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The Reduction of Aortic Abdominal Malondialdehyde Levels in Hypercholesterolemia Rats after Administration of Probiotics

Penurunan Kadar Malondialdehid Aorta Abdominal Tikus Hiperkolesterolemia setelah Pemberian Probiotik

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ABSTRACT

Background: One of the risk factors for hypercholesterolemia is a high-fat diet. Hypercholesterolemia can cause an increase in free radicals in the body, one of which is malondialdehyde (MDA). Probiotics are food additives that have a positive effect on digestive health. The potential of probiotics as antihypercholesterolemia still requires further study.
Objectives: To determine the effect of adding probiotics on MDA levels of the abdominal aorta in a hypercholesterolemic rat model.
Methods: Nineteen male Wistar rats were divided into 5 groups: negative control (C-), positive control (C+), and three probiotic groups (T1, T2, and T3). The negative control group received standard food while the positive group received standard food and shortening. The probiotic group received standard feed and white butter, with probiotics at three different doses as treatment for 10 weeks. After termination, the abdominal aortic MDA levels were checked. Analysis of the data obtained used the Kruskal-Wallis test.
Results: The mean levels of abdominal aortic MDA were 1.78 ± 0.11 nmol/g, 5.23 ± 0.51 nmol/g, 4.02 ± 0.02 nmol/g, 3.46 ± 0.16 nmol/g, and 2.20 ± 0.06 nmol/g for groups C-, C+, T1, T2, and T3, respectively. The statistical analysis showed that there was a significant difference in the abdominal aortic MDA levels ($p<0.05$). The T3 group showed the lowest abdominal aortic MDA levels of all.
Conclusions: The administration of probiotics to male Wistar rats induced by shortening had a significant effect on the abdominal aortic MDA levels.

INTRODUCTION

Based on the facts stated on the official website of the World Health Organization (WHO) (2021), 17.9 million people died from cardiovascular diseases in 2019[1]. This data increased by 0.6 million compared to that in 2010[1,2]. This number requires attention and alertness as it represents 32% of the total global deaths[1]. Efforts to prevent and reduce the number of deaths due to cardiovascular diseases are crucial. Among the ways to prevent the development of cardiovascular diseases is to reduce the major risk factors. The main underlying cause of such disease is atherosclerosis. Atherosclerosis is a vascular disease caused by accumulation of fat, inflammatory response, and fibrosis of the wall of an artery[3]. Atherosclerotic lesions in the aorta occur in the abdominal aorta more frequently than in the thoracic aorta although the mechanisms involved in such vulnerability have not been fully understood[4].

The key factor in atherosclerosis is high levels of cholesterol in the blood commonly called hypercholesterolemia[5]. In hypercholesterolemia, there is a disturbance in cholesterol metabolism. Such metabolic process can produce free radicals[6]. Lipid peroxidation by free radicals will increase the levels of toxic aldehyde compounds. Malondialdehyde (MDA) is among these toxic aldehyde compounds[7]. The condition of hypercholesterolemia can be influenced by such factors as excessive consumption of fatty foods, lack of physical activity, and too little fiber intake[8]. Among the fatty foods frequently consumed by Indonesians is white butter. It is widely used in the process of cake and bread making[9].

The development of therapy for hypercholesterolemia seeks alternative forms of therapy, including the use of probiotics[10]. Probiotics are living organisms found in food that can provide antihypercholesterolemic effects[11]. Probiotics have some significant effects on cholesterol levels. Studies have

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shown decreases in triglycerides and low-density lipoprotein (LDL) owing to probiotics, thereby reducing the total cholesterol levels in the blood[12]. Probiotics have several mechanisms of action in reducing cholesterol levels, including deconjugation of bile salts by the Bile Salt Hydrolase (BSH), assimilation of cholesterol, and conversion of cholesterol to coprostanol[13]. The use of probiotics is considered a beneficial adjunctive therapy in dyslipidemia[10,14]. Based on the high prevalence of hypercholesterolemia, people's high-fat diets, and facts about probiotics from previous research, this study aims to examine the effect of probiotic administration on the abdominal aortic MDA levels of hypercholesterolemic male Wistar rats. The research was carried out on experimental animals because the observation was made on the abdominal aorta variable, which is more appropriate for application to experimental animals. The probiotics used in this study were probiotics with registered trademark and fixed levels.

