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Effectivity of Pedada Fruit (*Sonneratia caseolaris*) Extract to The Level of SGOT and SGPT in Rat Treated by Paracetamol Induction

Efektivitas Ekstrak Buah Pedada (Sonneratia caseolaris) terhadap Kadar SGOT dan SGPT Tikus Putih yang Diinduksi Parasetamol

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Abstract

The study was aimed to determine the effectiveness of pedada fruit extract as a hepatoprotector in the experimental rat that fed by toxic dose of paracetamol. The total of 30 white rats (Wistar strain, two months age and 150-200 g weight) were randomly divided into 5 groups. Group I (normal control) only given distilled water for 7 days). Group II (negative control) that given distilled water for 7 days and then treated by 270 mg/head single dose of paracetamol. Group III, IV, and V (treatment group) were given a pedada fruit extract at a dose of 28 mg/head/day, 56 mg/head/day, and 84 mg/head/day for 7 days and then treated by 270 mg/head single dose of paracetamol. On the 9th day of treatment, the blood samples were taken and were further measured for its SGOT and SGPT level using photometry enzymatic method. The result of LSD test on SGOT and SGPT data showed that III, IV, and V groups were not significantly different to the group I ($p>0.05$). However, it significantly different with the group II ($p<0.05$). Data of SGOT showed that group IV were significantly different ($p<0.05$) with the group V. Whereas, the data of SGPT among groups III, IV, and V were not significantly different ($p>0.05$). The result of linier regression test indicated that dose 28 mg/head was the most effective dose. It was concluded that pedada fruit extract was able to provide a hepatoprotective effects in rats that fed by toxic dose of paracetamol and most effective dose as a hepatoprotector was 28mg/head/day.

Abstrak

Penelitian ini bertujuan untuk mengetahui efektivitas ekstrak buah pedada sebagai hepatorotektor tikus putih yang diberi parasetamol dosis toksik. Sebanyak 30 ekor tikus putih (strain Wistar jantan berumur dua bulan dengan berat badan 150-200 g) dibagi secara acak dalam lima kelompok. Kelompok I (kontrol normal) diberi aquadest selama tujuh hari. Kelompok II (kontrol negatif), diberi aquadest selama tujuh hari dilanjutkan pemberian parasetamol 270 mg/ekor dosis tunggal. Kelompok III, IV, dan V (kelompok perlakuan) diberi ekstrak buah pedada pada dosis 28 mg/ekor/hari, 56 mg/ekor/hari, dan 84 mg/ekor/hari selama tujuh hari dilanjutkan pemberian parasetamol 270 mg/ekor dosis tunggal. Hari ke-9 darah diambil dan diukur kadar SGOT dan SGPT dengan metode fotometri enzimatik. Hasil uji LSD data SGOT dan SGPT menunjukkan bahwa kelompok III, IV, dan V tidak berbeda nyata terhadap kelompok I ($p>0,05$), namun berbeda nyata terhadap kelompok II ($p<0,05$). Data SGOT kelompok IV berbeda nyata ($p<0,05$) dengan kelompok V. Data SGPT tidak ada perbedaan nyata ($p>0,05$) antara kelompok III, IV, dan V. Hasil uji regresi linier, dosis 28 mg/ekor adalah dosis paling efektif. Disimpulkan bahwa ekstrak buah pedada mampu memberikan efek hepatoprotektor pada tikus yang diberi parasetamol dosis toksik dan dosis yang paling efektif sebagai hepatoprotektor adalah dosis 28 mg/ekor/hari.

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INTRODUCTION

Liver is the largest organ in the body and the most complex one. it composed of liver cells (hepatocytes) that play role in the metabolism of nutrients, drug and toxicant. The liver performs more than 500 functions, including (1) production of bile (2) production and secretion of glucose, proteins, vitamins, fats and other compounds (3) breakdown of hemoglobin (4) conversion of ammonia to urea (Haws, 2008). Liver is the main place of amino acid metabolism in the body and also the main place urea synthesis. It is the only organ that has all lines to form and break down the amino acid through transamination reaction. The enzyme that catalyzes this reaction is known as transaminase or aminotransferase (Marks et al., 2000). Therefore, liver is one of organs that contain a lot of aminotransferase enzymes.

