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The Role Cardioprotective of Edible Bird's nest (*Collacalia fuciphaga*) Extract Through Suppression of Oxidative Stress

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ABSTRACT

Background: Heart organs can be damaged due to an increase in free radicals that are not balanced by antioxidants. Edible Bird's Nest (Collocalia fuciphaga) contains many amino acids and vitamins that are thought to stimulate antioxidant activity. The cardioprotective nature of swallow's nest is expected to be the basis of management for cases of heart disease.

Methods: The design of this study is experimental . This study showed levels of MDA (free radical decomposition), catalase activity (endogenous antioxidants) and histology of heart tissue after bieng given edible bird's nest extract (doses 10, 20 and 40 mg/kgBW) for 32 days.

Results: Edible Bird's extract was compared to the control: MDA levels decreased significantly (0.007; 0.038; 0.030 nmol/mg tissue), increased catalase activity (1.32; 1.21; 0.83 IU/mg tissue); Cardiomyocytes at 40x magnification showed a normal nucleus in the center.

Conclusion: Edible Bird's extract can suppress oxidative stress, through decreasing MDA, increasing catalase activity, and normal cardiomyocyte histology.

Keywords: Edible Bird's (Collocalia fuciphaga), Antioxidants, Free Radicals, Oxidative Stress, Heart

INTRODUCTION

Edible Bird's birds are insectivorous birds that can produce nests. Types of Edible Bird's nest that can be eaten and traded include *Colloccalia fuciphaga* (white nest) and *Colloccalia maxima* (black nest). Indonesia is the highest exporter of Edible Bird's nest in the world. The areas that produce the largest Edible Bird's nests in Indonesia are Central Java, East Java and West Java.[1] Edible Bird's nest is widely used by the Chinese community as a nutritional enhancer in food and medicine to increase endurance, increase cell proliferation, help with hormone formation, increase metabolism, anti-aging, and increase antioxidant activity in the body [1,2].

Edible Bird's nest contains carbohydrate components (sialic acid, galactosamine, glucosamine, galactose and fructose), essential amino acids (histidine, leucine, threonine, valine, methionine, and phenylalanine), non-essential amino acids (serine, aspartic, arginine, lysine. , and proline), fatty acids, and vitamins (vitamin A, vitamin D, vitamin E, and vitamin C) [3,4]. Edible Bird's nest has antiviral, antioxidant, and immune-boosting effects [5]. Edible Bird's nest extract can thicken the skin in the dermal layer, and increase the strength of femur bones due to an increase in calcium levels in the bones [2,5]. The nutritional content of bird's nest is affected by the place of breeding, temperature, and food intake [6].

Free radicals are unpaired compounds that are highly reactive and unstable, so to stabilize them they must bind to other molecules [5]. Free radicals normally exist in the body. If the excess free radicals in the body can cause damage to cells, tissues and organs [7,8].

The damage is exacerbated by exogenous factors such as UV rays, radioactivity, exposure to chemicals, drugs, insecticides, and others. As a result, there is oxidative stress (imbalance between oxidants and antioxidants) in cells [9]. Free radicals can act as both oxidants and reductants [10,11]. Physiologically, when free radicals are in the body, the body will carry out self-defense by triggering the release of antioxidants. However, if the balance between antioxidants and free radicals is disturbed, there will be an oxidative stress mechanism that will damage

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molecules, namely lipids, proteins, and nucleic acids, both in structure and function, resulting in oxidative damage to body cells that cause disease [12,13,14].

· Antioxidants are molecules that can donate electrons in order to neutralize free radicals, because antioxidants are low-molecular-weight and can interact with free radicals to break the chain of reactions before cell damage occurs in organs [15]. Antioxidants act as hydrogen donors, electron donors, and enzyme inhibitors. , and peroxide decomposers. Antioxidants are of two types, namely enzymatic (superoxide dismutase, catalase, and glutathione) and nonenzymatic (ascorbic acid, glutathione, melatonin, vitamin E, and uric acid) [15,16].

One of the ways of oxidative stress is when free radicals damage lipids which have double carbon bonds in the process of lipid peroxidation. The results of lipid peroxidation undergo decomposition to produce malondialdehyde (MDA) products. Increased MDA levels indicate an increasing number of free radicals in the body. Therefore, MDA is used as an indicator (biomarker) of oxidative stress in the body [10, 11].