METHODS

This was an experimental study with the treatment given in the form of a high-cholesterol diet. A total of 3 g of white butter was administered per day to induce hypercholesterolemia. Intervention with probiotics at increasingly graded doses for 10 weeks was made after the induction of hypercholesterolemia[15].

Research Subjects

The experimental animals involved were 19 male white Wistar rats (*Rattus norvegicus*). The rats were divided into five treatment groups. Each group received different treatment. The negative control group (C-) received 20 g/day of standard BR-II feed, ad libitum drinking water, and 3 cc of distilled water per day through a feeding tube. The positive control group (C+) was given standard feed and 3 g/day of white butter through a feeding tube. Meanwhile, the T1 group was given standard feed, 3 g/day white butter, and probiotics at a dose of 1.65 x 106 cfu/g/day. The T2 group was given standard feed, 3 g/day white butter, and probiotics at a dose of 5.5 x 106 cfu/g/day. The T3 group was given standard feed, 3 g/day white butter, and probiotics at a dose of 1.65 x 107 cfu/g/day. The duration of treatment was 10 weeks conducted in a laboratory of the Faculty of Medicine, Universitas Islam Indonesia.

Induction of Hypercholesterolemia

Hypercholesterolemia was induced by administering 3 g of white butter per day to each experimental animal. White butter was administered through a feeding tube, first by melting and then cooling it before being administered to the experimental animals. The dose of the white butter was 3 g/day with a duration of administration of 10 weeks[15]. Hyperlipidemia in rats is characterized by a total cholesterol level of >130 mg/dl, LDL level of >60 mg/dl, triglyceride level of >100 mg/dl, and HDL level of < 50 mg/dl[16].

Probiotics

The probiotics used in this study were powdered probiotics from the brand Lacto-B®. The probiotics contain $4.7x10^7$ cfu/g Lactobacillus acidophilus bacteria and have obtained a distribution permit from the Food and Drug Supervisory Agency (BPOM) as a health supplement. The doses of the probiotics administered referred to those in previous research[17], which were 1.65 x 109 cfu/kg (0.04 g Lacto-B®) for T1, 5.5 x 109 cfu/kg (0.12 g Lacto-B®) for T2 , and 1.65 x 1010 cfu/kg (1.2 g Lacto-B®) for T3. These doses emulated those from previous research, in which 1.65 x 109 cfu bacteria/kg was a low dose, 5.5 x 109 cfu bacteria/kg was a medium dose, and 1.65 x 1010 cfu bacteria/kg was a high dose[17]. Prior to administration through a feeding tube, the probiotics were diluted using 0.5 cc of distilled water.

Measurement of Abdominal Aortic Malondialdehyde

The abdominal aortic homogenate was prepared by crushing all the abdominal aorta of the rat. A total of 500 µl of 0.9% NaCl was added for the homogenization process. The homogenate liquid was collected and then centrifuged at a speed of 8000 rpm for 20 minutes. A total of 100 µl of centrifugation supernatant was placed in a microtube, and 550 µl of distilled water was added for another homogenization. Then, 100 µl of 1% Na-Thio and 100 µl of 1 N HCl were added and then homogenized. After the process of heating for 10 minutes, the tube was cooled and then centrifuged. The abdominal aortic MDA measurement was carried out using a spectrophotometer at a wavelength of 532 nm to measure the absorbance[19].

Data Analysis

The data on the abdominal aortic MDA levels of the rats was analyzed using the Kruskal-Wallis test with the Mann-Whitney post hoc test.

Research Ethics

The research has passed the ethical review and obtained the approval letter No. 33/Ka.Kom.Et/70/KE/2019 from the Health Research Ethics Committee of the Faculty of Medicine of Universitas Islam Indonesia.

RESULTS AND DISCUSSION

Based on the results of spectrophotometric measurements, the mean and standard deviation for each treatment group is shown in Table 1. They are 1.78 ± 0.11 nmol/g in group C-, 5.23 ± 0.51 nmol/g in group C+, 4.02 ± 0.02 nmol/g in group T1, 3.46 ± 0.16 nmol/g in group T2, and 2.20 ± 0.06 nmol/g in group T3 (Table 1). The results of the ANOVA statistical test showed that there were significant differences among the groups.

