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JOURNAL TEMPLATE HEPATOPROTECTIVE EFFECT OF BLACK CUMIN (Nigella sativa) AGAINST THE LIVER Aspartame-induced Rattus norvegicus BASED ON HISTOPATHOLOGICAL FEATURES Katrine Adiansyah Dwi Mukharomah1*, Fitria Diniah Janah Sayekti1 1Medical Laboratory Technology, STIKES Nasional Surakarta, Surakarta, Indonesia Jl. Raya Solo-Baki Kwarasan, Grogol, Sukoharjo ; Telepon, : 0271-5723399 *Corresponding author, e-mail: fitria.diniah@stikesnas.ac.id Article history Posted, Nov 12nd, 2022 Reviewed, Marc 3rd, 2023 Received, ……. Abstract Background: Foods and beverages containing artificial sweeteners in the form of aspartame are widely consumed in various countries including Indonesia, and have increased every year. Excessive consumption of aspartame can increase the occurrence of hepatotoxicity in the liver such as changes in the histopathological picture of the liver characterized by degeneration and cell necrosis (cell death). Hepatoprotectors are compounds that have antioxidant benefits so that they can protect the liver by reducing oxidation reactions in liver damage. One compound that functions as a hepatoprotector is black cumin (Nigella sativa). Aims: This study aims to determine the effect of black cumin administration on macroscopic and microscopic observations of liver organs in male white rats induced by aspartame. Methods: This study was experimental with 5 treatment groups including 1 normal group, 1 negative group and 3 aspartame and black cumin treatment groups. Liver tissue is observed macroscopically based on color, texture and size, while microscopically it is done by assessing the presence of normal cells, degeneration and necrosis. The results. The results of microscopic observations showed that the negative control and treatment groups showed cell damage in the form of cell degeneration and necrosis. The results of the study based on the ANOVA test obtained a significance value of < 0.05 which means there is an average difference between groups and continued with the Tukey test. Conclusions: Based on Tukey's test, the fourth group (K4) is a treatment group with the most effective dose of black cumin in preventing liver cell damage to white rats, which is 0.2 ml / 200 g body weight / day. Keywords: : Aspartame, Black Cumin, Hepatoprotective, Macroscopic, Microscopic 1. Introduction Foods and drinks that contain artificial sweeteners in the form of aspartame are widely consumed in various countries including Indonesia. Cahyadi (2008) stated that the use of synthetic sweeteners such as aspartame is widely chosen by the food and beverage industry because the price is relatively cheap and has 200 times the sweetness content compared to sugar (sucrose). These foods and drinks can pose various kinds of health hazards if consumed in excessive amounts. Health problems that arise are related to organs such as the liver, kidneys, stomach, pancreas, esophagus, brain, and others (Muhartono et al., 2019). According to data from the Food and Drug Supervisory Agency (2014), for the food and beverage category, the maximum limit of aspartame consumption is 50 mg / kg body weight. Excessive consumption of aspartame can cause significant changes in the histopathological picture of rat livers characterized by hydrophyic degeneration of hepatocyte cells and cell necrosis (cell death). When aspartame enters the human body, it is broken down into three compounds, namely aspartic acid, phenylalanine, and methanol (Sumarny et al., 2020). The use of aspartame is not allowed for people who have brain damage because the content of phenylalanine can cause severe brain damage (Maulana et al., 2018). Taking a low dose of aspartame can increase methanol levels in the body (Sumarny et al., 2020). While taking aspartame with excessive doses can increase the occurrence of hepatotoxicity in the human liver. In the study of Rafwiani et al (2018), giving

energy drinks containing artificial sweeteners in the form of aspartame at doses of 50 mg / kg body weight and 75 mg / kg body weight orally for 28 days can cause damage to rat liver histopathology with the onset of hydrophyic degeneration of hepatocyte cells and cell necrosis in the liver of male white rats. The liver has many functions such as metabolism, storage, the process of removing waste substances in the body, synthesis, and the process of cleansing toxins in the body. The function of detoxification in the liver is to prevent or eliminate harmful substances that enter the body. Potentially toxic compounds will be carried to the liver through the portal vein. The liver will mutate this compound through first pass metabolism (Costanzo, 2014). Hepatoprotectors are compounds that contain molecules that prevent the oxidation process so that they can reduce liver damage and can protect liver cells from toxic substances that harm the liver (Jiwandini et al., 2020). Black cumin or Nigella sativa contains many active ingredients, especially thymoquinone, which can help overcome toxicity by chemicals. The antioxidant properties of thymoquinone can prevent the effects of ROS (Reactive Oxygen Species) produced. Increasing catalase activity and playing a role in protecting liver tissue from damage is the use of thymoquinone (Rizky, 2018). This study aims to determine the effect of black cumin administration on macroscopic and microscopic observations of liver organs in aspartame-induced white rats. This research has passed the code of ethics test with letter number KEPK/UMP/42/VIII/2023. 