Disease caused by impaired liver function is a major problem in the world of health. Until now, liver disease affects hundreds of millions people around the world, causing acute and chronic illness and approaching 1.4 million people die every year (WHO 2013). Liver damage is caused by microorganisms such as viruses and bacteria, while the use of drugs, alcohol, chemicals and environmental toxins can also lead to lever damage (Eswaraiah et al. 2013). Chemical and drug that can lead to liver damage (hepatotoxicity), are alcohol, carbon tetrachloride (CCl_4), galactosamine, paracetamol, isoniazid and rifampicin, antibiotic, peroxidised oil, and aflatoxin (Sowjanya et al. 2013).

One indicators of liver damage is increasing the level of liver enzymes in the serum, including the level of SGPT and SGOT (Wahyuni 2005). Serum Glutamate Pyruvate Transaminase (SGPT) and Serum Glutamate Oxaloacetate Transferase (SGOT) is an aminotransferase enzyme that catalyzes the reversible transfer of amino acid group of amino acid to alpha-keto acid (Sacher & McPherson 2004). SGPT and SGOT enzymes are sensitive indicators of liver cell damage (Barlett, 2004). Liver damage can lead to permeability membrane damage so the intracellular enzyme freely exit and enter the extracellular space and blood vessels (Krysanti & Widjanarko 2014).

Diseases caused by liver damage can occur to all level of people in any level of age, gender or economic level. Therefore, the use of natural materials as traditional medicine has started to be developed. This increases community awareness of the side effects caused by synthetic drugs that is greater than the natural drug or medicine (Armansyah et al. 2010). In addition, the price is much cheaper than synthetic drugs, natural medicine is faster and easier to obtain. Therefore, it is necessary to find an alternative treatment to prevent liver damage by using traditional medicine such as *Pedada* fruit (*Sonneratia caseolaris*).

Pedada fruit (*Sonneratia caseolaris*) has 24 components including eight steroids, nine triterpenoids, three flavonoids and four derivatives of benzenecarboxylate (Varghese et al., 2010). The component has function as an anti-inflammatory, analgesic, antioxidant, anti-allergic, anti-fungal and anti-microbial. Triterpenoids also serves as the prevention and treatment of hepatitis (Peteros & Uy 2010). Flavonoids in *Pedada* fruit (*Sonneratia caseolaris*) also have antioxidant activity (Shadu et al. 2006).

There are three bioactive components of methanol extracts of *Pedada* fruit (*Sonneratia caseolaris*), which are oleanolic acid, β-sistosterol-β-D-glukopyranoside and luteolin. Oleanolic acid in *Pedada* fruit was able to inhibit α-glucosidase enzyme and act as active component of antihyperglicemic (Tiwari et al. 2010). Oleanolic acid has hepatoprotective activity, anti-inflammatory, antimicrobial, hypoglycemic, antimutagen, antioxidants and antifertility (Furtado et al., 2008). Oleanolic acid is derived from triterpenoids which protects from various hepatotoxins in animals (Reisman et al., 2009). In a low dose, oleanolic acid generates adaptive response, whereas at high doses it can cause hepatotoxicity (Liu 2005).

According to Charoenteeraboon et al (2007) research, parts of *Sonneratia caseolaris* like calyx, seeds, fruit skins, pulp, seeds, petals, pneumatophore, and stamen have hepatoprotective activity. Hepatoprotective (liver protector) is a drug compound that has the therapeutic effect, to restore, maintain, and treat the damage of liver function. Based on its content, therefore the effectiveness of *Pedada* fruit against liver damage in rats was conducted.

As previously mentioned, one of the drugs that can lead liver damage is paracetamol which is in fact widely used by the society, the misuse of paracetamol can cause poisoning. Paracetamol or acetaminophen is an analgesic and antipyretic drug that is used for the treatment of various conditions of arthritis, rheumatism, joint pain and other diseases such as headache, pain during menstruation (dysmenorrhea), muscle pain (myalgia), and nervous system pain (neuralgia). Paracetamol overdose is often associated with acute liver and kidney damage in humans and experimental animals (Pierro & Rossoni 2013).

