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Effectiveness Of Watermelon (Citrullus lanatus) Red Flesh Extract On Reducing Coronary Artery Foam Cells and Thinning Of The Aortical Intima In Wistar Rats (Rattus norvegicus strain Wistar) Atherosclerosis Model

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ABSTRACT

Introduction: Atherosclerosis (AS) is a process of narrowing of the lumen of arteries due to progressive plaque buildup. Foam Cell and plaque appear as a result of lipoprotein metabolism disorders which result in inflammatory reactions. The incidence of AS in the world is increasing, resulting in various complications that can lead to death. Lycopene is contained in the red flesh of watermelon, which is an antioxidant that can control free radicals and can reduce the risk of AS.

Objective: To determine the effectiveness of watermelon (Cittrulus lanatus) red flesh extract on reducing coronary artery foam cells and thinning of the aortic intima in Wistar rats (Rattus norvegicus strain Wistar) atherosclerosis model.

Method: This research was an experimental study (true experimental) using the Post Test Only Control Group Design method, which measures the number of coronary artery foam cells and the thickness of the aortic intima in Wistar rats (five groups) after administration of a hypercholesterolemic diet and watermelon red flesh extract at a dose of 250,500,750 mg /kgBW. Data analysis was carried out using One-Way ANOVA and Post Hoc Bonferroni tests.

Results: The One-Way ANOVA statistical test showed results of 0.020 for foam cells and 0.008 for thickness of the intimal tunica, which means that there was a real influence of watermelon red flesh extract on decreasing foam cells and significant thinning of the intimal tunica in the treatment group. Furthermore, the Post Hoc Bonferroni test showed that the dose of 750 mg/kgBW had the most effect on reducing foam cells ($p=0.046$) and thinning the intima ($p=0.015$).

Conclusion: Watermelon (Citrullus lanatus) red flesh extract at a dose of 750 mg/kgBW has a significant effect on reducing the number of foam cells and thinning of the aorta of the Wistar rat model of atherosclerosis.

Keywords: Watermelon (Citrullus lanatus) red flesh extract, foam cell, tunica intima, plaque, lycopene, atherosclerosis.

INTRODUCTION

Atherosclerosis (AS) is a process of narrowing of the lumen of arteries due to progressive plaque buildup. Plaque or atheroma appears as a result of metabolic disorders of lipoprotein which results in an inflammatory reaction (Prameswari, 2020). Plaque occurs due to an inflammatory reaction in the form of an accumulation of activated leukocytes in the subendothelial space of blood vessels. Microscopic changes in blood vessel walls in the AS process are caused by foam cells, lipid accumulation in extra cells, migration and recruitment of monocytes, and extracellular matrix deposition (I Gede Gita Sastrawan, 2019).

The incidence of AS in the world is increasing every year, resulting in various complications that lead to death. AS is a cardiovascular disease and is the main cause of blood vessel disease throughout the world and the main cause of death in various countries (Sirilus, 2022). According to the World Health Organization (WHO) in 2015, deaths due to heart and blood vessel disease are estimated to increase to 20 million people and will continue to increase until 2030 and cause deaths in 23.6 million people. Global Burden of Disease reports that the number of deaths due to cardiovascular disease in the world in 2019 was 18.5 million (32.84%) and the number of deaths in Indonesia was 651,481 people (38.19%) (Lu'lu' et al ., 2022).

Currently the treatment for AS is statins which are the first line drugs in the treatment of hyperlipidemia and primary prevention of AS. However, the use of statins cannot be separated from various undesirable effects such as myopathy, loss of cognitive function, pancreatic and liver dysfunction (Simatupang & Oleh, 2020). Additionally some patients cannot tolerate recommended doses of statins and most do not achieve adequate reductions in low-density lipoprotein cholesterol (LDL-C), despite high-dose statin therapy. (Luquero et al., 2021; Przybylska & Tokarczyk, 2022)

