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Bioactivity and Health Effect of Black Garlic on Hydroxy Methylglutaryl-CoA Reductase Enzyme Activity in Male Obese *Rattus Norvegicus Strain Wistar*

Bioaktivitas dan Efek Kesehatan Bawang Hitam terhadap Enzim Reduktase Hidroksi Metilglutaril-KoA Pada Tikus Putih Jantan Obesitas

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Abstract

Obesity is a condition of abnormality or excess fat accumulation in adipose tissue. HMG-CoA reductase is an enzyme that can catalyse HMG-CoA into mevalonate, which is needed in cholesterol biosynthesis. Inhibition of the HMG-CoA reductase enzyme is an effective drug target mechanism to overcome dyslipidemia. Black garlic, which is high in antioxidants such as SAC, flavonoids, and polyphenols, is an effective mechanism. This study tested the bioactivity and health effects of black garlic on the activity of HMG-CoA reductase enzyme. This type of experimental study on male rats uses a post-test control-only group design. The sample in this study was 25 experimental animals divided into five groups, group negative control with a regular diet, group positive control with a high-fat diet, group treatment 1 with a high-fat diet and black garlic dose of 200 mg/rats, group treatment 2 with a high-fat and black garlic diet dose of 400 mg/rats, and group treatment given a high-fat diet and black garlic dose of 800 mg/rats. The results of the study showed that the average value and standard deviation of HMG-CoA in the negative control group were 1,044 and 0.088, the positive control group 2,136 and 0.487, the 1 group treatment 1,292 and 0.194, the 2 group treatment 1,296 and 0.206 and the three treatment group 1,201 and 0.201 nmol/min/mg protein. Based on the results of the hypothesis test, the significance level for the five groups was 0.004, indicating a significant difference in the average HMG-CoA levels in groups K1, K2, P1, P2, and P3. Black garlic significantly decreased HMG-CoA reductase activity in rats fed a high-fat diet, supporting its potential as a natural therapeutic agent for dyslipidemia management.

***Keywords:* Black Garlic; HMG-CoA; Mevalonate; Obesity; Rattus Novergicus.**

Abstrak

Obesitas merupakan kondisi ketidaknormalan atau kelebihan akumulasi lemak pada jaringan adiposa. HMG-CoA *reductase* merupakan enzim yang dapat mengkatalisis HMG-CoA menjadi mevalonate yang diperlukan dalam biosintesis kolesterol. Penghambatan terhadap enzim HMG-CoA *reductase* merupakan mekanisme target obat yang efektif untuk mengatasi dyslipidemia adalah black garlic yang tinggi antioksidan seperti SAC, flavonoid, dan polifenol. Penelitian ini menguji bioaktivitas dan efek kesehatan bawang hitam terhadap aktivitas enzim HMG-CoA reduktase. Jenis penelitian *experimental* pada hewan coba tikus jantan dengan desain penelitian *post-test control only group design*. Sampel dalam penelitian ini hewan coba sebanyak 25 ekor yang dibagi menjadi 5 kelompok yaitu kelompok kontrol negetif dengan diet normal, kelompok kontrol positive dengan diet tinggi lemak, kelompok perlakuan 1 dengan diet tinggi lemak dan black garlic dosis 200 mg/ekor tikus, kelompok perlakuan 2 dengan tinggi lemak dan diet black garlic dosis 400 mg/ekor tikus, dan kelompok perlakuan 3 diberikan diet tinggi lemak dan *black garlic* dosis 800 mg/ekor tikus. Hasil penelitian didapatkan nilai rata-rata dan standar deviasi HMG-CoA pada kelompok K1 negatif 1.044 dan 0,088, kelompok K2 positif 2.136 dan 0,487, kelompok P1 1.292 dan 0,194, kelompok P2 1.296 dan 0,206 dan kelompok P3 1.201 dan 0,201 nmol/min/mg protein. Berdasarkan hasil uji hipotesis, signifikansi dari lima kelompok tersebut sebesar 0.004 yang berarti terdapat perbedaan yang signifikan atau nyata bermakna rata-rata HMG-CoA pada kelompok kontrol negatif, kontrol positif, perlakuan 1, perlakuan 2, dan perlakuan 3. Bawang hitam secara signifikan menurunkan aktivitas enzim HMG-CoA reduktase pada tikus dengan diet tinggi lemak, sehingga mendukung potensinya sebagai agen terapi alami untuk manajemen dislipidemia

