Mandala of Health
Vol.18, No.2, September 2025, Hal. 185-194
ISSN: 0216-3098
DOI: 10.20884/1.mandala.2025.18.2.17250

THE EFFECT OF HEPATOPROCTECTIVE PROPOLIS ON THE HISTOPATHOLOGY OF THE LIVER CELL MICE INDUCED BY PARACETAMOL

Shofa Salsabila[1], Noor Yazid[2*], Nanik Marfu'ati[3]
[1]Faculty of Medicine, Muhammadiyah Semarang University
[2]Department of Anatomical Pathology, Faculty of Medicine, Muhammadiyah Semarang University
[3]Department of Biokimia, Faculty of Medicine, Muhammadiyah Semarang University

ABSTRACT

The overdose of paracetamol utility may increase N-acetyl-p-benzoqui-noneimine (NAPQI) and produce the free radicals, which will cause liver cell damage. Propolis contains antioxidants which have the ability to capture free radicals The aim of this study is to identify the hepatoprotective effect of propolis doses of 0.4 ml and 0.8 ml on the histopathological appearance of the liver of mice induced by paracetamol. This research was an experimental research using the Post Test Only Control Group Design method. The sample of this study were 24 Swiss Webster mice divided into 4 groups: group (K-) not given propolis and paracetamol; group (K+) was given paracetamol at a dose of 338 mg/kgBB; group (P1) was given a dose of 0.4 ml of propolis and group (P2) 0.8 ml and then induced by paracetamol at a dose of 338 mg/kgBB. This research was conducted for 14 days and on the 15th day termination was carried out to observe the histopathological picture of the liver tissue. There was a statistically significant hepatoprotective effect of propolis in the histopathological picture of the liver in the K- group under normal circumstances (score 1), the K+ group was dominated by necrosis (score 4), the P1 group was dominated by normal cells (score 1) and the P2 group was dominated by hydropic degeneration (score 3). The Kruskal-Wallis test showed a significant difference in all treatment groups with $p<0.001$. The results of the Mann-Whitney test showed that between the K– group and the K+ group and the P2 group there was a significant difference, between the K+ group and the P1 and P2 groups there was a significant difference, and between the P1 group and the P2 group there was a significant difference with $p<0,05$. There was a hepatoprotective effect of propolis on the histopathological of the liver of mice induced paracetamol. Propolis dose of 0.4ml was more optimal in preventing damage to the liver of mice than a dose of 0.8ml.

Keywords: Hepatoprotective, paracetamol, propolis.

Correspondence author:

Noor Yazid,
Department of Anatomical Pathology, Faculty of Medicine, Muhammadiyah Semarang University,
Kedungmundu Street No. 18, Kedungmundu, Tembalang, Semarang, Central Java.
Email: yazid_ad@yahoo.com

INTRODUCTION

Acetaminophen or paracetamol is a non-opioid antipyretic and analgesic drug that has been used since 1893 (Gunawan, Setiabudy, 2011). The Food and Drug Administration states that the safe dosage of paracetamol for adults and children over 12 years of age is a maximum of 4 grams per day and should not be used for more than 10 days (Setyo, 2013). Paracetamol is the most widely consumed drug in Indonesia, with a demand of 9,000 tons per year (Directorate General of Pharmaceuticals, 2022). Inappropriate use of acetaminophen can lead to overdose. A single dose of 10-15 grams of paracetamol per day can cause symptoms of hepatotoxicity (Sin, Billy, 2017). The United States Regional Poisons Center states that paracetamol poisoning is the second most common cause of liver transplantation (Caparrotta, 2018). This results in 56,000 emergency room visits, 2,600 cases requiring intensive care, and 500 deaths per year due to paracetamol poisoning. Fifty percent of these cases are accidental overdoses (Caparrotta, 2018; Amirudin R, 2007). Paracetamol is the primary cause of acute liver failure (Bunchorntavakul, 2013). The Indonesian Food and Drug Administration (BPOM) recorded 201 cases of paracetamol poisoning in Indonesia from 2002 to 2005, 175 of which were suicide attempts (Corey, 2010; Zulizar, 2013; Sa'diyah, 2020).