Catalase, also called hydroperoxidase, is an endogenous enzymatic antioxidant that catalyzes free radicals, namely hydrogen peroxide (H_2O_2) into water (H_2O) and oxygen (O_2), thus helping to prevent oxidative stress and tissue damage [16,17]. The catalase enzyme is found in large quantities in in the blood, bone marrow, mucous membranes, kidneys, and liver, and in small amounts in the brain, heart, and skeletal muscle [18,19].

The heart is one of the vital organs whose function is to pump blood throughout the body. All components in the blood such as oxygen, nutrients and free radical compounds will be distributed throughout the body. Thus, free radicals can affect organ function, one of which is the heart. This causes damage to the tissue or cells, thus triggering disease and heart defects [18]. Blood basically has several components that the body needs, and functions as a substance dealer, namely metabolism, oxygen, and the results of metabolic processes in the form of free radicals that are distributed through the body's blood vessels [19]. Free radicals circulating in the body can affect organ function, one of which is is an organ of the heart, which can cause heart cell damage due to oxidative stress that triggers heart disease which disrupts its physiological function [20].

Antioxidants are substances that can protect the body from free radicals. Antioxidants consist of endogenous antioxidants (in the body) and exogenous antioxidants (outside the body). The mechanism of antioxidants is to capture free radicals and inhibit free radical oxidation activity by inhibiting radical formation [8].

This cardioprotective effect study was conducted with the aim of knowing the ability of bird's nest to protect the heart from damage. The parameter used was the measurement of the MDA level and catalase enzyme activity of the heart organ in sprague dawley rats. This is to determine the role of Edible Bird's nest as a cardioprotective from oxidative stress..

MATERIALS AND METHODS

The design used in this study is an experimental design. Measurement of MDA levels, catalase activity and cardiac histology images were carried out at the Biochemistry and Histology Laboratory of the Faculty of Medicine, State Islamic University Syarif Hidayatullah, Jakarta, Indonesia. There were 5 treatment groups for 32 days and the 31st and 32nd day were given H_2O_2 1% orally. The treatment groups were as follows: positive control (vitamin E 1000 IU 4.08 ml/g), normal (without being given anything), Doses of Edible Bird's nest extract 10, 20 and 40 mg/KgBW of sprague dawley rats.

The mice were terminated according to a procedure using ether in a closed tube and the heart was weighed. The partially obtained heart was put in a buffer solution of 10% formalin to observe the histology of the tissue and as much as 25 mg in PBS pH 7,4 of tissue was homogenated to measure MDA levels and catalase activity. Data were analyzed using ANOVA or Kruskal Wallis test dependent on result of the distribution was normal or homogeneous using the SPSS version 23 program.

The Measurement of MDA Levels. The 250 µl homogenate was put in a test tube, then added with 500 µl of cold 10% TCA solution. Centrifugation at 4000 rpm for ten minutes. The supernatant was taken and transferred to another tube and 750 µl of 0.67% TBA solution was added. Incubate at 100oC for ten minutes. After cooling, the absorbance was read using a spectophotometer with a wavelength of 532 nm. The calculate the MDA level using the standard MDA curve.

The Measurement of Catalase Activity. The volume 50 µl of heart tissue homogenate was added to the microtube and then 50 µl of PBS 7.4 solution was added, and 950 l of H_2O_2 solution. Read the absorbance with a UV spectrophotometer with a wavelength of 240 nm at 0.1, 2, and 3 minutes. The calculate the catalase activity using the standard MDA curve.

Preparation of Histology and Hematoxylin-Eosin (HE) Staining. After being fixed in a formalin buffer, the tissue was dehydrated in graded alcohol. Furthermore, the clearing process is carried out in alcohol-toluol (1: 1); then the embedding process in the toluol-paraffin mixture overnight at a temperature of 60°C. The tissue is made of Paraffin blocks and cuts after freezing using a microtome. The tissue was subjected to a HE staining process and observed under a microscope.

