the form of SGPT and SGOT, lactate dehydrogenase, and serum bilirubin. Serum SGPT levels are a more sensitive indicator of liver damage because very few conditions other than the liver affect serum SGPT levels (Siti Boedina Kresno, 1995). Carbon tetrachloride (CCl4) is a common xenobiotic used to induce lipid peroxidation and poisoning that leads the liver disorder. The CCl4 reactive

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metabolites in the body can cause cell death including liver cells (Syahrin et al., 2016). In the other study, Intraperitoneal administration of CCl4 in rats has been reported can induce liver fibrosis (Supriono et al., 2019).

Hepatoprotectors are medicinal compounds that have a therapeutic effect, to restore, maintain, and treat damage from liver function. Hepatoprotections work by protecting the liver from damage caused by toxins, drugs, and other disorders (Aditya et al., 2016). Flavonoids, alkaloids, saponin, and polyphenols are known to have activity as hepatoprotectors (El-Newary et al., 2021; Liem et al., 2018), which are also known to be contained in Notika leaf (*Archboldiodendron calosercium* (Kobuski)). The presence of phenolic and flavonoid content in Notika leaves can prevent liver damage from free radicals including CCl4 by lipid chain-breaking antioxidants mechanism (Maulina, 2015).

The exploration of the pharmacological activity of the Notika plant is still limited. Some studies reported that the ethanolic extract of the Notika plant can reduce total cholesterol levels, which is thought to be through an antioxidant mechanism (Nuralifah et al., 2019). In this study, 96% ethanol was used as the solvent for extracting the samples because it is more uniformly selective and can extract more polar compounds including phenolic and flavonoid, non-toxic, and neutral (Syamsul, et.al., 2016). Currently, no studies are reporting the activity of this plant as a hepatoprotector. Carbon tetrachloride (CCl4) is a common method that can be used in modeling animals with liver damage. Therefore, in this study, the hepatoprotector activity of the Notika leaf ethanolic extract was investigated by measuring the SGOT and SGPT levels, and histopathological profile of the animal liver.

## METHODOLOGY

### Material

The tools used in this study were rotary vacuum evaporator (Rotavapor, Buchi), blender (Philips®), analytical balance (Precisa®), measuring cup (Pyrex®), hot plate (Stuart®), funnel (Pyrex®), beaker (Pyrex®), measuring flask (Pyrex®), oven (Gallenkamp Civilab-Australia®), porcelain cup, droppings, stirring stick, jar, syringe and cannula for giving extracts orally and tools for making preparations for liver histology, namely: cutting board, scalpel knife, tweezers, tissue cassette, automatic processing machine, vacuum machine, blocking machine, microtome machine, microtome knife, 46°C water bath, spectrophotometer, object glass, cover glass, special shelf for staining, oven, electric microscope and rat cage.

The materials to be used in the research are crude extracts of *Notika* leaves (*Archboldiodendron calosericeum* (Kobuski)); male white rat Wistar strain; Physiological 0.9% NaCl, CCl4, coconut oil, aquadest, 0.5% Na CMC, rat feed ingredients and ingredients for making preparations for liver histology: The main ingredients are pieces of animal liver tissue that have been fixed with 10% formalin solution. The required solution is ether, 96% ethanol, 70% alcohol. 80%, 90%, 95%, and 100%, xylol, paraffin, hematoxylin solution, and eosin solution.

### Method

#### Extract preparation

Notika leaf samples (*Archboldiodendron calosericeum* (Kobuski)) were obtained from Madi Village, East Paniai District, Papua, and were determined at the Biological Research Center, LIPI Cibinong. Leaf samples were prepared in dry simplicia, then ground into powder by using a blender (Philips). The simplicia powder (500 mg) was macerated using 96% ethanol (1:10 w/v) for 3x24 hours. Every 1x24 hours the sample was filtered, the residue was macerated again while the filtrate was collected and concentrated using a rotary vacuum evaporator (Rotavapor® RII butchi) to obtain a crude extract. The crude extract was weighed by using an analytical balance (Precisa®), and the yield was calculated.