The recommended dose is 1-2 g/day. It

does not irritate the stomach, kidney cell and liver cell, but high doses (> 2 g / day) of paracetamol may affect complications in the intestines, stomach, kidney function and liver damage (Malar & Mettilda 2012). In single dose (15 g or more), paracetamol can cause liver damage through toxic metabolites of NAPQI (N-Acetyl-P-benzoquinone imine) (Clark et al. 2012). At therapeutic doses, NAPQI reacts with sulfhydryl groups of glutathione into non-toxic metabolites and it is excreted through the urine. Whereas in excessive doses of NAPQI, it increases beyond the ability of glutathione to detoxify, so the metabolite reacts with liver cells that lead necrosis centrilobular (Darsono 2002).

The formation metabolites NAPQI in large numbers and decreasing the number of hepatic glutathione causes oxidative stress cell and necrosis or liver damage (Gopalakrishnan & Kalaiarasi 2013). Oxidative stress can disrupt the hepatocyte membrane integrity resulting in the release of various enzymes from hepatocytes, for example SGOT and SGPT (Armansyah et al. 2010). Liver damage can increase blood lipid peroxide because lipid peroxide of the body cannot longer be detoxified in the liver (Heirmayani 2007). Giving *Pedada* fruit could inhibit the occurrence of lipid peroxide and it is able to increase glutathione that is responsible for maintaining the antioxidant (Furtado et al., 2008).

Based on the description, liver damage can be detected by measuring levels of SGOT and SGPT in the blood. On the other hand, *Pedada* fruit content has a role as hepatoprotector. Therefore, this study will assess the effectiveness of *Pedada* fruit extract (*Sonneratia caseolaris*) as hepatoprotector of white rat (*Rattus novergicus*) induced by toxic dose of paracetamol.

METHODS

This research was a lab experiment. The design used was Post Test Randomized Control Design with Completely Random Design. Experimental animals used in this research are 30 male Wistar strain rats aged two months, weight of 150-200 g that were obtained and maintained in LPPT Unit 4 Gajah Mada University.

Hepatoprotector test material used was 85% methanol extract of *Pedada* fruit (*Sonneratia caseolaris*) from Randusanga, Brebes area. Ripe fruit was cleaned, cut into small pieces, and dried for 15 days under the sunlight. Then it is blended up into coarse powder, and extracted by using soxhlet method. The extraction was stored in refrigerator at a temperature of 7-10 ° C (Hasan et al. 2013). Hepatotoxic inducer material used is paracetamol doses of 270 mg/rat /single dose.

Thirty rats were randomly divided into five groups. Group I (control normal) were given only distilled water for seven days. Group II (control negative), were given distilled water for seven days and then continued by giving single dose of paracetamol of 270 mg/rat. Group III, IV, and V (treatment group) were fed by *Pedada* fruit extract at dose of 28 mg/rat/day, 56 mg/rat /day, and 84 mg/rat/day for seven days and then continued by giving single dose of paracetamol of 2,7ml/each single dose. On the 9th day, blood samples were taken to measure the level of SGOT and SGPT.

Blood samples were drawn through *plexus retroorbitalis* by using microhematocrit and collected in 1.5 mL eppendorf tubes to the brim, and then waited for 60 minutes in order to separate serum from blood. Furthermore, it was centrifuged at 4000 rpm for 10 min or 12,000 rpm for 2 minutes to get serum. Then the activity of SGOT and SGPT was read by using enzymatic photometric method.

The data were normally distributed and homogeneous, then One Way ANOVA test with 95% significance level was performed. The result showed that it has significant effect, then LSD test with 95% significance level was performed to determine the most effective dose by using the Linear Regression test. Data analyses were performed by using Statistical Product and Service Solutions (SPSS) 16.0 for Windows (Santosa 2005).

RESULTS AND DISCUSSION

The results showed that each group of rats showed variations of the level of SGOT and SGPT. Shapiro-Wilk test results indicated that the data of SGOT and SGPT were normally distributed ($p > 0.05$) and variant of data was homogeneous ($p > 0.05$). One Way ANOVA test result showed the level of SGOT and SGPT had significance value of 0.000 or less than 0.05 significance level ($p < 0.05$), it means that the *Pedada* fruit extract can give significant effect on the level of SGOT and SGPT of rats that are given the toxic dose of paracetamol. To find out the difference of five treatment groups, further LSD test at 5% level was conducted. Result of statistical test of SGOT and SGPT can be seen in Table 1.

