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HEPATOPROTECTIVE EFFECT OF HONEY AND BLACK CUMIN COMBINATION AGAINST SOFT DRINK-INDUCED *Rattus norvegicus* LIVER BASED ON HISTOPATHOLOGICAL FEATURES

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ABSTRACT
Carbonated soft drinks are drinks that can cause damage to the liver if consumed excessively. The combination of honey and black cumin as an antioxidant agent has hepatoprotective and antioxidant effects with a capacity of 3-4 times compared to honey or black cumin seeds alone. The aim of this research was to determine the effect on macroscopic and microscopic observations of the liver of Rattus norvegicus given a combination of honey and black cumin in graded doses, namely concentrations of 25%, 50% and 75% after being induced by soft drinks and the damage that occurred when given in doses and the specified time. This research was carried out experimentally at the Cytohistotechnology Laboratory Sekolah Tinggi Ilmu Kesehatan Nasional. The research was divided into 6 groups, namely 3 control groups and 3 treatment groups. The results of macroscopic observations showed differences in colour, size, fatty and similarities in liver texture. The results of microscopic observations showed normal cells and damage such as hydropic degeneration, parenchymatous degeneration, pyknosis necrosis, karyorrhexic necrosis, and karyolysis necrosis. The results of the test using One Way ANOVA and followed by Post Hoc Duncan can be concluded that giving a combination of honey and 75% black cumin as much as 2 mL/200 gr weight of rats can have a protective effect on macroscopic and microscopic examination of the liver of Rattus norvegicus after being induced by soft drinks.

Keywords: hepar; histopathology; honey and black cumin combination; macroscopic; soft drink

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INTRODUCTION

Carbonated drinks are drinks made by absorbing carbon dioxide into drinking water, with or without various additives. Caffeine, saccharin, fructose, benzoic acid, sorbic acid, aspartame, and phosphoric acid are substances commonly added to carbonated drinks. Currently, the consumption of carbonated soft drinks has increased significantly around the world, including Indonesia, especially among young people (Berawi and Dzulfikar, 2017). According to the Beverage Marketing Corporation, carbonated beverage consumption reached 29.8 billion gallons in the United States in 2012, and reached 14.5 billion litres in the United Kingdom in 2013. According to a Nusa Research Indonesia survey in 2014, the figure was 30%. The number of respondents who consumed carbonated drinks two to three times a week in the past three months. Several epidemiological studies have shown that chronic consumption of these carbonated drinks is associated with obesity, kidney disease, liver disease and osteoporosis (Basu et al., 2013).

Hepar is the largest organ in the human body (1300-2000 g) and has important functions in nutrient metabolism (proteins, carbohydrates, fats, vitamins, minerals, etc.) and detoxification functions (Iswan et al., 2019). Hepar also plays a role in detoxifying the types of drugs and toxins that enter the body. Potentially toxic compounds are transported to the liver via the

portal vein. Hepar modifies these compounds by first pass metabolism (Costanzo, 2014). Hepatoprotectors are effective compounds and or substances that can protect liver cells from toxic substances that can damage the liver. These compounds are able to repair liver tissue that is no longer functioning. Usually hepatoprotectors are ingredients with antioxidant properties that can reduce oxidative reactions that cause liver damage (Jiwandini et al., 2020).

The combination of honey and black cumin oil as antioxidants showed that the hepatoprotective effect was greater. This may be characterised by complete recovery from biochemical abnormalities caused by hepatotoxic substances. The hepatoprotective effect of honey against hepatotoxicity may be related to the ability of honey to reduce lipid peroxidation and enhance the antioxidant defence system. Black cumin seeds contain the bioactive compounds thymoquinone and polyunsaturated fatty acids (PUFAs) which have various positive effects in disease cure and liver protection. In addition, the combination of the two active ingredients increases antioxidant capacity by 3-4 times greater when compared to using black cumin seeds or honey alone (Syarif et al., 2019). Based on the research of Syarif et al. (2019), it was found that there was a significant increase in the treatment group given a combination of black cumin oil and honey by using a dose of honey that was more than the dose of black cumin oil against hepatic damage to Rattus norvegicus due to sisplatin compared to the group given black cumin oil or honey alone. The purpose of this research was to determine whether or not there is an effect on macroscopic and microscopic observations of the liver organ of Rattus norvegicus which has been given a combination of honey and black cumin with graded doses, namely 25% concentration, 50% concentration, and 75% concentration after being induced by a soft drink and to determine the damage that occurs if given in the specified dose and time with hematoxylin-eosin dye.