#### Simplified characterization

Determination of Water Soluble Extracts A total of 5 grams of simplicia powder was added with 100 mL of distilled water-chloroform (2.5 mL of chloroform and aquadest to 100 mL, shaken until dissolved), put in a stoppered flask, shaken for 6 hours, and allowed to stand for 18 hours. Filter, and separate the filtrate and residue. The filtrate (20 mL) was heated at 105$^{o}$C by using an oven (Gallenkamp Civilab -Australia) until dry and constant weight. Calculate the content in percent water-soluble juice, calculated from the dried material (Depkes RI, 2000).

#### Determination of Concentration of Soluble Essence in Ethanol

A total of 5 grams of simplicia powder was added with ethanol 96% (p.a) 100 mL, put in a corked flask, shaken for 6 hours, and allowed to stand for 18 hours. The sample was filtered rapidly to separate the filtrate and residue. The filtrate (20 mL) was evaporated at a temperature of 105$^{o}$C to dryness and constant weight. Calculate the content

in percent ethanol-soluble extract of 96%, calculated from the dried material (Depkes Ri, 2000).

**Determination of Water Content**

Simplicia (1 g) is placed in a porcelain dish that has been tarred previously. Simplicia put in the oven for 30 minutes and cooled. Then it was weighed until a constant weight was obtained. If a constant weight has not been obtained, it is necessary to re-dry in the oven (Gallenkamp Civilab-Australia) (Depkes RI, 2000).

**Determination of Total Ash Content**

The extract (1 g) was placed in a pre-tapped cup. Then the sample was ignited in a furnace at a temperature of 600$^{o}$C until it became ash, then cooled and weighed until a constant and stable weight was obtained (Depkes RI, 2000).

**Phytochemical screening**

The phytochemical screening method of the ethanolic extract of Notika (Archboldiodendron Calosericeum (kobuski)) leaves was used with modifications (Yamin et al., 2020).

Alkaloid

The extract was dissolved with 5 mL of HCl and then put in a test tube. Added 3 drops of Dragendroff's reagent into the tube. The formation of an orange precipitate on the tube indicates the presence of alkaloids.

Flavonoid

The extract was added with ethanol solvent, 0.2 g of magnesium powder was added and 2 mL of concentrated HCl solution was added. The formation of an orange-red solution indicates the presence of flavonoids.

Terpenoid

The extract was added 0.5 mL of anhydrous acetic acid and 2 mL of concentrated sulfuric acid. The formation of a blue-green solution indicates the presence of terpenoids.

Saponin

The extract was added with 10 mL of hot water and then cooled, shaken vigorously for 10 seconds. A solid foam is formed for at least 10 minutes.

Tanin

The extract was added with 1 mL of 1% Fe (III) chloride solution. If a dark blue, dark blue or greenish-black color is formed, it indicates the presence of tannin compounds.

**Preparation of Tetrachloride Induction Solution (CCl4)**

Tetrachloride solution (CCl4) at a dose of 0.4 ml/kgBW was prepared by weighing 4.24 g of carbon tetrachloride (CCl4), then dissolved in coconut oil and made up to 100 mL (Wahyu Atmaja K.J, Santi Purna Sari, 2010).

**Experimental animals**

The experimental animal was a 3-month-old male white rat Wistar strain weighing 200-300 grams, obtained from the E-mentik farm, Kendari, Southeast Sulawesi. The animals were approved as experimental animals with ethical number 020a/UN29.17.1.1/ETIK/2022 from the Medical Faculty of Halu Oleo University. Animals were acclimatized for a week before being used and given standard feed. The animals were divided into five treatment groups each group consisting of six rats. Group I normal control (Na CMC 0.5%); Group II negative control (Na CMC 0.5% for seven days and added CCl4 on the eighth day); Group III (ethanol extract of Notika leaves at a dose of 125 mg/kgBW for seven days and added CCl4 on the eighth day); Group IV (ethanol extract of Notika leaves at a dose of 250 mg/kgBW for seven days and added CCl4 on the eighth day); Group V (ethanol extract of Notika leaves at a dose of 500 mg/kgBW for seven days and added CCl4 on the eighth day). On the ninth day of treatment, blood samples were taken to measure the levels of SGOT and SGPT, and the liver was taken for histopathological examination of the liver (Panjaitan et al., 2011).

