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Lipid Profile and Malondialdehyde (MDA) Level after Administration of *Syzygium aromaticum* in Sprague Dawley Rats with Dyslipidemia

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Abstract
Dyslipidemia leads the process of oxidative stress and increased the levels of malondialdehyde (MDA). Syzygium aromaticum has an antioxidant effect and lowering lipid profile. This study aims to evaluate the changes in MDA level after administration of Syzygium aromaticum in various doses of administration. 30 male Sprague Dawley rats are divided into 6 groups: normal group (normal diet), negative control (high fat diet/HFD only), positive control (HFD and simvastatin), group 1 (HFD and Syzygium aromaticum 150mg/body weight) group 2 (HFD and Syzygium aromaticum 250mg/body weight) and group 3 (HFD and Syzygium aromaticum 500mg/body weight). The evaluation of lipid profile was performed pre and post experimental procedure (day 0 and day 42). After six weeks rats were terminazed by ketamine-xylazin injection intramuscularly, and had their liver collected for the examination of MDA levels. One-way anova test showed significant differences in lowering MDA levels in groups 2 dan 3 (HFD and Syzygium aromaticum doses 250 and 500mg/KgBB). It can be concluded that the administration of Syzygium aromaticum extract aromaticum reduced oxidative stress with MDA parameters.

Keywords: MDA, Dyslipidemia, Syzygium Aromaticum

1. Introduction

Dyslipidemia is a lipoprotein metabolism disorder, characterized by an increase in total cholesterol, low-density lipoprotein cholesterol, triglyceride levels, and, or a decrease in high-density lipoprotein cholesterol levels (Lao et al., 2021). Previous research has proven that dyslipidemia is associated with cardiovascular disease and stroke (Kopin & Lowenstein, 2017). Dyspilidemia causes 50% of ischemic heart and cerebrovascular disease which are the main causes of morbidity and mortality in the world (Aradine E et al., 2020). Exessive lipid stored in adipose tissue in the body, leads to obesity. Obesity followed by increased fat (lipid) metabolism causes reactive oxygen species (ROS) production. Increased ROS in adipose cells can cause the balance of oxidation-reduction (redox) reactions to be disrupted, resulting in decreased antioxidant enzymes in the circulation. This situation is called oxidative stress (Wahjuni, 2015). Increased oxidative stress causes dysregulation of adipose tissue, and is the initial pathophysiology of metabolic syndrome, hypertension and atherosclerosis (Arshad et al., 2021). Oxidative stress

can be evaluated by measuring the end products of oxidative damage to proteins and amino acids, one of which is malondialdehyde (MDA). Malondialdehyde is the end product of degradation of lipid peroxidation that is the reason of widely used as a parameter of oxidative stress (Niki, 2009).

Syzygium aromaticum (clove) has high anti-oxidative effect. Indonesia is one of the largest clove producers in the world. Based on previous research, *Syzygium aromaticum* contains an active compound of 70-96% euginol (Towaha, 2012). The compound euginol ($C_{10}H_{12}O_2$) is a derivative of guaiacol with an additional alkyl chain known as IUPAC 2 methoxy-4-(2 propenyl) phenol. Phenolic compounds contained in a number of plants are considered secondary metabolites which have an important role in antioxidant activity (Alawiyah et al., 2019)(Selles et al., 2020). *Syzygium aromaticum* also has the potential to reduce blood lipid profiles (Rouhi-Boroujeni et al., 2015).

This study aims to determine MDA levels as a marker of oxidative stress in the pathogenesis of dyslipidemia in Sprague dawley rats administered with Syzigium aromaticum in several dose groups. Research on *Syzygium aromaticum* related to dyslipidemia and oxidative stress has widely carried out. The novelty of this research is to evaluate the MDA level as end product of oxidative stress in dyslipidemia. This research is expected to increase knowledge regarding the involvement of oxidative stress and become the basis for using natural ingredients as additional therapy in the management of dyslipidemia in the future.

2. Method

All experiments were performed strictly in accordance with the recommendations of the guide for the care and use from iRATco Animal Laboratory (Bogor, Indonesia). The experiment was approved by the local ethics committee of Faculty of Medicine & Health, University of Muhammadiyah Jakarta with registered number 09/PE/KE/FKK-UMJ/I/2023 (Indonesia).