AS is a progressive (gradual) disease, difficult to identify in the early phase and requires preventive measures to prevent the severity of the disease. Therefore, the role of phytochemical compounds (carotenoids) is needed to support therapy for patients at high risk of complications. Based on the results of cell culture research, the compound lycopene has been proven to prevent the occurrence of AS as shown by in vitro research, lycopene as the most effective keratenoid in suppressing monocyte adhesion to endothelial cells, resulting in a decrease in the number of monocytes at the lesion site, phagocytic activity by macrophages and foam cells. thus preventing the formation of plaque which will cause AS (Selvia & Vradinatika, 2020). Lycopene is found in the red flesh of watermelon. Watermelon (Citrullus lanatus) is a fruit that can be consumed directly or processed first. Watermelon can be found in various seasons at affordable prices. The antioxidant compounds contained in watermelon besides lycopene are vitamin C, cucurbitacin E. (Meidayanti, 2020). Lycopene, which is also known as α-carotene, is an antioxidant that can control free radicals and is more efficient than vitamin E, so it can reduce the risk of AS. The lycopene content of red-fleshed watermelons is 40% higher than tomatoes. The lycopene content in 100g of watermelon is

around 4.81mg and in tomatoes around 3.03mg (Naz et al., 2014). The choice of watermelon red flesh extract refers to research which states that the lycopene content increases at higher storage temperatures. The process of making watermelon red flesh extract goes through several procedures at high temperatures which of course affect the lycopene levels. Research data shows that at a temperature of around 5ºC the lycopene content in watermelon per 100g is around 7.8 – 8.1 mg. Meanwhile, at a temperature of 20ºC it increases by around 8.1 – 12.7 mg per 100g (Naz et al., 2014).

Based on the background and explanation above, the author wants to conduct research regarding the red flesh extract of watermelon (Cittrulus lanatus) as a prevention of AS to reduce coronary artery foam cells and thinning of the aortic intima in Wistar rats (Rattus norvegicus strain Wistar) model of atherosclerosis.

RESEARCH METHODS

This type of research was True Experimental Post Test Only Control Group Design. The research was conducted at the Biomedical Laboratory, Faculty of Medicine and Pharmacy Laboratory, Faculty of Health Sciences, University of Muhammadiyah Malang in August 2023 for 7 weeks.

The population selected in this study were all male Wistar rats (Rattus norvegicus strain Wistar). The samples used were 2-3 months old with a body weight of 150-200 grams, healthy mice, with active criteria, clear eyes and thick fur. In determining the research sample size, it will be determined using the Sample Size Calculation in Animal Studies, 2017 formula, the sample size required was around 3-5 Wistar rats in each group. Group Negative Control (given standard feed (AD2 pellets), Group Positive Control (Hypercholesterolemia (AD2 pellets + 9:1 Margarine), Group P1: Hypercholesterolemia (AD2 pellets + 9:1 Margarine) + red fruit flesh extract watermelon dose 250 mg/head/day for 28 days, Group P2: Hypercholesterolemia (AD2 pellets + Margarine 9:1) + administration of watermelon red flesh extract dose 500 mg/head/day for 28 days, Group P3: Hypercholesterolemia (AD2 pellets + Margarine 9 :1) + administration of watermelon red flesh extract at a dose of 750 mg/head/day for 28 days. The sampling technique used simple random sampling.

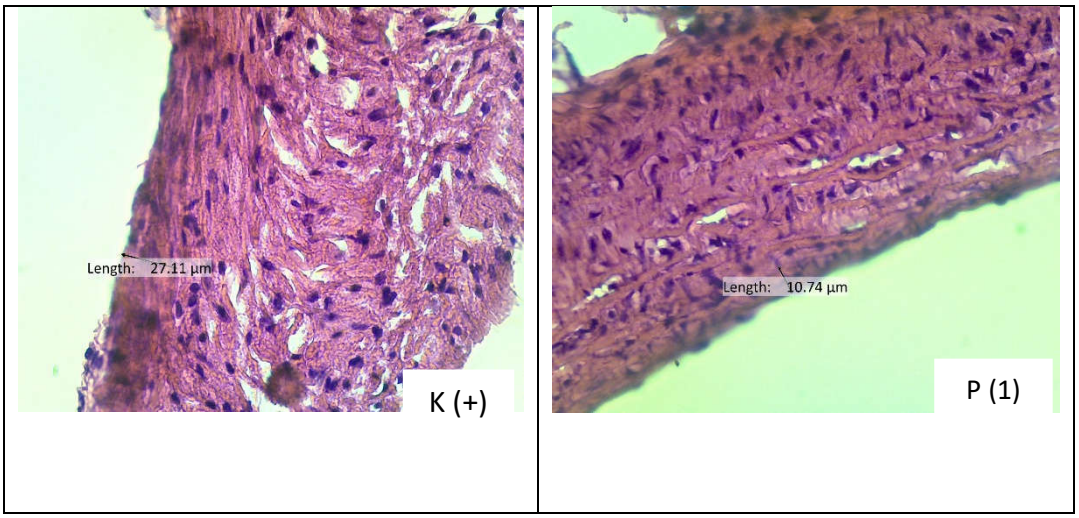
The red flesh extract of the watermelon in the research was made at the Pharmacy Laboratory, Faculty of Health Sciences, University of Muhammadiyah Malang using the following procedure: The watermelon fruit was cut open and separated into the red flesh, white flesh and skin, blended into watermelon juice, mixed with the solvent n-hexane, acetone, and 96% ethanol with a ratio (F/S) of 100 ml: 200 ml, placed in a three-neck flask at a temperature of 70ºC until the extraction process is complete for 90 minutes. Place the extraction results in an Erlenmeyer. The extraction results are put into a separating funnel and shaken for 15 minutes to obtain polar and