**Determination of SGOT and SGPT levels**

Determination of SGOT and SGPT levels was carried out based on the method with modifications. In summary, the SGOT assay used reagent 1 (TRIS, L-aspartic, MDH, LDH) and reagent II (2-oxoglutarate, NADH). SGPT levels were determined using reagent I (TRIS, L-alanine, LDH) and reagent II (2-oxoglutarate, NADH). The reagent used in each determination was a mixture of reagents 1 and 2. The reagent mixture was pipetted as much as 1000 L reacted with 100 L of serum samples, and incubated at 37°C for 1 minute. The absorbance of the sample was read using a spectrophotometer with a wavelength of 365 nm (Muhammad Reza Ramadhani, Mochammad Saiful Bachri, 2015).

**Histopathological examination of the liver**

The obtained liver was washed using a physiological solution of NaCl 0.9% for 30 minutes, then fixed using formalin 10%. After that, the tissues were dehydrated using 70%, and 80%

**Table I. Characteristics of Simplicia**

| Characterization Type | Results | Standard | Literature |
|---|---|---|---|
| Ethanol soluble extract content | 50.04 % | ≥9.7 % | Depkes RI, 2000 |
| Water soluble juice content | 32.01 % | ≥ 18% | Depkes RI, 2000 |
| Water content | 3.99 % | ≤ 10 % | Depkes RI, 2000 |
| Ash content | 5.11% | ≤7% | Depkes RI, 2000 |

alcohol. 90% and 95% were carried out for 24 hours and followed by 100% alcohol for 1 hour, respectively. After being dehydrated, it was followed by purification using xylol three times, each for 1 hour. Then paraffin infiltration is carried out, incisions with a thickness of 4-5 microns. The results of the incision are placed on a slide, and stained with Hematoxylin-Eosin (HE), then observed under a light microscope.

**Data Analysis**

Data of SGPT and SGOT were analyzed by using ANOVA oneway with IBM SPSS statistics.

## RESULT AND DISCUSSION

### Results

**Simplified characterization**

The results of the simplicial characterization of Notika leaves in Table 1 show the ethanol-soluble extract content, water-soluble extract content, water content, and ash content according to the standard.

**Extraction**

The weight of the ethanolic extract of Notika leaves obtained was 158.36 g, and the percent yield of the initial simplicia weight was 2.77.

**Phytochemical Screening**

The results of the phytochemical screening of the ethanol extract of the Notika leaf extract in Table 3 show the presence of flavonoids, saponins, tannins, terpenoids, and the absence of alkaloids.

**Determination of SGOT and SGPT levels**

The levels of SGOT and SGPT of test animals in each group were measured before and after administration of the ethanol extract of the leaves of *Notika* (*Archboldiodendron calosericeum* (kobuski)). The results showed that the induction of the CCl4 solution caused the SGOT and SGPT levels of the test animals to increase significantly ($p<0.05$) (Figures 1 and 2). SGOT and SGPT levels of test animals after being given ethanol extract of Notika leaves at doses of 125, 250, and 500 mg/kgBW in each treatment group decreased. The greatest decrease in SGOT and SGPT levels was seen in the group given the 500 mg/kgBW notika leaf ethanol extract, which was 28.6 U/L and 29.2 u/L, respectively, which were significantly different ($p<0.05$). to the negative control and the group that was given a dose of 125 mg/kgBW, while the positive control had no difference ($p > 0.05$).

**Histopathology of the Liver**

The histopathological profile of normal control group liver cells (Figure 3a) showed normal conditions with clearly visible central veins, sinusoidal channels, and portal tracts. The induction of the CCl4 solution caused liver damage to the test animals. Histopathological observations showed that there was cell damage in the form of necrosis, namely the shape of the cell nucleus that was compacted and dark in color in the liver tissue indicated by yellow arrows (Figure 3b).