Paracetamol metabolism occurs in two phases, where most paracetamol is conjugated by phase II enzymes to form glucuronides and sulfa derivatives. A small portion of paracetamol undergoes oxidation by phase I enzymes, namely cytochrome P450, to form free radicals, namely the toxic and reactive metabolite NAPQI (N-acetyl-p-benzoquinonemine). NAPQI binds with endogenous antioxidants in the form of glutathione (GSH) in the liver to form a non-toxic substance. If the amount of paracetamol consumed exceeds the therapeutic dose, the reserves of glucuronide and sulfate derivatives in the liver will be depleted, resulting in the formation of excessive amounts of the reactive metabolite NAPQI. As long as glutathione is available, NAPQI will be detoxified, preventing hepatotoxicity. However, if glutathione continues to be used up, it will eventually be depleted, leading to the accumulation of toxic and reactive NAPQI metabolites. These metabolites will react with nucleophilic groups found in liver cell macromolecules, such as proteins, causing hepatotoxicity that leads to liver necrosis. NAPQI accumulated in the body will bind to cells and mitochondrial proteins, which will then damage the mitochondrial structure and produce oxidative stress. Oxidative stress and mitochondrial damage cause hepatocellular damage. To overcome this, exogenous antioxidants in the form of propolis are needed (Huang, 2014; Suseno, 2009; Anindyaguna, 2022).

Propolis is a substance that has hepatoprotective properties. Propolis contains compounds such as amino acids, terpenoids, and polyphenols (phenolic acids, esters, and flavonoids). Of these three substances, the flavonoids contained in propolis have the greatest benefit, namely their antioxidant properties. The antioxidants in propolis function as hepatoprotectors that inhibit the activity of hepatic stellate cells (HSC), prevent hepatocyte apoptosis, and reduce fibrosis. Propolis can also work as an immunoregulator that can improve immunity, thereby protecting liver cells from damage by suppressing the activity of Kupffer cells in producing reactive oxygen species (ROS) and cytokines that exacerbate inflammation (Krisnansari, 2014; Kumar, 2013; As'ari, 2009; Brown, 2009).

Previous research conducted by Apriany in 2011 found that the least damage to liver cells occurred when a dose of 0.4 ml of propolis was administered, but the type of

liver cell damage that occurred was not explained in detail. In a study by Alviana, 2017, which used a 0.15 ml dose of propolis, it was shown that propolis has a function as an antioxidant that traps free radicals that cause damage to Mus musculus (mouse) liver cells due to exposure to 250 mg/kgBW of paracetamol. However, this study only used one dose of propolis (Darma, 2011; Price, 2012). Therefore, the researchers wanted to increase the propolis dose to 0.4 ml and 0.8 ml to identify the effect of propolis administration as a hepatoprotector in Mus musculus induced with 338 mg/kgBW paracetamol. The doses of 0.4 ml and 0.8 ml were chosen to determine the differences in their effects as hepatoprotectors on the histopathological picture of the liver of mice that were then induced with paracetamol (Utami, 2017; Malar, 2012).

RESEARCH METHODS

This study was conducted in the biology laboratory and anatomical pathology laboratory in Semarang, Indonesia. The samples used in this study were Swiss Webster strain mice. The samples in this study were divided into four groups, namely K- (not given propolis or paracetamol), K+ (given paracetamol at a dose of 338mg/kgBW without propolis), P1 (given propolis at a dose of 0.4ml and paracetamol at a dose of 338mg/kgBW) and P2 (given propolis at a dose of 0.8ml and paracetamol at a dose of 338mg/kgBW). Thus, the sample used consisted of 24 mice, with 6 mice per group. Sampling in this study was performed using simple random sampling. The inclusion criteria for this study were clinically healthy mice (active, undamaged, uninjured, and without defects), aged between 2 and 3 months, male, and weighing ± 20 grams. The exclusion criteria for this study were mice that died during the adaptation period, mice whose weight decreased from their previous weight, and mice that were not actively moving. The mice were then adapted for 7 days in a laboratory at a temperature of 30°C in dark conditions with standard feed in the form of pellets and water.

The data collection was conducted in four stages, namely editing, coding, processing, and data cleaning, which were analyzed using SPSS (Statistical Package for Social Sciences) software in four stages, namely univariate analysis, normality test, homogeneity test, and bivariate analysis using the Kruskal Wallis test and Mann Whitney test.