non-polar layers. Place the non-polar layer in a measuring cup. (Mariani, Rahman and Supriadi, 2018).

Analysis of research data using SPSS for Windows ver. 2.4 . The data will be analyzed using the normality test stage with the Shapiro-Willk test. Data is said to be normal if $p > 0.05$. Normality test is carried out as a condition for carrying out the One Way ANOVA test. Homogeneity test with Lavene's test to determine the homogeneity of normally distributed data variants if the normality test finds $p > 0.05$, One Way ANOVA test to determine the comparison of the number of foam cells and thickness of the intima between administration of watermelon red flesh extract. It is said that there is a significant difference if a p value <0.05 is obtained. Post hoc Bonferroni test as a continuation test of the General Linear Model test. This test is used to determine significant differences when data was homogeneous between research treatment groups. If the data is not homogeneous, the Mann-Whitney post hoc test is used. Next, a linear regression analysis test is carried out to determine how big the effect of giving various doses of watermelon red flesh extract and foam cells is and the thickness of the intima (Parama Santosa et al., 2018).

RESULTS AND DISCUSSION

The study was conducted to compare the number of decreases in coronary artery foam cells and thinning of the aortic intima in the hypercholesterolemia group without treatment with three hypercholesterolemia groups given watermelon (Citrullus lanatus) red flesh extract using a light microscope.



