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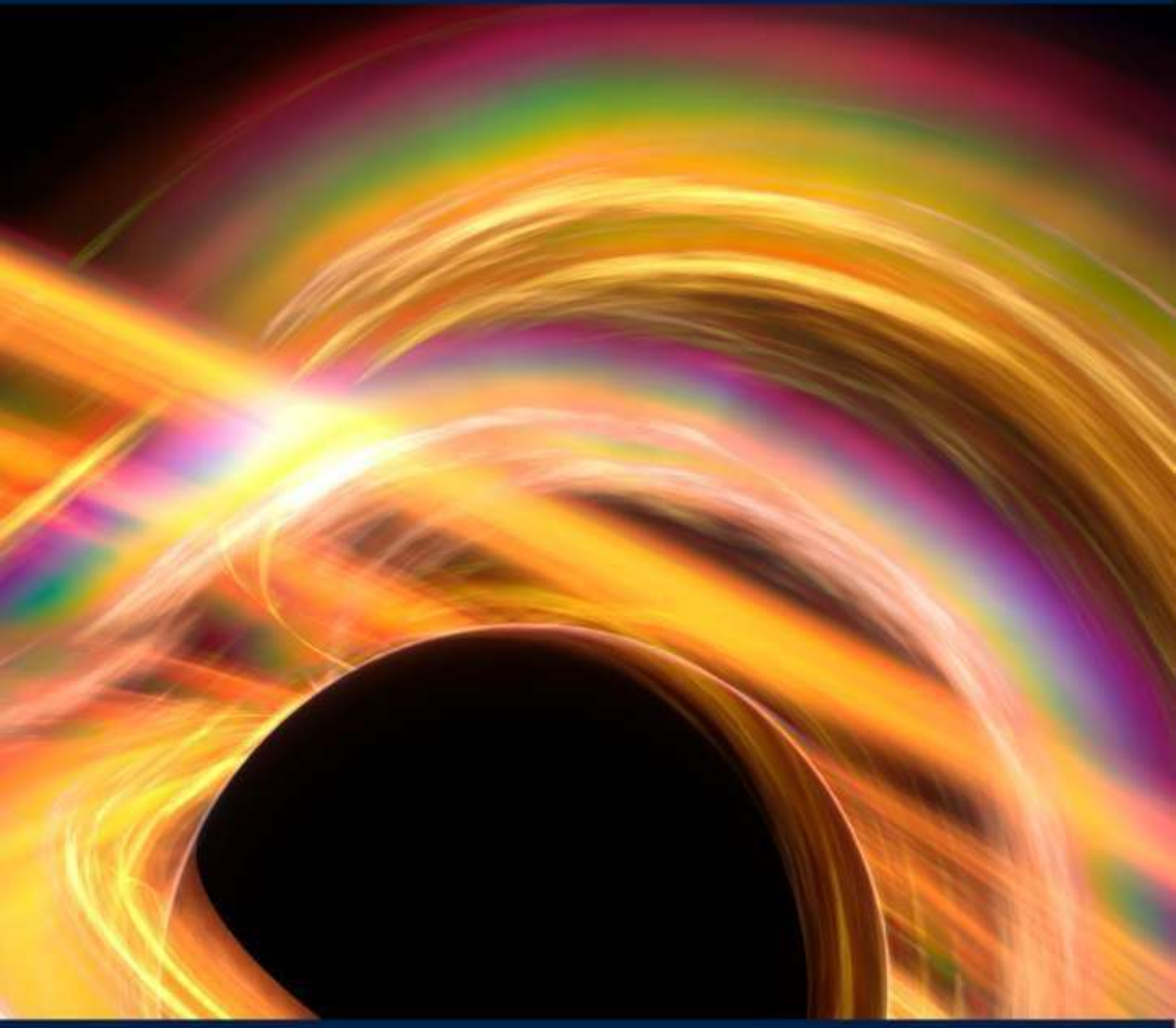