The average level of SGOT and SGPT in group II (control negative) was higher (119.18 U / L and 69.80 U / L) than group I (normal control) (Table 1). Based on the result of further LSD test showed that group II (control negative) had significant difference ($p < 0.05$) of group I (control

Table 1. Statistics Test Result of SGOT and SGPT Level (U/L).

Group	SGOT (Rerata ± SD)	SGPT (Rerata ± SD)
(Control normal)	89,05 ± 9,08[a]	49,72 ± 10,56[a]
(Control negatif)	119,18 ± 8,21[b]	69,80 ± 1,59[b]
(Pedada fruit extract dose of 28 mg)	88,08 ± 11,29[a]	48,62 ± 3,09[a]
(Pedada fruit extract dose of 56 mg)	78,42 ± 5,97[ac]	52,08 ± 10,99[a]
(Pedada fruit extract dose of 84 mg)	96,08 ± 12,86[ad]	55,10 ± 6,83[a]

Note : Numbers followed different letters in the same column showed significant difference ($p < 0,05$) of LSD test at 5% level.

normal). It means that the paracetamol of dose of 270 mg/rat can bring damage effects on the rats' liver. According to Clark et al. (2012), a single dose of paracetamol (15 g or more) can cause liver damage by toxic metabolites of NAPQI (N-acetyl-para-benzoquinoneimine)

Paracetamol toxic dose lead to increase of N-acetyl-para-benzoquinoneimine (NAPQI) formation and lipid peroxide concentration. Lipid peroxides are formed due to liver cells are not able to prevent oxidation caused by free radicals of N-acetyl-para-benzoquinoneimine. Antioxidant process is only done naturally by enzymes contained in the body that have smaller number than free radicals, thus hepatic glutathione is getting decreasing. This is consistent with Rustandi (2006) that the group of rats that were given paracetamol increased lipid peroxide concentrations during treatment with concentration of 60.42% that was higher than the normal group.

The formation of high amounts of reactive metabolites NAPQI and decreasing the number of hepatic glutathione will enhance the Radical Oxygen Species (ROS). The increasing of ROS that is not accompanied by the increasing of antioxidant will lead oxidative stress. Free radicals damage cell membranes, mitochondria and endoplasmic reticulum resulting the increasing of cytosolic Ca^{2+}. The increasing of cytosolic Ca^{2+} will activate the phospholipase, protease, endonucleases, and ATPase enzymes which phospholipids decreasing, membrane proteins and cytoskeleton disruption, DNA fragmentation, and ATP decreasing. These conditions will initiate the death of liver cells (necrosis) or liver damage (Sulistyowati et al. 2013). Liver damage will cause the release of intracellular enzymes, including SGOT and SGPT. The intracellular enzyme will increase its level in the serum so it can be indicator of liver damage (Wahyuni 2005).

Hepatoprotector effect in *Pedada* fruit extracts was shown from the average difference level of SGOT and SGPT among group II and group III, IV, and V. Rats given *Pedada* fruit extract and paracetamol toxic dose had lower average level of SGOT and SGPT compared to rats who were not given *Pedada* fruit extracts but given toxic dose of paracetamol. Statistical analysis by LSD test, showed that group II had significant difference to the groups III, IV, and V. This means that *Pedada* fruit extracts at dose of 28 mg/rat/day, 56 mg/rat/day, and 84 mg/rat/day were able to provide hepatoprotector effect due to the consumption of toxic doses of paracetamol. Hepatoprotector effect showed by *Pedada* fruit extracts was probably caused by the presence of secondary metabolites that have antioxidant and hepatoprotector activity.

According to Wu et al. (2009), there are nine compounds contained in methanol extracts of *Pedada* fruit (*Sonneratia caseolaris*) including (-)-(R) -nyasol; (-)-(R) -4'-O-methyllnyasol; 3,8-dihydroxy-6H-benzo [b, d] Pyrans-6-one; 3-hydroxy-6H-benzo [b, d] Pyrans-6-one; oleanolic acid; maslinic acid; luteolin; luteolin 7-O-β-glucoside; and benzyl-O-β-glucopyranoside. Luteolin and luteolin 7-O-β-glucoside are flavonoid compounds that have antioxidant activity (Shadu et al. 2006). Flavonoids are supposed to influence in inhibiting liver damage by binding free radicals produced by paracetamol so the impact to the liver is reduced.

