



Hepatoprotective Activity of Ethanol Extract of Figs Leaves (*Ficus carica* L.) with SGOT & SGPT Parameters in *Sprague Dawley* Female Rats Induced by Paracetamol

(Efek Hepatoprotektif Ekstrak Etanol Daun Tin (*Ficus carica* L.) dengan Parameter SGOT dan SGPT pada Tikus Betina *Sprague Dawley* yang Diinduksi Paracetamol)

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ABSTRACT

Background: Long-term usage of paracetamol damages liver cells characterized by the increasing levels of *Serum Glutamic Pyruvic Transaminase* (SGPT) and *Serum Glutamic Oxaloacetic Transaminase* (SGOT). Figs (*Ficus carica* L.) leaves contain high flavonoid compounds that able to act as hepatoprotector agents which inhibited the process of liver damage. **Objectives:** This study aims to determine the dose characteristics and hepatoprotective activity of figs (*Ficus carica* L.) leaves extract. **Material and Methods:** The hepatoprotective activity of figs extract (*Ficus carica* L.) was determined by measuring SGPT & SGOT levels in rat blood. 42 rats were prepared, divided into 7 groups: normal control group, negative control given paracetamol with a dose 40 mg/200 g BW, positive control given hepamax®, base control given Na CMC, and 3 test dose groups given figs leaves extract with a dose of 40 mg/200 g BW, 80 mg BW/200 g BW and 160 mg/200 g BW. The treatment was carried out for 14 consecutive days. Paracetamol was given for 14 days, while positive control, 3 test dose groups and base control were given on day 7 to day 14. Rats blood samples were taken through the orbital sinuses on day 1, day 5, day 10 and day 14 after treatment began. SGPT & SGOT levels were determined using spectrophotometry with analytical methods using specific SGPT & SGOT reagent kits. **Results:** The results showed that the leaves extract of figs (*Ficus carica* L.) proved to be able to reduce the levels of SGPT & SGOT with the most potent dosage was 40 mg/200 g BW. However, the reduction of SGPT & SGOT levels were not significantly different from other treatments. **Conclusions:** Figs (*Ficus carica* L.) leaves extract showed activity as a hepatoprotective agent, based on the reduction of SGPT & SGOT levels in rat after 14 days of treatment.



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ABSTRAK

Latar Belakang: Penggunaan parasetamol dalam jangka panjang merusak sel hati yang ditandai dengan peningkatan kadar Serum Glutamic Pyruvic Transaminase (SGPT) dan Serum Glutamic Oxaloacetic Transaminase (SGOT). Daun tin (*Ficus carica* L.) mengandung senyawa flavonoid tinggi dan diduga dapat berperan sebagai agen hepatoprotektor sehingga dapat menghambat proses kerusakan hati. **Tujuan:** Penelitian ini bertujuan untuk mengetahui karakteristik dosis dan aktivitas hepatoprotektif ekstrak daun tin (*Ficus carica* L.). **Bahan dan Metode:** Aktivitas hepatoprotektif ekstrak etanol daun tin (*Ficus carica* L.) ditentukan dengan mengukur kadar SGPT & SGOT dalam darah tikus. Sebanyak 42 ekor tikus dibagi menjadi 7 kelompok yaitu kelompok kontrol normal, kontrol negatif yang diberi parasetamol, kontrol positif diberi hepamax®, kontrol basis, dan 3 kelompok dosis uji yang diberi ekstrak etanol daun tin (*Ficus carica* L.) dengan dosis 40 mg/200 g BW, 80 mg/200 g BW dan 160 mg/200 g BW. Perlakuan dilakukan selama 14 hari berturut-turut. Paracetamol diberikan selama 14 hari, sedangkan kontrol positif, kontrol dosis uji ekstrak dan kontrol basis diberikan pada hari ke-7 sampai hari ke-14. Sampel darah tikus diambil melalui sinus orbital pada hari ke-1, hari ke-5, hari ke-10 dan hari ke-14 setelah perlakuan dimulai. Kadar SGPT & SGOT ditentukan menggunakan spektrofotometri dengan metode analisis menggunakan reagen kit SGPT & SGOT. **Hasil:** Hasil penelitian menunjukkan bahwa ekstrak daun tin (*Ficus carica* L.) terbukti mampu menurunkan kadar SGPT & SGOT dengan dosis paling poten yaitu 40 mg/200 g BW karena mempunyai kekuatan untuk menurunkan kadar SGPT & SGOT yang tidak berbeda secara signifikan dari dosis 80 mg/200 g BW dan 160 mg/200 g BW tikus. Kesimpulan: ekstrak etanol daun tin (*Ficus carica* L.) menunjukkan aktivitas sebagai agen hepatoprotektif, karena dapat menurunkan kadar SGPT & SGOT pada tikus setelah 14 hari perlakuan.