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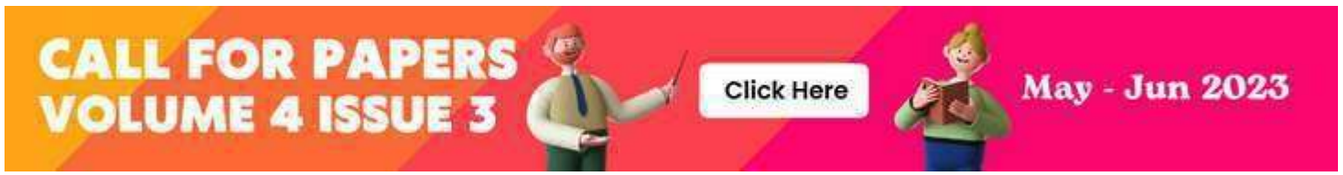

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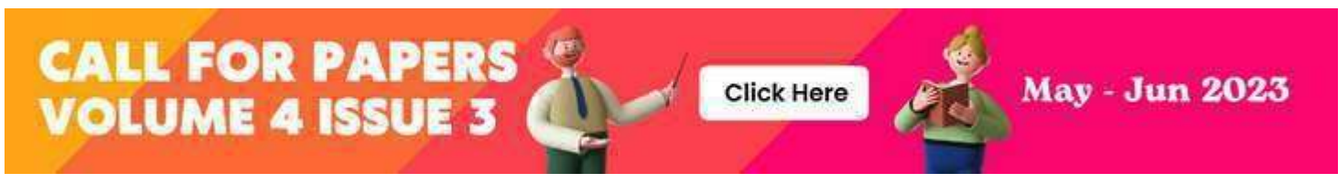

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The Effect of Administering *Apis dorsata* Forest Honey on Liver Histopathological Changes of Rats (*Rattus norvegicus*) Exposed to Physical Stress

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ABSTRACT
The objective of this study was to determine the effect of *Apis dorsata* forest honey on the liver histopathological changes of white rats (Rattus norvegicus) exposed to physical stress. This study used 24 rats which were divided into 4 groups. The positive control group (C+) was only given a stressor and distilled water orally, the treatment group 1 (T1) was given a stressor + honey 2g/rat/day, T2 was given a stressor + honey 4g/rat/day, and T3 was given a stressor + honey 6g/rat/day. All treatments were carried out within 14 days. The results showed that there was a significant difference ($p<0.05$) between the C+ control group (3.44a ± 0.622; 3.52a ± 0.109; 1.76a ± 0.384) and the treatment group1 /T1 (1.13b ± 0.389; 2, 48c ± 0.438; 0.84b ± 0.260) in terms of reduced level of liver damage, however, there was no significant difference ($p> 0.05$) between the C+ control group (3.44a ± 0.622 ; 3 .52a ± 0.109; 1.76a ± 0.384) and treatment group2 / T2 (3.72a ± 0.268; 3.64ab ± 0.260; 1.90a ± 0.400) and T3 (3.84a ± 0.167; 3.88a ± 0.178; 2 .48a ± 0.840). It can be concluded that the administration of *Apis dorsata* honey to rats exposed to physical stress within 14 days can reduce the level of liver damage with an effective dose of 2g/rat/day. However, excessive consumption of honey causes adverse effects on the liver as seen in the T2 and T3 treatment groups with doses of honey 4g/rat/day and 6g/rat/day which can increase the risk of liver damage.

Keywords: liver damage; swimming exercise; wild honey

INTRODUCTION

Physical exercise is an activity that moves the body in a planned, structured, and repeated manner. Physical exercise is intended to maintain or increase physical fitness. However, if physical exercise is carried out excessively, it can have a bad impact on health. Excessive physical exercise can result in physical stress.

Excessive physical stress will lead to disruption or inhibition of physiological processes in the body. Physiologically, increased oxygen consumption in the respiratory chain during physical stress conditions will result in oxidative stress. Increased ROS causes lipid peroxidation which will result in cell damage [1,2]. Oxidative stress itself can be formed due to an imbalance between pro-oxidants and antioxidants in the body. The occurrence of peroxidation reactions of lipids, proteins, enzymes, and DNA is the cause of oxidative damage due to oxidative stress[3,4]. One of the affected organs is the liver.

Hu et al.[5] in their research found that swimming exercises performed once and seven times in experimental rats led to an increase in lipid peroxidation in the liver tissue.