Oleanolic acid is a pentacyclic triterpenoid compounds that can be found in plants in the form of the free acid and has important role in inhibiting lipid peroxide and increasing glutathione (Furtado et al.2008). Oleanolic acid compound is seen to be able to protect liver cells from toxic materials. Oleanolic acid is an Nrf2-ARE pathway activator, where this pathway has an important role in the regulation of genes that control the expression of proteins in detoxifying and eliminating electroph (Nguyen et al., 2009).

Nrf2 (nuclear factor erythroid 2-related factor 2) is a transcription factor that induces antioxidant and cytoprotective genes or known as Human Antioxidant Response Element (ARE) (Reisman et al. 2009). ARE is enhancer sequence

action or element arrangement found in the promoter region of many genes in detoxification and antioxidant enzymes. Oleanolic acid is ARE inducer that stimulates Nrf2-ARE pathway so this line will work optimally. Oleanolic acid will increase the activity of Nrf2, then this Nrf2 activates transcription by identifying the parts of the connective tissue of ARE so antioxidant genes such as glutathione will be expressed. The increasing of antioxidants in the body such as glutathione will also increase the Total Antioxidant Status (TAS). Increasing will inhibit the occurrence of free radical and electrophilic caused by toxic dose of paracetamol.

Based on the result of LSD test of SGOT, it showed that the group III, IV, and V did not have significant differences ($p > 0.05$) to group I (control normal). Group III (28 mg dose) did not have significant differences ($p > 0.05$) to group IV (56 mg dose) and group V (dose 84 mg). Meanwhile, there was significant differences ($p < 0.05$) between group IV and V group, although both of those groups can still prevent the increasing of SGOT level.

The average levels of SGPT of groups III, IV, and V are 48.62 (U / L), 52.08 (U / L), and 55.10 (U / L). Based on the results of LSD test with 95% significance level, it was found out that among those three dose groups, they did not have significant differences ($p > 0.05$) to the control normal group (49.72 U / L). So, based on the result of LSD test of SGOT and SGPT showed that *Pedada* fruit extract at doses of 28 mg/rat / day, 56 mg/rat/day, and 84 mg/rat /day already provided hepatoprotective effect due to the giving of toxic doses of paracetamol and the dose of less than 28 mg/rat also had possibilities of having hepatoprotective effect, while the dose of 84 mg/rat gave hepatotoxic effects.

In this research, to determine the most effective dose of *Pedada* fruit extract as hepatoprotective in rats, the statistical test of linear regression was performed. Regression analysis of SGOT data indicated there was relationship between dose of *Pedada* fruit extract and SGOT level with the linear regression equation model of $Y = 69.867 + 0{,}315X$ (Figure 1). It means that when the dose of *Pedada* fruit extract is 0 (zero) then SGOT level will be at 69.867 point and every increasing of 1 (one) dose of extract, SGOT level will increase 0.315. Positive coefficient (+0.315) means that there was a positive relationship between the increasing of *Pedada* fruit extract dose, and the increasing of SGOT level, so it was less effective as hepatoprotector. Dose of 28 mg/rat/day had lower Y value (78.687) compared to dose of 56 mg/rat/day and 84 mg/rat/day (87.507 and 96.327). So, *Pedada* fruit extract at dose of 28 mg / head / day dose was the most effective in lowering SGOT level because it has the lowest predictive value of SGOT (Y) level.

Regression analysis of the SGPT data indicated that there was relationship between *Pedada* fruit extract dose and SGPT level with linear regression equation model of $Y = 45.453 + 0{,}116X$ (Figure 2). It means that when the dose of *Pedada* fruit extract is 0 (zero) then SGPT level will be at 45.453 SGPT levels and and every increasing of 1 (one) dose of extract, SGPT level will increase 0.116. Positive coefficient (+0.116 means that there was a positive relationship between the increasing of *Pedada* fruit extract dose, and the increasing of SGPT level, so it was less effective as hepatoprotectior. Dose of 28 mg/rat/day had lower Y value (48.701) compared compared to dose of 56 mg/rat/day and 84 mg/rat/day (51.949 and 55.197). So, *Pedada* fruit extract at dose of 28 mg / head / day dose was the most effective in lowering SGPT level because it has the lowest predictive value of SGPT (Y) level.

