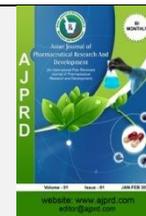


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Research Article

Hepatoprotector Effect of Corn Silk Ethanol Extract (*Stigma maydis*) on Paracetamol-Induced White Male Rats

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ABSTRACT

Objectives: Corn silk (*Stigma maydis*) is one part of the corn plant that contains useful chemical compounds, including flavonoid compounds. The ability of flavonoid compounds to capture free radicals that cause liver damage. The purpose of this study was to determine the hepatoprotective effect of corn silk ethanol extract on male white rats induced by paracetamol and to determine the effect of varying doses of corn silk ethanol extract as a hepatoprotector.

Data Sources Study Selection: This study is an experimental study testing the hepatoprotective effect of corn silk ethanol extract using male white rats

Summary of contents of the article: This study using 20 male white rats which were divided into 5 groups, namely negative control given NaCMC, positive control induced by toxic dose of paracetamol, and group of corn silk ethanol extract doses of 250, 500, 1000 mg/kgBW. The measurement parameters were the levels of SGOT and SGPT enzymes, the ratio of liver weight, and histopathological examination of the liver. The data obtained were analyzed descriptively, statistically with two-way and one-way ANOVA followed by Duncan's test and. The results showed that administration of corn silk ethanol extract could reduce levels of SGOT and SGPT enzymes, and analysis using two-way ANOVA showed that there was a significant difference in levels of SGOT and SGPT in the test group with ($p < 0.05$). The ratio of liver weight was analyzed by one-way ANOVA. The results showed that there was no significant difference to the ratio of organ weight in the test group with ($p > 0.05$). Histopathological picture showed improvement of liver parenchymal morphology on administration of corn silk ethanol extract.

Conclusion: Based on the results of the study, it was concluded that the presence of a hepatoprotector effect on the ethanol extract of corn silk and that there was an influence of the dose variation on the hepatoprotector effect with a dose of 1000 mg/kgBW was more effective as a hepatoprotector.

Keywords: Corn Silk Ethanol Extract, Hepatoprotector, Paracetamol

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INTRODUCTION

The liver is the center of the body's metabolism with very complex functions, but the liver is the organ that is most often affected by injury, so it is often the cause of liver damage that ends up in liver failure.¹

The prevalence of liver damage in the world shows a serious number to watch out for.² Until now people with hepatitis in the world have reached 2 billion people with the

number of deaths of more than 350 thousand people per year. Patients with hepatitis also have a high risk of experiencing more serious liver function disorders such as cirrhosis and liver cancer.³ Data from the Ministry of Health (Ministry of Health) 2010, in Indonesia, liver disease ranks third after infectious and pulmonary diseases.⁴ One of the causes is the use of drugs that are hepatotoxic. Liver damage caused by hepatotoxic effects can be very severe.

One of the drugs that can cause hepatotoxicity is paracetamol. Hepatotoxicity can occur in a single dose of 10-15 grams of paracetamol. This occurs due to the formation of reactive toxic metabolites *N-acetyl-p-benzoquinonimin* (NAPQI) and free radicals through the biotransformation process by cytochrome P450 enzymes with the help of CYP2E1 isoenzymes. Toxic reactive metabolites and free radicals can disrupt the integrity of cell membranes and liver damage occurs.⁵

Drugs commonly used in the treatment of liver disease include antivirals, diuretics and antibiotics. In addition, natural remedies can also be used to prevent liver damage, for example, curcumin or ginger.

Corn (*Zea mays*) is the most productive plant that grows in both tropical and subtropical countries.⁶ One part of the corn plant is corn silk. Corn silk is considered a waste whose utilization has not been maximized, such as being used as animal feed or thrown away, even though corn silk has the potential as medicine. Corn silk is rich in phenolic compounds, especially flavonoids.⁷ Corn silk has many medicinal properties, including curing kidney stones, nephritis, cystitis, inflammation, prostatitis, kaliuretics, urinary tract infections, nephrotoxicity, depression,⁸ hypertension,⁹ hyperglycemia¹⁰, hyperlipidemia¹¹, hypokalemia, gout¹², hyperthyroidism¹³, gonorrhea and has activity as an antioxidant, antibiotic, antidiabetic and antitumor.¹⁴ Corn silk contains protein, vitamins, carbohydrates, Ca²⁺, K⁺, Mg²⁺ and Na⁺ salts, essential oils, and steroids, such as sitosterol and stigmaterol, alkaloids, saponins, tannins, and flavonoids.¹⁵