Keywords*: *Black Garlic; HMG-CoA; Mevalonate; Obesity; Rattus Novergicus.

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Introduction

Obesity has reached epidemic proportions worldwide, with over 1 billion people classified as obese in 2022, representing 13 % of the global population. Projections indicate that by 2035, around 1.9 billion adults, approximately 25 % of the world's population, will be affected. Looking further ahead to 2050, it is estimated that 3.80 billion adults, representing more than half of the anticipated global adult population, will be living with overweight or obesity. [1]. Indonesia's obesity rate increases by 3.9 per cent annually. Southeast Asia has the highest obesity rate. Obesity is caused by the accumulation of lipids in adipose tissue. Lipids are broken down into fatty acids and glycerol during lipolysis, which can be oxidised to provide energy. Cholesterol can also be produced by the liver with the help of an enzyme called hydroxymethylglutaryl-CoA (HMG-CoA) reductase, which is then released into the bloodstream [2]. Cholesterol synthesis occurs from the breakdown of carbohydrates, proteins, or fats in the form of acetyl-CoA. Cholesterol formation occurs through an enzymatic reaction in the mevalonate pathway, where the enzyme HMG-CoA reductase plays a role in catalysing the conversion of HMG-CoA to mevalonate [3–5].

This risk can lead to metabolic syndrome, which can lead to dyslipidemia. Dyslipidemia causes impaired lipoprotein metabolism, characterised by increased total cholesterol, increased low-density lipoprotein cholesterol, increased triglycerides, and decreased high-density lipoprotein cholesterol [6,7]. Treating dyslipidemia can also involve traditional remedies such as black garlic. Black garlic, a processed garlic product, has biological functions such as antioxidant, anti-inflammatory, anticancer, anticardiovascular, antidiabetic, anti-obesity, antibacterial, and immunomodulatory properties [8]. Black garlic can reduce body weight, adipose tissue mass, serum triglycerides, cholesterol, and low-density lipoprotein [9,10]. Black garlic inhibits 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase [11]. Inhibition of HMG-CoA reductase effectively reduces cholesterol production by activating regulatory sterol-binding proteins, which in turn upregulate HMG-CoA reductase and LDL receptors within hepatocyte membranes, leading to increased extrahepatic tissue activity, resulting in lower cholesterol levels [3,4].

Black garlic contains slightly different substances from garlic. Heating will cause the change of GSAC (γ-glutamyl-S-allylcysteine) to SAC (S-allyl cysteine) [12]. This heating process induces many chemical reactions in garlic, such as enzymatic browning and the Maillard reaction, which causes the colour to change from white and yellow to dark brown [13,14]. Black garlic contains biologically active compounds such as SAC, S-allylmercaptocysteine (SAMC), allyl sulphides, diallyl polysulphides, flavonoids, polyphenols, leucine, isoleucine, cysteine, phenylalanine, tyrosine, fructans, and methionine [15,16]. The SAC content in black garlic is higher than in white garlic due to the heating process. Black garlic contains 106.1 mg/kg of SAC, five times higher than garlic, which has a SAC content of 21.0 mg/kg. The heating process reduces the alliin content in garlic, while SAC increases [16,17].