METHOD

This research was conducted at the Cytohistotechnology Laboratory Sekolah Tinggi Ilmu Kesehatan Nasional in August 2023 - December 2023 using experimental analytical research. This research passed the KEPK/UMP/41/XII/2023 ethical review.

Tools and Materials

The tools used consisted of animal cages, ruler, macro knife, microtome knife and cutting board, cassette tissue, pencil, label paper, timer, analytical balance, stainless steel bowl, measuring cup, micropipette, blue tip, sonde, scissors, tweezers, object glass, deck glass, microtome, microscope, floating bath, and painting chamber. Materials used include Rattus norvegicus hepatic tissue, soft drinks, alcohol (70%, 80%, 95%, 96%), absolute alcohol, haematoxilin eosin, honey and black cumin oil combination solution, xylol, distilled water, cotton, Canada balsam, NaCl 0.9%, paraffin, filter paper, neutral buffer formalin 10%, and filter paper. Preparation of Honey and Black Cumin Combination Solution: The ratio used is 1:1 so that 1 mL of forest honey with 1 mL of black cumin oil is mixed until homogeneous.

Treatment Group: Using 6 groups, namely the normal control group, which is only given water and feed of the same type, the negative control group, which is induced by soft drinks 2 mL / 200 g weight/ day without giving a combination of honey and black cumin. The positive control group is induced by a combination of honey and black cumin 2 mL/200 g weight/day without induction of soft drinks. The first treatment group (K1) was induced with soft drinks 2 mL/200 g weight/day and a combination of honey and black cumin with a concentration of 25% as much as 2 mL/200 g weight/day. The second treatment group (K2) was induced by soft drinks 2 mL/200 g weight/day and a combination of honey and black cumin with a concentration of 50% as much as 2 mL/200 g weight/day. The third treatment group (K3) was

induced by soft drinks 2 mL/200 g weight/day and a combination of honey and black cumin with a concentration of 75% as much as 2 mL/200 g weight/day.

This research used 30 male white rats (Rattus norvegicus) wistar strain, and each group consisted of 5 Rattus norvegicus which were adapted for 7 days and treated for 21 days (Saputra and Sayekti, 2021). This sampling was carried out by simple random sampling. Observations were made macroscopically (colour, texture, and size) and microscopically (normal cells and damage such as hydropic degeneration, parenchymatous degeneration, pycnotic necrosis, cariorrhexis necrosis, and cariolysis necrosis). The preparation procedure consisted of fixation, dehydration, clearing, embedding, blocking, microscopy and haematoxilin-eosin staining (Damaira and Sayekti, 2022). Observations were made in 5 field of view using 400x magnification for each preparation. The assessment used was that each cell criterion found was given a value. Normal cells (1), degeneration in the form of both parenchymatous and hydropic (2), pycnotic necrosis (3), karyorrhexis necrosis (4), and karyolysis necrosis (5). The data obtained were processed using SPSS. Data results were tested using the One Way ANOVA test and if the results obtained <0.05, namely between groups have a difference in average, then the Post Hoc test is carried out using the Tukey test.