Kata kunci: Daun tin; Hepatoprotektor; Paracetamol, SGPT; SGOT

INTRODUCTION

Liver disease in Indonesia is considered the high category. One of the causes of liver disease is the use of hepatotoxic drugs. Hepatocytes (liver parenchyma cells) make up a large part of this organ. Hepatocytes are responsible for the central role of the liver in body metabolism. These cells are located between the sinusoids which contain blood and bile ducts (Corwin, 2010). The use of paracetamol as an analgesic and antipyretic has been widely known by the general public and is known as OTC drug. Inappropriate medication can result in an overdose of paracetamol which can lead to liver failure and then death within a few days. The toxic dose of paracetamol varies widely. In adults, hepatotoxicity occurs with a single dose of 10-15 grams (200-250 mg / kg) of paracetamol, doses of 20-25 g or more are likely to cause death. The general symptoms during the first day of acute paracetamol toxicity are not clearly visible. Events such as anorexia, nausea and vomiting and abdominal pain can occur within the first 24 hours and can last for several weeks. Liver disorders are estimated to occur on the second day, with symptoms, namely an increase in serum transaminase and lactate dehydrogenase activity and normal serum bilirubin levels (Katzung, 2010). The enzyme most often associated with hepatic cell damage is aminotransferase, which causes hepatic parenchymal cell damage to increase levels of Serum Glutamic Pyruvate Transaminase (SGPT) and Serum Glutamic Oxaloacetic Transaminase (SGOT) in plasma. SGPT is more specific than SGOT. SGPT is more in the myocardium than in hepatic cells, also SGOT is in striated muscles, kidneys, and brain (Bastiansyah, 2012).

The fig (*Ficus carica* L.) plant comes from the Mediterranean. There have been many studies on the content and benefits of fig plants both leaves, fruit and roots, one of the benefits traditionally is that the leaves can be used to treat various diseases of the respiratory tract, cardiovascular, gastrointestinal tract and also as an antispasmodic and anti-inflammatory (Mawa et al, 2013). Flavonoid are the main compound in this plant and different extracts have been found have different biological activity (Gani et al, 2018). The main free flavonoid in fig leaves was found is luteolin, quercetin, and a free aglycone like methoxy-isoflavone and biochanin (Vaya, 2006). Quercetin is a group of flavonols, one of six subclasses of flavonoids containing high antioxidants that can be used as potent a chemopreventive and can be used to reduce growth of breast, lung, colon, and ovarian cancer cells (Sahoo et al, 2011). Bioavailability of quercetin is less than 17% in rats and 1% in humans (Kakran et al, 2011). Flavonoids, compounds known as antioxidants, reduce free radicals and inhibit the induction of inflammatory mediators that have the potential to cause damage to hepatocyte cells. The way it works is by increasing the activity of the enzyme catalase, superoxide dismutase, which is an endogenous antioxidant, and increasing the production of glutathione (GSH). Antioxidants namely vitamins A, C, and E can act as hepatoprotectors which may reduce oxidative stress by capturing electrophile structure compounds, namely paracetamol metabolites (NAPQI) which act as hepatotoxic so that they can cause liver damage (Wardah et al, 2016). The high flavonoid content in the leaves, researchers are very interested in exploring the benefits of fig leaves (*Ficus carica* L.) in Indonesia by conducting a phytochemical analysis of compounds from fig leaves (*Ficus carica* L.) and testing the hepatoprotector activity of fig leaves (*Ficus carica* L.) with SGOT & SGPT parameters in female *Sprague-Dawley* rats induced with paracetamol.