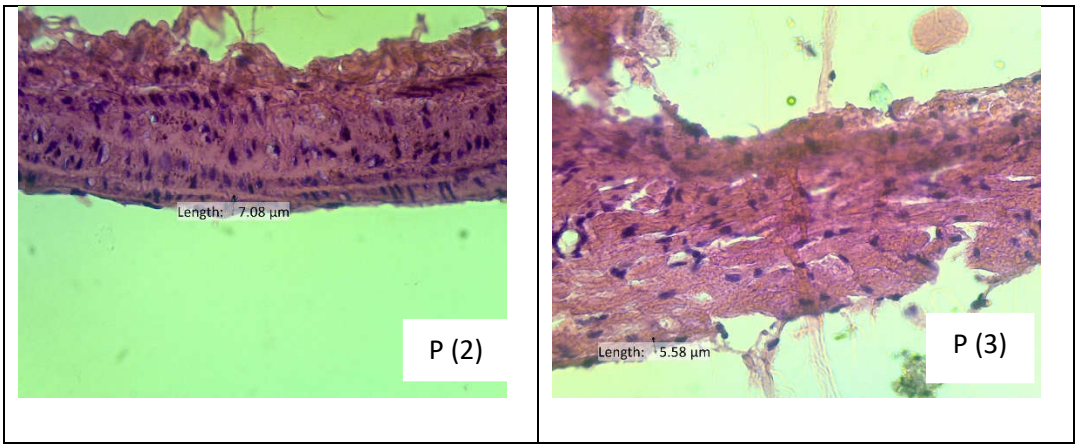
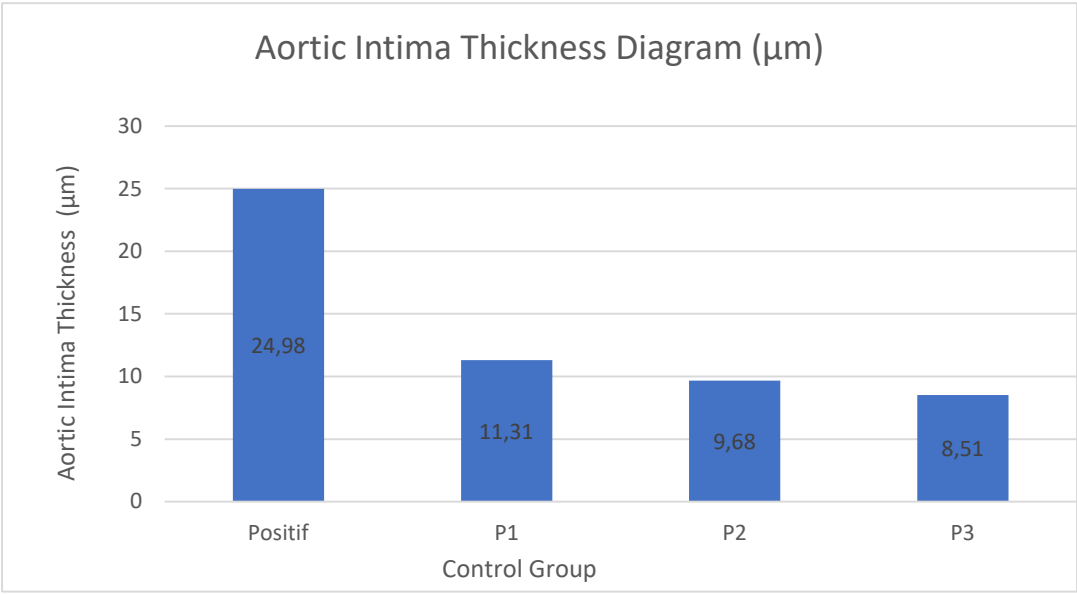


Figure 1. Thickness of the aorta's intima. The thickest aortic intima can be seen in the group of mice fed a high fat (K+) diet. The aortic wall in the group of atherosclerosis model mice given 250 mg (P1) and 500 mg (P2) watermelon red flesh extract was thinner, and the thinnest among the group of mice given 750 mg watermelon red flesh extract (P3).(H-E staining, 400x magnification).

Diagram 1. Aortic intima thickness diagram. The control group (K+) had the thickest average aortic intima thickness, while the treatment group (P3) had the thinnest average aortic intima thickness among the other treatment groups.



