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Original Article

Effect of Leunca Fruit (Solanum nigrum L.) on Oxidative Stress in rats fed a High Fat High Sucrose Diet

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ABSTRACT

Decreased levels of superoxide dismutase (SOD) and increased levels of malondialdehyde (MDA) are markers of oxidative stress and indicate obesity. Leunca fruit (Solanum Nigrum L) is a plant that contains antioxidants that can reduce the level of oxidative stress in obesity. The purpose of this study was to determine the effect of leunca fruit administration on SOD and MDA levels in obese rats. This type of research is true experimental with a post-test-only research design where 30 male Sprague Dawley rats were divided into five groups consisting of 2 control groups K(-) and K(+) and three treatment groups (P1, P2, P3). Groups K+, P1, P2, and P3 were fed a high-fat and sucrose diet (21% lard, 34% sucrose). The K (-) control group is a group of healthy rats that only receive standard feed without being given leunca fruit. Group K (+) is a group of obese rats without leunca fruit. Leunca fruit was given for six weeks at a dose of 0.8g (P1), 1.6g (P2), and 2.4g (P3). Serum SOD levels were measured by ELISA method and MDA levels were measured by TBARS method. Statistical analysis using One Way Anova test. Administration of leunca fruit with graded doses can significantly increase SOD activity p=0.000 ($p<0.05$) and can significantly reduce MDA levels in obese rats in each treatment group p=0.000 ($p<0.05$). Leunca fruit with a dose of 2.4g/BB rat is the most effective dose to increase SOD levels and reduce MDA levels. The limitation of this study that there is no weighing of the remaining rat feed at each meal, so that the percentage of rat intake is was unknown.

INTRODUCTION

Obesity is a condition in which there is an excess or abnormal accumulation of fat in the body and is measured in terms of increased body mass index, which may pose a danger to health.[1,2] High-fat and high-energy food sources cause high energy intake, while low energy expenditure is caused by a lack of physical activity and a sedentary lifestyle.[3] Based on data from the World Health Organization (WHO) by 2022, there will be more than 1 billion people worldwide with obese.[4] The prevalence of obesity in Indonesia is increasing from year to year. Basic Health Research (Riskesdas) data in 2018 shows the prevalence of adults aged >18 years who are obese, namely 2007 (10.5%), 2013 (14.8%) and 2018 (21.8%) with BMI>27.0.[5]

The imbalance between reactive oxygen species (ROS) and antioxidant system will lead to oxidative stress.[6] Obese individuals have increased levels of Malondialdehyde (MDA) and decreased Superoxide dismutase (SOD) activity, which characterizes oxidative stress. Oxidative stress occurs due to increased production of ROS in obese fat tissue that can damage all cell

components such as proteins, lipids, and DNA.[7] MDA is one of the radical oxidative markers and a compound that is derived from the peroxidation of polyunsaturated fatty acids[8]. It has been used as a biomarker to measure oxidative stress in various biological samples. Excess production of MDA is caused by an increase in free radicals[9]. SOD acts as an endogenous antioxidant,[10] and an important antioxidant defense against oxidative stress in the body.[11] Moreover, high-fat food consumption can also increase oxidative stress, weight gain, and lead to the progression of insulin resistance.[12,13] In obesity, endogenous antioxidants cannot control high levels of oxidative stress so it is necessary to intake foods that contain an antioxidant compound derived from natural products.[14]

One of the plants that have potential as an antioxidant is *Solanum Nigrum Linn*, or in Indonesia, known as leunca or ranti. Commonly consumed by the people as a vegetable salad, vegetable and chili sauce. Leunca is one of the Solanaceae family groups that grows in dry land; easy to grow, adaptable, and relatively cheap. This plant originated from Europe and West Asia, then Leunca spread in Indonesia, namely in West Java Island, Sumatra and eastern Indonesia with different local names.[15]

