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The Effect of the Extra Virgin Olive Oil Administration towards the Malondialdehyde and Vascular Endothelial Growth Factor Levels on the Hypertensive Pregnant Rats

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ABSTRACT

Background: Hypertension and pregnancy cause placental ischemia which will produce the toxic free radicals that cause the oxidative stress and increase the malondialdehyde (MDA) level. Oxidative stress also decreases the Vascular Endothelial Growth Factor (VEGF) level. Extra Virgin Olive Oil (EVOO) contains antioxidants that can break free radical chain reactions. This study aims to determine the effect of the EVOO administration on the MDA and VEGF levels on the hypertensive pregnant rats.
Methods: A post-test only control group design study was conducted on 30 pregnant rats consisting of a negative control group (K-), a positive control group (K+) and 3 treatment groups as a hypertension model (Pl, P2, P3), NaC1-induced hypertension model 6 % on day 6 to day 12 of pregnancy. All treatment groups were given EVOO except K+, from day 13 to day 19. On day 20, all the rats were executed. The MDA examination used a spectrophotometer and the VEGF examination used ELISA. The data was tested by using the one way ANOVA test which was statistically significant if $p < 0.05$.
Results: The results of this study showed that there was a significant decrease on the mean of the MDA level after the EVOO administration, especially in the P3 group, which was 1,532 mmol/l (p 0.000) and a significant increase on the mean of the VEGF level after the EVOO administration, especially in the P3 group, which was 68,892 ng/l. (p 0.000). It means that there is an effect of the EVOO administration on the MDA and VEGF levels of hypertensive pregnant rats.
Conclusion: The conclusion of this study is that the EVOO administration can decrease the MDA level and increase the VEGF level on hypertensive pregnant rats.

Keywords: *EVOO, MDA, VEGF, Hypertension*

INTRODUCTION

The World Health Organization (WHO) records the incidence of hypertension and pregnancy reaching 1.8%-18% in developing countries (1). The high prevalence rate makes hypertension and pregnancy the second leading cause of maternal and infant mortality. Sajith et al., (2014) found that hypertension and pregnancy cause 50,000 deaths per year of the total maternal deaths (2).

Hypertension and pregnancy (HAP) are the factor dominating maternal mortality. In 2014, this factor contributed 21.5%; in 2015 it was 24.7%; in 2016 it was 26.9%, in 2017 it increased to 27.1% (3). The West Sumatra Provincial Health Office noted that in 2019 the maternal mortality rate due to this factor reached 40% which this mortality rate was the second highest cause after bleeding (4).

Hypertension and pregnancy are characterized by the blood pressure of 140/90 mmHg or more. The blood pressure is raised higher than 30/15 mmHg since early pregnancy or based on pre-pregnancy examinations (5). A study (6) concludes that one of the early causes of hypertension and pregnancy is thought to stem from reduced uteroplacental perfusion causing the placenta to experience ischemia and hypoxia resulting in the production of highly toxic hydroxyl radicals, which in turn will damage endothelial cell membranes which are rich in unsaturated fatty acids into lipid peroxides. The final product is Malondialdehyde (MDA). One of the markers of oxidative stress in patients with hypertension and pregnancy is an increase on the MDA level (6). In hypertension, VEGF is bound by high sFlt-1 so that the levels of free VEGF circulating in the circulation are low/decreased (7).

The negative impact of oxidative stress caused by hypertension and pregnancy as stated above is that the body needs a balancing compound to minimize the adverse effects occurring due to an imbalance between antioxidants and free radicals in the body and neutralize oxidative stress. Extra virgin olive oil (EVOO) includes olive oil of the best quality because the stages of the production process are short, so it contains very high antioxidant compounds, especially tocopherols and vitamin E (8). Tocopherols in olive oil have been shown to reduce the production of reactive oxygen species (ROS) and produce free radical reduction effects (9).

METHODS

Design and Sample

This was an experimental study using a post-test only control group design. The sample was 30 pregnant rats with a body weight of 200-250 grams, aged 2-3 months who were hypertensive due to induction of NaCL 6% 3 mL/kg BW. The sample was divided into 5 groups consisting of: negative control group (K-), positive control (K+) and 3 treatment groups as hypertension model (Pl, P2, P3), hypertension model induced NaC1 6% on day 6 to day 6. -12 pregnancies. All treatment groups were given EVOO except K+, from day 13 to day 19. The maintenance of experimental animals in this study was carried out in the Pharmacy Laboratory of Universitas Andalas Padang on November 2021 – January 2022. The MDA examination used a spectrophotometer and the VEGF examination used Elisa Kit For Rats. The data were processed by using ANOVA test with 5% and followed by post hoc test.