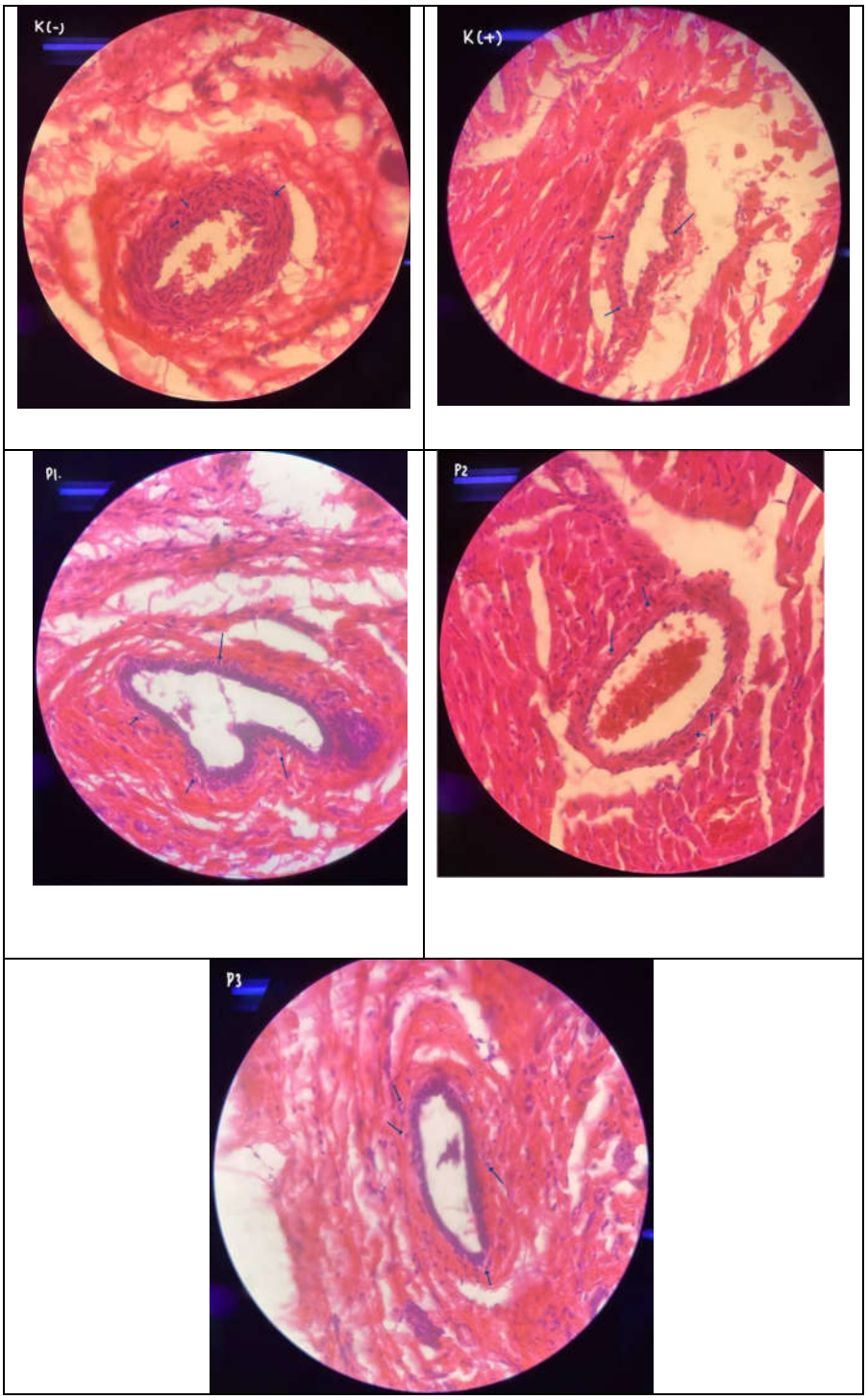


Figure 2. Coronary artery foam cells. You can see the most coronary artery foam cells in the group of mice fed high-fat (K+) food. Coronary artery foam cells in a group of atherosclerosis model mice that were given 250 mg (P1) and 500 mg (P2) watermelon red flesh extract. Coronary artery foam cells were more numerous, and the foam cells were the most abundant among group of mice given 750 mg watermelon red flesh extract (P3). (H-E staining, 400x magnification).