There are many nutrients in leunca fruit such as minerals, vitamins (A,C,E), and proteins. They also contain many free radical scavengers compounds, such as flavonoids, phenolic acid, alkaloids, solanine, quinones, tannins, that act as antioxidants so leunca can be said to be a good source of antioxidants.[16,17] Leunca fruits contain phytochemicals such as diosgenin (1.2%),[18] similar to tomatoes. Diosgenin can be useful in the treatment of diabetes by increasing adipocyte differentiation and by inhibiting inflammation in adipose tissue and increasing the levels of antioxidant enzymes SOD and GPx, and minimizing the level of lipid peroxidation.[19]

Flavonoids, Vitamin C, and Vitamin E are known as antioxidants that can protect cells from the negative effects of free radicals by binding and neutralizing free radicals as well as preventing, reducing, and inhibiting the oxidation process.[20] Currently, leunca, with its complete nutritional content and rich benefits, has not been optimally used in several regions in Indonesia. The researchers want to improve the antioxidant potential of leunca fruits as a functional food to prevent obesity. This study aims to determine the effect leunca fruit with different doses on increasing superoxide dismutase (SOD) enzyme activity and decreasing malondialdehyde (MDA) in obese rats divided into several treatment groups.

METHODS

Research Design. The type of research is true experimental with the form of research design randomized post-test only with a controlled group design. The study was conducted after intervention in rat serum for the measurement of superoxide dismutase (SOD) enzyme activity and malondialdehyde (MDA) levels. The experimental animal research was conducted from February 5 to March 2024 at the Laboratory of the Center for Food and Nutrition Studies, Gadjah Mada University, Yogyakarta.

Animal Study. Thirty male Sprague Dawley rats (8-11 weeks old), weighing 150-200 grams, lee index≤300 and healthy and without disabilities. The sample size is determined based on WHO[21] requirements for the minimum sampling size of herbal medicine trials, with the number of each treatment group consisting of 5 rats to avoid dropout samples; one rat was set as a reserve, so the total sample size was 30 rats. Rats were divided into 5 groups, namely healthy control group K(-), high fat sucrose diet control group K(+), treatment group 1 (P1), treatment group 2 (P2), and treatment 3 (P3).

Leunca Fruit. Leunca fruit was obtained from a vegetable shop in Yogyakarta. A total of 1/2 kg of launch fruit was sorted and then washed with clean running water and then stored in the freezer to maintain the content of launch fruit and given to rats when the intervention was carried out with a variety of doses. Determination of leunca fruit dose was based on a human daily intake of 30-60g[22] with frequency of eating 3 times a day. Leunca fruit intervention treatment using half and double dose method.

Table. 1 Dose of leunca fruits in rats

Human Intake	Rats Intake
Half dose: 15g x 3= 45g	0.018x45g=0.8g
Normal dose: 30g x 3= 90 g	0.018x90g=1.6g
Double dose: 45g x 3=135 g	0.018x135=2.4g

The calculation of the average daily intake of leunca fruit in human converted to rat doses follows the calculation of the dose of Evaluation of Drug Activities Pharmacometrics[23]. The dose of humans weighing 70kg converted to rats weighing 200g is 0.018. So, it converted to rat dose for intervention with dose variations of 0.8g, 1.6g, and 2.4g/200gBB. Variations of leunca fruit doses are (P1) 0.8g, (P2) 1.6g and (P3) 2.4g given to obese rats.

Treatment period. Each rat was acclimatized for 7 days with standard feed (CP594) and drinking water 10%/head/day *ad libitum*. Leunca fruit intervention by sonde and conditioning of rats to obesity with Hight Fat Sucrose Diet (HFSD) were given concurrently. HFSD diet given in the form pork oil (20%), and sucrose (34%). Body weight weighing of rats was carried out before, during, and after the intervention. The dosage variations of leunca fruit are 0.8 g, 1.6 g, and 2.4 g. This study not weigh the remaining weigh the remaining food of the rats at each meal, so the percentage of rat intake was unknown and the activity pattern of the rats during the interventions was not monitored, which could potentially bias the study.