RESULT

Table 1.
Results of Macroscopic Observations of Rattus norvegicus Hepar

Group	Macroscopic					Conclusion
	Colour	Texture	Size		Lean	
			Long (cm)	Width (cm)		
Normal group (K1)	Brownish Red	Chewy	4,3	3,5	No	Normal
Negatif group (K2)	Blackish Red	Chewy	4,1	3,2	Availab le	Discolouration and fatty liver
Positive group (K3)	Brownish Red	Chewy	4,3	3,5	No	Normal
First treatment (K4)	Brownish Red	Chewy	4,2	3,4	No	Normal
Second treatment (K5)	Brownish Red	Chewy	4,3	3,3	No	Normal
Third treatment (K6)	Brownish Red	Chewy	4,3	3,5	No	Normal

Based on the results of research on the Hepatoprotective Effect of the Combination of Honey and Black Cumin on Hepar Rattus norvegicus Induced by Carbonated Beverages from macroscopic observations (Table 1), it was found that there were differences in colour, size, and fatty between the control and treatment groups but there were similarities, namely having a chewy texture. Macroscopic observation is still not enough to analyse the hepatoprotective effect so it is necessary to do the next stage, namely microscopic observation.

Microscopic Observation

The examination results of microscopic observation of the hepatic Rattus norvegicus obtained results in the normal control group (K1) found the presence of normal cells (Figure 1) and in the negative control group (K2) (Figure 2), the first treatment (K4) (Figure 4), the second treatment (K5) (Figure 5), and the third treatment (K6) (Figure 6) found the presence of normal cells and damage such as hydropic degeneration, parenchymatous degeneration, pycnotic necrosis, necrosis karyorrhexis, and necrosis karyolysis. The positive control group (K3) (Figure 3) had damage but no hydropic degeneration damage. The third treatment group (K6) showed that the number of normal cells had started to increase compared to the first treatment group (K4) and the second treatment group (K5).

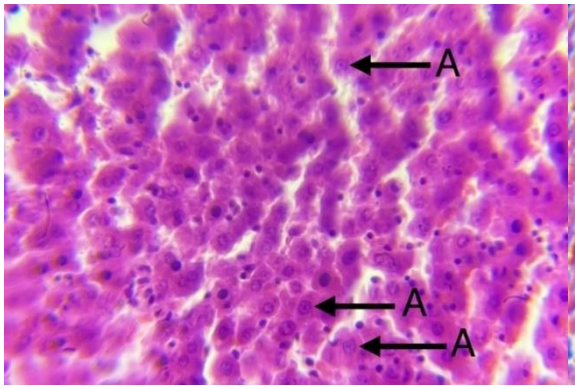

Figure 1. Normal Group (K1)

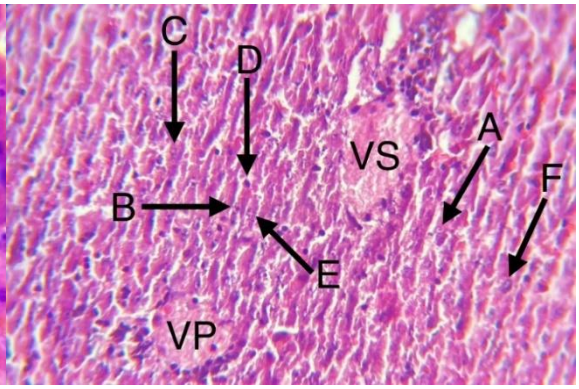

Figure 2. Negative Group (K2)

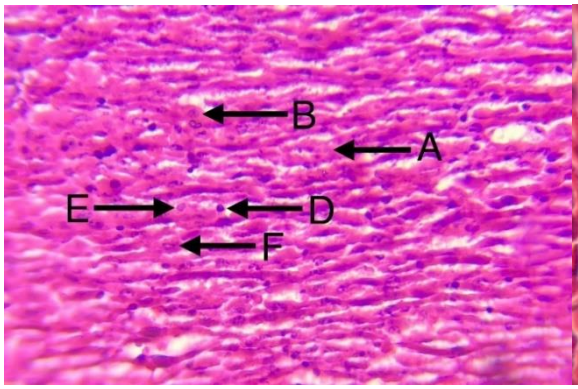

Figure 3. Positive Group (K3)