Necrosis was seen in the liver histopathological profile of the negative control group and not seen in the normal control group. Liver cell necrosis was also seen in group III (Notika ethanol extract dose of 125 mg/kgBW) and group IV (250 mg/kgBW), but in group V the liver cells experienced an improvement in conditions where the central vein was visible and no necrotic cells were found (Figure 3e).

**Discussion**

This study analyzed the hepatoprotective activity of the ethanol extract of *Notika* leaves. This research uses *notika* leaf powder which will be extracted using the maceration method. The maceration method is used because there is no need for a heating process so it is unlikely that natural materials will be damaged or decomposed. The principle of the extraction process is that the solvent penetrates or diffuses the mass of the solvent on the surface of the inert solid into the solid pore and then due to a difference in concentration, the solute mixture in the solvent diffuses out from the surface of the inert solid. Furthermore, the solute (solute) comes out of the pore of the inert solid and mixes with the solvent that is outside the solid. The results of the extraction were then processed using a rotary

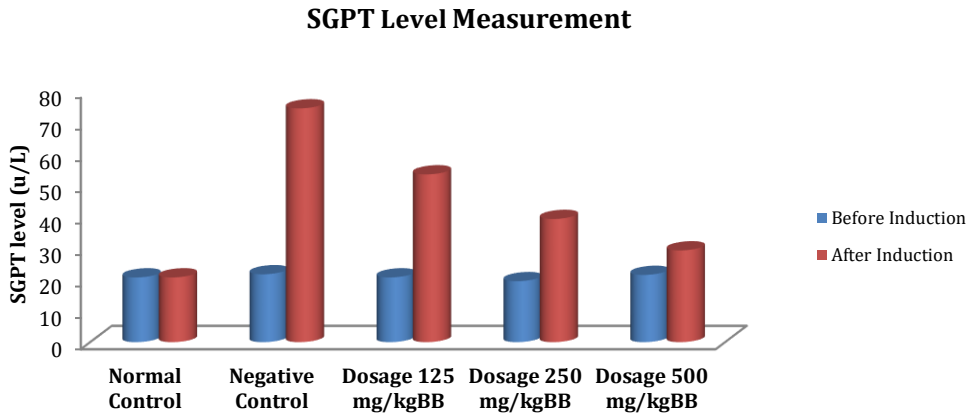


**Figure 1. Graph of SGPT levels before and after treatment**

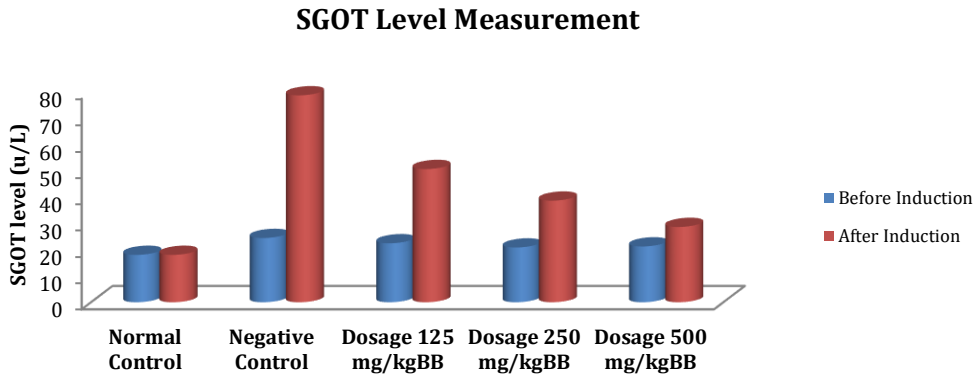


**Figure 2. Graph of SGOT levels before and after treatment**

**Table II. Notika leave phytochemical screening results**

| Phytochemical Test | Reactor | Reference | Results | Conclusion |
|---|---|---|---|---|
| Alkaloids | Dragendorf | Formation of a brown or red-orange precipitate | Black | Negative |
| Flavonoids | Mg + HCl P | Changes in color to red or orange (Setyowati, 2014). | Orange light brown precipitate | Positive |
| Saponins | Water | The emergence of foam (Nafisah, 2014). | Foam formed | Positive |
| Tannins | $FeCl_3$ | Formation of a blackish-green color in the extract after adding 1% FeCl3 (Setyowati, 2014). | blackish green | Positive |
| Terpenoids | Liebermann -Burchard | A positive result is the formation of a brown color (Setyowati, 2014). | blackish green | Positive |