Table 1. Mean and SD of abdominal aortic MDA levels

Group	n	Mean ± SD	p-value
C-	4	1.78 ± 0.11 nmol/g	0.002*
C+	4	5.23 ± 0.51 nmol/g	
T1	3	4.02 ± 0.02 nmol/g	

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Group	n	Mean ± SD	p-value
T2	4	3.46 ± 0.16 nmol/g	
T3	4	2.20 ± 0.06 nmol/g	

C-: negative control group, C+: positive control group, T1: treatment group 1, T2: treatment group 2, T3: treatment group 3
SD: standard deviation, n: number of experimental animals
*) significant results from the Kruskal-Wallis statistical test

From these results, it was found that the negative control group (C-) had the highest mean of SOD (superoxide dismutase) level while the SOD level in group C+ had the lowest mean. In the treatment group, the greater the probiotic doses, the greater the mean abdominal aortic SOD levels. Meanwhile, the statistical analysis using the Shapiro-Wilk normality test resulted in p >0.05 in groups C-, C+, T2, and T3, whereas in group T1 the value was p <0.05. This indicated that the research data was not normally distributed, leading to a failure to fulfill the One-Way ANOVA test requirement. The Kruskal-Wallis test was then carried out as an alternative, resulting in p = 0.002. The obtained p value indicated that there was at least a significant difference in the abdominal aortic MDA levels between two groups. To identify such differences, a Mann-Whitney post hoc test was carried out among the groups.

Based on the results of data analysis, it was found that the average abdominal aortic MDA levels of the rats from the lowest to the highest were in groups C- (1.78 nmol/g), T3 (2.20 nmol/g), T2 (3.46 nmol/g), T1 (4.02 nmol/g), and C+ (5.23 nmol/g). This indicated that administering a white-butter diet at a ratio of 1:5 for 10 weeks could increase the abdominal aortic MDA levels of male Wistar rats. This was shown by the abdominal aortic MDA level of male Wistar rats in the negative control that was lower than that in the positive control group.

From previous research, it was found that male Wistar rats given a white-butter diet and standard feed at a dose ratio of 1:5 and 1:10 for 6 weeks could experience an increase in abdominal aortic wall thickening compared to the negative control group although the changes were insignificant[15]. Another study involving Wistar rats induced by high cholesterol for 10 weeks resulted in increased serum and aortic MDA levels. The MDA levels in the serum and aorta of the control group were 5.70 ± 0.55 nmol/ml and 4.04 ± 0.39 nmol/ml, respectively. Meanwhile, in the hypercholesterolemia group, the MDA levels in the serum and aorta reached 8.90 ± 0.27 nmol/ml and 6.16 ± 0.90 nmol/ml. These results showed that there was a significant difference in the MDA levels (p <0.01) between the hypercholesterolemia group and the control group[20].

The results of this study showed that group C- had the lowest mean abdominal aortic MDA levels. This group did not receive induction of hypercholesterolemia, so it was unlikely to form many free radicals. On the other hand, in the group C+, the mean abdominal aortic MDA level was the highest. This condition was caused by the consumption of high cholesterol without any treatment to reduce the cholesterol levels. Such condition resulted in a high number of free radicals in the body, leading to an increased MDA level[21].

In hypercholesterolemia, the homeostasis of cholesterol level is maintained by the body by converting cholesterol into bile acids. In this process, the 7α-hydroxylated compounds are the first-stage and most important compounds. Such compounds will be catalyzed by the cholesterol 7α-hydroxylase enzyme, a microsomal enzyme that requires oxygen, cytochrome P450, and NADPH in its catalysis process. This process then produces superoxide free radicals (O_2^-) as a byproduct. This condition leads to oxidative stress, in which an imbalance occurs between the number of free radicals and that of antioxidants in the body[22].

Continuous oxidative stress conditions can lead to lipid peroxidation. This process produces a final by-product in the form of MDA compounds that can be used as a biomarker to assess the oxidative stress levels[23]. When the number of free radicals in the body increases beyond normal limits, additional antioxidants are needed from an external source. One form of antioxidants from outside the body is probiotics. Probiotics possess several mechanisms that can help increase the number of antioxidants in the body to fight free radicals[24].