MATERIAL AND METHODS

Materials

The materials used are distilled water, fig leaves purchased from Zam-Zam Therapy House, ethanol 70% (*Brataco*), paracetamol 500 mg tablets (*Kimia Farma*), Hepamax®, colloidal suspension Na-CMC 1% w / v, Mayer's reagent, 1% FeCl₃, the mobile phase is a mixture of n -butanol, acetic acid and water (technical grade), TLC plate silica gel Kiesegel 60 F254 0.25 mm (Merck), and Reigerd's SGPT & SGOT reagent kit (Merck).

Methods

This research was conducted for approximately eight months in June 2019-February 2020 at the Pharmaceutical Technology Laboratory and Pharmacy Research Laboratory, Faculty of Medicine and Health Sciences, University of Muhammadiyah Yogyakarta. This study was approved by the UMY Ethics Committee Number 039/EP-FKIK-UMY//VI/2020.

Extraction

The extract was prepared using the maceration method using 70% ethanol solvent for 5 days followed by remaceration for 2 days. Then phytochemical screening tests carried out included examination of alkaloids, tannins, saponins and flavonoids.

Preparation of colloidal Na-CMC 1% w / v

100 ml of aquadest was heated at 70°C. add 1 gram of Na-CMC gradually while stirring until a homogeneous colloid solution is formed. The dosage of test preparation given to experimental animals was 40 mg/200 g BW, 80 mg/200 g BW, 160 mg/200 g BW which were given orally.

Preparation of Test Animals

In this study, 42 female white rats (*Sprague dawley*) weighing 150-200 g were used which were randomly divided into 7 treatment groups. The normal group is the group that is not given treatment. The negative group was given only Paracetamol 40 mg/200 g BW of rats as toxic dose the positive group was given Hepamax® (Syilimarin) at a dose of 20 mg/g BW of rats and the base group was given 1% Na-CMC as a control group. The treatment was carried out for 14 consecutive days. Paracetamol was given for 14 days, while positive control, base control and 3 test dose groups given figs extract (*Ficus carica* L.) with a dose of 40 mg/200 g BW, 80 mg/200 g BW and 160 mg/200 g BW were given on day 7 to day 14. Rats blood samples were taken through the orbital sinuses on day 1, day 5, day 10 and day 14 after treatment began. The first SGPT and SGOT enzyme values were measured before giving paracetamol and ethanol extract of fig leaves (*Ficus carica* L.). The aim was to determine the initial value of the SGPT and SGOT enzymes contained in rat blood serum so that these initial values could be compared with the values when given paracetamol and ethanol extract of fig leaves (*Ficus carica* L.).

RESULTS AND DISCUSSION

The plant determination showed that the fig leaves from the *moraceae* family were true *Ficus carica* L. From the extraction process, 62.9 grams of thick extract of fig leaves were obtained so that the yield obtained was 12.58%. Screening test for chemical compounds in fig leaves extract. The alkaloid content of fig leaves extract was tested by means of the extract being tested by adding a specific reagent, namely Mayer's reagent. The results obtained in this test are the negative ethanol extract of fig leaves containing alkaloid compounds without the formation of white deposits and only forming a precipitate. The principle of this analytical method is the precipitation reaction that occurs due to ligand replacement. The nitrogen atom which has the lone pair on the alkaloid can replace the iodo ion in the reagents.