Research by Sarepoua et al., 2013, explained that the active compounds of corn silk are phenolic compounds such as flavonoids that act as strong antioxidants.¹⁶ The results of Ramadani et al, 2020 research, have tested the hepatoprotective effect of corn silk infusion on male wistar rats, the results obtained after treatment, can reduce levels of the enzyme *Alkaline Phosphatases* (ALP) and increase levels of *glutathione* (GSH).¹⁷ The results of another study from Karami et al 2013, in vitro tested the hepatoprotective effect of corn silk against ecstasy dose-induced injury (MDMA) using isolated rat liver perfusion system, the results showed liver protection by increasing *glutathione* (GSH) levels and showed histopathological improvement. liver cells.¹⁸

From the description above, the researchers wanted to conduct research on the hepatoprotective effect of corn silk ethanol extract in vivo using male white rats induced by paracetamol with varying doses of corn hair ethanol extract 250 mg/kg BW, 500 mg/kg BW, and 1000 mg/kg BW.

METHODS

This research was carried out from March 2021 to May 2021 at the Pharmacology Laboratory of the Perintis Indonesia University, the Perintis Padang Foundation and the Anatomical Pathology Laboratory, Faculty of Medicine, Andalas University (UNAND) Padang.

Equipment

Maceration bottle, rotary evaporator, analytical balance, animal scale, centrifuge, mindray BA-88A clinical

photometer, microscopy, EDTA tube, dropper, measuring cup, capillary tube, test tube, mortar, stamper, watch glass, microtube, oral syringe, scissors, cotton, vial.

Material

Corn silk ethanol extract, aquadest, paracetamol, 70% ethanol, chloroform, sodium carboxy methyl cellulose (Na-CMC), SGOT and SGPT reagents, hematoxylin and eosin dyes, xylol, paraffin.

Experimental animals

Experimental animals used were 20 male wistar strains of white rats aged 2-3 months with a body weight of 180-200 grams. These 20 rats were divided into 5 large groups, where each group consisted of 4 rats.

Sampling

The sample used in this study was corn silk taken at the Aina Payakumbuh F1 corn factory, West Sumatra.

Sample Identification

Sample identification was carried out at the Andalas Herbarium (ANDA) Department of Biology, Faculty of Mathematics and Natural Sciences, UNAND, Padang.

Sample Extraction

Corn silk is cleaned of dirt and weighed as much as 2 kg, dried, then chopped. Then the sample was put into a maceration bottle and 70% ethanol was added until it was submerged. left in the dark for 5 days while stirring. Filter the maceration results using filter paper. maceration until a clear maceration is obtained, combine the obtained maceration results, evaporate with a rotary evaporator until to obtain a thick corn silk ethanol extract.

Evaluation of Corn Silk Ethanol Extract

Extract evaluation included: organoleptic examination, determination of yield, determination of ash content, determination of drying shrinkage, and phytochemical tests for flavonoids, tannins, saponins, alkaloids, terpenoids and steroids.

Experimental Animal Preparation

Experimental animals used were 20 male wistar strains of white rats aged 2-3 months with a body weight of 180-200 grams. These 20 rats were divided into 5 large groups, where each group consisted of 4 rats. Before being treated, the rats were acclimatized for 7 days by being given adequate food and water. The mice used were healthy mice and did not show a significant change in body weight of more than 10% and visually showed normal behavior.

Experimental Animal Treatment

Rats were divided into 5 groups, each group consisted of 4 Rats

Group 1 negative control: 0.5% NaCMC suspension was given on days 1-6, followed by days 8-13. Days 7 and 14 examination of SGOT & SGPT enzyme levels. Day 15 of surgery.

Group 2 positive control: induced by paracetamol 1.25 g/kgBW on day 1-6, followed by day 8-13. Days 7 and 14 examination of SGOT & SGPT enzyme levels. Day 15 of surgery.

