

Cardioprotective effect of virgin coconut oil (VCO) on rats induced by doxorubicin

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Article History:

Received on: 20 Jun 2019

Revised on: 28 Aug 2019

Accepted on: 07 Sep 2019

Keywords:

Cardioprotective,
virgin coconut oil,
Creatinin kinase - MB,
Lactate dehydrogenase

ABSTRACT

Cardiotoxicity is caused by anticancer drugs, one of the anticancer drug is doxorubicin. doxorubicin triggered free radicals reaction in heart muscle cells this results in the death of heart muscle cells or cardiomyopathy, in this condition, the heart can't pump blood properly and caused heart failure, virgin coconut oil (VCO) has antioxidant such as polyphenol that can neutralize the free radicals formed by doxorubicin. The aimed of this research was to evaluate the activity of cardioprotective effect of VCO on rats by induced doxorubicin with accumulative dose of 15 mg/kgbw for 21 days, by administering a 5 mg/kgbw dose in a week, and for 21 days of the rats given doses 2 VCO ml, 4 ml and 6 ml subsequently conducted an examination of CK-MB and LDH in the blood. The result showed that the effect cardioprotective from VCO reduce the levels of serum CK-MB (Creatinin kinase - MB) and the LDH (Lactate dehydrogenase) as the biomarker of heart. Group dose 6 ml showed the level of CK-MB $2110.37 \pm 184,173$ mg/dl and the level of LDH 2903.9 ± 70.0743 mg/dl and differ significantly ($p < 0.05$) with the negative control group induced doxorubicin. VCO is highly recommended to be food supplements for the patient used anti-cancer.



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ISSN: 2456-818X

DOI: <https://doi.org/10.26452/jibps.v4i3.1430>



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INTRODUCTION

Cardiovascular disease and cancer is the leading cause of death worldwide. In the United States, Cardiovascular disease and cancer is the highest contributor towards chronic disease burden, estimated each of 14 - 15 million people with cardiovascular symptoms and a history of cancer and this number continues to rise along with the increase of the population. Factors affecting the increase including lifestyles, such as diet, physical activity, smoking,

and less alcoholism [1, 2].

Although in General cardiovascular disease (CVD) and cancer are considered as two separate types of diseases, but they have similarities and the possibility of mutual interaction, including some of the same risks such as obesity, hyperglycemia, hypertension, smoking, frequent exposure to oxidants, alcohol consumption, hypertriglyceridemia, radiation, microbes, viruses and bacteria, chronic diseases and autoimmune disease that induces inflammation, in which the role of inflammation is to promote carcinogenesis and the development of tumors. Risk factors of cardiovascular disease have a major impact on the related cardiotoxicity on the treatment of cancer drug. [1]

Doxorubicin (DOX) are anthracyclines, a chemotherapy agent that is widely used and is now part of a standard therapy regimen for different types of cancer such as hematopoietic cancer, breast cancer, ovarian cancer, and thyroid cancer. Doxorubicin triggered free radicals reaction in heart muscle cells these results in the death of heart muscle cells or

cardiomyopathy, in this condition, the heart can't pump blood properly and caused heart failure [3].

VCO is beneficial for the skin and hair care, stress relief, weight loss, lowering cholesterol and blood fat levels, immunomodulatory effect, keeping stable blood pressure, circulatory disorders and Alzheimer's disease, anti-inflammation, analgesic and antipyretic [4].

High polyphenol content in virgin coconut oil was able to maintain a normal level of parameters in the tissue and serum, and increasing antioxidant enzyme such as SOD and GSH so that can bind into reactive oxygen in plasma and peroxidation in microsomal lipids [4]. Figure 1

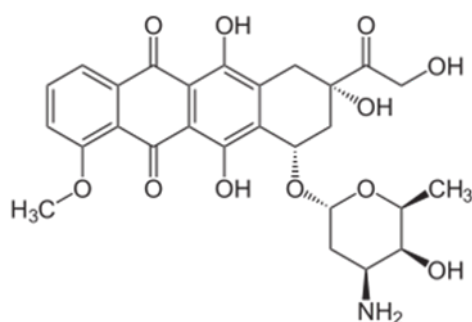


Figure 1: Structure of doxorubicin

MATERIALS AND METHODS

Material

Microplate Reader, pH meter (OHAUS Starter300 Portable) Beaker glass (IWAKI CTE33), Multiskan Go Reader (Thermo Fisher Scientific 1510), analytical measure, Eppendorf tube, vial 1 ml, Spatula, Micropipet (1-10 μ L, 50-200 μ L, 100-1000 μ L) (Eppendorf), Termometer, automated plate washer, VCO (Indonesian Palm Oil), Ketamine (Sigma P-4417), Doxorubicin (Merck 109057), CMC-Na (Sigma P-4417).