vacuum evaporator to separate the extract and solvent so that a thick ethanol extract of *notika* leaves was obtained as much as 158.36 g.

The phytochemical screening carried out in this study aims to provide an overview of the classes of compounds contained in the plants studied. The phytochemical screening methods carried out included tests for alkaloids, flavonoids, saponins, tannins, and terpenoids. This test was carried out to identify the secondary metabolite compounds present in the extract of the *notika* leaf plant. Furthermore, after the identification of

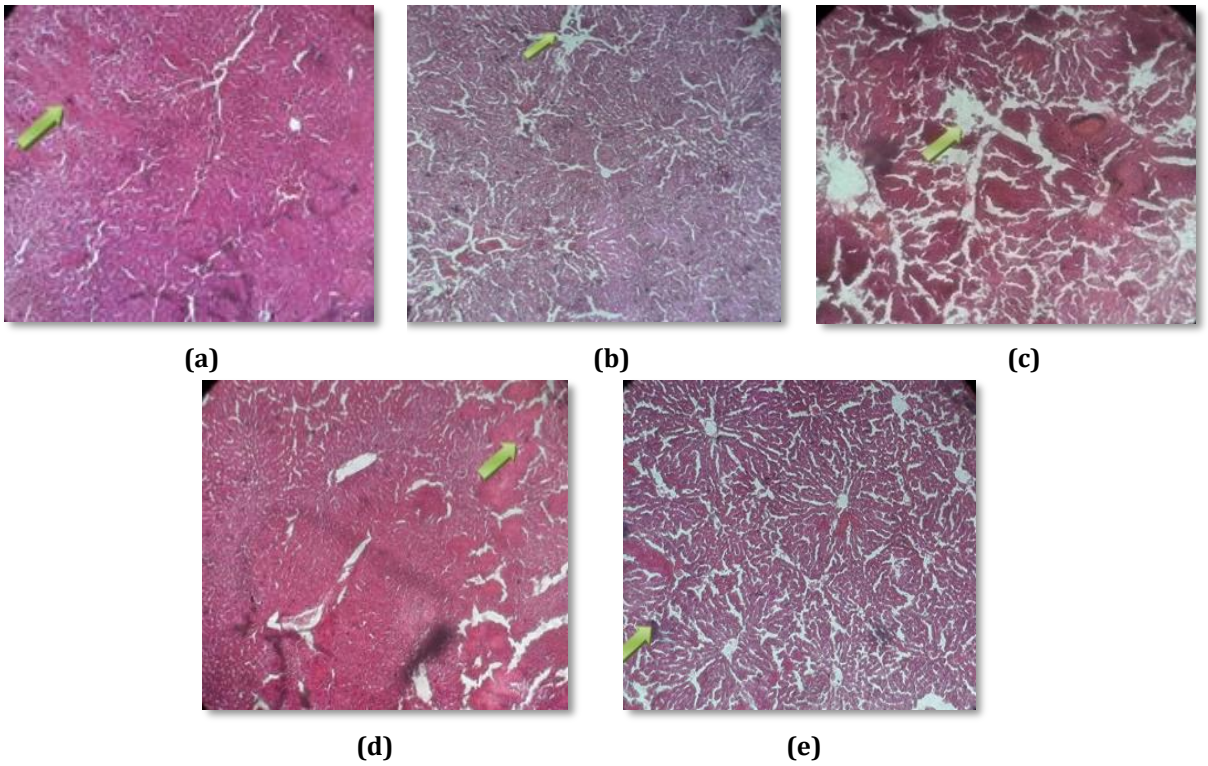


**Figure 3. Histopathological description of the liver of rat (Rattus norvegicus) with HE staining, magnification 400x. In the normal control group, the liver structure was still in normal condition (a), and the control group was negative, showing that the liver cells were entirely necrotic (b), at a dose of 125 mg/kgBW, liver cell damage or necrosis was found (c), 250 mg/kgBW was found. the presence of damage or necrosis of liver cells (d), 500 mg/kgBW does not find any damage or necrosis of liver cells (e). Signs ➡ cell necrosis, ➡ central vein. White bar: 1 cm.**