Group 3: corn silk ethanol extract (EERJ) 250 mg/kgBW on day 1-6, then extract + induction paracetamol 1.25 g/kgBW on day 8-13. Days 7 and 14 examination of SGOT & SGPT enzyme levels. Day 15 of surgery.

Group 4: corn silk ethanol extract (EERJ) 500 mg/kgBW on day 1-6, then extract + induction paracetamol 1.25 g/kgBW on day 8-13. Days 7 and 14 examination of SGOT & SGPT enzyme levels. Day 15 of surgery.

Group 5: corn silk ethanol extract (EERJ) 1000 mg/kgBW on day 1-6, then extract + induction paracetamol 1.25 g/kgBW on day 8-13. Days 7 and 14 examination of SGOT & SGPT enzyme levels. Day 15 of surgery.

Make Paracetamol Suspension

Paracetamol in 0.5% NaCMC suspension is made by weighing 0.5 grams of NaCMC then sprinkled in a mortar containing hot distilled water, leave for 15 minutes, then grind until a transparent mass is formed, enter the weighed paracetamol powder and grind ad homogeneously. The volume is made up to 100 mL.

Make Corn Silk Ethanol Extract Suspension

0.5 grams of NaCMC powder was weighed, sprinkled into a mortar filled with hot distilled water, and left for 15 minutes, then ground until a transparent mass was formed, add 2.5 grams of corn hair ethanol extract for a dose of 250 mg/kgBW crushed until homogeneous and add 100 mL of water. Then for doses of 500 mg/kgBW and 1000 mg/kgBW it was done in the same way.

Observed Parameters:

Test of SGOT and SGPT Enzymes Levels

The rat blood samples were centrifuged at 3000 rpm for 15 minutes to obtain the serum. After that, the levels of SGOT and SGPT enzymes were analyzed. A total of 100 microliters of rat blood serum were mixed with 1000 microliters of reagent, then measured using a mindray BA-88A clinical photometer.

Determination of Liver Weight Ratio

Animals that have been sacrificed are dissected, then the liver is taken, cleaned and weighed. The ratio of liver weight to animal body weight can be determined using the equation:

$$\text{Liver Weight Ratio} = \frac{\text{Animal liver weight}}{\text{Animal weight}} \times 100\%$$

Histopathological Observation

Histopathological observations of liver tissue were carried out after the animals were sacrificed, these tissue samples were immersed in 10% formalin solution and implanted in paraffin wax, cut 4 mm thick and stained with hematoxylin-eosin. The finished preparations were labeled, then examined microscopically using a microscope at the top

object magnification 100x, the bottom object 400x to observe liver cell necrosis.

Data Analysis

From the results of testing the hepatoprotector effect of corn silk ethanol extract (*Stigma maydis*) on male white rats induced by paracetamol, it was processed descriptively and statistically with one-way and two-way ANOVA using SPSS 25 and continued with Duncan's test to determine the comparison of the average values of each treatment. tested. For the ratio of liver weight using one-way ANOVA statistical test. The results of the measurement of SGOT and SGPT enzyme levels were statistically analyzed by two-way ANOVA. And the histopathological results were analyzed descriptively.

RESULTS AND DISCUSSION

This study aims to determine the hepatoprotective effect of corn silk ethanol extract (*Stigma maydis*) on male white rats induced by paracetamol and to determine the effect of varying doses of corn silk ethanol extract as a hepatoprotector.

Corn silk ethanol extract was obtained by maceration method using 70% ethanol as solvent. Maceration was chosen because it is good for compounds that are not resistant to heat and has several advantages including simple equipment used and easy processing. The 70% ethanol solvent was chosen because it has selective properties, is neutral, has good absorption, and molds are difficult to grow in 70% ethanol, is economical, is able to extract most of the chemical compounds contained in simplicia.¹⁹

The filtrate from the maceration was evaporated using a vacuum rotary evaporator with the aim of removing the solvent so that a thick extract was obtained, then the viscous extract obtained was dried in a water bath to obtain corn silk ethanol extract, from 401 grams of dry sample obtained 49.9944 grams of corn silk ethanol extract with yield calculations. obtained by 12.46%.