After 6 weeks of intervention, the body weight of the rats was measured. Analysis SOD enzymes and MDA levels was performed after the intervention of Leunca Fruit. The results of the analysis SOD enzymes were measured using Enzyme-Linked Immunosorbent Assay (ELISA) method. Blood plasma MDA levels were measured using the Thiobarbituric Acid Reactive Substance (TBARS) method.

Data Analysis. The IBMS SPSS 21 program was used to analyze the data. Since there are fewer than 50 samples in the data, the Shapiro-Wilk test is used to check the normality test. Data is considered normal when $p>0.05$. A statistical analysis is considered significant if $p <0.05$. Using the one-way ANOVA test, statistical analysis is performed to ascertain the variation in SOD and MDA levels in six groups. The data were significant and regularly distributed, they were followed by post-hoc LSD testing.

RESULT

This study was conducted using experimental rats that were intervened by leunca fruit and induced by HFSD. There were 6 group of rats, namely healthy control K(-), HFSD control K(+), and leunca fruit treatment groups of 0.8 g dose (P1), 1.6g dose (P2), 2.4g dose (P3). The body weight of the rats was increased every week during the intervention.

SOD and MDA levels were measured after rats were given leunca fruit intervention for 42 days in rat serum. Analysis of the One-Way Anova tests to determine whether there are differences in increasing SOD levels and decreasing MDA showed significant changes between groups with different doses of leunca fruit with a value of $p <0.05$. LSD Post Hoc analysis of SOD and MDA levels showed there were significant differences between each group K(-), K(+), P1, P2, and P3 with p value <0.05.

Table 1 shows significant differences between each group ($p<0.05$). The treatment group (P3) with a dose of 2.4g/BB rats showed high mean SOD levels 71.3% and low mean MDA 2.11 nmol/ml compared to the K-, P1, and P2 groups.

Table. 1 SOD and MDA Levels After Leunca Fruit Intervention in Obese Rats

Treatment Group	n	SOD Levels (%)	MDA Levels (nmol/ml)
Health Control K(-)	6	81.1±3.06[a]	1.53±0.15[a]
Obese Control K(+)	6	31.9±3.06[b]	9.93±0.20[b]
Treatment 1 (P1)	6	41.8±3.06[c]	6.09±0.27[c]
Treatment 2 (P2)	6	63.1±3.06[d]	3.05±0.18[d]
Treatment 3 (P3)	6	71.3±3.06[e]	2.11±0.17[e]
P		0.000	0.000

Note: P = One way ANOVA test, *[abcde]= Post Hoc LSD* test

DISCUSSION

Excessive production of ROS occurs in obesity. ROS production occurs through the activation of enzymes in the cytosol, mitochondria, and membrane. Increased ROS production and depletion of antioxidant result in oxidative stress. The generated oxidative stress causes intracellular cell damage and redox changes, leading to the accumulation of irreversible oxidation products resulting in increased endothelial dysfunction, leading to insulin resistance, hypertension, dyslipidemia and metabolic syndrome.[24]

Oxidative stress in obesity can supress endogenous antioxidant such as SOD in the body and one of the main pathologies that the body can observe includes increased concentrations of MDA a marker that indicates cellular damage, especially in lipid peroxidation. Excessive levels of adipokines realesed by adipocytes will increase ROS production.[25]

Superoxide Dismutase Level

Obese conditions cause increased level of mechanical stress on the work function cardiorespiratory and body metabolism which affects the total number of free radicals and one of the SOD enzymes as an antioxidant in the body that can protect cells. So, in the case of obesity, conditions can continue to reduce SOD levels and increase the number of free radicals in the body. Therefore, antioxidants are needed from outside, which are obtained by consuming food sources of antioxidants that can neutralize free radicals in the body.[26]