Tools and Materials

The tools used in this study were experimental animal cages, stomach probes, electronic scales, surgical instruments (tweezers, scalpels, scissors, wax tables, and needles), hepatology histopathology observation tools (binocular microscope, object glass, and deck glass), histology preparation tools (paraffin molds, oven, and microtome), syringe. The materials used in this study were animal feed and drink, male mice, propolisKU, paracetamol, materials for making histological preparations (10% formalin buffer solution, xylol solution, paraffin, alcohol with levels of 50, 60, 70, 80, 96%, 100%), HE staining materials (xylol solution, absolute ethanol, 95% and 50% alcohol, Mayer's hematoxylin, Canada balsam), and aquadest.

Research Procedures

1. Preparation

The researchers prepared 24 mice that would be adapted for one week to a temperature of 30°C in dark conditions, fed a standard diet of pellets and water.

2. Randomisasi
   The adapted mice were randomly grouped into four treatment groups, namely negative control (K-) consisting of 6 mice, positive control (K+) consisting of 6 mice, paracetamol 338mg/kgBW and propolis 0.4ml (P1) treatment consisting of 6 mice, paracetamol 338mg/kgBW and propolis 0.8ml treatment (P2) consisting of 6 mice.
3. Administration of parasetamol and propolis
   Group K- mice were fed a standard diet ad libitum for 7 consecutive days. Group K+ mice were fed a standard diet ad libitum and administered 338 mg/kg body weight of paracetamol via a feeding tube for 3 days, namely on days 12, 13, and 14. Group P1: Mice were fed standard chow ad libitum and administered paracetamol at 338 mg/kg body weight for 3 days, specifically on days 12, 13, and 14, 60 minutes after receiving 0.4 ml of propolis via a feeding tube. Group P2: Mice were given standard feed ad libitum and paracetamol 338 mg/kgBW for 3 days, namely on days 12, 13, and 14, administered 60 minutes after the administration of 0.8 ml of propolis using a feeding tube. Propolis administration in treatments 1 and 2 was given for 14 consecutive days.
4. Organ procurement procedure
   After treatment was completed on day 15, all experimental animals were euthanized using ketamine anesthesia and cervical vertebral dislocation. The right lobe of the liver was then removed to be prepared for histology using paraffin blocks and HE staining. This process was carried out on day 15 so that the effects of the treatment would be clearly visible.
5. Procedure for preparing specimens with staining HE
   In this stage, the liver is fixed for up to 4 hours in a 10% formalin solution, then repeated twice with a new solution. The preparation is then stained using hematoxylin and eosin.
6. Scoring System with Scoring Histopathology Manja Roenigk
   Scoring Histopathology Manja Roenigk with a score of 1 (normal cells), score 2 (parenchymal degeneration cells), score 3 (hydropic degeneration), and score 4 (necrosis cells).

Data Analysis

The data obtained were processed using SPSS (Statistical Package for Social Sciences) software with a significance value of 0.05 in univariate and bivariate analyses. Univariate analysis was intended to obtain an overview of the histopathology of the mouse liver. Univariate analysis in this study was obtained from calculating the damage value of liver cell samples. Bivariate analysis was used to understand the significant differences between the entire treatment group and between the two treatment groups. This study used the Kruskal Wallis test, followed by the Mann Whitney test.

RESULTS AND DISCUSSION

This study was conducted in the biology laboratory and anatomical pathology laboratory in Semarang, Indonesia. The samples used in this study were 24 Swiss Webster strain mice. Sampling was conducted using simple random sampling. This study was conducted over a period of 14 days and there were no dropouts, meaning that no mice died

during the study period. In this study, all samples met the inclusion and exclusion criteria, so all samples could be used.

Table 1. Hepatic Damage Degree Results

Group	N	Normal	Parenchymal degeneration	Hydropic degeneration	Nekrotic	*Score*	Total field area
K-	6	18*	10	1	1	1	30
K+	6	0	3	8	19*	4	30
P1	6	16*	5	7	2	1	30
P2	6	0	2	21*	7	3	30

Description: *The number of damage scores that dominate each group.