2.1 Animal and Experimental Design

Thirty 8-12 weeks-old male Sprague Dawley weighing 120-150 g were purchased from iRATco animal lab provider (Bogor, Indonesia) and divided into 6 groups. 5 rats each group was divided randomly and given intragastric administration of vehicle CMC 0,5% (normal control), high fat diet only (negative control), and simvastatin (positive control). The other three treatment groups were treated with dosages 150, 250, and 500 mg/kg/day of SA ethanolic extract. The body weight of each rat was monitored weekly for six weeks. The evaluation of lipid profile was performed pre and post experimental procedure (day 0 and day 42). After six weeks rats were terminazed by ketamine-xylazin injection intramuscularly, and had their liver were collected for the examination of MDA levels.

2.2 Diet

Two kinds of diet were used in this study; standard and high-fat diet. Normal diet with total energy 3600 (kkal/kg) consists of total protein 12.58%, total fat 4%, total carbohydrate 72.7%, fiber 5%, Ash 3.89%, Calcium 0.5% and Phosphat 0.19%. High-fat diet with total energy 5700 (kkal/kg) consists of total protein 14%, total fat 50%, total carbohydrate 36%, fiber 3.5%, Ash 5.3%, Calcium 1% and Phosphat 0.7%.

2.3 Syzygium aromaticum Extract

Dried cloves were purchased from IPB Biopharmacy Center (Bogor, Indonesia). Clove was extracted by using 96% ethanol through the maceration method in Indonesian Medicinal and Aromatic Crops Research Institute (IMACRI) (Bogor, Indonesia). The clove extract was produced by measuring 50 g of clove powder then was extracted using 96% ethanol solvent at 1:5 ratio (w/v). Furthermore the extracted sample was macerated for 24 hours, while being stirred using the magnetic stirrer at room temperature. The maceration product was filtered using Whatman no 41 filter paper. The unfiltered sample was re-macerated twice with the same method. The

macerated production was concentrated by the vacuum evaporator at 30-45°C and preserved at -20°C for further steps.(Ode et al., 2023)