In line with this, Jawi et al.[6] explained in their research that maximum physical activity in the form of swimming which was carried out once in mice was able to significantly increase SGOT and SGPT levels and cause degeneration to necrosis in liver cells. Research conducted by Thirumalai et al.[7] reported that intense swimming training increased ROS production in the muscles. Another study conducted by Lima et al.[8] reported that swimming exercises carried out until fatigue caused an increase in ROS in the liver organs due to mitochondrial dysfunction.

Oxidative stress can be prevented by administering antioxidants that can neutralize these free radicals so that further reactions due to oxidative stress can stop and cell damage can be avoided. One of the antioxidants derived from natural ingredients is honey. Honey can be used as an antioxidant because it contains compounds such as flavonoids, polyphenols, vitamin C, manganese, beta-carotene, and other active substances that could protect the liver[9]. Honey which has higher antioxidants than other honey is produced by *Apis dorsata* bees.

In line with research conducted by Moniruzzaman et al.[10] stated that the flavonoid compound in *Apis dorsata* forest honey has the highest content, namely 65.65 mg catechin/kg) compared to *Apis melliera* forest honey (21.95 mg catechin/ kg) and *Apis cerana* forest honey (25.81 mg catechin/kg).

MATERIALS AND METHODS

Ethical Clearance

This study was approved by the Animal Care and Use Committee, Faculty of Veterinary Medicine, Universitas Airlangga with certificate number 1.KEH.041.04.2022.

Preparation of Experimental Animals

This study used 24 female Wistar rats (*Rattus norvegicus*) aged 3 months with an average body weight of 200 grams obtained from the Rattus Breeding Center, Malang, East Java, and they were acclimatized for 7 days. This study was divided into 4 treatment groups using a random sampling system so that each group consisted of 6 rats.

Forest Honey Preparation

The forest honey used in this study was forest honey that comes from *Apis dorsata* bees. The forest honey was administered after the rats were exposed to physical stress according to a predetermined dose based on the previous research[11] in which the dose value was converted to 2g/rat/day for treatment group 1, 4g/rat/day for treatment group 2, and 6g/rat/day for treatment group 3 for 14 days.

Treatment Procedure

The physical stress given was in the form of forced swimming[12] which was carried out on a drum with a height of 70 cm, a bottom diameter of 36 cm, and an upper diameter of 47 cm which was filled with water ¾ of the height of the drum for 5 minutes for 14 days. This study consisted of 4 treatment groups, namely C+ which was treated with swimming only; T1 which was treated with swimming and honey given using sonde 2g/rat/day; T2 treated with swimming and honey 4 g/rat/day and T3 treated with swimming and honey 6 g/rat/day. On the 15th day, the rats were terminated by dislocation of the cervical vertebrae. Next, liver histopathological preparations were made and viewed under a Nikon Eclipse-E100 light microscope. The research was conducted at the Faculty of Veterinary Medicine, Universitas Airlangga.

Data Analysis

The data obtained in the form of values on changes in the liver histopathological images of white rats (*Rattus norvegicus*) were arranged in tabular form and then analyzed. To find out different changes in the liver histopathological images of white rats, statistical tests were carried out using the Kruskal-Wallis test. The degree of change was processed using ranking research and if there was a significant difference, it continued with the Mann-Whitney test. All analyses were performed using computer software.

RESULTS

Based on the observation of liver histopathological images and the variables which are considered to represent pathological conditions in cells and tissues, the changes observed in this study are degeneration, necrosis, and congestion.

TABLE 1: Mean Rank ± SD of damage in rats (*Rattus norvegicus*) hepatocytes.

Group	Mean Rank ± SD		
	Degeneration	Necrosis	Congestion
C+	$3.44^{a} \pm 0.622$	$3.52^{a} \pm 0,109$	$1.76^{a} \pm 0.384$
T1	$1.13^{b} \pm 0.389$	$2.48^{c} \pm 0,438$	$0.84^{b} \pm 0.260$
T2	$3.72^{a} \pm 0.268$	$3.64^{ab} \pm 0,260$	$1.90^{a} \pm 0.400$
T3	$3.84^{a} \pm 0.167$	$3.88^{a} \pm 0,178$	$2.48^{a} \pm 0.840$

Different superscripts showed significant differences ($p<0.05$).