2. Research Methods Tools and Materials The tools used in this study include: experimental animal cages, macros knives, microtome knives and cutting boards, cassete tissue, pencils, label paper, timers, analytical scales, stainless bowls, measuring cups, micropipettes, blue tips, sondes, scissors, tweezers, glass objects, deck glass, microtomes, microscopes, floating baths, and painting chambers. The materials used in this study include: white rat liver tissue, aspartame, alcohol (70%, 80%, 95%, 96%), absolute alcohol, hematoxcilin eosin, black cumin solution, xylol, aquadest, cotton, Canada balsam, NaCl 0.9%, paraffin, filter paper, neutral buffer formalin 10%, and filter paper. Treatment Provision White rats (Rattus norvegicus) are treated for 7 days of acclimatization to the laboratory environment such as temperature, air, and humidity. Acclimatized rats were divided into 5 groups, namely 1 experimental animal treatment group that was not given aspartame and was not given black cumin as a normal control, 1 group as a negative control that was given aspartame 100mg / 200 g body weight / day without black cumin, and 3 experimental animal treatment groups given aspartame at a dose of 100mg / 200 g body weight / day and black cumin with a stratified dose of 0.1 mL / 200 g BB / day, 0.2 mL/200 g BB/day, and 0.3 mL/200 g BB/day. Treatment given for 21 days. Animal Termination Process White rats were terminated using ether a day after giving pure aspartame and black cumin for 21 days, termination was done by cotton given ether then put in a container without air circulation then closed tightly, make sure the rat was euthanized and then liver organs were taken to be examined. Creation of Network Preparations Histological tissue processing is carried out in a manual way. The tissue is cut with a sharp knife of about 5mm then washed or rinsed with a 0.9% NaCl solution to clean the blood that is still in the tissue. Once clean, insert the tissue into a tissue cassette and then fixate it using a 10% NBF solution for 11/2 hours to preserve the tissue. Furthermore, the process of removing water from the tissue so that the tissue can be thinly sliced, namely dehydration, is carried out by inserting the tissue in stratified alcohol, which is 80%, 90%, 95% and absolute alcohol (2 times) for 5 minutes each. Then clearing was carried out using xylol I solution for 1 hour and xylol II for 2 hours. Furthermore, embeding and blocking is a process to replace the clarifying material with liquid paraffin so that the tissue is easily cut using microtomes, the paraffin block is allowed to stand at room temperature for 10 hours and then incubated in the freezer. Then cutting, which is the process of cutting tissue on the block using microtomes at a thickness of 3-5 mm and taken with a glass object in a floating bath at a temperature of 55-60°C. Previously, glass objects were given glycerol albumin so that the tissue could stick perfectly to the surface of the glass object. Furthermore, staining hematoxylin and eosin is carried out. The first staining process is deparafinization by inserting tissue in xylol 2 times for 5 minutes, then put in alcohol for 5 minutes. Then the preparation is flooded with aquadest for 10 minutes. After that, soaking hematoxylin paint with a time of 5 minutes, then the preparation is washed with flowing water. When finished, the tissue is soaked in eosin paint with 2 minutes and rinsed with xylol. Furthermore, network mounting is carried out with enthelan. Finally, the preparation has been covered with deck glass. Observed using a microscope at 400x magnification (Damairia, 2021). 3. Results and Discussions This study aimed to determine the hepatoprotective effect of black cumin with stratified doses, namely 0.1 mL/200 g BB/day, 0.2 mL/200 g BB/day, and 0.3 mL/200 g BB/day on macroscopic and microscopic images of aspartame-induced white rat liver at a dose of 100 mg /200 g body weight of rats tested for 21 days. The observations analyzed are macroscopic and microscopic images on the histology of white rat livers. Previously, black cumin was carried out phytochemical tests, namely tests of metabolite compounds contained in the content of black cumin in the form of flavonoids, interquinones, terpenoids, and saponins. Flavonoids, interquinones, terpenoids and saponins are chemicals contained in black cumin. The chemical content consists of several active components that can overcome the toxicity caused by chemicals. One of the active components of black cumin that is useful as a hepatoprotector is thymoquinone. The presence of thymoquinone can be seen by interquinone test on black cumin. The following are the phytochemical test results contained in table 1. Table 1. Black Cumin Phytochemical Test Results Content Information Flavonoid The formation of red color Antarkuinon The formation of a brownish-red color Terpenoid The formation of a brownish-red color Saponin Froth