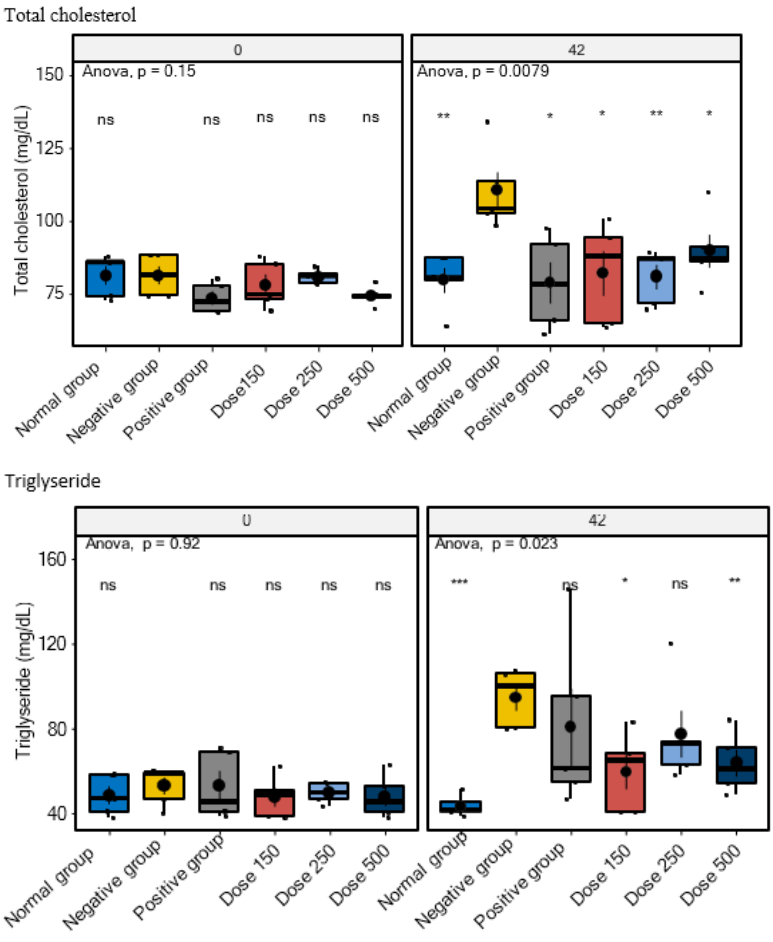
2.4 Lipid Profile and MDA Measurement

Rats were stopped from being given food 24 hours before the blood test. Blood was taken from sinus orbitalis. Lipid profile examined using enzimatic methode using glory diagnostic kit. MDA was examined with spectrophotometry using modification of thiobarbituric acid (TBA) method. A total of 400 µl of sample was reacted with 200 µl of 20% trichloroacetic acid (TCA) for deproteinization. Then vortexed and centrifuged at 5000 rpm for 10 minutes. The supernatant formed was taken and 400 µL of 0.67% TBA was added. Sample was vortexed and incubated in a water heater at 96°C, 10 minutes later removed and cooled to room temperature. Then read the absorption at a wavelength of 530 nm.(Rakita et al., 2020)

3. Results

3.1 Lipid Profile

To ensure that the experimental animals had dyslipidemia, the blood lipids were examined and compared between groups post-treatment on day 42.



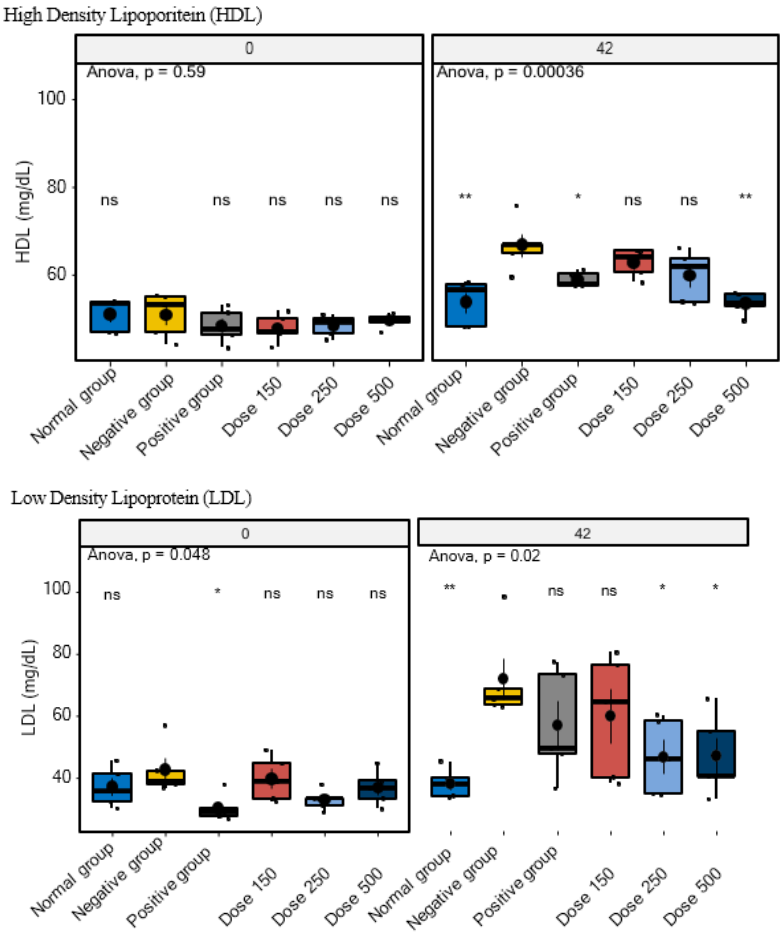


Figure 1. Serum lipid profile parameters of different experimental groups

Values were expressed as mean ± SD (n = 5). *Bonferroni-test, indicates a significant diff (p < 0,05)

Figure 1. shows specific comparison between all experimental groups in lipid profile. Total cholesterol increased in the group treated with high-fat diet, but in the group given *Syzygium aromaticum* extract, total cholesterol level decrease significantly ($p<0.05$). Triglyceride levels increased in the group treated with a high-fat diet, but triglyceride levels showed a significant decrease in the group treated with the *Syzygium aromaticum* extract at dose of 150 and 500 mg/kgbody weight ($p<0.05$). HDL levels increased in the group treated with high fat diet, but HDL decrease in the group treated with *Syzygium aromaticum* extract dose of 500 mg/kg BW ($p<0.05$). LDL levels increased in group treated with high fat diet, but decrease significantly in the group treated with *Syzygium aromaticum* extract doses of 250 and 500 mg/kg BW ($p<0.05$).