The measurement SOD levels was conducted in the serum of obese rats after the intervention of leunca fruit for 42 days. After the OneWay Anova test, showed a significant difference in the increase in SOD levels in the control group and the treatment group. The K (+) group decreased SOD levels compared to the K(-) group. The decrease in SOD levels was caused by excess ROS products due to the HFSD diet of 42 days. Endogenous antioxidants in obese individuals are lower than endogenous antioxidants in healthy individuals.[27] At increased adipose tissue, the antioxidant enzyme activities such as SOD, glutathione peroxidase (GPx), and catalase (CAT) were revealed to be significantly reduced. As a result, high production of ROS and decreased antioxidant capacity lead to different abnormalities, among which are dysfunction of the endothelium, marked by decreased bioavailability of vasodilators, especially nitric oxide (NO), and increased levels of endothelium-derived contractile factors which support atherosclerosis disease.[28]

The analysis of the LSD post hoc test showed that there was a significant increase in SOD levels in the P1, P2, and P3 groups compared to K(+). The leunca fruit administration of the P3 group at a dose of 2.4g had a higher increase in SOD levels compared to the K(+) obesity group. The increase was caused by the high content of antioxidants and flavonoids in leunca fruit. This is in line with previous research that antioxidants in leunca fruit shown as an antiobesity agent to reduce body weight and body fat by inhibiting the proliferation and accumulation of lipids in adiposity and regulating lipid metabolism.[29]

Leunca fruits contain bioactive compounds, such as tannins, flavonoids, and alkaloids, that exhibit antioxidants by inhibiting oxidative stress damage. Gallic acid, catechins, and isoquercetrin in leunca fruits also have antiobesity, antioxidant, and anti-inflammatory characteristics.[29] Flavonoids can improve health by providing biological functions, such as reducing ROS production, inducing apoptosis, and antitumorigenic activity. Flavonoids have

phenolic hydroxyl groups, which make them highly potent antioxidants that work against ROS and are involved in the process of lipid peroxidation initiation.[30] Studies showed that leunca fruit at a daily dose of 2.4g could prevent the formation of lipid damage by preventing a decrease in SOD levels.

Studies conducted on rats have shown that consuming leunca fruit as a source of gallic acid which has strong antioxidant characteristics and the ability to counteract free radicals and protect biological cells, tissues, and organs from damage caused by oxidative stress through a series of enzymatic and nonenzymatic antioxidants such as SOD, GPx, CAT, Vitamin C, Vitamin E. Gallic acid can reduce MDA levels and ROS formation through free radical scavenging activity.[31]

Malondialdehyde Level

ROS production and the generation of oxidative stress associated with obesity are strongly related to immune system activity in adipose tissue and low-grade chronic systemic inflammation. ROS responsible for lipid peroxidation spreads in the cell when oxidative stress occurs. Cell and tissue damage caused by radicals can lead to increased lipid peroxidation so that endogenous antioxidant levels are decreased.[32]

The result of the study on MDA levels in the rats group after the administration of leunca fruit for 42 days. The One-Way Anova Test showed a significant difference between the control group and the leunca fruit treatment group in terms of reducing MDA levels. Compared to the levels of the K(-) group, MDA levels in the K(+) group were higher. This is following the research from Ashar (2023), which states that MDA levels in obesity are higher (1.7 ± nmol/ml) compared to non-obesity (1.5 ± nmol/ml).[8] This is caused by the administration of the HFSD diet, thereby causing an increase in ROS production, which is characterized by high MDA levels. Obesity is marked by increased oxidative stress, which can be recognized by the increased MDA levels.[33] This is following research (Viviana et al., 2019), which states that rats fed a high-fat diet and consuming potato starch can increase SOD levels in rats.[34]