Based on these data, Manja Roenigk histopathology scores were obtained for each group based on the number of cells that dominated or were most numerous in each treatment group. Group K- obtained a score of 1 (normal cells), group K+ obtained a score of 4 (necrosis), group P1 obtained a score of 1 (normal cells), and group P2 obtained a score of 3 (hydropic degeneration) (Guyton, 2012; Eroschenko, 2012).

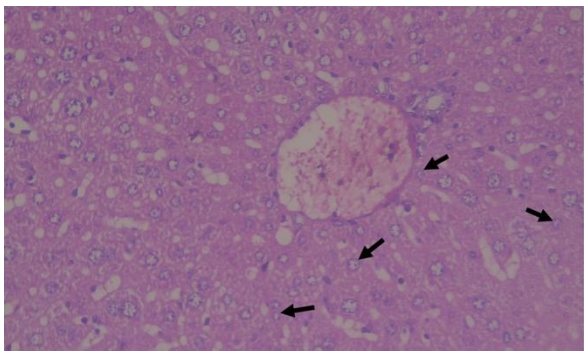

Figure 1. Histopathological image of mouse liver at 400x magnification in the negative control group (K-), dominated by normal cells (thick arrows).

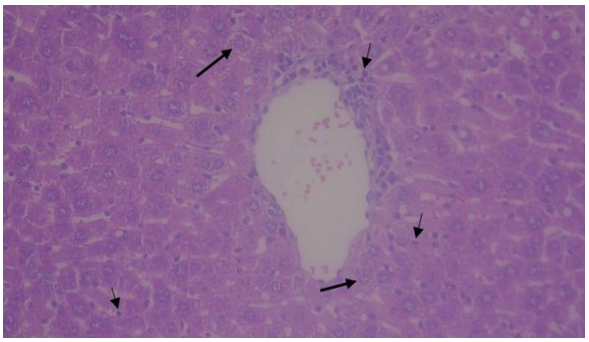

Figure 2. Histopathological image of mouse liver magnified 400x in the positive control group (K+). Cells undergoing hydropic degeneration (thick arrows) and necrosis (thin arrows) are visible.

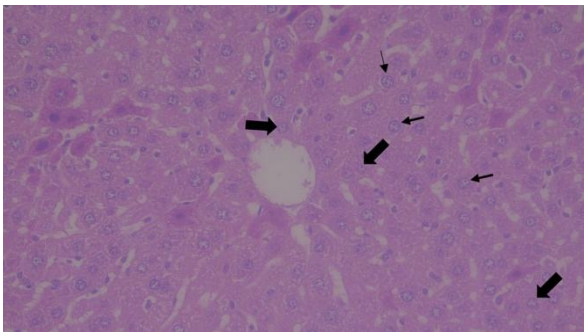

Figure 3. Histopathological image of mouse liver at 400x magnification treatment group 1 (P1). The tissue is dominated by normal cells (thick arrows), cells undergoing parenchymal degeneration (thick arrows), and hydropic degeneration (thin arrows).

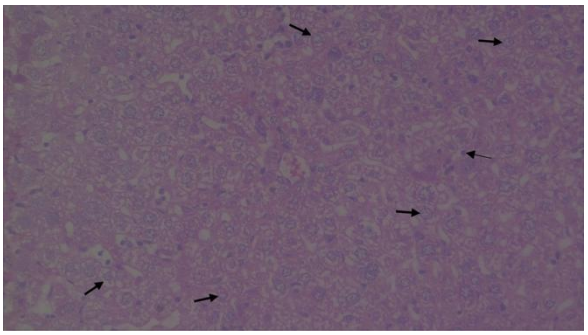

Figure 4. Histopathological image of mouse liver at 400x magnification in treatment group 2 (P2). The tissue is dominated by hydropic degeneration (thick arrows) and necrosis (thin arrows).

Table 2. Descriptive table and Kruskal-Wallis test results of histopathological findings in paracetamol-induced mouse livers

Group	Hepatic Mice Histophatology				p
	Normal	Parenchymal degeneration	Hydropic degeneration	Nekrotic	
K–	5	1	0	0	<0,001*
K+	0	0	1	5	
P1	5	0	1	0	
P2	0	0	5	1	

Note: * Significant (p< 0.05)

Table 2 shows the results of microscopic observations tested with data analysis using the Kruskal Wallis and Mann Whitney statistical tests. In the statistical calculation using the Kruskal Wallis test, a p-value of <0.001 was obtained, so it can be concluded that there are significant differences between all groups.