Then the extract was evaluated including: organoleptic which showed a thick extract form, distinctive smell, and blackish brown in color. Then the drying shrinkage test got 8.5% and the ash content test got 1.02%. All the tests met the requirements according to the 2017 Herbal Pharmacopoeia. Then in the phytochemical screening test, corn silk ethanol extract was positive for flavonoids and tannins.

After evaluation, the corn silk ethanol extract was made in the form of a suspension. The purpose of being made in the form of a suspension is that the test preparation is evenly dispersed during treatment. The suspension used is 0.5% NaCMC because it is inert and does not affect the efficacy of the extract, the suspension is stable. Good resistance to microbes.

In this study, paracetamol (acetaminophen) was used as an inducer of liver damage. If used above the therapeutic window, it can cause liver damage. Paracetamol will form toxic reactive metabolites (*N-acetyl-p-benzoquinone*) and free radicals through a biotransformation process by cytochrome P450 enzymes with the help of CYP2E1

isoenzymes. Reactive metabolites that are toxic and free radicals can disrupt the integrity of cell membranes and lead to liver damage. Liver damage mainly occurs in the centrolobular area because *cytochrome* P450 enzymes are abundant in that area.⁵

The main indicator observed for impaired liver function was the activity of transaminase enzymes which included *Aspartate Aminotransferase* (AST) or *Serum Glutamic Oxaloacetic Transaminase* (SGOT) and *Alanine Aminotransferase* (ALT) or *Serum Glutamic Pyruvic Transaminase* (SGPT). Transaminase enzyme is an intracellular enzyme, if there is cell damage such as impaired liver cell wall permeability due to a disturbance, its activity will increase.²⁰ Increased activity of SGOT and SGPT enzymes can be caused by the administration of excessive doses of paracetamol.

From the results of the measurement of SGOT enzyme levels on Day 7, the negative control group, positive control, the dose of EERJ 250 mg/kgBB, EERJ 500 mg/kgBB, and EERJ 1000 mg/kgBW obtained an average of 20.75 U/L, respectively. , 58.5 U/L, 26.5 U/L, 26.5 U/L, 25.75 U/L. Day 14 The negative control group, the positive control, the doses of EERJ 250 mg/kgBW, EERJ 500 mg/kgBW, and EERJ 1000 mg/kgBW were 21.5 U/L, 87 U/L, 54 U/L, respectively. 45.5 U/L, 29.75 U/L.

From the results of the measurement of SGPT enzyme levels on day 7, the negative control group, positive control, the dose of EERJ 250 mg/kgBW, EERJ 500 mg/kgBW, and EERJ 1000 mg/kgBW respectively were 33.35 U/L, 53.5 U/L, 27.25 U/L, 25 U/L, 22.75 U/L. Day 14 Negative control group, positive control, dose of EERJ 250 mg/kgBW, EERJ 500 mg/kgBW, and EERJ 1000 mg/kgBW with the averages respectively 30.5 U/L, 86.25 U/L, 51 U/L, 44 U/L, 31.5 U/L.

On day 7 the positive control group given paracetamol showed higher levels than the other groups. The negative control group and the extract dose group were still in the normal range. And on day 14 the levels of SGOT and SGPT enzymes seemed to increase except in negative controls. The positive control group given continuous paracetamol induction had higher levels than the 7th day. Under normal conditions paracetamol will be absorbed by the body and then conjugated with glucuronic acid and sulfuric acid, a small portion is hydroxylated with cytochrome P450 to become *N-acetyl-p-benzoquinonimin* (NAPQI) metabolites. This NAPQI will be converted by glutathione into cystine and mercapturic metabolites which will then be excreted in the urine, but if paracetamol is consumed in excess of the therapeutic dose, the reserves of glucuronic acid and sulfuric acid in the liver will be depleted, resulting in the formation of excess NAPQI reactive metabolites. As long as the level of glutathione to detoxify NAPQI is still available, there will be no hepatotoxicity reaction. However, when glutathione continues to be used, glutathione depletion will occur and there will be accumulation of toxic and reactive NAPQI metabolites.²¹