Research by Hasim et al. (2018) found that consuming black garlic for six weeks can lower blood LDL concentrations in obese adults [18]. Research by Tran et al. (2018) found that a single clove of black garlic improves dyslipidemia. Research by Huang et. al. (2015) found that black garlic can reduce dyslipidemia in male Sprague-Dawley rats with diabetes mellitus [19]. Research by Huang et al. (2023) found that black garlic can reduce body weight, serum triglycerides, and liver lipid profiles in male Wistar rats on a high-energy diet [20]. Research on black garlic has been extensive in recent years. However, research investigating its therapeutic effects remains very limited. Therefore, the author is interested in researching the bioactivity and health effects of black garlic on the activity of HMG-CoA reductase enzyme in obese male *Rattus Novergicus*.

Experimental Section

Plant collection and identification

The Black Garlic used is fermented single-clove garlic. The garlic is a local Indonesian variety native to Bogor Regency, West Java, and its surroundings. The garlic is fermented for 21 days at a temperature of 70 degrees Celsius and 80% humidity. This Black Garlic is a product processed by Serambi Botani IPB with MD 655628009776. This black garlic is weighed according to each dose for each rat, namely 200 mg/rat, 400 mg/rat, and 800 mg/rat. The black garlic is ground until smooth and mixed with aquades solution to make it easier to administer to the rats.

Equipment and Chemicals

A serum examination was performed using the HMG-CoA reductase test kit from Sigma-Aldrich Co. (St Louis, MO, USA). The concentration of the HMG-CoA reductase stock solution was 0.5–0.75 nmol/min/mg protein. The absorbance was measured at 340 nm after 10 minutes using a spectrophotometer, and the results were expressed in nmol/min/mg protein.

Animals

The Biomedical Laboratory, Faculty of Medicine, Andalas University, provided healthy, active adult male Wistar rats weighing 200 g and aged 2 months. They were maintained in the laboratory, fed standard feed, and had access to drinking water ad libitum. This study was conducted with the approval of the Ethics Committee of the Faculty of Medicine, Andalas University, and in accordance with ethical standards in medical research (ethics permit number: 520/UN.16.2/KEP-FK/2024, issued on October 4, 2024).

Method

Stage 1: Establishment of an Obese Rat Model

Male Wistar rats weighing 200g were fed a high-fat diet (HFD; 2 ml goat oil and 1 ml egg yolk) for 16 weeks, administered via a tube every morning between 9:00 and 10:00 a.m. WIB. After 16 weeks, body weight and body length were measured to determine the Lee obesity index (equivalent to human BMI), calculated using the formula

$$\text{Lee Obesity Index} = \frac{\sqrt[3]{w}}{L}$$

Description: W is the weight of the rats (g) and L is the length of the rat's body from nose to anus (cm). Rats with a Lee index value of 0.300 or higher are considered obese.

Stage 2: Experiment

Based on the sample calculation results using Federer's (1991) formula, the minimum sample size was 5 for each treatment group. Therefore, the total number of rats used in this study was 25 for the five treatment groups, with a minimum reserve of 20%. The total number of rats was 35, divided into five groups of 7 each. These treatment groups were administered for 28 days:

1. Negative Control Group (K1): Normal diet and placebo probe (water).
2. Positive Control Group (K2): High-fat diet (HFD) and placebo probe (water).
3. Treatment Group 1 (P1): High-fat diet (HFD) and black garlic probe (200 mg/rats).

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4. Treatment Group 2 (P2): High-fat diet (HFD) and black garlic probe (400 mg/rats).
5. Treatment Group 3 (P3): High-fat diet (HFD) and black garlic tube at a dose of 800 mg/rats.

Body weight, body length, and activity levels were monitored weekly. Activity levels were assessed by observing aggressive or sedentary behaviour. Body weight was measured by weighing the rats, and body length was measured from nose to anus with a tape measure after the rats were anaesthetised with chloroform. HMG-CoA reductase enzyme parameters were determined on the last day of the experiment using Serum examination using the HMG-CoA reductase test kit from Sigma-Aldrich Co. (St Louis, MO, USA) using a spectrophotometer and the results were expressed in nmol/min/mg protein.

