October – December, 2024
Original Article
DOI: http://dx.doi.org/10.30867/action.v9i4.1940
Pages: 647 – 654
AcTion: Aceh Nutrition Journal
p-issn 2527-3310; e-issn 2548-5741

Effect of Dangke administration on serum TNF-a and liver SOD levels in rats induced by a high-fat, high-sugar diet

Pengaruh pemberian dangke terhadap kadar TNF-a serum dan SOD liver pada tikus yang diinduksi diet tinggi lemak tinggi gula

Uzifatun Nur Y.F. Lapatta[1*], Diana Nur Afifah[2], Adriyan Pramono[3], Ninik Rustanti[4]

[1] Master program of nutrition science of postgraduate, faculty of medicine, Diponegoro University, Semarang, Central Java, Indonesia.
E-mail: uzifatunnur1999@gmail.com
[2] Department of Nutrition Science, Faculty of Medicine, Diponegoro University, Semarang, Central Java, Indonesia.
E-mail: diananurafifah@live.undip.ac.id
[3] Department of Nutrition Science, Faculty of Medicine, Diponegoro University, Semarang, Central Java, Indonesia.
E-mail: adriyanpram@gmail.com
[4] Department of Nutrition Science, Faculty of Medicine, Diponegoro University, Semarang, Central Java, Indonesia.
E-mail: ninik.rustanti@fk.undip.ac.id

***Correspondence Author:**
master program of nutrition science of postgraduate, faculty of medicine, Diponegoro University, Jl. Prof. Sudarto, Tembalang, Semarang City, Central Java, 50275, Indonesia.
E-mail: uzifatunnur1999@gmail.com

Article History:
Received: July 10, 2024; Revised: August 07, 2024; Accepted: August 19, 2024; Published: December 04, 2024.

Publisher:
Politeknik Kesehatan Aceh
Kementerian Kesehatan RI

Abstract

Dangkes contain lactic acid bacteria that improve obesity by controlling the intestinal flora, improving the micro-ecological balance in the gut, and boosting the immune system. This study aimed to analyze the differences in serum TNF-α and liver SOD levels in obese rats fed a Dangke diet. The research was conducted from December to January 2024 at the PSPG PAU UGM using a true-experiment design post-test with only the control group. Male Sprague-Dawley rats (n=30) were randomly divided into five groups: healthy rats (KS), obese rats given standard feeding (K-), obese rats received L-Bio (K+), obese rats were given Dangke at a low dose (P1), and obese rats received Dangke at a high dose (P2). Intervention for 28 days. Data analysis was performed using one-way ANOVA tests and further post-hoc Bonferroni tests. The result obtainded that Dangke with dose dose of 3,6 g/200 gBB was effective in decreasing TNF-α levels and increasing SOD levels (p<0,05). P2 had the lowest mean TNF-α level (7,33 ± 0,22) compared to K+ (8,59 ± 0,22) and P1 (8,88 ± 0,18). P2 had the highest SOD levels compared to K+ (62,56 ± 4,06) and P1 (61,47 ± 4,71). In conclusion, Dangke effectively overcame inflammation and oxidative stress in obesity.

Keywords: Dangke, TNF-α, SOD, oxidative stress, obesity

Abstrak

Dangke mengandung bakteri asam laktat yang dapat memperbaiki obesitas dengan mengontrol flora usus, menjaga keseimbangan mikro-ekologi di usus, dan meningkatkan sistem kekebalan tubuh. Penelitian ini bertujuan untuk menganalisis perbedaan pemberian Dangke terhadap kadar TNF-α serum dan SOD liver pada tikus obesitas. Penelitian dilakukan pada Desember-Januari 2024 di PSPG PAU UGM dengan menggunakan desain true-eksperiment post-test only with control group. Tikus jantan galur spraguey dawley (n=30) dikonfigurasi secara acak menjadi lima yaitu kelompok tikus sehat (KS), tikus obesitas yang diberikan pakan standar (K), tikus obesitas diberi L-Bio (K+), tikus obesitas diberi Dangke dengan dosis rendah (P1), tikus obesitas diberi Dangke dengan dosis tinggi (P2). Diintervensi selama 28 hari. Analisis data menggunakan uji One Way ANOVA dan uji lanjut post hoc Bonferroni. Hasi, pemberian Dangke dengan dosis 3,6 g/200gBB efektif dalam penurunan TNF-α dan peningkatan SOD (p<0,05). P2 memiiki rerata kadar TNF-α (7,33 ± 0,22) terendah dibandingkan dengan K+(8,59 ± 0,02) dan P1 (8,88 ± 0,18). P2 memiliki kadar SOD tertinggi dibandingkan K+ (62,56 ± 4,06) dan p1 (61,47 ± 4,71). Kesimpulan, Dangke efektif mengatasi peradangandan stress oksidatif pada obesitas.

Kata Kunci: Dangke, TNF-α, SOD, stress oksidatif, obesitas.

Introduction

According to the World Health Organization (WHO), obesity is a global public health problem that requires special attention (Mutia et al., 2022). The prevalence of obesity based on World Health Organization (WHO) data has tripled since 1975. In 2016, as many as 650 million or 13% of the world's population aged > 18 years were in a state of obesity (Ayuningtyas et al., 2022). According to the 2018 Basic Health Research, the prevalence of obesity in adults in Indonesia increased from 14,8% to 21,8% in 2013. The prevalence of obesity was higher in women (29,3 %) than in men (14,5%). Meanwhile, the prevalence of central obesity at the age of ≥15 years is approximately 31%, with a prevalence of 46,7% in women and 15,7% in men; therefore, treatment and therapy are needed to deal with the incidence of obesity.