The extract group showed that there was a decrease in the levels of the SGOT and SGPT enzymes compared to the positive control, the higher the dose of the extract, the lower the levels of the SGOT and SGPT enzymes. The dose

of 1000 mg/kgBW showed the lowest levels with the average levels of SGOT and SGPT enzymes, which were 29.75 U/L and 31.5 U/L. These data indicate that the most effective dose in reducing levels of SGOT and SGPT enzymes in rats compared to other doses is the dose of corn silk ethanol extract of 1000 mg/kgBW. It is suspected that the flavonoid content in the ethanol extract of corn silk can be potential as an antioxidant as well as a hepatoprotector. These compounds are widely known as hepatoprotection and are closely related to the prevention of several diseases such as liver disease.²²

Based on the results of statistical analysis with two-way ANOVA test on levels of SGOT and SGPT enzymes, corn silk ethanol extract has a hepatoprotective effect which is characterized by a significance value of $p < 0.000$ ($p < 0.05$), which means that there is a significant difference between groups given the preparation. test, the positive control group and the negative control group on the difference in examination days.

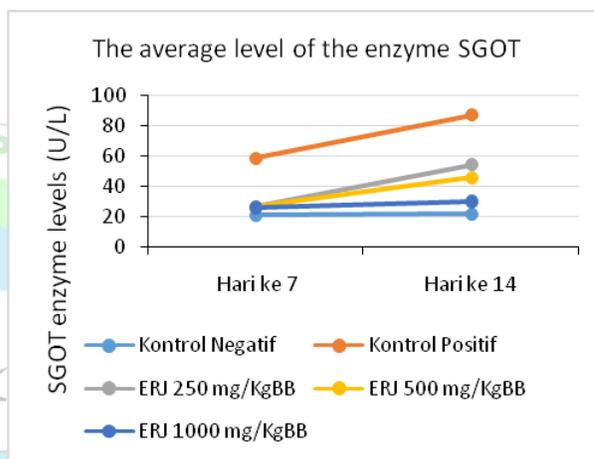


Figure 1: Diagram of the Comparison of Average SGOT Enzyme Levels on Day 7 and Day 14.

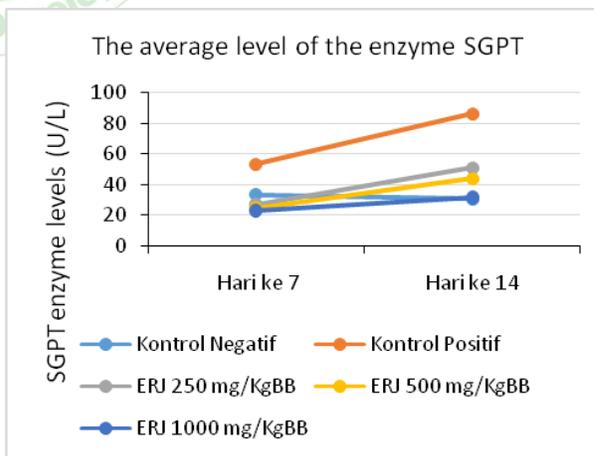


Figure 2: Diagram of the Comparison of Average ALT Enzyme Levels on Day 7 and Day 14.

The next parameter observed in this study was to calculate the ratio of liver weight by calculating the weight of the animal's liver divided by the animal's body weight before being sacrificed multiplied by 100%. The average results obtained in the negative control group, positive control, doses of 250 mg/kgBW, 500 mg/kgBW, and 1000 mg/kgBW respectively were 3.77%, 3.91%, 3.75%, 3.74%,

and 3.63%. From these results, it can be seen that in the positive control group the ratio of liver weight was slightly higher than the other groups. At a dose of 1000 mg/kgBW

showed a lower liver weight ratio. The ratio of liver weight that is greater than normal conditions can describe the occurrence of liver swelling due to necrosis of liver cells. The occurrence of necrosis results in a large number of damaged cell particles and organelles (*debris*) causing inflammation or inflammation and the accumulation of fluid masses, which in turn occurs in the accumulation of white blood cells in the area which are in charge of phagocytosis until normal conditions occur.²³ Based on the results of statistical analysis with one-way ANOVA test to liver weight ratio, a significance value of p was 0.938 ($p > 0.05$), which means there was no significant difference between the groups given the test preparation, the positive control group and the negative control group.