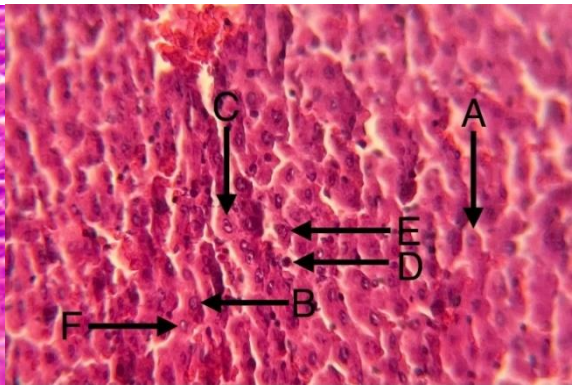

Figure 4. First Treatment Group (K4)

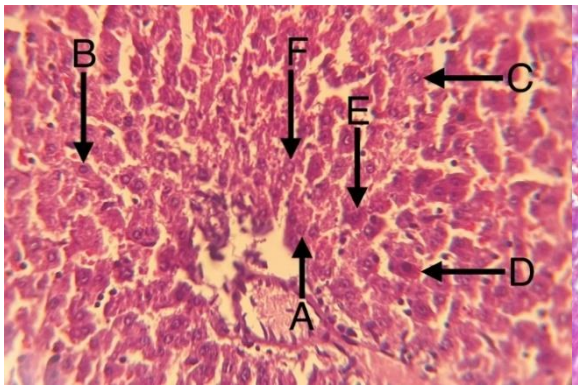

Figure 5. Second Treatment Group (K5)

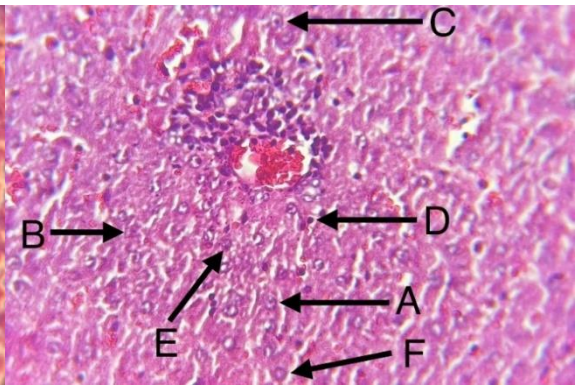

Figure 6. Third Treatment Group (K6)

Histopathological picture of Rattus norvegicus Hepar with Hematoxylin-Eosin staining with 400x magnification.

Description: A = Normal Cells, B = Parenchymatous Degeneration, C = Hydropic Degeneration, D = Pycnotic Necrosis, E = Karyorrhexis Necrosis, F = Karyolysis Necrosis, VP = Portal Vein, VS = Central Vein (Source: Personal Documentation, 2023).

The data obtained were then tested with SPSS (Statistical Program for Social Science). The results obtained from the One-Way Analysis of Variance Test (ANOVA) test <0.05, so between groups have differences in average. The results of Duncan's Post Hoc Follow-up test are groups that are in the same column as the normal control group, namely the positive control group (K3) and the third treatment group (K6). It was found that the group giving a combination of honey and black cumin 75% as much as 2 mL/200 g weight of rats can provide hepatoprotective effects.

DISCUSSION

The results of macroscopic observations in groups K1, K3, K4, K5, and K6 obtained a brownish red liver colour which indicates that the normal colour of the liver. According to Fortes (2017) the normal colour of the liver is brownish red, this is caused by the flow of blood into the liver. There are differences in size between groups in both the control and treatment groups. According to Guyton and Hall (1984) differences in size can be influenced by feed and drinking water because these factors are extrinsic factors. The liver has a relationship with body weight because the liver metabolism food substances that will be used for activity or stored as food reserves. The negative control group (K2) found that there were white beetroot which is fatty liver. The fatty liver can be caused by excessive amount of free fatty acids entering the liver, disturbance in the triglyceride cycle, increased fatty acid synthesis, decreased fatty acid oxidation, and decreased Very Low Density Lipoprotein (VLDL) synthesis and secretion. Macroscopic observation is not enough to analysis the hepatoprotective effect, so the next step is microscopic observation.