The difference of the result between the level of SGOT and SGPT was because SGOT is the enzyme that is not only produced by the liver but the heart, skeletal muscles, kidney and brain, too while SGPT is the enzyme that can be found most in the liver in large numbers (Sadikin 2005). Therefore, more specific parameter to indicate the damage of liver cells is by observing the SGPT enzyme activity, because most of this enzyme is mostly produced in the liver (Kendran et al. 2013). The increasing of SGOT level also happens when liver tissue is damaged, both of the enzyme activities are measured to measure the liver damage (Sadikin 2002). In addition, both of SGOT and SGPT enzymes can routinely be checked in daily examination to determine the condition of the liver (Sibuea et al.2005). In this research, *Pedada* fruit extract is most effective used as hepatoprotector in rat by emphasizing of looking at the results of SGPT level measurement.

Based on the result of linear regression test it showed that the higher dose of *Pedada* fruit extract, the lower the effectiveness of rats hepatoprotector induced by toxic dose of paracetamol. This is due to compound that is antagonists towards hepatoprotector. According to Liu (2005), oleanolic acid contained in *Pedada* fruit has hepatoprotector activity in low doses and hepatotoxic in high doses. The possibility of the compound (-) - (R) -nyasol, (-) - (R) -4'-O-methyllnyasol, and maslinic acid also affects the increasing of SGOT

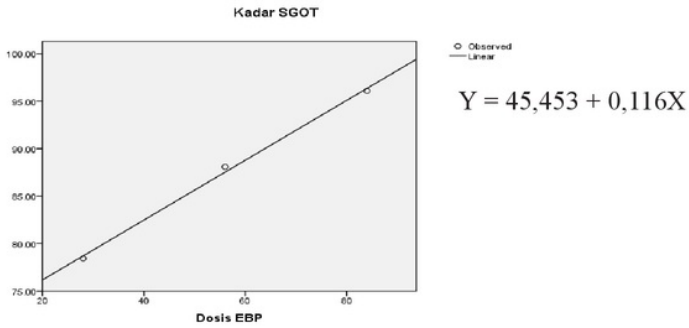

Figure 1. Linear Regression Line between Dose of *Pedada* Fruit Extract and SGOT

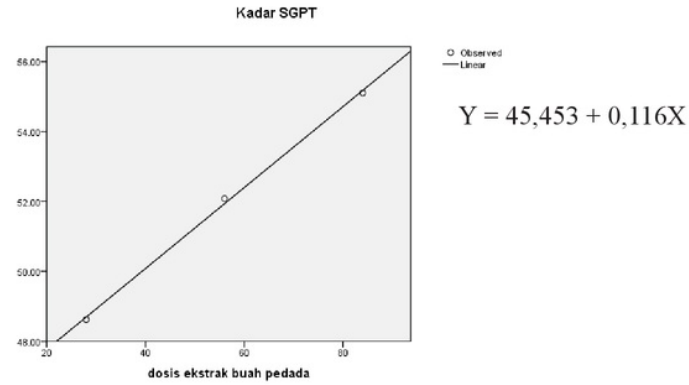

Figure 2. Linear Regression Line between Dose of *Pedada* Fruit Extract and SGPT

and SGPT level. All those compounds have cytotoxic properties in the body (Wu et al., 2009). The higher dose of *Pedada* fruit extract, the higher the oleanolic acid content, (-) - (R) -nyasol, (-) - (R) -4'-O-methyllnyasol, and maslinic acid so its activity is no longer as hepatoprotector.

Pedada fruit extract dose used in this study refers to Hasan et al (2013) research, about methanol extract activity of *Pedada* fruit as hypoglycemic. The study explained that the highest dose of *Pedada* fruit extract of 400 mg/kg body weight was able to lower blood sugar level in mice effectively compared to doses of 50 mg/kg, 100 mg/kg and 200 mg/kg. In this study, dose of 200 mg/kg in mice or equal to 28 mg/rat was the most effective dose to prevent liver damage due to toxic dose of paracetamol, but apparently it has not been used as a treatment for liver damage. Therefore, it is necessary to conduct further research on the use of *Pedada* fruit extract as treatment for of liver damage disease.

The results showed that the methanol extract of *Pedada* fruit was able to provide hepatoprotector effect by preventing the increasing of SGOT and SGPT level in rats that were given toxic dose of paracetamol and the most effective dose used as hepatoprotector is 28 mg/rat/day.