This study shows the results of the Mann Whitney test to determine the differences between research groups by looking at the greater values of each group. From the results of the Mann-Whitney test, the histopathological description of paracetamol-induced liver in mice showed that there was a significant difference between group K– and groups K+ and P2, between group K– group and the P1 group, there was no significant difference between

the K+ group and the P1 and P2 groups, and there was a significant difference between the P1 group and the P2 group.

Table 3. Mann-Whitney test results for histopathological findings in paracetamol-induced mouse livers

Group		p
I	**II**	
K–	K+	0,002*
	P1	0,902
	P2	0,002*
K+	P1	0,002*
	P2	0,027*
P1	P2	0,006*

Note: * Significant (p< 0.05)

The results of this study show that there is a statistically significant difference in the number of liver cell damages between the K- group (not given propolis and paracetamol) and the K+ group (given paracetamol at a dose of 338mg/kgBW without propolis) in the microscopic image of the liver. Administration of a 338 mg/kg body weight dose of paracetamol to the K+ group for 3 days on days 12, 13, and 14 can damage liver cells without causing death in mice (Aman, 2017; Widjaja, 2007). These results prove that paracetamol is effective in damaging mouse liver cells (Darma, 2011; Bunchorntavakul, 2013; Al, 2018).

In the K-group (not given propolis and paracetamol) and the P2-group (group given 0.8 ml of propolis followed by 338 mg/kgBW of paracetamol), there were statistically significant differences. In the K-group, microscopic observations of the liver showed that most cells were normal, but there was also parenchymal degeneration, hydropic degeneration, and necrosis, resulting in a score of 1 for the K-group. Group P2 was dominated by a score of 3 (hydropic degeneration), indicating that a 0.8 ml dose of propolis is not the optimal dose for preventing damage to mouse liver cells. There was no statistically significant difference between the K- group (not given propolis and paracetamol) and the P1 group (given a 0.4 ml dose of propolis followed by a 338 mg/kg body weight dose of paracetamol). The administration of a 0.4 ml dose of propolis provided more optimal protection in preventing liver cell damage, with the P1 group dominated by normal cells, indicating that this dose is optimal for preventing liver cell damage in mice as it can restore liver cells to their normal condition (Darma, 2011; Toprakci, 2013).

There were also significant differences between the K+ group (given 338 mg/kg body weight of paracetamol) and the P1 group (given 0.4 ml of propolis followed by 338 mg/kg body weight of paracetamol) and the P2 group (given 0.8 ml of propolis followed by 338 mg/kg body weight of paracetamol). . Group P1 was able to provide protection and was more optimal in preventing liver cell damage caused by paracetamol compared to group P2, which used a 0.8 ml dose of propolis. This is in line with the results of a previous study by Monika Bhadauria (2012), which showed that the normal dose of propolis for adults is 5-6 drops/day or 0.335-0.402 ml/day, which is safe for consumption.

Therefore, administering a propolis dose of 0.8 ml caused an overdose in mouse liver cells because the liver cells did not return to their normal state (Monika, 2012). Furthermore, previous research by Diah Krisnansari (2014) showed that propolis doses of 0.054 ml and 0.108 ml exhibited hepatoprotective activity against liver damage. Based on these research results, propolis doses of 0.054 ml and 0.108 ml were able to prevent liver damage caused by carbon tetrachloride induction, and propolis could be used as an alternative to prevent the liver fibrosis process (Krisnansari, 2014; Wilmana, 2007).

The results of this study show that group P1 (the group given a 0.4 ml dose of propolis followed by a 338 mg/kg body weight dose of paracetamol) and group P2 (the group given a 0.8 ml dose of propolis followed by a 338 mg/kg body weight dose of paracetamol) had statistically significant differences and different amounts of liver cell damage. Group P1 was dominated by a score of 1 (normal cells), while group P2 was dominated by a score of 3 (hydropic degeneration). These results are consistent with previous research by Apriany Darma (2011), which showed that administering 0.2 ml and 0.4 ml doses of propolis can have a hepatoprotective effect against paracetamol. In that study, normal cells were more dominant in the group given a 0.4 ml dose of propolis. This indicates that a 0.4 ml dose of propolis is more optimal in preventing liver cell damage caused by paracetamol.