Based on table 1 on the results of the Mann-Whitney test analysis, showed that degeneration, necrosis, and congestion of the positive control group (C+) show significant differences with those of the T1 treatment group, but it does not show significant differences with those of the T2 and T3 treatment groups. The damage level of the T1 treatment group, which is treated with *Apis dorsata* forest honey at a dose of 2 g/rat/day shows a significant decrease compared to the positive control group (C+). This shows that *Apis dorsata* forest honey at a dose of 2 g/rat/day has antioxidants that can neutralize free radicals. The T2 and T3 treatment groups do not appear to have any significant differences compared to the control group. This shows that the dose of *Apis dorsata* forest honey also affects liver tissue or cells. The high dose of forest honey administered has a detrimental effect on the body.

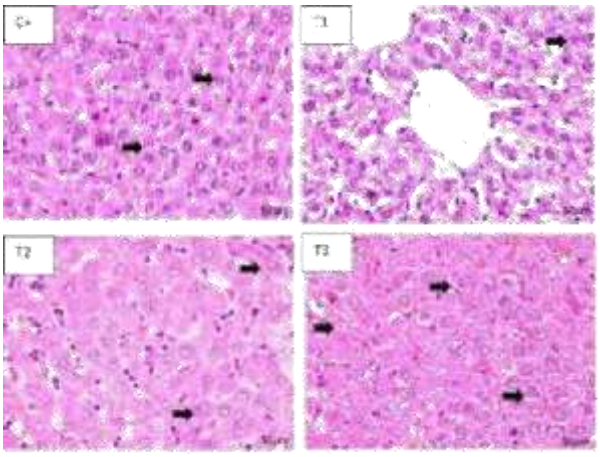

FIGURE 1: Liver histopathological images of white rats (*Rattus norvegicus*) that has degeneration in various treatment groups. C+ group is treated with only physical stress; the T1 group is treated with physical stress and honey 2 g/rat/day; the T2 group is treated with physical stress and honey 4 g/rat/day; the T3 group is treated with physical stress and honey 6 g/rat/day. The C+ group has the highest degeneration as many swollen cells are found. It is not significantly different from T2 and T3 groups as these groups have many swollen cells. Whereas, the T1 group has a low degeneration level as there is a decrease in swollen cells. The black arrow indicates hydropic degeneration (H&E Staining; Nikon Eclipse-E100, Magnification 400x).

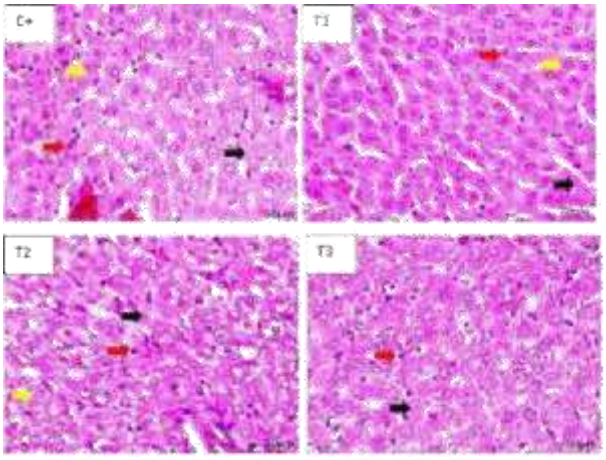

FIGURE 2: Liver histopathological images of white rats (Rattus norvegicus) that has necrosis in various treatment groups. C+ group is treated with only physical stress; the T1 group is treated with physical stress and honey 2 g/rat/day; the T2 group is treated with physical stress and honey 4 g/rat/day; the T3 group is treated with physical

stress and honey 6 g/rat/day. It shows that the C+ group has the highest necrosis level as the nucleus disappears, the nucleus is fragmented into small parts, and the nucleus is condensed. It is not significantly different from T2 and T3 groups as they show the same as the C+ group. Whereas, the T1 group has a low necrosis level as the nucleus disappears and there is a decrease in the nucleus which is fragmented into small parts as well as a condensed nucleus. The black arrow indicates karyolysis, the yellow arrow indicates karyorrhexis, and the red arrow indicates pyknosis. (H&E Staining; Nikon Eclipse-E100, Magnification 400x).