Treatment dose

A total of 30 rats were divided into 5 groups. All groups were conditioned first to be pregnant where each cage contained 1 male and 3 female for mating. Negative controls were only given standard feed; positive controls were induced with 6% NaCL; 3 treatment groups were induced with 6% NaCL on day 6 to day 12, then given EVOO orally at a dose of 0.90 mL/kg BW, 1.80 mL/kg body weight and 3.60 mL/kg on day 13 to day 19.

Furthermore, the MDA and VEGF levels were checked by taking the Rattus Norvegicus blood under anesthesia, and then 3 mL of blood was drawn through the orbital medial canthus by using a non-EDTA hematocrit capillary pipette. To obtain serum, the blood was then centrifuged at 3500 rpm for 5 minutes. Serum was packaged by using dry ice and sent to the biochemistry laboratory of Universitas Andalas for the MDA level examination using the Thiobarbituric Acid Reactive Substance (TBARS) method and to a biomedical laboratory for the VEGF level examination using the Enzyme Linked Package Immunosorbent Assay (ELISA) method.

Data Analysis

The data were analyzed to see the normality by using the Shapiro Wilk test with ($p>0.05$) then followed by the One-way ANOVA test to see the relationship between variables. Furthermore, the analysis was continued with multiple comparison

tests (post hoc test) of the LSD types to see the differences between groups.

RESULTS

Malondialdehyde

Table 1: The mean of the MDA level in each group based on treatment

Group	Mean of MDA (mmol/L) Mean ± SD	*p-value*
K-	1,72 ± 0,15	0,000
K+	2,56 ± 0,13	
P1	2,27 ± 0,21	
P2	2,05 ± 0,08	
P3	1,53± 0,04	

The mean of the MDA level in group K- was 1.72 mmol/L. In group K+ it was higher than the other groups, which was 2.56 mmol/L. In group P1 it was 2.27 mmol/L; in group P2 it was 2.05 mmol/L; in group P3 it was 1.53 mmol/L. Based on the One-way ANOVA test, there was a significant difference between the control group and the treatment group on the MDA level with p value = 0.000 (p <0.05).

Vascular Endothelial Growth Factor

Table 2. The Mean of the VEGF level in each group based on treatment

Group	Mean of VEGF (ng/L)Mean± SD	*p-value*
K-	71,15± 1,78	0,000
K+	54,87± 1,09	
P1	57,05± 0,34	
P2	65,93± 1,94	
P3	68,89± 1,61	

The mean of the VEGF level in group K- was 71.15 ng/L. In group K+ it was lower than the other groups, which was 54.87 ng/L. In group P1 it was 57.05 mmol/L; in group P2 group it was 65.93 ng/L; in group P3 it was 68.89 ng/L. Based on the One-way ANOVA test, there was a significant difference between the control group and the treatment group on the VEGF level with p value = 0.000 (p <0.05).

DISCUSSION

The results of this study showed that the pregnant rats in the positive control group induced by 6% NaCl without the EVOO administration had an increase on the mean of the MDA level which was higher (2.56±0.13 mmol/L) than in the negative control without 6% NaCl and without the EVOO administration (1.72±0.15 mmol/L). This is in line with study on the MDA level after giving 6% NaCl for three days on pregnant rats in the treatment group which was higher (1.75±0.04 mmol/L) than in the control group (0.58±0.02 mmol/L).) (10).

In addition, other studies have also shown that abnormal lipid metabolism and high lipid peroxide concentrations occurring in hypertension and pregnancy contribute to the oxidative stress and vascular dysfunction (11).

Nevertheless, this is in accordance with the theory that the increase of the vascular resistance by NaCl results in the release of free radicals that can cause the damage to all biological membranes by damaging proteins, lipids, nucleic acids, and glycogen (12). In this case, the oxidation process of long-chain unsaturated fatty acids (PUFA) or known as lipid peroxidation in cell membranes produces lipid peroxide radicals, hydroperoxides, and aldehyde products such as MDA and if the levels are increased, cells experience the oxidative stress, which then triggers hypertension gradually with the formation of reactive oxygen species causing renal vasoconstriction (13). This is thought to have caused the increase in the MDA level on pregnant rats given 6% NaCl in this study.