CONCLUSION

This study has limitations in that no research was conducted on the biochemical content of propolis and only an assessment was made using histopathological parameters. This study concluded that propolis can act as a hepatoprotector by reducing liver cell damage and improving the histological structure of the liver lobules. Histopathological damage in the form of liver cell necrosis decreased significantly in group P1. This is consistent with Apriany's 2011 study, which found a reduction in liver cell damage when administering a 0.4 ml dose of propolis.

ACKNOWLEDGEMENT

The researchers would like to thank various parties who have supported this research, including the Faculty of Medicine at Muhammadiyah Semarang University and the biology and anatomical pathology laboratories in Semarang, Indonesia, which have granted permission for the research to be conducted.

REFERENCES

Al C, Gluud C, Brok J, Na B. Interventions for paracetamol (acetaminophen) overdose (Review) SUMMARY OF FINDINGS FOR THE MAIN COMPARISON. *Cochrane Database of Systematic Rev*. 2018;(2):1–90.

Aman I, Okky I, Alex P. Pemberian ekstrak floret pisang raja (Musa x paradisiaca) dapat mencegah penurunan kadar superoksida dismutase (SOD) pada hati mencit (Mus musculus) BALB/c dengan aktivitas fisik berlebih. Fakultas Kedokteran Universitas Udayana. 2017. Available from : https://erepo.unud.ac.id/id/eprint/12582/1/dbd775dx98384b7d5577xx8919b94cae.pdf

Amirudin R. Fisiologi dan Biokimia Hati : Buku Ajar Ilmu Penyakit Dalam. 4th ED. Jakarta: Departemen Ilmu Penyakit Dalam FK UI; 2007. 415–9 p.

Anindyaguna A, Mustofa S, Indria D. Drug-Induced Liver Injury Akibat Penyalahgunaan Parasetamol. Medula Fakultas Kedokteran Universitas Lampung. 2022.

As'ari H. Efek Pemberian Madu Terhadap Kerusakan Sel Hepar Mencit (*Mus musculus*) Akibat Paparan Parasetamol. [Skripsi]. Fakultas Kedokteran Universitas Sebelas Maret; 2009.

Brown R. Hive Products : Pollen, Propolis and Royal Jelly. Bee World; 2009. 70 p.

Bunchorntavakul C RK. Acetaminophen-related hepatotoxicity. Clin Liver Dis. 2013;17(4):587-07.

Caparrotta, Thomas M., Daniel J. Antoine and JW. Dear. "Are Some People at Increased Risk of Paracetamol-Induced Liver Injury? A Critical Review of the Literature." European Journal of Clinical Pharmacology [Internet]. 2018;147–60. Available from: https://pubmed.ncbi.nlm.nih.gov/29067481/

Corey R, Leonard M EB. Acetaminophen : old drug, new warnings. Medicine (Baltimore) [Internet]. 2010;77(1):19–27. Available from: https://pubmed.ncbi.nih.gov/20048026

Darma AW. Efek Hepatoprotektor Propolis Terhadap Kerusakan Sel Hepar Mencit (*Mus musculus*) Yang Diinduksi Parasetamol. [Skripsi]. Fakultas Kedokteran Universitas Sebelas Maret; 2011.

Direktorat Jenderal Farmasi dan Alat Kesehatan. Kemenkes Terus Berupaya Mencapai Ketahanan Farmasi Nasional Untuk Parasetamol. Kementerian Kesehatan Republik Indonesia. 2022.

Eroschenko VP. DiFiore's Atlas of Histology with Functional Correlations. 11th ed. Philadelphia: Wolters Kluwer Health; 2012. 313–330 p.

Guyton H. Buku Ajar Fisiologi Kedokteran. 11th ed. Jakarta: Penerbit Buku Kedokteran EGC; 2012.

Huang S, Cui PZ, Kai W, George Q LH. Recent Advances in The Chemical Composition Of Propolis. Faculty Of Pharmacy University Of Sydney; 2014.