Statistical Analysis

The data are presented as the mean ± standard deviation (SD) from three independent experiments ($p<0.05$). All statistical analyses were performed using IBM SPSS Statistics for Windows version 22.0 (IBM Corp., Armonk, NY).

Research Result and Discussion

The results of the HMG-CoA Reductase enzyme activity Serum examination using the HMG-CoA reductase test kit from Sigma-Aldrich Co. (St Louis, MO, USA) using a spectrophotometer were expressed in nmol/min/mg protein.

Table 1. Mean and Standard Deviation of HMG-CoA Reductase Enzyme Activity

Group	N	Rate (X±SD) nmol/min/mg protein HMG-CoA
Negative Control (K1)	5	1.044 ± 0.088
Positive Control (K2)	5	2.136 ± 0.487
Treatment 1 (P1)	5	1.292 ± 0.194
Treatment 2 (P2)	5	1.296 ± 0.206
Treatment 3 (P3)	5	1.204 ± 0.201
Total	25	1.3944 ± 0.46164

This research was conducted with 25 male Wistar strain *Rattus novergicus* and 10 reserve rats. The animals were divided into five groups: negative control 1, a negative control with a regular diet; positive control 2, a high-fat diet; Treatment 1, a high-fat diet and black garlic at a dose of 200 mg/rat; Treatment 2, a high-fat diet and black garlic at a dose of 400 mg/rat; and treatment 3, a high-fat diet and black garlic at a dose of 800 mg/rat. The results of the study were obtained Based on table 1, it can be seen that the average value mean and standard deviation of HMG-CoA in the negative control were 1,044 and 0.088, the positive control 2,136 and 0.487, the treatment 1 (P1) 1,292 and 0.194, the treatment 2 (P2) 1,296 and 0.206 and the treatment 3 (P3) 1,201 and 0.201 nmol/min/mg protein.

Table 2. Mean ranks and statistics test of HMG-CoA Reductase Enzyme Activity

Group	N	Mean rank (nmol/min/mg protein) HMG-CoA
Negative Control (K1)	5	5.10
Positive Control (K2)	5	23.00
Treatment 1 (P1)	5	12.90
Treatment 2 (P2)	5	13.00
Treatment 3 (P3)	5	11.00
Chi-Square		15.397
Sig		0.004

Based on the results of the hypothesis, the Kruskal-Wallis test, the significance of the five groups was 0.004, which means there was a significant or real difference in the average HMG-CoA in the negative control, positive control, treatment 1, treatment 2, and treatment 3. Black garlic supplementation significantly decreased HMG-CoA reductase activity in rats fed a high-fat diet. The results of the Dunn test showed that the positive control group had a significant p-value of <0.05 for all groups. The significant values for the

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negative control group were (p value 0.000), treatment group 1 (p value 0.001), treatment group 2 (p value 0.001), and treatment group 3 (p value 0.000).

Discussion

The results of the HMG-CoA Reductase enzyme. This research was conducted with 25 male Wistar strain Rattus novergicus and 10 reserve rats. The animals were divided into five groups: negative control 1, a negative control with a regular diet; positive control 2, a high-fat diet; Treatment 1, a high-fat diet and black garlic at a dose of 200 mg/rat; Treatment 2, a high-fat diet and black garlic at a dose of 400 mg/rat; and treatment 3, a high-fat diet and black garlic at a dose of 800 mg/rat. Based on the average mean and standard deviation values of the HMG-CoA reductase enzyme, it can be seen that in the negative control group, the HMG-CoA reductase enzyme was very low. In the positive control group given the HFD diet, there was an increase in the HMG-CoA reductase enzyme, while in treatments 1, 2 and 3 given the HFD diet and black garlic, there was a decrease in the HMG-CoA reductase enzyme. There were significant differences between the five groups with a p-value <0.05. Black garlic significantly reduced HMG-CoA reductase activity in rats fed a high-fat diet. Dunn's test results showed that the positive control group had a significant p-value <0.05 for all groups.