The results of the study in the treatment group given the EVOO with various doses, showed that there was a decrease on the mean of the MDA level, respectively P1 (2.27±0.21 mmol/L), P2 (2.05±0.08 mmol/L), and P3 (1.53±0.04 mmol/L). This is in line with the study that the EVOO administration with various doses for 14 days had an effect on decreasing the mean of the MDA levels on the rats from 8.88±0.63 mmol/L to 7.49±0.85 mmol/L (14).

This is in accordance with the theory that tocopherol can effectively minimize the oxidative stress, lipid peroxidation and toxic

effects of reactive oxygen species in biological systems (14). Furthermore, the theory also states that the mechanism of the EVOO action to reduce the MDA level is as a chain breaker class antioxidant. In this case, the -tocopherol contained in it functions to break the various free radical chain reactions by transferring the hydrogen tocopherol to peroxyl free radicals from double unsaturated fatty acids (PUFA) which has undergone peroxidation to form new and more stable compounds. Therefore, -tocopherol is the most active and most important form of tocopherol for the body's biological activities. -Tocopherol controls lipid peroxides by donating hydrogen ions into the reaction, thereby converting the peroxyl radicals (products of lipid peroxidation) into less reactive tocopherol radicals, which in turn will break the chain reaction and limit the damage (18).

Moreover, the results of the study in group P3 given EVOO at a dose of 3.60 mL/kg BW had a very significant decrease in the MDA level compared to the other groups. It can be seen from the mean of group P3 which was close to the mean of the negative group, namely 1.53±0.04 mmol/ L. This is in line with the study that giving EVOO to the treatment group showed the significant results as evidenced by the mean value of the treatment group which was close to the normal value, namely 1.60±0.18 mmol/L. It means that EVOO can decrease the production of MDA produced by placental cells (15).

However, other studies have also suggested that the biochemical imbalances in hypertension and pregnancy occur in the presence of increased oxidative stress. Lipid peroxide, as an end product of oxidative stress, is involved in endothelial cell damage, vasoconstriction and imbalance between thromboxane and prostacyclin. MDA is a marker of lipid peroxidation in hypertension and pregnancy. Thus, antioxidants are needed as an important treatment for compensating lipids associated with hypertension and pregnancy (16).

Furthermore, this is in line with the theory that tocopherol is antioxidants breaking the lipid peroxidation chain and inactivate free radicals by converting them into more stable products (17). The formation of sufficient amounts of antioxidants from -tocopherol in cells can defend the body against oxidative stress. Furthermore, the theory also states that the administration of antioxidants in high levels is able to inhibit the oxidation of target molecules so that they can fight or neutralize the free radicals. In addition, it is also suspected that -tocopherol is about 40 – 60% of the food that can be absorbed by the intestine, so increasing the amount consumed will increase the percentage that is absorbed. Some of -tocopherol performs its function as an antioxidant. Therefore, it can be understood that giving a high dose of EVOO will cause tocopherol to increase resulting in inhibition of fatty acid peroxidation which in turn decreases the MDA level, when compared to the low doses (18).

In contrast to the results of other studies which showed that giving EVOO had no effect on decreasing the MDA level with a p value of 0.310. This was because EVOO was only given at a low dose (0.45 mL) which at that dose the antioxidants in EVOO, especially tocopherol, did not able to reduce the oxidants/free radicals under oxidative stress as indicated by the high MDA level (19).

The results of this study showed that the pregnant rats in the positive control group induced by 6% NaCl without the EVOO administration had a lower decrease in the mean of the VEGF level (54.87 ± 1.09 ng/L) than in the negative control rats without induced NaCl and without given EVOO (71.15±1.78 ng/L). This is in line with the study on the VEGF level after given 6% NaCl for six days on the pregnant rats in the treatment group which was lower (60.02±1.52 ng/L) than in the control group (75.16±1.09 ng/L) (20).

Another study showed that hypertension caused by decreased

intrauterine perfusion on the pregnant rats was closely associated with the increased sFLT-1 level. Pathological pregnancy can cause hypoxia and ischemia of placental tissue, then release toxic cytokines into maternal blood circulation, resulting in endothelial cell damage, proliferation, and differentiation of trophoblast cells. It can therefore lead to decreased VEGF secretion and increased levels of sFLT-1 in maternal blood circulation (21).