Krisnansari D, Sulistyo H, Dwi W. Potensi Hepatoprotektor Propolis Terhadap Hepar Tikus Putih (*Rattus norvegicus*) Yang Diinduksi Karbon Tetrakhlorida. Fakultas Kedokteran dan Ilmu Kesehatan; 2014.

Kumar S, Abhay K. Chemistry and Biological Activities Of Flavonoid: An Overview. Scientific World. 2013;

Malar, V. dan Bai SM. Beware of Paracetamol Toxicity. *J Clin Toxicol*. 2012;2(6):1–3.

Mescher AL. Jungqueira Histologi Dasar Teks dan Atlas. 12th ED. Jakarta: EGC; 2012.281-190 p.

Monika B. Propolis Prevents Hepatorenal Injury Induced by Chronuc Exposure To Carbon Tetrachloride. Evidenced Based Complementary and Alternative Medicine. 2012. Available from : https://doi.org/10.1155/2012/235358

Price, SA., Wilson L. Patofisiologi Konsep Klinis Proses Penyakit. 6 vol 1. trans. H. Pendit MW, editor. Jakarta: EGC; 2012.

Ramadan, Amer, Gamal S, Sawsan S M. Hepatoprotective and Hepatotheraupeutic Effects Of Propolis Against D-Galactosamine/Lipopolysaccharide-Induced Liver Dmage in Rats. Pharmaceutical Science. 2015.

Sa'diyah K. Pengaruh Ekstrak Propolis Terhadap Pertumbuhan Sel Hepar Tikus (*Rattus norvegicus*) Secara In Vitro. Universitas Islam Negeri Maulana Malik Ibrahim; 2020.

Setyo Rini et al. Efektifitas Ekstrak Etanol Putri Malu (*Mimosa pudica Linn*) Sebagai Nefroprotektor Pada Tikus Wistar Yang Diinduksi Parasetamol Dosis Toksik.

Pustaka Kesehat [Internet]. 2013;1:15–9. Available from: https://repository.unej.ac.id/handle/123456789/57445

S. Gunawan, R. Setiabudy, Nafrialdi, Elysabeth. Farmakologi Dan Terapi. Jakarta: FK UI; 2011. 236–46 p.

Sin, Billy, Kimberly Koop, Michelle Liu, Jun Yen Yeh and PT. Intravenous Acetaminophen for Renal Colic in the Emergency Department: Where Do We Stand? American Journal of Therapeutics [Internet]. 2017;12–9. Available from: https://pubmed.ncbi.nlm.nih.gov/27779484/

Suseno D. Aktivitas Antibakteri Propolis *Trigona spp*. Pada Dua Konsentrasi Berbeda Terhadap Cairan Rumen Sapi. Institut Pertanian Bogor; 2009.

Toprakci M W. Kompilasi Keterangan-Keterangan Mengenai Propolis [Internet]. 2013. Available from: http://www.zaaba313.coms.ph/catalog.html

Utami RA, Berata K, Samsuri MI. Efek Pemberian Propolis Terhadap Gambaran Histopatologi Hepar Tikus Putih Yang Diberi Parasetamol. Buletin Veteriner Udayana, editor. Fakultas Kedokteran Hewan Universitas Udayana; 2017.

Vidhya Malar HL MMBS. Beware of Paracetamol Toxicity. Clinical Toxicology. 2012;2.

Widjaja S. Antioksidan : Pertahanan Tubuh Terhadap Efek Oksidan dan Radikal Bebas. Fakultas Kedokteran Universitas Trisakti. 2007;16(1):162.

Wilmana PF, Gunawan S. Analgesik-Antipiretik Analgesik Anti-Inflamasi Nonsteroid dan Obat Gangguan Sendi Lainnya. Farmakologi dan Terapi. 5th ED. Jakarta: Gaya Baru; 2007. 237 p.

Zulizar AA. Pengaruh Parasetamol Dosis Analgesik Terhadap Kadar Serum Glutamat Oksaloasetat Transminase Tikus Wistar Jantan [Internet]. Medika Muda. Semarang: Fakultas Kedokteran Universitas Diponegoro;2013. Available from: https://meida.neliti.com/media/publications/110810-ID-none.pdf