Animals

Animals used in research is a rat (*Rattus norvegicus*) Wistar male 150 – 200 g. Before the study began, animal test adjusted for one week with the condition of the room temperature (22-25°C), under the cycle of 12 hours light/ dark, given the food and the drinking water. Ethics Commission from health and science commission, University of Sumatera Utara.

In vivo test cardioprotective effect of VCO

In vivo tested in an experiment by using 25 Wistar rats (*Rattus norvegicus*) male and weight 150 g - 200 g, as many as 25 and divided into 5 groups and each group consisted of 5 rats :

Normal : Suspension Na-CMC.

Negative control : Wistar rats (*Rattus norvegicus*) male induced by doxorubicin 15 mg/kgbw.

Group 2 ml VCO : Wistar rats (*Rattus norvegicus*) male induced by doxorubicin 15 mg/kgbw + 2 ml of VCO.

Group 4 ml VCO : Wistar rats (*Rattus norvegicus*) male induced by doxorubicin 15 mg/kgbw + 4 ml of VCO.

Group 6 ml VCO : Wistar rats (*Rattus norvegicus*) male induced by doxorubicin 15 mg/kgbw + 6 ml of VCO.

Rat induced by doxorubicin with an accumulative dose of 15 mg/kgbw over for 21 days, with the dose of administered 5 mg/kgbw once a week. Before treatment, the rats adapted for 14 days and then continued with the administered of doxorubicin and the treatment of rats for 21 days administered by the VCO with a dose of 2 ml, 4 ml, and 6 ml. on the last day of treatment the rats fasting 18 hours before performed surgery on the animal test. Rats administered by ketamine 70 mg/kgbw an intraperitoneal then continued to the surgery. Thoracic dissected and the blood was taken as much as 3 ml. The blood transferred into a microtube. Then the blood is centrifuged for 10 minutes at 3000-4000 rpm until it dived into 2 layers as serum and supernatant. A layer of serum is taken 1 ml and put into microtubes and stored in the refrigerator at a temperature of -4°C. Blood serum used to determine CK-MB, and LDH [5].

Determine of CK-MB and LDH

Measurement of the levels of CK-MB and LDH is performed by following the method described by Adeyemi, et al. (2015). As many as 50 μ l samples and 500 μ l of CK-MB reagent/LDH mixed in a test tube. Then the initial absorbance read after 1 minute at a wavelength of 340 nm. Next, the absorbance was measured again after 1, 2, and 3 minutes [5].

Statistical analysis

Test analysis was carried out by using one-way analysis of variance (ANOVA) followed by Post Hoc Test using the Tukey HSD test. P<0.05 was considered as statistical significance.

RESULT AND DISCUSSION

Result of CK-MB level

In this research, conducted an examination of CK-MB from the blood of rats. Results of serum CK-MB are obtained can be seen in Table 1.

Based on the known tables that the mean value of serum CK-MB level for the normal group is still in

Table 1: CK-MB level

No.	Doses	Mean CK-MB \pm SD (mg/dl)
1.	Normal	1180.5 \pm 42.5395
2.	Negative control	4706.97 \pm 283.111
3.	Group 2 ml VCO	2504.78 \pm 80.0021
4.	Group 4 ml VCO	2156.48 \pm 120.738
5.	Group 6 ml VCO	2110.37 \pm 184.173

The data presented in the form of Mean \pm SD. Data obtained results based on the results of the statistical tests, the levels of serum CK-MB normal have a significant difference ($p < 0.05$) with the negative control group, treatment group 2 ml dose, 4 ml dose treatment group, and 6 ml dose treatment group.