The Tannin test was carried out by adding the extract with 1% FeCl₃ solution drop by drop and the results obtained in the fig leaves extract formed a dark black color which indicated the formation of a complex compound between tannins and Fe₃⁺ which indicated a change in green, red, purple, blue or black color. Phytochemical test using FeCl₃ is used to determine whether the sample contains phenol groups. The presence of phenol groups is indicated by a blackish green or dark blue color after adding FeCl₃, so that it gives a positive result, it is possible that there are phenolic compounds in the sample and one of them is tannins because tannins are polyphenolic compounds. The classic way to detect simple phenolic compounds, namely adding extracts with 1% FeCl₃ solution in water, which causes a strong green, red, purple, blue or black color. The formation of a blackish green color in the extract after adding FeCl₃ because tannins will form complex compounds with Fe₃⁺ ions (Harborne, 1987).

Forth test is performed to determine or identify saponin compounds. In the fig leaves extract that has been added with 5 mL of aquadest then shaken. The foam remains for 30 seconds so the identification shows the presence of saponins. This foam or foam indicates the presence of glycosides which have the ability to form foam in water which is hydrolyzed into glucose and other compounds (Marliana dkk, 2005).

Phytochemical screening tests were carried out to obtain information about the chemical content of fig leaves as a parameter of extract quality in relation to their pharmacological effects. The results obtained indicate that the fig leaves contain tannins, saponnins and flavonoids. Flavonoids, especially quercetin, are able to act as hepatoprotectors, thereby inhibiting the process of liver damage (Sawi and Sleem, 2010). The identification of quercetin compounds with TLC was carried out using the stationary phase silica gel plate (GF254). GF254 silica gel is a silica gel that is free from water and contains gypsum (CaSO₄ H₂O) and compounds that fluoresce under UV254 light, but under UV366 light the plate will look dark. For the mobile phase used is ethyl acetate: methanol: water with a ratio (6.5: 2.85: 3). The result from TLC is shown in Figure 1.

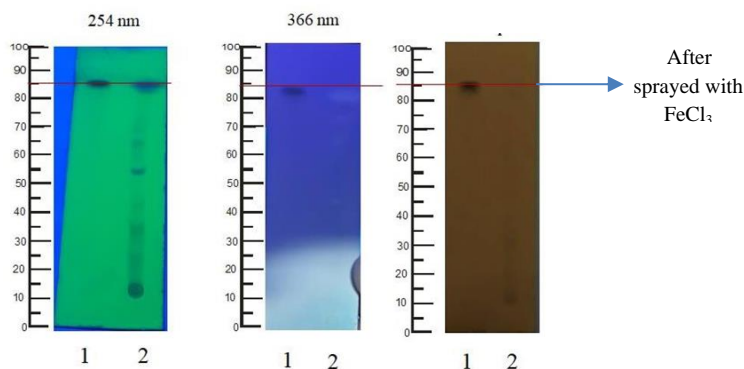


Figure 1. TLC Results of quercetin standar (1) and figs leaves extract (2)

Table 1. Data from the observation of SGOT levels

Group	SGOT Blood Levels (IU/L)±SD (day 1)	SGOT Blood Levels (IU/L)±SD (day 5)	SGOT Blood Levels (IU/L)±SD (day 10)	SGOT Blood Levels (IU/L)±SD (day 14)
Normal	56.069±7.94	56.06±7.94	56.06 ± 7.94	56.06 ± 7.06
Negative	64.66±6.42	91.94±9.01	87.22 ± 3.19	84.86 ± 0.96
Positive	58.17±1.91	87.15±3.61	60.71 ± 7.51	63.56 ± 12.37
Base	66.04±10.58	88.48±5.84	83.924 ± 3.20	84.91 ± 2.77
Dose I	62.81±6.11	91.40±10.36	63.36 ± 6.35	58.93 ± 5.95
Dose II	58.79±3.46	88.65±3.71	67.47 ± 12.09	54.81 ± 6.52
Dose III	56.17±7.29	85.85±1.95	70.89 ± 12.94	52.14 ± 4.95