In this study, there were three treatment groups of male Wistar rats given probiotic intervention at various doses. The probiotic doses in this study were based on previous research that administered probiotics at three different doses[17]. Probiotics at a dose of 1.65 x 1010 cfu/kg (high dose), 5.5 x 109 cfu/kg (medium dose), and 1.65 x 109 cfu/kg (low dose) for hypercholesterolemic rats could reduce the levels of total cholesterol, triglycerides, and LDL[17]. The mean abdominal aortic MDA levels from the lowest to the highest in the treatment groups were T3 (2.20 nmol/g), T2 (3.46 nmol/g), and T1 (4.02 nmol/g). This indicates that the higher the probiotic doses, the lower the MDA levels. Meanwhile, significant differences were found between T1 and T2, T1 and T3, and T2 and T3 MDA levels (p value <0.05). The lowest abdominal aortic MDA levels were found in the third treatment group (T3), which was the group of hypercholesterolemic male Wistar rats given an intervention with a high dose of probiotics. The low MDA levels are associated with the role of probiotics as an antihypercholesterolemia. Consuming probiotics can reduce hypercholesterolemia, thus lowering oxidative stress[13]. The results of this research are in line with a previous study that found a decrease in the total cholesterol levels after the administration of probiotic supplement[25].

Probiotics have several mechanisms of action in reducing cholesterol levels, including by assimilating cholesterol into bacterial cell membranes, deconjugating bile salts, converting cholesterol into coprostanol, producing short-chain fatty acids during probiotic growth, and influencing the carrier protein gene expressions[26]. Assimilation of cholesterol into bacterial cell membranes can reduce the amount of cholesterol absorbed from the small intestine into the blood, thereby reducing cholesterol levels in the blood serum[10]. Another mechanism is deconjugation of bile salts assisted by the

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Bile Salt Hydrolase (BSH). Unconjugated bile acids are less soluble than conjugated bile acids, making it more difficult for unconjugated bile acids to be absorbed by the lumen of the small intestine. These unconjugated bile acids will later be excreted from the body through feces[13]. In addition, probiotics produce short-chain fatty acids that can prevent the HMG-CoA performance, thereby inhibiting cholesterol biosynthesis. One of these short-chain fatty acids is butyrate[27].

Probiotics can inhibit cholesterol absorption in the intestine by inhibiting the Niemann Pick C1-like 1 (NPC1L1) transporter. The NPC1L1 transporter is expressed on the surface of enterocytes and assists the absorption of cholesterol in the intestinal lumen. The Niemann-Pick C1-like 1 (NPC1L1) protein plays a central role in intestinal cholesterol absorption and is the target of ezetimibe, a drug that inhibits NPC1L1 to reduce cholesterol absorption[28]. In addition, lactobacillus has the ability to mediate the expression of the NPC1L1 gene and other genes to inhibit cholesterol absorption[29].

Probiotics not only have an antihypercholesterolemic effect but also play a role as antioxidants[30]. Probiotics can reduce oxidative stress[31]. In addition, probiotics have the ability to chelate metal ions, that is the ability to capture metal ions and prevent metal ions from catalyzing oxidation. The results of this research indicate that strains of lactic acid bacteria, such as Lactobacillus casei KCTC 3260, have high antioxidant capacity by chelating Fe^{2+} or Cu^{2+}. Probiotics can also improve the work of antioxidant system of the host body cell through the antioxidant enzyme system. Like animals, probiotics also have an antioxidant enzymatic system. One of these antioxidants is SOD (superoxide dismutase)[32]. The SOD compounds can catalyze the breakdown of superoxide into hydrogen peroxide and water, and they are a chief regulator to control ROS levels (reactive oxygen species)[24]. Although the antioxidant pathway is considered as one of the mechanisms for lowering cholesterol levels, the pathway of such mechanism involves complex signals, thus requiring further studies[32].

CONCLUSIONS

There was an effect of probiotic administration on the abdominal aortic MDA levels of male Wistar rats in a model of white-butter-induced hypercholesterolemia. Abdominal aortic MDA levels are inversely proportional to the dose of probiotics being administered. The higher the probiotic doses, the lower the MDA levels. This study provides an overview of MDA levels specifically in the segment of abdominal aortic blood vessel. However, this study has yet to be completed with histopathological features. Therefore, it is recommended that future research can include histopathological observations of the abdominal aorta.

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Conflict of Interest and Funding Disclosure

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Author Contributions

ABCD: conceptualization, data curation, formal analysis, investigation, methodology, roles/writing-original draft; RLA: conceptualization, funding acquisition, investigation, methodology, project administration, supervision, validation; MDP: conceptualization, methodology, supervision, validation, writing-review & editing.

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