secondary metabolites in the ethanol extract of notika leaves, hepatoprotective activity was tested. Induction of carbon tetrachloride (CCl4) is one method of modeling test animals with tissue damage in the liver. The use of this compound can cause steatosis, centriolar necrosis, and cirrhosis, so its use is very appropriate to assess the hepatoprotective ability of a drug compound (Supriono et al., 2019). Liver damage caused by CCl4 is caused by the formation of trichloromethyl radicals (CCl3) from the metabolism of CCl4 compounds by cytochrome P450 2E1 (CYP2E1) in the liver. Trichloromethyl compounds with oxygen will form trichloromethyl peroxy (CCl3O2) which can attack the lipids of the endoplasmic reticulum membrane, causing lipid peroxidation reactions and disrupting calcium homeostasis which causes cell death, and fat accumulation (steatosis) in the liver.

The SGOT and SGPT values are indicators that can be used to assess damage to liver tissue, including those caused by CCl4 induction (Muhammad Reza Ramadhani, Mochammad Saiful Bachri, 2015). The success of animal modeling in this study was assessed based on the values of SGOT and SGPT and liver histopathological profiles of test animals in the negative and positive control groups. In this study, the SGOT and SGPT values of each test group after being induced by CCl4 compounds increased and differed significantly ($p<0.05$) from normal controls who were only given 0.5% NaCMC. There was a small rise after CCl4 treatment at dosages of 125 mg/kgBW and 250 mg/kgBW, indicating that these doses were less effective as hepatoprotectors. It was more effective as a hepatoprotector at a dose of 500 mg/kgBW because there was less increase after being induced by CCl4 at this level and the decline was better than in the other dose groups. Inhalation anesthetics like ether have been shown by Ganiswara (1995) to mildly impair liver function, allowing for a rise in SGPT readings. Collin et al.'s (1978) study, which claimed that ether might enhance the SGPT enzyme level in rats even if no abnormalities were visible, offers evidence in favor of this. The histopathological profile showed the presence of cell necrosis in the liver tissue in the negative control group and not in

the positive control group, thus animal modeling with liver damage was successful.

The hepatoprotective effect of the ethanolic extract of Notika (*Archboldiodendron Calosericeum* (Kobuski)) is probably caused by the secondary metabolites, such as flavonoids and saponins. Flavonoids have long been known to have antioxidant effects. This compound can break down lipid chains to prevent liver damage due to free radicals including CCl4 so that the function of cell membranes is maintained (Maulina, 2015). Several studies have shown the hepatoprotective effect of flavonoid compounds through antioxidant mechanisms in animals induced by CCl4 (Alghazeer et al., 2018), and induction of paracetamol (Zakaria et al., 2020). Saponins showed a hepatoprotective effect in CCl4-induced animals with antioxidant properties (Rachmawati et al., 2013), anti-inflammatory mechanisms, and regulating genes that play a role in cell apoptosis (Qu et al., 2012). In another study, saponin was also reported can inhibit the release of SGOT and SGPT after 14 days of administration (Liem et al., 2018).

## CONCLUSION

The secondary metabolites contained in notika leaves are flavonoids, tannins, and terpenoids. The ethanolic extract of notika leaf has a hepatoprotective effect based on the values of SGOT and SGPT and the histopathological profile of the liver at a dose of 500 mg/kgBW.

## ACKNOWLEDGEMENT

The authors would like to thank to Faculty of Pharmacy, Halu Oleo University for the facilities and research support provided.

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