RESULTS

The results of measuring MDA levels and catalase activity after giving Edible Bird's nest extract can be seen in Figure 1. The lowest cardiac MDA levels in the group giving Edible Bird's nest extract at doses of 10, 20 and 40

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mg/kg BW had MDA levels lower than the normal and positive groups. The low levels of MDA in the group giving Edible Bird's nest extract indicated the presence of antioxidants in the bird's nest. The lowest catalase activity was in the treatment group given the highest dose of Edible Bird's nest extract, namely 40 mg/KgBB, the highest catalase activity was in the treatment group given the lowest dose of Edible Bird's nest extract, namely 10 mg/ kgBW, followed by moderate dose of Edible Bird's nest extract 20 mg/KgBW. Based on the results of this study, it was found that the highest endogenous catalase antioxidant activity was found in the provision of low-dose Edible Bird's nest extract of 10 mg/KgBW, while the lowest endogenous catalase antioxidant activity was in the high-dose Edible Bird's nest extract of 40 mg/KgBW compared to positive control. The results of the Pearson correlation test showed a weakly tive correlation (R = 0.426). The higher the catalase activity in the Edible Bird's nest extract, the lower the MDA levels. Pearson correlation test results showed a strong negative relationship, because the higher the MDA level the catalase activity of the jatropha seed extract. It is possible that this enzyme works directly as an antioxidant to prevent lipid peroxidation.

The Qualitative observations of the histology of heart tissue can be seen in Figure 1. In this study, the histology of heart tissue is shown, the treatment of swallow's nest extract with low (10 mg / KgBW) and high (40 mg / KgBW) doses as a representation of the description of all treatment groups. The results showed that in general the shape of the cardiomyocyte cell membrane was normal and had a nucleus in good condition in the middle of the cytoplasm.

DISCUSSION

Antioxidants are substances that play a role in regulating free radicals and inhibiting the production of ROS by capturing radical compounds [7]. Endogenous antioxidants are antioxidants that come from the body, namely the enzymes superoxide dismutase (SOD), GSH-Px, catalase, and others. The Edible Bird's nest contains several types of vitamins, namely vitamin A, vitamin C and vitamin E which act as exogenous antioxidants [21]. The increase in the activity of the catalase enzyme, which acts as an endogenous antioxidant, can inhibit the formation of MDA in the lipid peroxidation process, thereby reducing MDA levels.

Free radicals are unpaired compounds that are highly reactive and unstable, so they require compounds that can make them unreactive and stable [22]. A type of free radical that is highly reactive is reaction oxygen species (ROS). This study used H_2O_2 as a form of non-reactive radical compound which was induced intramuscularly to test animals. Determination of the concentration of H_2O_2 given for two days is based on inducing free radicals and damaging liver tissue [21]. Giving Edible Bird's nest extract for 23 days has been able to provide an endogenous antioxidant effect that acts as a protector of organ tissues. H_2O_2 is a type of non-reactive radical that can trigger oxidative stress if it cannot be compensated for by catalase and GSH-Px which can break down H_2O_2 into stable compounds (water and oxygen). As a result, cleaning and formation of ROS are unbalanced, leading to a tendency for the formation of ROS which can cause damage to organs, one of which is the heart [23]. Hydrogen peroxide can significantly increase MDA levels in Schwann cells, thus indicating oxidative stress [24]. Oxidative stress is a marker the presence of excess ROS in the lipid peroxidation process. The lipid peroxidation process produces a product in the form of MDA which acts as a biomarker of oxidative stress.

In this study, the levels of MDA in the rat heart decreased significantly when giving Edible Bird's nest extract at a dose of 10, 20, and 40 mg/kg. This indicates a decrease in the lipid peroxidation process due to the role of amino acids and vitamins (vitamin A, vitamin C, vitamin D) in Edible Bird's nest as antioxidants. This study is in accordance with previous research on the content of amino acids and vitamins in Edible Bird's nest extract which can significantly increase the activity of SOD and catalase enzymes and reduce MDA levels in Drosophila melanogaster (Hu et al, 2016). Giving Edible Bird's nest extract at a dose of 30 mg/kgBB and 60 mg/kgBW can also significantly reduce MDA levels in mice [25]. Giving Edible Bird's nest extract at a dose of 3.4 mg/ml can significantly reduce MDA. The administration of vitamin C and Portulaca oleracea extract in mice significantly reduced MDA levels in the rat heart compared to the control group. This Portulaca oleracea extract has the same active compound as Edible Bird's nest [26].