In microscopic observation of hepatic organs, the preparations used were stained with Hematoxylin Eosin. Hematoxylin and eosin is a dual staining method with the first function of allowing the identification of certain tissue components with different stains. The second function is that it can be stained at different levels or degrees of colour to produce different colours. With this staining, a complex dark purple colour is obtained with hematoxylin staining, and with eosin staining, tissues that cannot be stained purple with hematoxylin dye will be stained from pink to red. Hematoxylin is the basic dye and colours the core of the tissue. Eosin is acidic and colours the cytoplasm and connective tissue in tissue samples (Tutik and Sayekti, 2022). Microscopic observations were assessed by scoring the presence of normal cells, hydropic degeneration, parenchymatous degeneration, pycnotic necrosis, karyorrhexis necrosis, and karyolysis necrosis. Observations were made as many as 5 field of view for each preparation and 1 group consisted of 5 preparations with 400x magnification. The data obtained from microscopic observations were then tested using SPSS. Damage in the form of cell degeneration or cytolysis is a cell disorder that occurs due to minor injury. Minor damage affects intracellular structures such as mitochondria and cytoplasm that disrupt the cell's metabolic processes. Cell degeneration damage is reversible. It can be repaired if the cause is immediately stopped or eliminated (Maulida et al., 2013).

If not eliminated or aggravated, the damage becomes irreparable and the cells die. Parenchymal degeneration is damage caused by the accumulation of water in the cell, which causes the failure of oxidation thus inhibiting the transport of proteins produced by ribosomes. This causes the cell to swell, affects the cytoplasm, and causes granules to form due to protein deposition. Hydropic degeneration is a lesion where the cytoplasmic structure appears pale and swollen. Hepatocytes damaged by hydropic degeneration will appear brighter when compared to cells damaged by parenchymal degeneration because the cells are transparent, contain more water to form vacuoles, and do not contain fat. The level of damage due to hydropic degeneration is greater when compared to parenchymal degeneration (Nazarudin et al., 2017). Necrosis is a condition of damage caused by irreversible death of living tissue cells due to toxic substances and radioactive radiation (Barata and Merdana, 2018). Necrosis is caused by various factors, such as toxic substances, metabolic disorders, and biological agent infections (Sijid et al., 2020). Microscopically, necrosis shows changes in the nucleus, namely loss of chromatin, the nucleus becomes wrinkled instead of blood vessels, the nucleus appears denser, black in colour (picnosis), broken (karyolysis), and or pale (decomposition of the nucleus). Condensation or blackening of the cell nucleus can occur due to intracellular damage in the form of membrane damage, mitochondrial damage, and golgi apparatus,

resulting in cells unable to release water and triglycerides that accumulate in the cell cytoplasm (Adikara et al., 2013).

Several studies on carbonated soft drinks have been conducted to determine the hepatoprotective effect on the liver of Rattus norvegicus with predetermined doses and times. In the study of Muhartono et al (2019) in treatment groups 1, 2, and 3 experienced histopathological liver damage which appeared in the form of parenchymatous degeneration (cloudy swelling), hydropic degeneration, and fatty deposits. In the study of Murti et al (2016) in treatment group 2, hepatocyte damage was found in the form of parenchymatous degeneration to zone 3 necrosis (severe). In the study of Selvira et al (2021) in treatment group 2, the most severe hepatocyte damage occurred, namely necrosis in zone 3 (centrolobular) and some extended to zone 2.Several studies on honey have been conducted to determine the hepatoprotective effect on the liver of Rattus norvegicus with a predetermined dose and time. In the study of Fairuz et al (2013), administration of 50% forest honey solution had a protective effect on liver damage in rats induced by ethanol. In the study of Sibarani et al (2013), honey can reduce liver cell damage in Rattus norvegicus induced by aspirin. In the study of Hartanto et al (2017), administration of Be pollen honey can reduce liver damage in Rattus norvegicus with a small number of cloudy swollen degenerated cells due to administration of ibuprofen.