Table 2. Data from the observation of SGPT levels

Group	SGPT Blood Levels (IU/L)±SD (day 1)	SGPT Blood Levels (IU/L)±SD (day 5)	SGPT Blood Levels (IU/L)±SD (day 10)	SGPT Blood Levels (IU/L)±SD (day 14)
Normal	22.42±4.03	21.53±4.64	21.53±4.64	21.53± 2.14
Negative	26.35±1.49	42.67±2.73	42.45±2.31	44.88 ± 2.34
Positive	23.84±0.81	42.99±6.29	50.83±3.09	23.56 ± 3.94
Base	19.99±1.69	45.46±2.53	47.11±4.35	48 ± 4.55
Dose I	22.66±2.45	54.77±3.83	40.84±2.91	24 ± 4.39
Dose II	22.05±1.14	45.52±4.89	44.74±1.35	24.49 ± 3.18
Dose III	19.51±1.01	52.55±0.88	51.69±3.21	23.16 ± 2.67

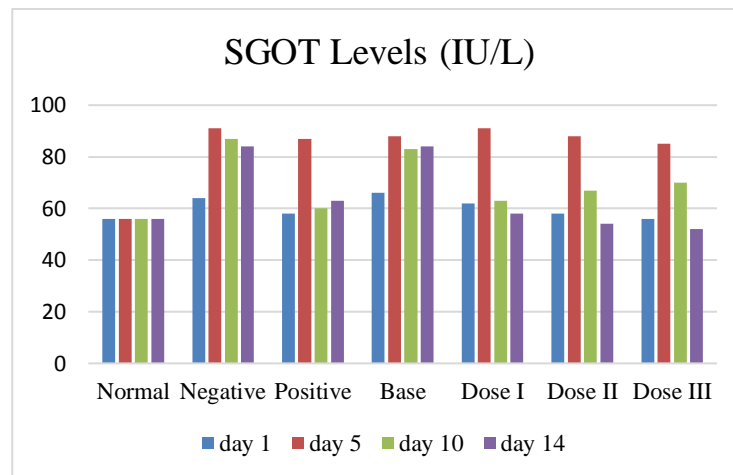


Figure 2. SGOT Blood Levels

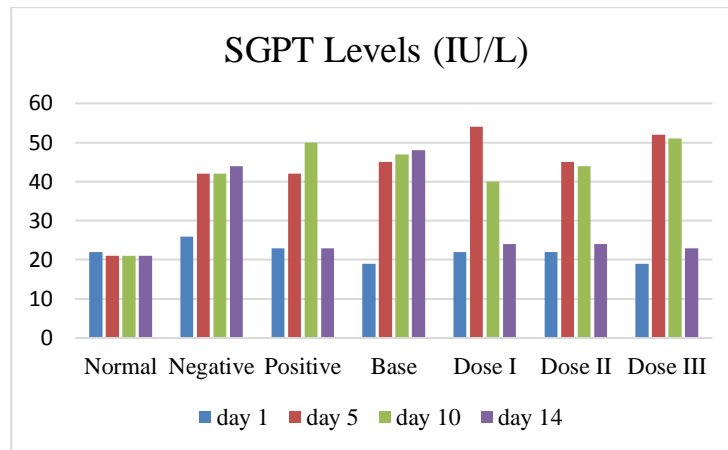


Figure 3. SGPT Blood Levels

Table 3. Results of One-way ANOVA Analysis

Groups	Statistical results (p<0.05)
Negative vs Normal	0.05
Negative vs Positive	0.07
Positive vs Base	0.07
Negative vs Dose I	0.02
Negative vs Dose II	0.01
Negative vs Dose III	0.00
Dose I vs Dose II	0.55
Dose I vs Dose III	0.33
Dose II vs Dose III	0.69

From the results of statistical tests using One-way ANOVA, the probability of both was less than 0.01 ($p < 0.05$), which means that fig leaves extract (*Ficus carica* L.) with a gel base of Na-CMC had an effect on reducing SGPT and SGOT levels of *Sprague dawley* rats. To determine the significant effect between dose on the reduction of SGPT and SGOT levels, a further test was performed, namely the Least Significance Test (LSD). From the results of the LSD test, it was found that fig leaves extract based on Na-CMC gel had a significant effect on reducing SGPT and SGOT levels because the probability of the LSD test results was less than 0.05 ($p < 0.05$).