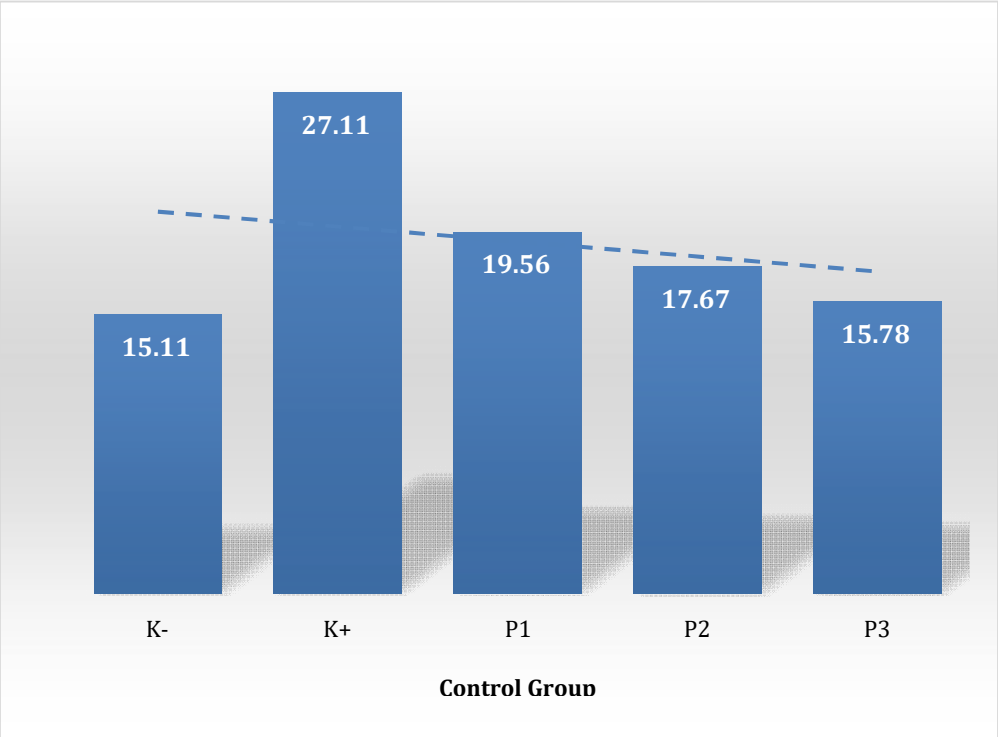


Diagram 2. Diagram of the number of foam cells. The control group (K+) had the highest average number of foam cells, while the treatment group (P3) had an average number of foam cells close to the control group (K-).

The research data was tested for normality using the Shapiro-Wilk method with a p value of >0.05 and a homogeneity test with a p value of >0.05. Thus, the research data has a normal and homogeneous distribution so that it meets the requirements of the One Way ANOVA test and the Bonferroni Post-Hoc test. The one way ANOVA test showed that each group had a value of sig = 0.008 on the thickness of the aortic intima and the number of foam cells sig = 0.020 or $p < 0.05$, which means that there was a significant effect of giving watermelon red flesh extract on the thickness of the tunica. aortic intima and foam cell count in Wistar rats. The Bonferroni test on the Bonferroni test table on the thickness of the aortic intima showed that the control group had a significant difference from all treatment groups with a significant value for each group of $p < 0.05$. At P3 p= 0.015. The number of foam cells showed that there was a significant difference between the positive control group and the negative control group and P3 treatment with a significance value of p=0.046. The Linear Regression Test for the thickness of the aortic intima showed an R Square (R2) value of 0.533, which means that the red flesh of watermelon extract had a 53.3% effect on the thickness of the aorta, while the remainder was influenced by other factors not examined in this study.

DISCUSSION

The results of the study showed that the positive control, namely feeding high-fat food without being given red watermelon fruit extract, had a higher average thickness of the aortic intima and a higher number of coronary artery foam cells than the negative control. This is in accordance with the theoretical basis which states that a high-fat diet can cause dyslipidemic conditions which result in oxidation reactions by ROS and will result in endothelial dysfunction and the formation of Ox-LDL. This will result in decreased NO bioavailability, decreased endothelin-1 production, inflammation, increased monocyte aggregation, and increased expression of adhesion molecules such as ICAM-1 and VCAM-1. Aggregated monocytes will turn into macrophages due to mCSF stimulation. The macrophages formed will bind to Ox-LDL, CD 36 receptors, and LOX-1 macrophages. This situation results in the formation of foam cells. After the formation of foam cells, several genes such as PDGF, FGF, HB-EFG, and TGF-β will be active so that smooth muscle cells (SMC) will proliferate and migrate from the tunica mendia to the intima of the arteries/aorta. This will continue continuously if the risk factors are not managed properly, which can result in the accumulation of foam cells and smooth muscle cells resulting in thickening of the intima until atherosclerotic plaque forms (Darwin, 2018). These results also support the theory that treatment with ethanol extract of the red flesh of watermelon (Citrullus lanatus) plays a role in reducing LDL cholesterol levels in male Wistar rats fed a high-fat diet. LDL is one of the precursors for the formation of foam cells and plaque, or it could be said that the formation of LDL runs linearly with the formation of foam cells and plaque. Previous research showed that there is antioxidant content in the form of lycopene and flavonoids as well as substances that have anti-hypercholesterolemia properties, namely citrulline, in red watermelon. These substances have the effect of inhibiting the work of the HMG-CoA reductase enzyme which plays a role in cholesterol synthesis and can reduce LDL levels (Santosa, Trimurtini & Hasan, 2018).