the range of normal values of 1180.5 mg/dl. A negative control group has a mean of serum CK-MB of 4706.97 mg/dl. 2 ml dose treatment groups of the VCO has a mean value of serum CK-MB of 2504.78 mg/dl. Dose treatment groups of 4 ml VCO has a mean value of serum CK-MB of 2156.48 mg/dl. Dose treatment groups of 6 ml VCO has a mean value of serum of 2110.37 mg/dl. Based on the known tables the highest mean of serum CK-MB in treatment group namely 2504.78 mg/dl in 2 ml dose treatment groups of the VCO. And the lowest mean serum CK-MB in treatment groups namely 2110.37 mg/dl in group treatment dosing 6 ml VCO. In addition, the bar chart can be seen in Figure 2.

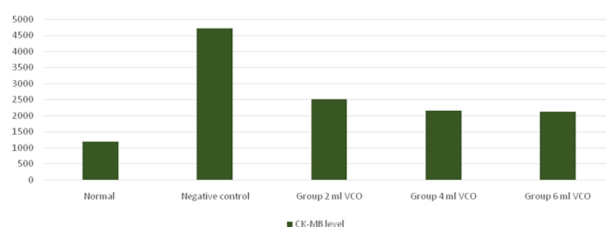
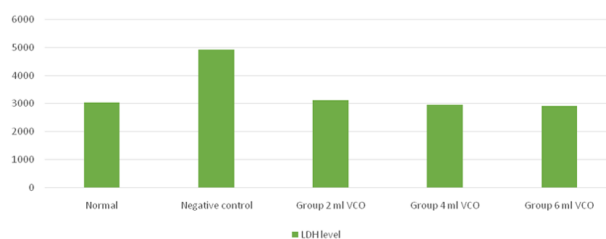
Result of LDH level

In this research, conducted an examination of LDH from the blood of rats. Results of serum LDH are obtained can be seen in Table 2.

Based on the known tables that the mean value of serum LDH level for the normal group is still in the range of normal values of 3026.15 mg/dl. A negative control group has a mean of serum LDH of 4912.15 mg/dl. 2 ml dose treatment groups of the VCO has a mean value of serum LDH of 3111.45 mg/dl. Dose treatment groups of 4 ml VCO has a mean value of serum LDH of 2951.95 mg/dl. Dose treatment groups of 6 ml VCO has a mean value of serum of 2903.9 mg/dl. Based on the known tables the highest mean of serum LDH in treatment group namely 3111.45 mg/dl in 2 ml dose treatment groups of the VCO. And the mean lowest serum LDH in treatment groups namely 2903.9 mg/dl in group treatment dosing 6 ml VCO. In addition, the bar chart can be seen in Figure 3.

Increased oxidative stress by doxorubicin caused damage to mitochondria, increases fat oxidation, and causes damage to heart cells. Cardiac cell strain is characterized by an increase in cardiac biomarkers including CK-MB and LDH.

In this study in the positive control group that was induced by doxorubicin CK-MB enzyme and LDH

**Figure 2: CK-MB level****Figure 3: LDH level**

increased, this was caused by damage to the heart muscle cells by doxorubicin. CK-MB is a biomarker that is widely found in heart muscle tissue compared to other tissues. The increase in CK-MB indicates the occurrence of damage to myocardial muscle cells caused by the production of reactive oxygenase (ROS) which increases because of doxorubicin, ROS rapidly damages the heart muscle cells. In this study, there were an increase in serum LDH (Lactate dehydrogenase) levels in the positive control group of doxorubicin induction compared to the negative (normal) and other treatment groups. LDH is an enzyme that is widely found in muscle tissue including the heart, kidneys, and liver. Increased serum LDH levels indicate damage to muscle tissue and in this study damage to heart muscle cells due to doxorubicin so that LDH levels increase [6].