This shows that the combination of vitamin C and vitamin E in Edible Bird's nest in the Edible Bird's nest extract group can significantly reduce MDA levels. Thus, the role of vitamin E in binding radical compounds in the form of hydroxyl compounds, lipid radicals, lipid peroxide radicals and other forms is helped by the presence of vitamin C (ascorbic acid). Vitamin C is an antioxidant that can bind to vitamin E radical compounds (tocopherol) to return to stable compounds (vitamin E), while vitamin C radicals can return to vitamin C with the help of the 4-hydroxyphenylpyruvate dioxygenase enzyme in the body In Edible Bird's nest extract dose 20 mg/ kgBW and 40 mg/kgBW showed higher MDA levels than the 10 mg/kgBW dose group. Vitamin C can act as an antioxidant and pro-oxidant [10]. Too high levels of vitamin C can result in the formation of oxidants (vitamin C radicals) higher than their role as an antioxidant. So, at doses of 20 and 40 mg/kgBW began to show results of higher MDA levels compared to doses of 10 mg/ KgBW. This study showed that giving Edible Bird's nest extract at a dose of 10 mg/kgBB for 30 days which was induced by H_2O_2 on the 31st and 32nd day reduced MDA levels better.

Antioxidants are substances that inhibit oxidative damage by inhibiting free radical activity. Antioxidants act as radical scavenger, hydrogen donors,

enzyme inhibitors, and peroxide decomposers. The classification of antioxidants is of three types, namely based on enzymes, their source, and their actions. Antioxidants are based on enzymes, namely enzymatic and non-enzymatic, and both are present in intracellular and extracellular forms. Enzymatic antioxidants consist of superoxide dismutase (SOD), catalase, and the glutathione system. Meanwhile, non-enzymatic antioxidants consist

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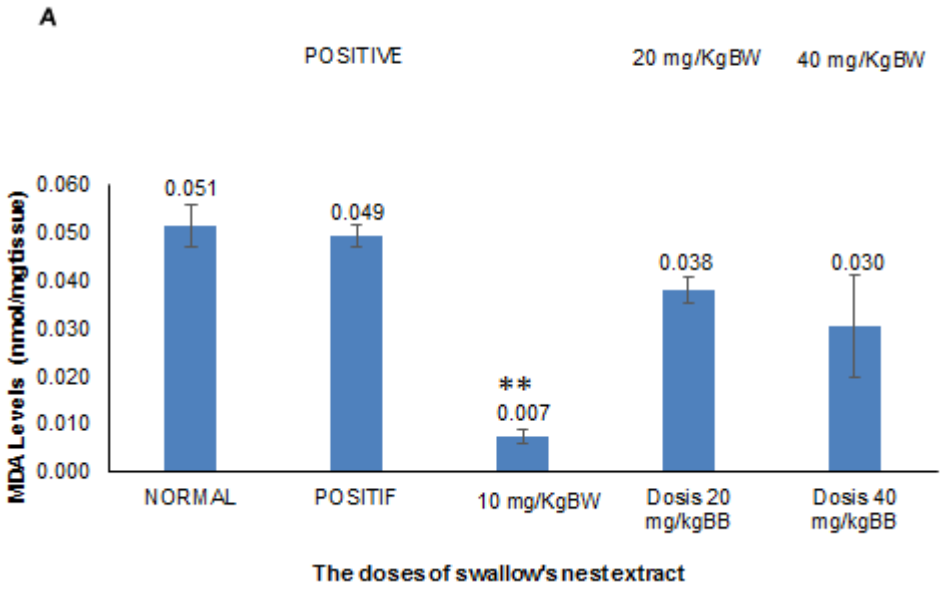
of ascorbic acid, glutathione, melatonin, and vitamin E. Antioxidants are based on the source, which consists of exogenous and endogenous. Exogenous antioxidants are ascorbic acid, vitamin E, beta carotene, lycopene, lutein, zinc, and selenium. And endogenous antioxidants, namely superoxide dismutase, catalase, glutathione peroxide, glutathione reductase, glucose-6-phosphate dehydrogenase, vitamin A, glutathione, and coenzymes. On the basis of its action, antioxidants are divided into preventive antioxidants which aim to reduce the rate of chain reaction initiation consisting of catalase, glutathione peroxidase, and selenium, and chain-breaking antioxidants which act in disrupting the propagation of chain reactions consisting of superoxide dismutase and vitamin E. Increased enzyme activity catalase which acts as an endogenous enzymatic antioxidant can inhibit the formation of free radicals, thereby preventing the occurrence of oxidative stress [27,28].