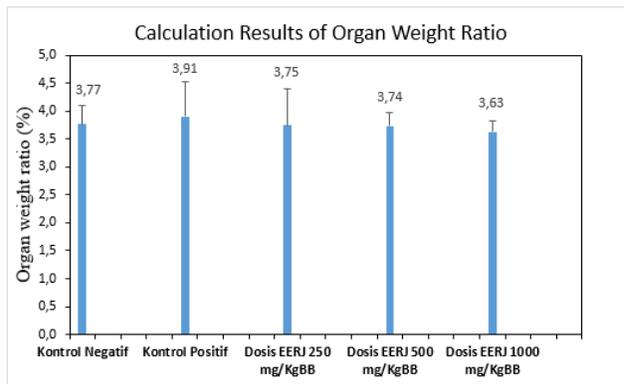


Figure 3. Diagram of the Calculation of the Average Weight Ratio of Liver Organs

In addition to testing the enzyme levels of SGOT, SGPT, liver weight ratio, histopathological tests were also carried out. Histopathological tests carried out were observations of degeneration to cell necrosis of rat liver tissue.

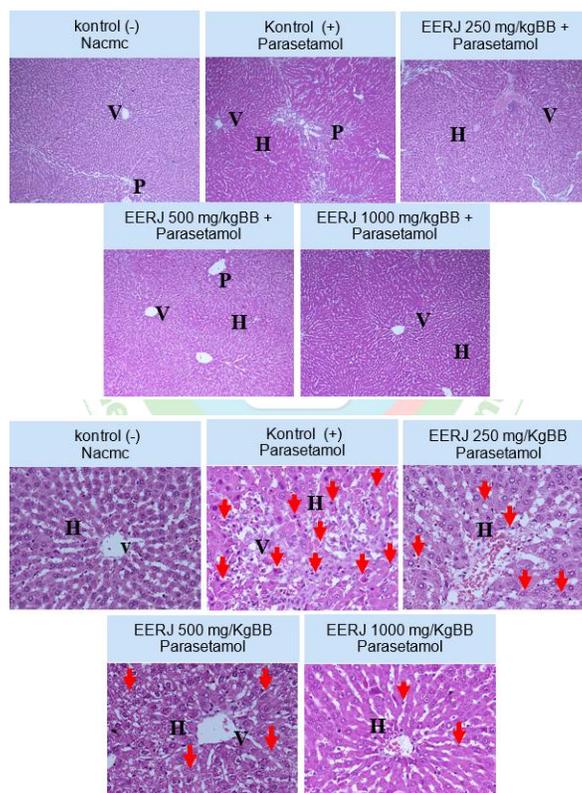


Figure 4. Histopathology Results

Based on the picture above, the histology of experimental animal liver tissue shows parenchyma with hepatocytes (H), central vein (V), and portal area (P). In group 1, negative control (normal animals) showed liver parenchyma with hepatocytes arranged in trabeculae, central veins and normal portal areas. There was no degeneration, significant cell death, and no blood vessel dilation (hyperemia) or bleeding (haemorrhage) was seen.

In the positive control group 2 which was only given paracetamol inducer showed parenchymal damage characterized by hepatocytes with degeneration and cell necrosis (red arrow), dilated blood vessels (hyperemia) and

bleeding (haemorrhage), and stroma with inflammatory cells.

In group 3, administration of corn silk ethanol extract 250 mg/kg BW to paracetamol-induced rats showed parenchyma characterized by hepatocytes with degeneration and cell necrosis (red arrow), dilated blood vessels (hyperemia) and bleeding (haemorrhage), and stroma with inflammatory cell infiltration. However, it showed improvement in the histological morphology of the liver parenchyma, reduced number of necrotic cells, and reduced areas of bleeding and inflammation compared to positive controls.