does not disappear with HCl addition Source : Primary data (August, 2023). The results of macroscopic observations 1. Table 1 is a discriptive data from macroscopic of white rat hearts can be seen in table 1 and figure observations of white rat liver organs from 5 groups. From the table above shows a color to the liver of white rats. The presence of white change in group K1 with groups K4 and K5. spots on the macroscopic liver is caused by fatty Macroscopic observations also showed that in the liver that blocks blood flow to the liver and causes K2, K3, K4, and K5 groups there were white spots the liver to pale in color (Lailatul, 2015). or spots which were a sign that there was damage Table 2. Results of macroscopic observations of white rat liver Macroscopis Group Color Information Normal Group (K1) Brownish red Normal negative group (K2) Brownish red There is a slack Aspartame and black cumin 0,1 ml (K3) Brownish red There is a slack Aspartame and black cumin 0,2 ml (K4) Blackish red There is a slack Aspartame and black cumin 0,3 ml (K5) Blackish red There is a slack Source : Primary data (September, 2023). Figure 1. Macroscopic picture of the liver of white rats. K1 = Normal group, K2 = Aspartame group, K3 = aspartame and black cumin 0.1 ml, K4 = aspartame and black cumin 0.2 ml, K5 = aspartame and black cumin 0.3 ml (Personal documentation, 2023). Figure 1 is a documentation of macroscopic observations on the liver of white rats. The results of macroscopic observations found color changes in each group. Based on the results of macroscopic observations, it can be seen that all groups have the same color, which is brownish red and there is no color change. However, white spots appeared in the form of fatty in groups K2, K3, K4 and K5 which is a sign that there is damage to the liver of white rats. The presence of white spots on the macroscopic liver is caused by fatty liver that blocks blood flow to the liver and causes the liver to be pale. In macroscopic white rat livers, spots or lipid droplets that appear are produced and synthesized as inclusion bodies. When synthesis is inhibited, fat accumulates and fills intracellular and extracellular spaces. Fat accumulation is caused by inhibition of fatty acid oxidation, which among other things is caused by excessive NADH formation. a a a a a Figure 2. Histopathological features of white rat liver in normal group (K1) with magnification of 400x. Remarks : A = Normal Cells (Personal documentation, 2023). b a a a c Figure 3. Histopathological features of white rat liver in the treatment group (K4) given aspartame and black cumin 0.2 mL with Hematoxylin-Eosin staining and 400x magnification. Remarks : A = Normal Cells, B = Hydropic Degeneration, C = Parenchymatous Degeneration, D = Pycnotic Necrosis, E = Caryorexia Necrosis and F = Carolysis Necrosis (Personal documentation, 2023). Based on Figure 2, microscopic observations in the K4 treatment group given observations on K1 show no degeneration and aspartame and 0.2 mL black cumin showed the necrosis. The picture on K1 obtained cell damage presence of relatively many normal cells and a in the form of parenchymatous degeneration cells relatively mild level of damage, namely cell and necrosis cells (pycnotic, cariorexic, swelling (parenchymatous and hydrophyic karyolysis). While in figure 3, microscopic degeneration. Table 3. ANOVA Test Analysis Results ANOVA Preparat Sum of Squares df Mean Square F Sig. Between Groups Within Groups 23.440 18.800 5 20 5.860 6.234 .940 .002 Total 42.240 24 Table 4. Tukey's Post Hoc Test Analysis Results Preparation Tukey HSDa Subset for alpha = 0.05 Treatment N 1 2 Group 1 (Normal Control) 5 1.00 Group 4 (Aspartame and Black Cumin 0.2 ml) 5 1.80 1.80 Group 3 (Aspartame and Black Cumin 0.1 ml)) 5 3.00 Group 5 (Aspartame and Black Cumin 0.3 ml) 5 3.20 Group 2 (Negative Control) 5 3.60 Sig. .691 .056 Means for groups in homogeneous subsets are displayed. a. Uses Harmonic Mean Sample Size = 5.000. Table 3 obtained p results < 0.05, namely there was a significant difference between the treatment group and the control group. So that continued the Post Hoc Tukey Based on the results obtained, it can be concluded that there is a significant difference

between the groups, where the K4 group (treatment group 2) is the most effective dose because it has the least difference with the K1 group (normal control) and it can be concluded that the administration of black cumin has a hepatoprotective effect on the histopathological picture of the liver of white rats after induction of artificial sweeteners in the form of aspartame. In the scoring assessment, if the preparation is found damage in the form of degeneration, both in the form of parenchymatose and hydropis, the data is still assessed 2. This degeneration damage is mostly found in each treatment except in the normal group or K1 group. Degeneration is a sign of liver damage due to reversible toxins and can still return to normal if exposure to these toxins is stopped. There are several types of cell damage, degeneration, including parenchymatous and hydropic degeneration. Morphological changes in dead cells are referred to as cell necrosis. Microscopically, necrosis can be seen from changes