Based on the LSD Post Hoc test analysis, it shows that there is a significant decrease in MDA levels in the P1, P2, and P3 groups compared to K(+). The decrease in levels in obese patients. So, the dose of 2.4g leunca fruits is effective and has benefits as a functional food, helping to improve oxidative stress conditions in obese patients. This is following the research of Peng (2020), which states that Solanum Nigrum L. leaf extract can be an antiobesity agent that can reduce body weight and body fat by reducing the number and levels of adipocyte lipids and regulating lipid metabolism.[29]

Leunca fruit contains the highest anthocyanin compound after berries.[35] Anthocyanins are generally effective in inhibiting α-glucosidase, α-amylase enzymes, and lipase, regulating insulin secretion, lowering glucose levels, regulating insulin secretion and preventing insulin resistance.[36] Obesity is also considered a chronic inflammation. Inflammation leads to the release of pro-inflammatory cytokines and the production of C-reactive protein (CRP), and increased pro-inflammatory response and leukocyte infiltration promote ROS production in obesity, resulting in oxidative stress. High levels of MDA can lead to various diseases such as Parkinson's, Alzheimer's, and Lou Gehrig's disease. The destructive effects of free radicals include DNA damage, and abberations or mutations.[37]

Leunca extract contains many polyphenolic compounds. The leaves are rich in polyphenols, including phenolic acid and flavones. Previous studies showed that the treatment of rats with solanum nigrum leaf extract was able to reduce oxidative stress and demonstrated the potential of this extract in preventing or reducing stress-induced diseases involving oxidative damage to cells, particularly the brain. The antioxidant activity may be due to the presence of polyphenolic compounds found in leunca. Studies show that oxidative stress is associated with pathological conditions, including central nervous system diseases and the physiological ageing process of the brain.[38]

The impact caused by oxidative stress is the oxidation of DNA which can initiate cancer, arterosclerosis and damage the cell member structure which results in a decrease in cell organelle function. If lipid that have a double carbon chain react with oxidant, lipid peroxidation will occur. Lipid hydroperoxide is the main product of lipid peroxidation. This structure is unstable so that it

can easily turn into MDA. Tha nature of MDA is more stable than other aldehyde products so that this compound is often used as a marker of oxidative stress. Plasma malondialdehyde levels in healthy individuals are 0.80±µmol/L.[39]

Flavonoids in leunca fruit can reduce oxidative stress and suppress MDA in rats fed a high-fat diet, it cannot be known for sure, but it can occur through several known mechanisms, namely (1) acting as a preventive antioxidant (preventing antioxidant) by preventing the occurrence of LDL peroxidation (hydroxyl groups (-OH) from flavonoids can reduce ROS (hydroxy radicals (OH*), ONOOH and HOCL) directly, (2) can prevent the propagation of peroxidation reactions (chain-breaking antioxidant or chain breaking peroxyl radical scavenger) by capturing peroxyl radicals (ROO*) to stop further peroxidation reactions.[40]

Leunca fruit contains antioxidants such as vitamin C. Vitamin C is a water-soluble antioxidant, protects intracellular and extracellular components, and plays an important role in capturing tocopherol radicals in active form. Vitamin C can also inhibit peroxidase that occurs in oxidative stress to reduce MDA levels.[40] In addition, bioactive compounds present in Solanum Nigrum extract can suppress preadipocyte differentiation and inhibit adipogenesis through modulating metabolic pathways.[41]

CONCLUSION

Leunca fruit at a dose of 2.4g/BB/day can significantly increase SOD levels and reduce serum MDA levels in mice induced by a high-fat high-sucrose diet when compared to the obese group without intervention, but SOD and MDA levels in the group given at a dose of 2.4g didn't reach a better level when compared to the healthy group. So, it can be concluded that the administration of leunca fruit effectively handles obesity. Furthermore, it is necessary to utilize leunca fruit as one of the food ingredients that can help manage obesity in the long term.

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