In group 4 administration of corn silk ethanol extract 500 mg/kgBW to paracetamol-induced rats showed parenchyma characterized by hepatocytes with degeneration and necrotic cells (red arrows), dilated blood vessels (hyperemia) and bleeding (haemorrhage), and stroma with inflammatory cell infiltration. However, it showed improvement in the histological morphology of the liver parenchyma, reduced number of necrotic cells, and reduced areas of bleeding and inflammation compared to positive controls and a dose of 250 mg/kgBW corn silk ethanol extract.

In group 5, administration of ethanol extract of corn silk 1000 mg/kgBW to paracetamol-induced rats showed parenchyma characterized by hepatocytes with degeneration and cell necrosis (red arrow), slightly dilated blood vessels (hyperemia) and minimal bleeding (haemorrhage), and stroma with mild inflammatory cells. The picture shows the best improvement in the histological morphology of the liver parenchyma compared to other doses of corn silk ethanol extract.

This indicates that the administration of corn silk ethanol extract can provide liver protection against exposure to the given toxic dose. The higher the dose of corn silk ethanol extract given, the more visible the improvement in liver tissue morphology.

Theoretically, the hepatoprotective effect of corn silk ethanol extract is due to the presence of antioxidants. Antioxidants are compounds that are able to ward off free radicals that enter the body.²⁴ The content of flavonoids and tannins in corn silk plays a role in protecting the liver against toxic substances seen from the morphology of liver tissue. Flavonoids are phenolic compounds that scavenge free radicals that enter the body. The mechanism of action of flavonoids is by binding or forming chelates which make these free radicals into non-toxic compounds so that these free radicals do not damage the liver.²⁵ Tannin compounds are included in the phenolic components that act as terminators of free radicals and as redox active metal ion chelators that allow to catalyze lipid peroxidation reactions. These phenolic antioxidants combine with the oxidation of lipids and other molecules due to the donation of hydrogen atoms to radicals. The phenoxy radical intermediates are relatively stable so they are no longer able to initiate further radical reactions.²⁶

CONCLUSION

From the research results of Hepatoprotector Effect Test of Corn Hair Ethanol Extract (*Stigma maydis*) Against Male White Rats Induced by Paracetamol, the following conclusions can be drawn:

1. Corn silk ethanol extract (*Stigma maydis*) on male white rats induced by paracetamol has a hepatoprotective effect.
2. The effect of variations in the dose of corn silk ethanol extract as a hepatoprotector, and a dose of 1000 mg/kgBW showed a better effect as a hepatoprotector.

REFERENCES

1. Sudoyo AW, Setiyohadi B, Alwi I, Simadibrata M, Setiati S. 2009. Textbook of Internal Medicine Volume II edition V. Interna

Publishing. Jakarta.