Free radicals are the product of normal cellular metabolism and the result of abnormal reactions stimulated by disease, metabolism, and the induction of xenobiotics [10]. Free radicals are in the form of compounds that have no electron paired, are unstable, and highly reactive. One of the most reactive and damaging free radicals is ROS, especially superoxide, O^{2-}, hydroxyl, OH•, and perihidroxyl. Hydrogen peroxide is a non-radical compound, reactive, and can trigger oxidative stress if it is not catalyzed by the enzyme catalase and GSH-Px. If H_2O_2 is broken down, it will become water and oxygen. If peroksida is not catalyzed, a lipid peroxidation mechanism will arise, which is a process that involves a secondary source of free radicals, reacting with other molecules, giving rise to biochemical lesions. The process of lipid peroxidation can occur in cell membranes, in double-chain saturated fatty acids, and one of them is in the heart organ [27,28].

Pro-oxidants are reactions and chemical compounds that have the potential to give rise to toxic oxygen species, and work against antioxidants. Normally, the amount of antioxidants and pro-oxidants is balanced. However, when there is an imbalance, antioxidants can also turn into pro-oxidants, namely ascorbate which reacts with superoxide and hydroxyl to produce monodehydroascorbate and hydrogen peroxide, ascorbate reacts with oxygen which is a source of superoxide radicals, and ascorbate reacts with Cu^{2+} ions to become hydroxyl radicals. If this imbalance persists, it will lead to oxidative stress and cell damage [28].

Catalase enzyme (CAT) is an endogenous, enzymatic, and preventive antioxidant. Catalase enzymes work by catalyzing H_2O_2 into H_2O and O_2. This enzyme can oxidize 1 molecule of hydrogen peroxide to oxygen, and this enzyme will reduce the second hydrogen peroxide molecule to water simultaneously. There are two mechanisms of the catalase enzyme as an antioxidant, namely catalytically and perosidatically. Catalytically, the catalase enzyme will use the hydrogen peroxide (H_2O_2) molecule as a substrate or electron donor, and other H_2O_2 molecules as an oxidant or electron acceptor [24, 25]. And this shows that H_2O_2 is the substrate of the catalase enzyme. Peroxidatically, this occurs when 1 H_2O_2 molecule is used as an electron acceptor and other compounds as electron donors.



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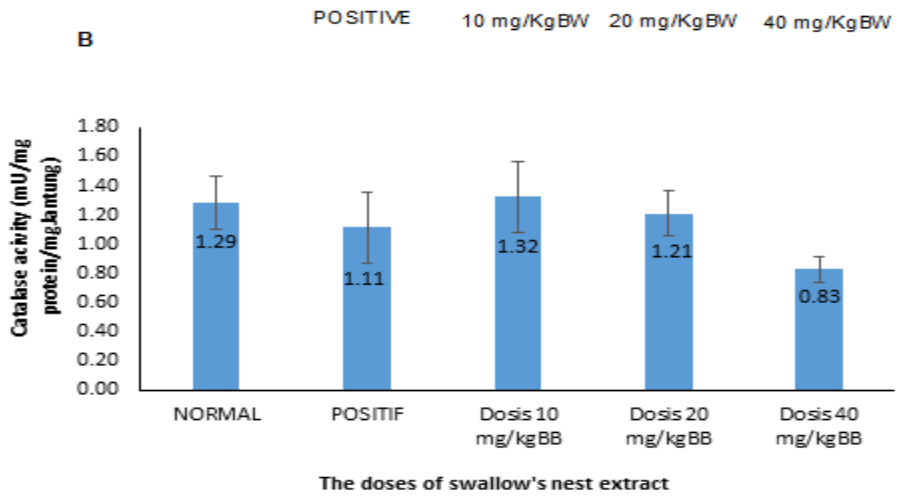

Figure 1: (A) The heart MDA levels after being given swallow's nest extract (ANOVA, p <0, 01). (B) The cardiac catalase activity after being given swallow's nest extract (Kruskal-Wallis, p> 0.05). Results of the correlation between MDA levels and catalase activity showed a low positive correlation (Pearson Corelation; R = 0.426).