This research was conducted to find out the effect of administration VCO against CK-MB and LDH level due to the toxicity of doxorubicin. Given in multiple doses to know the VCO can reduce heart damage caused by doxorubicin toxicity, CK-MB and LDH as indicators that decreasing of CK-MB and LDH level indicate that the VCO helpful reduced damage to the

Table 2: LDH level

No.	Doses	Mean LDH \pm SD (mg/dl)
1.	Normal	3026.15 \pm 248.124
2.	Control negative	4912.15 \pm 154.786
3.	Group 2 ml VCO	3111.45 \pm 127.35
4.	Group 4 ml VCO	2951.95 \pm 144.25
5.	Group 6 ml VCO	2903.9 \pm 70.0743

The data presented in the form of Mean \pm SD. data obtained results based on the results of the statistical tests, the levels of serum LDH normal have a significant difference ($p < 0.05$) with the negative control group, treatment group 2 ml dose, 4 ml dose treatment group, and 6 ml dose treatment group.

heart of a rat [7].

Doxorubicin is an anthracycline class of drugs that are widely used as an anticancer drug but doxorubicin can cause cardiotoxicity so the use of doxorubicin is clinically limited. Cardiotoxicity caused by doxorubicin can be an arrhythmia, cardiomyopathy, right ventricular heart failure and congestive heart failure [8].

Oxidative stress is the biggest factor that causes cardiotoxicity imbalance between reactive oxygenase species (ROS) and endogenous antioxidants increasing oxidative stress. Doxorubicin at a dose of 500 mg / m² increases oxidative stress. Cardiomyocytes are very much found in mitochondria, and ROS is mostly produced in mitochondria. In mitochondria, doxorubicin is converted into semiquinone which has one free electron and can act with O₂ to form -O superoxide anion (oxidative stress). In the presence of endogenous antioxidants SOD (Superoxide dismutase) converts oxidative stress to more stable and less toxic H₂O₂ [8].

The group giving doses of 2 ml, 4 ml, and 6 ml of VCO affected reducing serum levels of CK-MB and LDH in male Wistar (*Rattus norvegicus*) mice induced by doxorubicin. VCO contains medium chain fatty acid (MCFA) and binds polyphenol antioxidants. According to research [9] polyphenols contained in VCO are gallic acid, ferulic acid, quercetin, alpha-tocopherol, and metylcatecin. The ferulic acids found in VCO increase endogenous antioxidants in the body including SOD and GSH. Endogenous antioxidant enhancements including SOD will neutralize the -O superoxide anion formed by doxorubicin. [10]

VCO possess a promising hepatoprotective effect and this hepatoprotective effect of VCO may be attributed, partly to its antioxidant activity [11]. Virgin coconut oil (VCO), known in Indonesia as "minyak kelapa murni", is one type of coconut oil that has recently gain a lot of attention due to various claimed medicinal values, such as antioxi-

dant, antimicrobial, antiviral, antihypercholesterol and antithrombotic activities, administration of VCO is capable of increasing antioxidant enzymes and reduces lipid peroxidation content [12]. According to [10] VCO is organic and produced through a low heat process from freshly harvested, hand-selected organically grown coconut. This cold process extraction conserves all of the functional components of coconuts (i.e., tocopherols, sterols, and squalene) and, at the same time, also maintained the structure of its fatty acid as no polymerization takes place. This accounts for the preservation of most of its natural antioxidants properties [9]. According to Van Immerseel *et al.* [13], lauric oil, a saturated carbon-12 medium chain fatty acid, encompasses the majority (48%– 50%) of the nutritional content of VCO followed by a considerable amount of short-chain fatty acids such as capric, caproic, and caprylic acids that has antioxidant activities its can reduce the level of CK-MB and LDH.

CONCLUSION

Virgin coconut oil has antioxidant compounds that can neutralize the reactive oxygen species produced by doxorubicin. This study that the effect of virgin coconut oils can reduce the production of CK-MB and LDH in the rats after induced by doxorubicin, Group dose 6 ml showed the level of CK-MB 2110.37 \pm 184,173 mg/dl and the level of LDH 2903.9 \pm 70.0743 mg/dl and differ significantly ($p < 0.05$) with the negative control group induced doxorubicin. VCO is highly recommended to be food supplements for the patient used anti-cancer.

Funding Support

The authors declare that they have no funding support for this study.

Conflict of Interest

The authors declare that they have no conflict of interest.

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Cite this article: Sukirman Lie, Nyoman Ehrich Lister I., Edy Fachrial, Jenny. **Cardioprotective effect of virgin coconut oil (VCO) on rats induced by doxorubicin.** *J Inv. Bio. Pharm. Sci.* 2019; 4(3): 1-5.

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