Research entitled S-Alk(en)yl cysteine of garlic inhibits cholesterol synthesis by deactivating HMG-CoA Reductase in cultured rat hepatocytes found that it can reduce HMG-CoA reductase activity by 30-40% without changing the amount of mRNA or enzyme protein [21,22]. Research on the effects of black garlic (Allium sativum) extract on lipid metabolism in rats fed a high-fat diet [23]. The results of the study on black garlic extract given for 5 weeks showed a significant decrease in mRNA expression of HMG-CoA reductase and ACAT compared to the control group on a high-fat diet and a decrease in SREBP-1c expression that led to decreased lipid and cholesterol synthesis. Several related studies have been conducted, including those on the effect of black garlic on cholesterol, which yielded statistically significant differences in cholesterol levels before and after black garlic administration in patients with type II diabetes mellitus. Other studies have shown that black garlic has quite sound effects on atherosclerosis and hyperlipidemia by lowering cholesterol [24,25].

Obesity is a condition of excessive fat accumulation in adipose tissue [26]. Fat metabolism begins with the hydrolysis of triacylglycerol into glycerol and fatty acids, where glycerol can enter the glycolysis or gluconeogenesis pathway, while fatty acids are catabolized through β-oxidation in the mitochondria [27]. The liver also plays a role in cholesterol synthesis through the mevalonate pathway that occurs in the cytosol and endoplasmic reticulum, with the enzyme HMG-CoA reductase as the primary catalyst for the conversion of HMG-CoA to mevalonate, a cholesterol precursor [2,28–30]. Inhibition of this enzyme has been shown to effectively reduce cholesterol production through the regulation of LDL receptors and sterol-binding proteins [3,4]. Next, mevalonate undergoes a series of enzymatic reactions to form isopentenyl pyrophosphate (IPP), farnesyl pyrophosphate (FPP), and finally squalene, which, through cyclisation, is converted to lanosterol, then modified into cholesterol [19,28,31].

HMG-CoA can be formed in mitochondria and cytosol with different functions: in mitochondria, HMG-CoA plays a role in the formation of ketone bodies (acetoacetate, β-hydroxybutyrate, and acetone) and leucine oxidation products, while outside mitochondria, HMG-CoA plays a role in the synthesis of isoprenoids and cholesterol [11,23,32]. Cholesterol synthesis begins with the condensation of two acetyl-CoA molecules into acetoacetyl-CoA by the enzyme thiolase/ACAT, followed by the formation of HMG-CoA through the catalysis of HMG-CoA synthase, then reduced to mevalonate by the enzyme HMG-CoA reductase with the help of NADPH. Next, mevalonate is converted into the active isoprenoids isopentenyl-5-pyrophosphate (IPP) and dimethylallyl pyrophosphate (DMAPP) with the involvement of three ATP molecules [2,28,33,34].

HMG-CoA reductase is an enzyme involved in the formation of cholesterol and other isoprenoids in the body through the mevalonate pathway [3]. One mechanism for lowering blood cholesterol levels is through inhibiting mevalonate formation by inhibiting the HMG-CoA reductase enzyme [11,19]. Drugs that work through this pathway include statins such as simvastatin. Allium sativum is predicted to be a compound capable of inhibiting the HMG-CoA reductase enzyme, thereby lowering blood cholesterol levels [31]. HMG-CoA reductase is an enzyme that catalyses the conversion of HMG-CoA to mevalonate, which is essential for cholesterol biosynthesis. Inhibition of HMG-CoA reductase is an effective drug target mechanism for treating dyslipidemia [23,35].