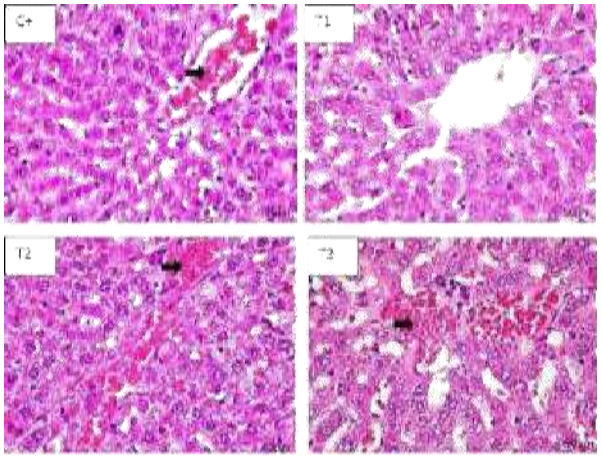

FIGURE 3: Liver histopathological images of white rats (Rattus norvegicus) that has congestion in various treatment groups. C+ group is treated with only physical stress; the T1 group is treated with physical stress and honey 2 g/rat/day; the T2 group is treated with physical stress and honey 4 g/rat/day; the T3 group is treated with physical stress and honey 6 g/rat/day. The C+ group has the highest congestion level as erythrocyte accumulation is found. It is not significantly different from T2 and T3 groups as there are many erythrocytes accumulated. Whereas there is no congestion in the C+ group as there is no erythrocyte accumulation. The black arrow indicates congestion. (H&E Staining; Nikon Eclipse-E100, Magnification 400x).

DISCUSSION

The positive control (C+) group showed quite high damage in the form of degeneration, necrosis, and congestion due to exposure to physical stress. It can be seen in Table 1 and Figures 1,2,3. Physical stress causes an increase in ROS in the body which will cause oxidative stress which cannot be neutralized by endogenous antioxidants13. As a result of insufficient endogenous antioxidants to combat oxidative stress that occurs in the body, lipid peroxidation cannot be prevented and causes damage to the liver tissue.

The body needs additional antioxidants to help fight oxidative damage. One of the antioxidants that have been proven to have a hepatoprotective effect is *Apis dorsata* forest, honey. This honey contains sufficiently high flavonoid compounds to prevent oxidative stress14. This is proven by the T1 treatment group that was treated with *Apis dorsata* honey using a sonde 2 g/rat/day which showed a significant difference ($p<0.05$) compared with the positive control group without being treated with *Apis dorsata* forest honey based on Table 1.

Flavonoid compounds help reduce the effects of free radicals as flavonoids have a role as an antioxidant by being a metal chelating agent and neutralizing ROS due to their double -OH group (>C=C<)15. The chelating role of flavonoids is to chelate Fe in the Fenton reaction in the oxidative phosphorylation process so that it cannot react with H2O2 (hydrogen peroxide) to form *OH (hydroxyl radicals) and reduce lipid peroxidation.

In addition, flavonoids also have a role as a ROS neutralizer by giving one of the H+ (hydrogen) ions to *O2 (superoxide) and LOO* (lipid peroxyl radical)16.

The choice of dose for Apis dorsata forest honey is very influential on the condition of liver tissue or cells. It is shown by the T2 group treated with Apis dorsata forest honey at a dose of 4g/rat/day and the T3 group treated with Apis dorsata forest honey at a dose of 6g/ rat/day which indicated damage and it was not significantly different ($p<0.05$) compared to the positive control group (C+) without being treated with Apis dorsata forest honey. Too high a dose can adversely affect hepatocytes17. This is in line with the statement of Wilson et al.18 which stated that consuming honey for a long time would increase the risk of liver damage, especially at high doses of honey. The duration of honey consumption and how much honey is consumed have an important role in the research results. The doses used in the T2 and T3 groups were too high for the body to accept, resulting in adverse effects on the body.

CONCLUSIONS

Based on the research which has been conducted, it can be concluded that the administration of Apis dorsata forest honey can repair the liver damage of rats (Rattus norvegicus) exposed to physical stress only for the T1 treatment group. Increasing the dose is not always followed by the level of cell repair.

ACKNOWLEDGMENT

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