It can be seen in table 3 that the results of the analysis for the normal, negative, positive and basic groups did not show a significant difference because they did not meet the requirements ($p < 0.05$). However, the negative group with test groups 1, 2 and 3 showed a significant difference between groups of ($p < 0.05$) so that there was a significant difference in the group given fig leaves ethanol extract (*Ficus carica* L.) and those that were not given that is the negative group.

In this study, paracetamol was used as an inducer of liver damage. If used above the treatment window it can result in liver damage. Paracetamol will form toxic reactive metabolites (N-acetyl-p-benzoquinone) and free radicals through the biotransformation process by the CYP450 enzyme with the

help of CYP2E1 isoenzymes. Reactive metabolites that are toxic and free radicals can interfere with the integrity of cell membranes and lead to liver damage. Giving paracetamol at a dose of 1000 mg / kg has been able to show liver damage which is characterized by increased levels of the SGPT enzyme (Abraham, 2005) (Roy and Das, 2010).

Liver damage mainly occurs in the centrolobular area because of the many cytochrome P450 enzymes there (Podolski and Isselbacher, 2002). Damage to the cell membrane causes the liver to secrete SGOT and SGPT enzymes. From the research conducted, it was found that the average SGPT level of the negative control group on the 14th day was 44.88 ± 2.34 U / L and the average SGOT level results in the negative control group on the 14th day was 84.86 ± 0.96 U / L. This shows that the paracetamol used as an inducer can cause liver damage, which shows the high levels of SGPT and SGPT in the negative control group given paracetamol compared to the SGOT and SGPT levels in the normal group. The mean SGOT levels in the dose group of 40 mg/200 g BW, 80 mg/200 g BW, and 160 mg/200 g BW rats respectively on day 14 were 58.93 ± 5.95 U / L, 54.81 ± 6.52 U / L, 52.14 ± 4.95 U / L. The mean SGPT levels in the dose group were 40 mg/200 g BW, 80 mg/200 g BW, and 160 mg/200 g BW of rats respectively on the 14th day, namely 24 ± 4.39 U / L, $24.49 \pm 3, 18$ U / L, 23.16 ± 2.67 U / L. There was a decrease in SGOT and SGPT levels at each dose of fig leaves extract in the three dose test groups. This research similar with the other study, that fig leaves extract in dose 200 mg/kg enhanced protection against CCl₄ induced hepatic damage (Aghel et al, 2011). Methanolic extract of fig leaves with oral dose 500 mg/kg showed significant role as hepatoprotective activity in CCl₄-induced liver damage in rat model by lowering alanine aminotransferase (SGPT), aspartate aminotransferase (SGOT), total serum bilirubin, and malondialdehyde (Krishna et al, 2007). It is indicated promising hepatoprotective activity that shown form in vitro test (Badgujar et al, 2014).

In the comparison of levels shown in Tables 1,2,3 and figures 2 and 3. There was a decrease in the levels of the SGPT and SGOT enzymes from the three doses, but these decreases did not show a significant difference between the three doses. At a dose of 40 mg/200 g BW, rats had shown a decrease in SGPT & SGOT levels in serum, although the two levels, 80 mg/200 g BW and 160 mg/200 g BW of rats, also met the normal levels of SGPT and SGOT.

CONCLUSION

The ethanol extract of fig leaves (*Ficus carica* L.) contains a flavonoid which is thought to be quercetin, which is a potential hepatoprotective agent. In the analysis, the results showed that there was no significant difference in the value reduction in SGPT and SGOT levels between doses, and the dose of 40 mg/200 g BW is the most effective dose which has properties as a hepatoprotective agent.

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CONFLICT OF INTEREST

Authors declare that there is no conflict of interest

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