Several studies on black cumin have been conducted to determine the hepatoprotective effect on the liver of Rattus norvegicus with predetermined doses and times. In the study of Afdin et al (2018), the administration of black cumin (Nigella sativa) extract had a hepatoprotective effect on liver damage in male Rattus norvegicus induced by ethanol. In the study of Sari et al (2021), the administration of black cumin extract in graded doses was able to repair the damage to hepatocyte cells that occurred. In the study of Amalia et al (2021) in treatment group 1 which was given black cumin extract and induced with paracetamol, the results showed visible improvements in the form of a reduction in the number of cells undergoing degeneration and necrosis, as well as proliferation of kuppfer cells, although bleeding was still found in some areas. In the study of Hendrawan et al (2023) in treatment group 3, the results showed that black cumin had a protective effect on the histopathological picture of hepatocytes in the liver of Rattus norvegicus induced by organophosphates with low degeneration and focal necrosis values.

The negative control group (K2), positive control (K3), first treatment (K3), second treatment (K4), and third treatment (K5) resulted in the presence of normal cells and damage such as hydropic degeneration, parenchymatous degeneration, pycnotic necrosis, karyorrhexis necrosis, and karyolysis necrosis. The negative control group (K2) was found to have degeneration and necrosis damage with a considerable amount of necrosis damage. The positive control group (K3) found a large number of normal cells and no hydropic degeneration and very rarely found necrosis damage. Parenchymatous degeneration includes mild damage, hydropic degeneration includes moderate damage or more severe than parenchymatous degeneration damage and necrosis is included in severe damage. In the treatment group. In the third treatment group (K6) when compared to the first treatment group (K4) and the second treatment group (K5), normal cells were found in greater numbers and the damage began to decrease.

From the results of this research, the negative control group, namely the soft drink group, experienced the most severe damage when compared to other groups. In the third treatment group with a combination of honey and black cumin with a concentration of 75% showed

significant healing results from soft drink-induced hepatic damage. This is in accordance with research by Syarif et al (2019) that the combination of black cumin oil and honey can provide a synergistic protective effect against hepatotoxicity in Rattus norvegicus caused by cisplatin.
The microscopic observation data obtained were then tested using SPSS. The data obtained were tested using the One-Way Analysis of Variance Test (ANOVA) test and the results obtained <0.05 the six treatment groups had differences in average, so the Post Hoc Duncan further test was carried out with the aim of knowing whether there was a difference in the effect of the combination of honey and black cumin on the histopathological picture of the liver of Rattus norvegicus. The results showed that there were differences between groups. Groups that are in the same column as the normal control group (K1) are the positive control group (K3) and the third treatment group (K6). Giving a combination of honey and black cumin 75% as much as 2 mL / 200 g weight rats can provide a protective effect on macroscopic and microscopic examination of the hepar of Rattus norvegicus after being induced by soft drinks.

CONCLUSION

The results showed that macroscopic observation of hepatic tissue had differences in colour, size, and fatty but there were similarities in hepatic texture between groups. Microscopic observations showed that there were normal cells and damage to the hepatic cells of the control and treatment groups, except for the normal control group which showed only normal cells. Statistical test results from microscopic observations are significant differences between groups. Giving a combination of honey and black cumin 75% as much as 2 mL / 200 g weight rats can provide a protective effect on macroscopic and microscopic examination of the hepatic Rattus norvegicus after being induced by soft drinks.

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