This is consistent with the theory that the induction of 6% NaCl triggers the sympathetic nervous system (SNS) to produce marinobufagenin (MBG) which acts as an inhibitor of the Na+/K+ pump and thereby alters Na retention (excess Na+) and increases vascular resistance of endothelial dysfunction. The increase of the vascular resistance results in the endothelial damage due to the release of ROS and causes arterial stiffness (loss of elasticity of arteries) and ultimately hypertension. In hypertension, it is believed that the blood vessels fail to provide adequate blood flow to the placenta, causing ischemia. As a result, the placenta produces a variety of factors, especially elevated the sFlt-1 level and decreased the VEGF level that cause glomerular endothelial damage on rats. Thus, the importance of a balance between the proangiogenic and antiangiogenic factors for endothelial cell survival (22).

Another theory also states that in hypertension conditions also cause trophoblasts to produce antiangiogenic factors such as sFlt-1 and an increase in the sFlt-1 level which can cause endothelial dysfunction and hypoxia. Furthermore, VEGF and sFLT-1 play an important role in endothelial dysfunction. VEGF is mainly expressed on the surface of the placental syncytiotrophoblast and trophoblast cells during pregnancy. It is expressed in the vasculature during early pregnancy and is abundant in trophoblast cells in normal pregnancy. Nevertheless, in hypertension and pregnancy, the VEGF level decreases (23).

The results of the study in the treatment group given EVOO with various doses showed that there was an increase on the mean of the VEGF level, respectively P1 (57.05±0.34 ng/L), P2 (65.93±1.94 ng/L), and P3 (68.89±1.61 ng/L). This is in line with a study which the EVOO administration with various doses affected the increase in the VEGF level on rats from 57.88±1.49 ng/L to 65.62±2.33 ng/L (19).

Another study also demonstrated the increased uterine and placental tocopherol concentrations following oral tocopherol supplementation during late gestation on the pregnant rats. In this study, it was shown that the increase in VEGF on the female rats given tocopherol supplements had an antioxidant effect that could increase the VEGF level, which was increased through the VEGFR1 (low sFlt1) and VEGFR2 (high KDR) (24).

This is in accordance with the theory that EVOO is able to increase the VEGF level because it can function as an antioxidant that can delay the oxidation process. EVOO compounds can delay the oxidation process because the -tocopherol content can break the radical ion chain by releasing the hydrogen radicals so that a stable derivative is obtained. This indicates that -tocopherol (αT) can increase the expression of vascular endothelial growth factor (VEGF). Thus, it can act as an active lipid mediator enhancing the VEGF expression, angiogenesis, and vasculogenesis (25).

The results of the study in group P3 given EVOO at a dose of 3.60 mL/kg BW showed that there was a very significant increase on the mean of the VEGF level compared to other groups, it can be seen from the P3 group average which was close to the mean of the negative group, namely 68.89±1.61 ng/ L. This is in line with research which states that relatively high concentrations of tocopherol can be used for treatment because it is absorbed into the body as an efficient whole molecule. The synthesis of -tocopherol in certain cells requires a sufficiently high concentration to

carry out its proper and relevant subcellular function for signaling. In experimental studies it was demonstrated that -tocopherol can regulate angiogenesis in endothelial cells by triggering the production and secretion of VEGF from cells in the vascular system (eg. from vascular smooth muscle cells, monocytes/macrophages, renal cells, or trophoblasts) (26).

This is in line with the theory that giving a higher dose of Extra Virgin Olive Oil (EVOO) also allows the antioxidants in EVOO to delay the oxidation process. In this case, the main antioxidant inhibiting the oxidation process in EVOO is tocopherol, cleaving free radical chains by donating hydrogen radicals thereby causing more stable derivatives during reaction formation (27). A study on the EVOO tocopherol antioxidant activity also shows the possibility that tocopherol acts as hydrogen donors and it also donates positive electrons thereby stabilizing hydroxyl radicals. -Tocopherol is essential for normal reproduction and many other bodily functions. This type is found in many cell membranes, and if it does not function then free radicals will affect the function of membranes, DNA, and other cell components. It is the most active form of vitamin E, and it is a powerful biological antioxidant (28).

CONCLUSION

It can be concluded that the oral administration of Extra Virgin Olive Oil give a significant effect on decreasing the MDA level and increasing the VEGF level on the hypertensive pregnant Rattus Norvegicus.

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