that occur in the cell nucleus or cytoplasm. There are 3 kinds of necrosis, namely pycnosis necrosis, cariorexis necrosis, and karyolysis necrosis. Necrosis of picnosis is characterized by reduced cell nucleus size, loss of chromatin and dark color. Caryorexic necrosis is characterized by rupture or destruction of the cell nucleus and scattered chromatin fragments within the cell. Carolysis necrosis is characterized by the loss of the ability of cell nuclei in staining so that they do not look or appear pale (Nazarudin et al., 2017). The picture of necrosis that occurred in the K2 negative control group was different from all test groups because this group was only given the artificial sweetener aspartame which can be damaging, while K3, K4, and K5 with the treatment of artificial sweeteners aspartame and black cumin with stratified doses of each group showed differences between degeneration and necrosis. This situation shows that the dose of cumin used is varied enough to produce varying effects as well. The K3 black cumin treatment group has begun to show improvements in liver histopathological features when compared to the K5 group. When compared to the K4 group given black cumin at a dose of 0.2 mL/200 g BB rats, the decrease was smaller with an improved degree of necrosis. The histopathological picture in the negative control group showed the result that there was a small amount of degeneration and a considerable amount of necrosis in the field of view of each preparation. It showed that the artificial sweetener aspartame at a dose of 100 mg / 200 g body weight / day for 21 days caused damage to the liver cells of white rats. The effects of consuming aspartame for the body, especially the liver, have been mentioned in several studies such as in the study of Haliem et al (2018) male white rats induced aspartame at a dose of 250 mg / kg bb / day for 2 months showed histopathology of liver tissue with irregular nuclear hepatocytes, cytoplasm containing many vacuoles and few mitochondria, and cell necrosis. Histopathological features in groups K3, K4, and K5 have been related to the administration of black cumin with stratified doses. In the damage scoring of each treatment, it was found that the K4 group given black cumin at a dose of 0.2 mL / 200 g BB rats gave the most effective results where normal cells were found and reduced damage was found. The second treatment group (K4) used a dose of 0.2 mL / 200 g body weight of rats which dose is the standard daily consumption of black cumin which has been able to provide hepatoprotective effects on the liver of white rats induced by artificial sweetener aspartame. The first (K3) and third (K5) treatment groups showed damage results that were not much different from the negative control group. That's because consumption of black cumin that is less than the normal dose and exceeds the normal dose can cause damage to the liver of white rats. In accordance with the research of Afdin et al (2018), ethanol-induced white rats in treatment group 5 given black cumin extracted with a concentration of 50% and 50% ethanol solution 0.01 mL/grBB for 14 days showed that black cumin that had been extracted had a hepatoprotective effect on the liver of white rats damaged by ethanol in the presence of mild fat degeneration in microscopic observations of white rat livers. Black cumin contains many active ingredients, especially thymoquinone, which can overcome toxicity by chemicals. The antioxidant properties of thymoquinone can reduce the effects of ROS (Reactive Oxygen Species) produced. Increasing catalase activity and playing a role in protecting liver tissue from damage is the use of thymoquinone (Rizky, 2018). In addition, thymoquinone content can also reduce oxidative stress and strengthen the effects of antioxidants in the body. (Mollazadeh et al., 2014). 4. Conclusions Based on the results of this study, it can be concluded that the administration of black cumin at a dose of 0.1 mL/200 g body weight /day; 0.2 mL/200 g body weight /day; and 0.3 mL/200 g body weight /day after induced artificial sweetener aspartame at a dose of 100 mg/200 g BB/day for 21 days exerted a protective effect against macroscopic and microscopic white rat livers. The most effective dose in preventing liver cell damage of white rats is the fourth group (K4) which is the second treatment group with aspartame 100 mg / 200 g body weight / day and black cumin 0.2 mL / 200 g body weight / day. References 1. Afdin, R.R. and Quzwain, F. 2018. Hepatoprotective effect of black cumin (Nigella sativa) extremist against liver damage of male white rats (Rattus norvegicus) of ethanol-induced Sparague Dawley strains. Jambi Medical Journal, 6(1) : 36 – 44. 2. Agustyani, V. N., Ikhda, C., &; Hamidah, N. 2021. Formulation and Physical Quality Test of Black Cumin Seed Extract (Nigella sativa) Toothpaste Preparation. Mulawarman Pharm Conf 13 (5), 232-238. 3. Food and Drug Supervisory Agency of the Republic of Indonesia. Regulation of the Head of the Food and Drug Agency of the Republic of Indonesia Number 4 of 2014 concerning Maximum Limits on the Use of Sweetened Food Additives. 2014:1–28 4. Damairia, Ema, R. 2021. 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