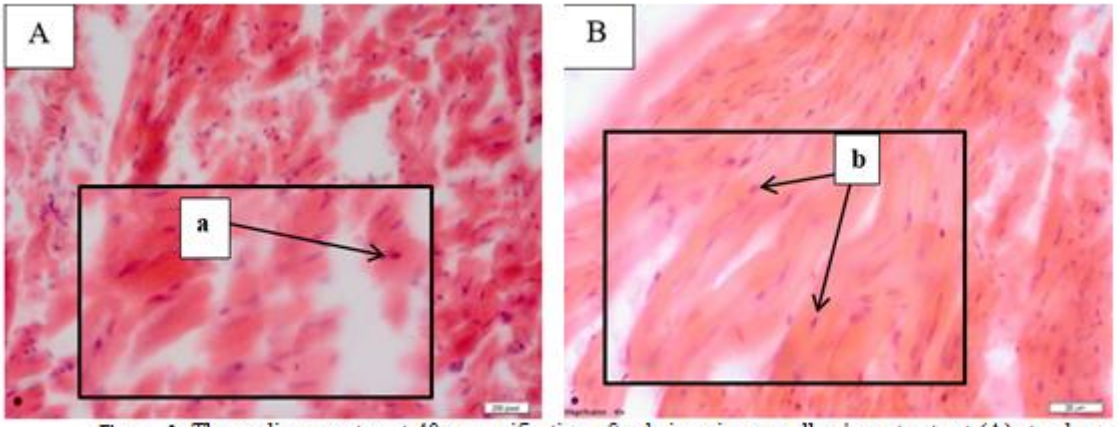

Figure 2: The cardiomyocytes at 40x magnification after being given swallow's nest extract (A) at a dose of 10 mg / kgBB (B) a dose of 40 mg / kgBB. Arrows (a) and (b) normal nucleus in the middle.

Compounds that can be electron donors are methanol, ethanol, formic acid, and nitrite ions.Previous research showed that Edible Bird's nest extract (Collocalia fuciphaga) in Drosophila melanogaster can significantly increase the activity of the enzyme catalase [27,29].

In the positive control group (giving H_2O_2 and vitamin E), it can be seen that CAT levels are lower than the low (10 mg / kgBW) and moderate (20 mg / kgBW) doses, and higher than the high doses. This is because ascorbic acid reduces vitamin E radicals, so that it becomes vitamin E, and the ascorbic acid that is left behind will bind to free iron and trigger the Fenton reaction, which causes radical compounds. The combination of vitamin C and vitamin E from high doses of bird's nest extract can trigger a decrease in catalase activity, and the combination of vitamin C and vitamin E in low-dose Edible Bird's nest extract does not cause a decrease in catalase activity because it is in optimal and balanced levels, so it doesn't trigger the addition of oxidants. Vitamin C or ascorbic acid has a mechanism as an antioxidant or pro-oxidant. The pro-oxidant properties of ascorbate will arise if the levels are in high doses, where excess ascorbate will react with free iron and a Fenton reaction occurs, causing radical compounds. These free radical compounds will trigger oxidative stress and damage the molecular structure of cells, one of which is an enzyme, so that the enzyme will be damaged and decrease its work activity [28,29].

The Edible Bird's nest extract (*Collocalia fuciphaga*) high doses (40 mg / kgBW), it was found that the results of catalase activity were lower than the positive control due to the vitamin C content that was too high at high doses. Ascorbic acid can act as an antioxidant or pro-oxidant, if the level of ascorbic acid is too high, it will trigger the formation of pro-oxidants so that there will be an imbalance in the amount of antioxidants and pro-oxidants, so that the research shows that in giving high doses of bird's nest extract, there is a decrease in the antioxidant activity of the catalase enzyme due to an increase in pro-oxidant vitamin C [25,27,28].

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The histological image of cardiomyocytes can be assessed from the cell nucleus and cytoplasm. Normal cytoplasm has the characteristics of being homogeneous and not experiencing swelling [30]. Preparations of treated heart tissue at doses of 10 mg/kgBW and 40 mg/kgBW indicate normal cell nucleus and cytoplasm conditions (Figure 1). The results of these preparations are supported by other research that the administration of Edible Bird's nest extract at a dose of 30 mg/ kg and 60 mg/kg of body weight does not cause damage to the liver tissue of rats.

CONCLUSION

Edible Bird's extract can suppress oxidative stress, through decreasing MDA, increasing catalase activity, and normal cardiomyocyte histology. The lowest levels of MDA and increase catalase activity in the heart of Sprague dawley rats were significantly given 10 mg/KgBW of Edible bird's nest extract. The heart tissue of Sprague dawley rats is not damaged were given bird's nest extract..

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CONFLICTS OF INTEREST

There are no conflicts of interest.

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