2. Poli, G. &Parola, M. 1997. *Oxidative Damage and Fibrogenesis*. Free Radic Biol Med. 22: 287-305. Ramadani AP, Tamhid HA, Sadrina TL, Jasno, Mustafidah M. 2020. Hepatoprotective Effect of Corn Silk Infusion in Male Wistar Rats. *Jurnal of Sciences and Data Analysis*. 2020; 1(1) 51-55.
3. World Health Organization (WHO). 2011. World hepatitis day [linked periodically]. http://www.who.int/csr/disease/hepatitis/world_hepatitis_day/en/ [7 February 2012].
4. Indonesian Ministry of Health. 2010. Bulletin of Health Data and Information Window. Ministry of Health of the Republic of Indonesia. Jakarta. 2010; 2(2):1-20.2.
5. Podolsky, D.K. &Isselbacher, K.J. 2002. *Diagnostic Tests in Liver Disease*. In: Harisson Principles of Internal Medicine. 13th Edition. EGC Medical Book Publisher. Jakarta.
6. Yusuf RP. 2009. Study of Farmers' Income in Corn Farming Business (Case in Sanggalangit Village, Gerokgak District, Buleleng Regency). *SOCA Journal of Socio-Economic Agriculture and Agribusiness*, 2009; 9(3):263-390.
7. Liu J, Songyi L, Zuozhao W, Cuina W, Erlei Wang, Yang Z. Supercritical fluid extraction of flavonoids from maydis stigma and its nitrite-scavenging ability. *Food and Bioprocess Processing*; 2011; 89(4):333-9.
8. Hasanudin, K., Hashim, P. and Mustafa, S. *Corn Silk (Stigma Maydis) in Healthcare: A Phytochemical and Pharmacological Review*. *Molecules*. 2012; 17. 9697-9715.
9. Anonymous. 1995. *Materia Medika Indonesia (Volume VI)*. Jakarta: Ministry of Health of the Republic of Indonesia.
10. Guo, J., Liu, T., Han, L. & Liu, Y. *The Effects of Corn Silk on Glycaemic Metabolism*. *Nutrition & Metabolism*. 2006; 6:47.
11. Zhang Y, Sui DY, Zhou JS. & Zhou HL. 2011. Microwave-assisted Extraction and Antihyperlipidemic Effect of Total Flavonoids From Corn Silk. *African Journal of Biotechnology*. 2011; 10(65), pp. 14583-14586.
12. Shamkhy, A., Al-Chalabi, R., Al-Amery, H. Effect of Corn Silk Extract on Kidney Stone Decomposition in Comparison with Alkalinizer agent (uralyte). *Int J Health Nutr*. 2012; 3(2): 1- 5.
13. Bhaigyabati T, Ramya J, Usha K. Effect of Methanolic Extract of Sweet Corn Silk on Experimentally Induced Hyperthyroidism in Swiss Albino Rats. *IRJP*. 2012; 3(3).
14. Nessa, F., Ismail, Z., Mohamed, N. 2012. Antimicrobial Activities of Extracts and Flavonoid Glycosides of Corn Silk (*Zea mays* L). *International Journal of Biotechnology for Wellness Industries*. 2012; 1:115-121.
15. Ebrahimzadeh MA, Pourmorad F, Hafezi S. Antioxidant activity of Iranian corn silk. *Turk J variety*. 2008; 32:43-9.
16. Sarepoua E, Tangwongchai R, Suriharn B, Lertrat K. Relationships Between Phytochemicals and Antioxidant in Corn Silk. *International Food Research Journal*. 2013; 20(5):2073-2079.
17. Ramadani AP, Tamhid HA, Sadrina TL, Jasno, Mustafidah M. 2020. Hepatoprotective Effect of Corn Silk Infusion in Male Wistar Rats. *Jurnal of Sciences and Data Analysis*. 2020; 1(1):51-55.
18. Karami M, S. Saeidnia, and A. Nosrati. 2013. Study of Hepatoprotective Activity of Feijoa sellowiana Fruit Methanol Extract Against MDMA Using Isolated Rat Liver Perfusion System. *Iran J Pharm Res.*; 2013; 12(1)85-91.
19. Indonesian Ministry of Health. 1979. *Indonesian Pharmacopoeia (Third Edition)*. Indonesian Ministry of Health. Jakarta.
20. Hastuti, T. 2008. Transaminase Enzyme Activity and Histopathological Overview of Mice Liver Given Kopyor Coconut After Paracetamol Induction.
21. Wilmana PF, Gunawan SG. 2007. *Analgesics, Non-Steroid Anti-Inflammatory and Other Joint Disorder Drugs*. Jakarta. FKUI Publishing Center.

22. Bandy. 2009. Evaluation of the Use of Intravenous Paracetamol in Inpatient Childhood Patients at Mas Amsyar Hospital Kasongan, Central Kalimantan. *Drug Use Evaluation.*; 2009; 1(2):422-426.
23. Wikanta T, Prehati R, Rahayu L, Fajarningsih ND. 2010. Effect of *Turbinariadecurrens* Ethanol Extract on Repair of Liver Damage in White Rats. *Journal of Postharvest and Marine and Fisheries Biotechnology.*: 2010; 5(1):19-28.
24. Winarsi, H., 2007, Natural Antioxidants and Free Radicals, Kanisius, Yogyakarta, pp.2007; 12(15):18:79-81.
25. Amic D, Davidovic D, Beslo D, Trinajstic N. 2003. Structure-Radical Scavenging Activity Relationships of Flavonoids. *Croatia Chemical Acta*, 2003; 76(1):55-61.
26. Nzaramba. (2008). Ischaemic preconditioning modulates the activity of Kupffer cells during in vivo reperfusion injury of rat liver. *Cell Biochem Funct* 2003; 21(4):299–305.