CONCLUSION

Based on the result of this research it can be concluded that methanol extract of *Pedada* fruit (*Sonneratia caseolaris*) was able to provide hepatoprotector effects in rats induced by toxic dose of paracetamol and the most effective dose used as hepatoprotector is 28 mg/rat/day.

REFERENCES

Armansyah, T., Amalia, S., Aliza, D., Vanda, H., Rahmi, E. (2010). Aktivitas hepatoprotektif ekstrak etanol daun kucing-kucingan (*Acalypha indica*

L.) pada tikus putih (*Rattus novergicus*) yang diinduksi parasetamol. *Jurnal Ilmiah Ilmu-Ilmu Peternakan,* 13(6), 292-298.

Bartlett, D. (2004). Acetaminophen toxicity. *Journal of Emerg Nurs,* 30, 281-283.

Charoenteeraboon, J., Wetwitayaklung, P., Limmatvapirat, C., Phaechamud, T. (2007). Hepatoprotective activity from various parts of *Sonneratia caseolaris*. *Journal of Planta Medica,* 73, 561.

Clark, R., Fisher, J. E., Sketris, I. S., Johnston, G. M. (2012). Population prevalence of high dose paracetamol in dispensed paracetamol/opioid prescription combinations: an observational study. *BMC Pharmacology and Toxicology,* 12(11), 1-8.

Darsono, L. (2002). Diagnosis dan terapi intoksikasi salisilat dan parasetamol. *Jurnal Farmakologi Fakultas Kedokteran Universitas Kristen Maranatha Bandung,* 2(1), 30-38.

Eswaraiah, M. C., Sindhu, N., Dipankar, B., Manasa, N. (2013). Hepatoprotective activity of *Averrhoa carambola* stem ethanolic extract on CCl_4 induced liver damage in rats. *International Journal of Pharmacy and Pharmaceutical Sciences,* 5(4), 406-4010.

Furtado, R. A., Rodrigues, E. P., Araujo , F. R. R., Oliveira, W. L., Furtado, M. A., Castro, M. B., Cunha, W. R., Tavares, D. C. (2008). Ursolic acid and oleanolic acid suppress preneoplastic lesions induced by 1,2-dimethylhydrazine in rat colon. *Journal of Toxicologic Pathology,* 36: 576-580.

Gopalakrishnan, S. & Kalaiarasi, T. (2013).Hepatoprotective activity of the ethanolic extract of the fruit *Cucumis trigonus* roxb. *International Journal of Pharmacy and Pharmaceutical Sciences,* 5(2), 268-272.

Hasan, M. N., Sultana, N., Akhter, M. S., Billah, M. M., Islamp, K. K. (2013). Hypoglycemic effect of methanolic extract from fruits of *Sonneratia caseolaris*, a mangrove plant from Bagerhat region, the Sundarbands Bangladesh. *Journal of Innovation & Development Strategy (JIDS),* 7(1), 1-6.

Haws, P. S. (2008). *Asuhan Neonatus: Rujukan Cepat*. H.Y. Kuncara, penerjemah. Terjemahan dari: *Care of The Sick Neonote: A Quick Reference For Healthy Care Providers.* Jakarta: Buku Kedokteran EGC

Heirmayani. (2007). Toksikopatologi hati mencit (Mus musculus) pada pemberian parasetamol. *Skripsi*. Bogor: Fakultas Kedokteran Hewan, Institut Pertanian Bogor.

Kendran, A. A. S., Gelgel, K. T. P., Pertiwi, N. W. L., Anthara, M. S., Dharmayuda, A. A. G., Angrreni, L. D. (2013). Toksisitas ekstrak daun sirih merah pada tikus putih penderita diabetes mellitus. *Jurnal Veteriner,* 14(4), 527-533.

Krysanti, A. & Widjanarko, S. B. (2014). Toksisitas subakut tepung glukomanan (*A. mulleri* Blume) terhadap SGOT dan natrium tikus wistar secara in vitro.*Jurnal Pangan dan Agroindustri,* 2(1), 1-7.

Liu, J. (2005). Oleanolic acid and ursolic acid: research perspectives. *Journal of Ethnopharmacology* 100, 92-94.