Treatment group 1 with 250 mg of watermelon red flesh extract, treatment group 2 with 500 mg of watermelon red flesh extract and treatment group 3 with 750 mg of watermelon red flesh extract had a thinner aortic intima thickness than the positive control group. Likewise, the number of foam cells also decreases. This is in accordance with the hypothesis, namely that administration of watermelon (Citrullus lanatus) red flesh extract can have an effect on thinning of the aortic intima and a decrease in foam cells in the Wistar rat (Rattus norvegicus strain Wistar) model of atherosclerosis. Watermelon contains lycopene, flavonoids, vitamin C, vitamin E and alkaloids, which are antioxidants that can neutralize ROS formed due to the atherosclerosis process. Lycopene is the most powerful antioxidant compound in watermelon. When compared with other antioxidant compounds such as vitamins C and E, the power of watermelon lycopene as a scavenger, which is a molecule that acts to neutralize free radicals, is much more effective. Its ability as an antioxidant is twice that of beta-carotene (provitamin A) and ten times that of vitamin E. Lycopene can suppress the secretion of Very low Density Lipoprotein (VLDL) cholesterol in the

liver by reducing the inhibition of the flow of free fatty acids in adipose tissue which will reduce the formation of cholesterol. Apart from lycopene as an antioxidant, lycopene also has non-oxidative activity by inhibiting the action of the HMG-CoA reductase enzyme which plays a role in cholesterol synthesis in the liver, thereby providing a hypocholesterolemic effect, activating LDL receptors, and can increase LDL degradation (Husna LA et al., 2019). Lycopene is also a caratonoid which effectively suppresses the adhesion of molecules and monocytes to endothelial cells, causing a decrease in the number of monocytes in lesions, a decrease in phagocytes and a decrease in foam cell formation, thereby preventing the formation of atherosclerotic plaque. (Selvia and Vradinatika, 2020).

The flavonoid content is very effective in reducing free radicals and several studies also state that flavonoids can reduce the risk of atherosclerosis by inhibiting LDL oxidation. Flavonoids can also increase the effectiveness of vitamin C and anti-inflammatories (Nisa et al., 2015). The mechanism for preventing free radicals by flavonoids can be divided into three, namely: slowing the formation of ROS, breaking down ROS and regulating/protecting with antioxidants. Meanwhile, the anti-inflammatory mechanism of flavonoids works by directly inhibiting the activity of COX and lipoxygenase enzymes which causes inhibition of the biosynthesis of prostaglandins and leukotrienes which are the end products of the COX and lipoxygenase pathways (Susila Ningsih et al., 2023). Apart from flavonoids, watermelon also contains alkaloids which also function as antioxidants because they contain nitrogen atoms in their structure, these atoms have lone electron pairs which function to reduce free radical activity in the body (Hasan et al., 2022).

Vitamin C is an antioxidant that is able to neutralize oxidative stress through the electron donation/transfer process. Vitamin C is also effective in preventing lipid peroxidation caused by the accumulation of ROS. Vitamin C acts by donating electrons to prevent other compounds from being oxidized and scavenging anions. Vitamin C as an exogenous antioxidant can reduce free radicals so that it can inhibit lipid peroxidation and prevent cell damage (Wibawa et al., 2020). Apart from vitamin C, vitamin E also acts as an antioxidant which can stop free radical chain reactions. Initially, vitamin E will capture free radicals, but vitamin E then turns into vitamin E radicals so it requires the help of vitamin C. Vitamin C together with vitamin E can inhibit oxidation reactions by binding vitamin E radicals which are formed in the process of breaking free radical reactions by vitamin E becomes free vitamin E, so it functions again as an antioxidant. With these different working mechanisms, if these two vitamins are used they will be able to inhibit free radical activity (Rusiani et al., 2019).

Thus, from the research results it was found that the results were in accordance with the hypothesis, namely that the administration of watermelon (Citrullus lanatus) red flesh extract could influence the thinning of the aortic intima and reduce the number of foam cells in the Wistar rat (Rattus norvegicus strain Wistar) model of atherosclerosis.

The limitations of this research are as follows: No watermelon extract content test was carried out, so it is not known for certain what compounds are contained in the red flesh extract of watermelon, no toxicity test was carried out on watermelon red flesh extract, so the optimal dose of red flesh extract is not known watermelon.

CONCLUSION

Watermelon (Citrullus lanatus) red flesh extract at a dose of 750mg/kg BW had a significant effect on reducing the number of foam cells and thinning of the aorta intima of Wistar rats. Extract of the red flesh of watermelon (Citrullus lanatus) has an effect of 53.3% on the thinning of the aortic tunica intima of Wistar rats.

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