Black garlic is the result of a 21-day fermentation of garlic. Its optimal content of the antioxidant compound S-allyl-cysteine (SAC) is achieved after 21 days of fermentation. Black garlic has a SAC twice as

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high and a DADS level 30 times higher than raw garlic [12]. SAC has no more than 4% of the toxicity of allicin and DADS [8]. At this fermentation stage, black garlic contains a total polyphenol content of 538.33 mg GAE/g (GAE: gallic acid equivalents). The increased SAC and polyphenol compounds function as antioxidants [36]. Black garlic contains 106.1 mg/kg of SAC, five times higher than garlic, which contains 21.0 mg/kg. This is because heating converts unstable compounds in garlic, including alliin, into more stable compounds, one of which is SAC. The heating process decreases the alliin content in garlic, while SAC increases [8,16,17].

The study assumed that each rat was an independent subject randomly allocated to a treatment group under uniform rearing conditions. HMG-CoA reductase enzyme activity was measured using a valid and reliable method for continuous-scale data. The Kruskal–Wallis test with Dunn's extended test was chosen based on the small sample size and non-normal distribution of the data. Biologically, a high-fat diet is expected to increase HMG-CoA reductase enzyme activity, while black garlic administration decreases this enzyme activity, depending on the dose administered. Administering black garlic to mice on a high-fat diet can reduce HMG-CoA reductase enzyme activity. This is based on the bioactive compounds in black garlic, such as S-allyl cysteine (SAC), flavonoids, and polyphenols, which act as antioxidants. These compounds can inhibit HMG-CoA reductase enzyme activity by binding to the hydroxymethylglutaryl-CoA reductase enzyme reaction and inhibiting other enzymes, such as squalene monooxygenase and lanosterol-14-demethylase, thereby reducing oxidative stress that triggers increased cholesterol synthesis. Therefore, the higher the dose of black garlic administered, the greater the potential reduction in enzyme activity.

The researcher's limitation was the relatively small sample size (five rats per group), so the results obtained may not fully represent the broader population. The study only used male Wistar rats, so the effects of black garlic on other sexes or species cannot be generalised. The black garlic doses used were limited to three variations (200 mg, 400 mg, and 800 mg/head), thus not reflecting broader or optimal dose effects. Measurements focused solely on HMG-CoA reductase enzyme activity without evaluating other biochemical parameters related to the overall lipid profile. The study was conducted over a long period. This study was conducted over a limited period of time, thus not being able to explain the long-term effects of black garlic administration.

Based on the study's limitations, several recommendations need to be considered for further research. A larger sample size is needed to ensure higher statistical power and generalizability of the results. The use of experimental animals of different sexes or species can provide a broader picture of the effects of black garlic. More diverse dosage variations and optimal dose testing are needed to determine the limits of effectiveness and safety. Further research should not only assess HMG-CoA reductase enzyme activity but also include other biochemical parameters such as total cholesterol, LDL, HDL, and triglyceride levels to provide a more comprehensive picture of the lipid profile. Longer-term studies are needed to evaluate the chronic effects and potential toxicity of black garlic. Furthermore, human clinical trials are essential to ensure the relevance of animal test results to therapeutic applications in humans.

Conclusion

Based on the findings of this study, it can be concluded that the administration of black garlic (*Allium sativum* L.) at doses of 200 mg, 400 mg, and 800 mg per rat significantly decreased the activity of the hydroxy methylglutaryl-CoA (HMG-CoA) reductase enzyme in male Wistar rats induced with obesity through a high-fat diet. This inhibitory effect was demonstrated by the significantly lower mean HMG-CoA reductase activity in all treatment groups (P1: 1.292; P2: 1.296; P3: 1.204 nmol/min/mg protein) compared to the positive control group (2.136 nmol/min/mg protein), with a statistical significance value of $p < 0.05$. This bioactivity is likely attributed to the antioxidant compounds in black garlic, such as S-allyl cysteine (SAC), flavonoids, and polyphenols, which interfere with the mevalonate pathway of cholesterol biosynthesis. These results strongly support the potential of black garlic as a promising natural therapeutic agent for managing dyslipidemia associated with obesity.

Conflicts of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article are original and that they will bear any liability for claims relating to the content of this article.

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