Malar, H. L. V. & Mettilda, B. S. M. (2012). Beware of paracetamol toxicity. *Journal of Clinic Toxicol,* 2(6), 1-3.

Marks, D. B., Marks, A. D., Smith, C. M. (2000). *Biokimia Kedokteran Dasar: Sebuah Pendekatan Klinis*. Jakarta: EGC Kedokteran.

Nguyen, T., Nioi, P., Cecil, B. (2009). The nrf2-antioxidant response element signaling pathway and its activation by oxidative stress.*Journal of Bio Chem,* 284(20), 13291-13295.

Peteros, N. P. & Uy, M. M. (2010). Antioxidant and cytotoxic activities and phytochemical screening of four Philippine medicinal plants.*Journal of Medicinal Plants Research,* 4(5), 407-414.

Pierro, D. F. & Rossoni, G. (2013). An amino acids mixture improves the hepatotoxicity induced by acetaminophen in mice. *Journal of Amino Acids,* 1-6.

Reisman, S. A, Aleksunes, L. M., Klaassen, C. D. (2009). Oleanolic acid activates Nrf2 and Protects from acetaminophen Hepatotoxicity via Nrf2-dependent and Nrf2-independent. *J Biochem Pharmacol,* 77(7), 1273-1282.

Rustandi, M. I. (2006). Potensi antioksidan ekstrak daun sangitan (*Sambucus javanica* Reinw ex Blume) sebagai hepatoprotektor pada tikus. *Skripsi*. Bogor: Fakultas Matematika dan Ilmu Pengetahuan Alam, Institut Pertanian Bogor.

Sacher, R. A. & McPherson, R. A. (2004). *Tinjauan Klinis Hasil Pemeriksaan Laboratorium.* Brahm U, penerjemah. Terjemahan dari *Widmann's Clinical Interpretation of Laboratory Tests.* Jakarta: Buku Kedokteran EGC

Sadikin, M. (2002). *Biokimia Enzim*. Jakarta: Widya Medika.

Shadu, S. K., Firoj, A., Takashi, O., & Masami, I. (2006).Flavonoids from *Sonneratia caseolaris. Journal of Natural Medicines,* 60(3), 264-265.

Sibuea, H., Panggabean, M. M., &Gulton, S. P. 2005. *Ilmu Penyakit Dalam.* Jakarta: Rineka Cipta.

Sulistyowati E, Purnomo Y, Nuri S, Audra F. (2013). Pengaruh diet sambal tomat ranti pada struktur dan fungsi hepar tikus yang diinduksi tawas. *Jurnal Kedokteran Brawijaya,* 27(3), 156-161.

Sowjanya, G., Swarnalatha, D., Shivakala, T., & Mobeena, S. K. (2013). Hepatoprotective activity- a review. *International Journal of Phytopharmacy,* 3(2), 37-49.

Tiwari, A. K., Viswanadh, V., Gowri, P. M., Ali, A. Z., Radhakrisnan, S. V. S., Agawane, S. B., Madhusudana, K., & Rao, J. M. (2010). Oleanolic acid – an α-glucosidase inhibitory and antihyperglycemic active compound from the fruits of *Sonneratia caseolaris*. *Journal of Medical and Aromatic Plants,* 1(1), 19-23.

Vargeshe, J. K., Belzik, N., Nisha, A. R., Resmi, S., & Silvipriya, K. S. (2010). Pharmacognostical and phytochemical studies of a mangrove (*Son-*

neratia caseolaris) from Kochi of Kerala State in India. *Journal of Pharmacy research,* 3(11), 2625-2627.

Wahyuni, S. (2005). Pengaruh daun sambiloto (*Andrographis paniculata, Ness*) terhadap kadar SGPT dan SGOT tikus putih. *Jurnal Gamma,* 1(1), 45-53.

Wu, S. B., Wen, Y., Li, X. W., Zhao, Y., Zhao, Z., Hu, J. F. (2009). Chemical constituents from the fruits of *Sonneratia caseolaris* and *Sonneratia ovata* (Sonneratiaceae). *Journal of Biochemical Systematics and Ecology,* 37, 1-5.

WHO [World Health Organization]. (2013). World hepatitis day [terhubung berkala].http://www.who.int/campaigns/hepatitisday/2013/event/en/index.html[12 November 2013].

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