3.2 The malondialdehyde level

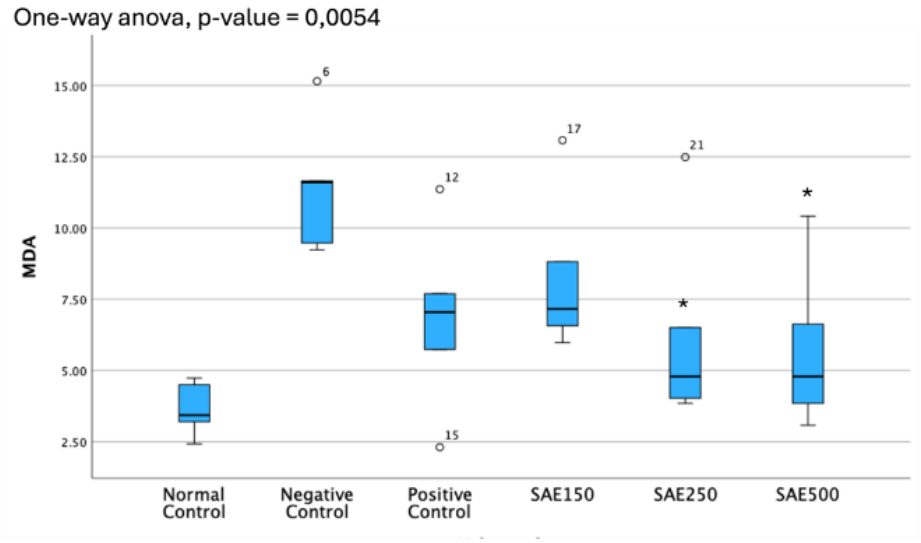


Figure 2: Malondialdehyde (MDA) levels (µmol/L)

MDA levels indicate the presence of oxidants in the liver. In this study, high fat diet groups showed an increase in MDA levels. Groups treated with Syzigum aromaticum extract showed significant decreased of MDA levels with a dose of 250 and a dose of 500 mg/kgBW (figure 2).

4. Discussion

4.1 Dyslipidemia and Oxidative stress

Reactive oxygen species (ROS) are bioproducts of cellular metabolism. There is a range of molecules with oxidizing properties known as ROS. Despite those molecules being implied negatively in aging and numerous diseases, their key role in cellular signaling is evident. ROS control several biological processes such as inflammation, proliferation, and cell death. (De Almeida et al., 2022) Dyslipidemia has been reported to involve a release of reactive oxygen species (ROS) which may lead to oxidative stress. The primary sources of endogenous ROS production are the mitochondria, plasma membrane, endoplasmic reticulum, and peroxisomes. Metabolic disorders such as obesity, dyslipidemia and diabetic mellitus are accompanied by chronic inflammation mediated by oxidative stress. Increased oxidative stress in metabolic disorders plays a role in causing mitochondrial dysfunction, accumulation of protein and lipid oxidation products and disruption of the antioxidant system. (Vona et al., 2019)(Pechánová et al., 2015)

4.2 Malondialdehyde and lipid peroxidation

One of the consequences of uncontrolled oxidative stress (imbalance between the prooxidant and antioxidant levels in favor of prooxidants) is cells, tissues, and organs injury caused by oxidative damage. It has long been recognized that high levels of free radicals or reactive oxygen species (ROS) can inflict direct damage to lipids. The primary sources of endogenous ROS production are the mitochondria, plasma membrane, endoplasmic reticulum, and peroxisomes. through a variety of mechanisms including enzymatic reactions and/or autooxidation of several compounds, such as catecholamines and hydroquinone. Different exogenous stimuli, such as the ionizing radiation, ultraviolet rays, tobacco smoke, pathogen infections, environmental toxins, and exposure to herbicide/insecticides, are sources of *in vivo* ROS production.(Ayala et al., 2014) Malondialdehyde (MDA) is an end-product of lipid peroxidation and a side product of thromboxane A2 synthesis. MDA's high reactivity and capability of forming adducts with multiple biological molecules such as proteins or DNA have attracted major attention over the last decades. . MDA's high reactivity is mainly based on its electrophilicity making it strongly reactive toward nucleophiles, such as basic amino acid residues. (Giera et al., 2012) MDA has been widely used

for many years as a convenient biomarker for lipid peroxidation of omega-3 and omega-6 fatty acids because of its facile reaction with thiobarbituric acid (TBA). The TBA test is predicated upon the reactivity of TBA toward MDA to yield an intensely colored chromogen fluorescent red adduct. (Niki, 2009) MDA is one of the most popular and reliable markers that determine oxidative stress in clinical situations [53], and due to MDA's high reactivity and toxicity underlying the fact that this molecule is very relevant to biomedical research community.

4.3 Syzygium aromaticum and Oxidative Stress

Syzygium aromaticum is not only a significant spice but has also been utilised in traditional medicine to treat a number of diseases. In the current study, stress caused by a high-fat diet was used to investigate the underlying protective mechanism of S. Aromaticum (clove) extract in a rat model. In the present study, we found that SA extract had ability to alter the lipid profile. It significantly decrease the dyslipidemia parameters which are characterized by the decrease in serum levels of total cholesterol, triglyceride, LDL-c, and an increase in HDL-c compared with the high fat diet only group. A study conducted by El-Rahman (Abd El-Rahman, 2015) showed that cloves could reduce the serum total cholesterol, trigycerides, LDL-c, and VLDL-c levels however increased HDL-c level significantly compared to the DC group. Pourlak et al (Pourlak et al., 2020) and Rabeh et al., (Rabeh et al., 2021) demonstrated that clove extract significantly decreased the dyslipidemia status by regulating lipid metabolism.

Finding from this study have also shown that administration of SA extract reduced the MDA level of treatment groups compared to high fat diet only group. MDA level is one of the indicator of lipid peroxidation and oxidative stress with the MDA resulting from the end product of polyunsaturated fatty acid peroxidation. Hyperlipidemia is associated with the increased oxidative stress and increased MDA levels. Many studies in both human and animal models found that elevated levels of MDA are associated with the hyperlipidemia and reduced antioxidant levels in the experimental subjects. Study conducted by Al Flyah (Al-flyah et al., 2010) have shown that cloves (*Syzygium aromaticum*) extract significantly reduced the MDA level of rats induced by alloxan. Pourlak et al.(Pourlak et al., 2020) also found that in the groups of rats that were treated with clove extract exhibited a significant reduction of MDA level compared to the control diabetes group. Study by Sharma et al (Sharma et al., 2023) demonstrated a phytochemical analysis of *Syzygium aromaticum* extract and found that as per the GC-MS, cloves have a higher content of eugenol and eugenol acetate, which possess strong antioxidant activities by hydrogen/electron transfer or directly trapping the free radicals.

The antioxidant activity of SA extract may be due to phenolic compounds such as eugenol, eugenol acetate, and thymol. SA extract can prevent cell damage by scavenging free radicals, chelating temporary metal ions, inhibiting oxidant enzymes, or by repairing a-tocopherol from a-tocofoxyl radical. Also, flavonoids can scavenge O2, OH, and peroxyl radicals and inhibit LPO activity, as result, SA extract can decrease MDA level.

The results of this study showed that SA extract has beneficial effects in lowering serum cholesterol, triglycerides, and LDL levels. SA extract also decreases MDA level. MDA is one of the most popular and reliable markers that determine oxidative stress in clinical situations. Therefore, because of these beneficial effects of *Syzygium aromaticum* / clove, it can be used as an effective herbal medicine in reducing and treating the dyslipidemia and oxidative stress induced by high fat diet.

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Conflicts of Interest: the Authors declare no conflict of interest.

Informed Consent Statement/Ethics approval: The experiment was approved by ethics committee of Faculty of Medicine & Health, Universitas Muhammadiyah Jakarta with registered number 09/PE/KE/FKK-UMJ/I/2023 (Indonesia).

Declaration of Generative AI and AI-assisted Technologies: This study has not used any generative AI tools or technologies in the preparation of this manuscript.

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