High-fat and high-sugar foods contribute to obesity and its related conditions worldwide. An increase in adipose tissue is a defining feature of obesity, a condition characterized by an imbalance between energy intake and expenditure (Kobi et al. 2023). Therefore, the primary cause of obesity remains a global concern. The pathophysiology of obesity involves multiple factors such as appetite, physical activity, and calorie consumption regulation. However, it still interacts with other elements, such as the availability of the healthcare system, significance of socioeconomic level, and environmental and genetic factors (Lin & Li, 2021). Some non-communicable diseases that arise due to obesity include cardiovascular disease (CVD), cancer, type 2 diabetes mellitus, and several neurodegenerative diseases (Ali Redha et al., 2021).

Obesity is a complex, heterogeneous, polygenic, immunometabolic illness. It is characterized by an altered gut microbiota and excess and dysfunctional adipose tissue, both of which affect human health (Fabersani et al. 2021). Under conditions of obesity, there is a change in the composition of the intestinal microbiota, causing intestinal dysbiosis, which is characterized by an increase in *Firmicutes* bacteria and a decrease in *Bacteroidetes* (Vetrani et al., 2022). Modifications in the gut microbiota have the potential to affect intestinal permeability, which in turn can lead to the translocation of lipopolysaccharide (LPS) and low-grade inflammation. As LPS activates Toll-like receptors (TLR4), which are expressed by neutrophils, dendritic cells, and macrophages, it plays a crucial role in the inflammatory process (Jeong, 2023).

It is currently known that lactic acid bacteria included in probiotics can both prevent and treat obesity by balancing the micro-ecological equilibrium in the colon, enhancing lipid metabolism, lowering blood cholesterol levels, and boosting the immune system (Zhang et al., 2022). Lactic acid bacteria are a form of probiotic that is considered a potential intervention in metabolic syndrome therapy (Djabir & Yustisia, 2023). Isolating microorganisms with probiotic potential from foods, including Kyoto pickles, kefir, kimchi, and sake, has been the subject of several investigations. Additionally, bacteria have been isolated from processed milk, including curd, fermented milk, horse milk, buffalo milk, breast milk, and dangerous foods (Fadhillah et al., 2015).

Dangkes are traditional food originating from Enrekang, South Sulawesi. It is prepared from cow milk, buffalo milk, and papaya sap using fermentation techniques. Dangkes contain lactic acid bacteria, which are beneficial to health (Djabir & Yustisia, 2023). Dangke contains natural lactic acid bacteria. Studies have shown that lactic acid bacteria isolated from Dangke include *Lactobacillus fermentum, Lactobacillus plantarum, and Lactobacillus acidophilus* (Burhan et al., 2017).

LAB are known to have an anti-obesity role that can suppress excess fat absorption, inhibit 3TL—LL adipose, reduce energy intake, reduce the weight of white fat tissue and average fat size, modulate the intestinal microbiota to lose weight, and inhibit the growth of pathogenic bacteria in the gastrointestinal tract. Pathogenic bacteria in the intestinal tract can stimulate the production and secretion of lipopolysaccharides (LPS) from intestinal epithelial cells and then bind cytokine receptors to hepatocytes and adiposites that trigger the release of pro-inflammatory cytokines (TNF-α. IL-6, and MCP1). In addition, BAL can also reduce the production of free radicals and relieve oxidative stress, which in turn increases SOD activity through intestinal microbiota improvement, resulting in increased SCFA. (Asetat, propionat, butirat) (H) Li et al., 2020).

Probiotic therapy using Dangke containing lactic acid bacteria can reduce the release of LPS, which triggers the production of pro-inflammatory cytokines from the intestinal epithelial cells through changes in the gut microbiota, thus altering the short-chain fatty acid pathway (SCFA) and bile acid synthesis. Such changes lead to a reduction in fat accumulation, suppression of weight gain, and risk of insulin resistance (Kober et al., 2024).

In a previous study, rats that were fed a high-fat diet and administered *Lactobacillus plantarum* for six weeks showed a reduction in the levels of TNF-α, Interleukin-6, Il-1b, and interferon (IFN)-y, and *Lactobacillus plantarum* intervention could inhibit tissue damage and inflammation due to obesity in rats fed a high-fat diet (Gan et al., 2020). In rats fed a high-fat diet and given yoghurt supplementation for eight weeks, glucose intolerance was prevented, specific liver enzyme activities were normalized, and oxidative stress markers in the plasma and liver levels were reduced (Lasker et al., 2019).

Therefore, researchers are interested in conducting research by administering kaju dangke containing lactic acid bacteria, which act as antioxidants in rats induced by a high-fat, high-sugar diet to manage obesity. The researchers aimed to analyze the differences in the effects of Dangke administration on serum TNF-α and liver SOD levels in obese rats.

Methods

The True-experimental study used a completely randomized design with a randomized post-test only and a control group design. This study was conducted at the Center for Food and Nutrition Studies Laboratory of Gadjah Mada University, Yogyakarta between November 2023 and January 2024. Thirty-eight-week-old rats weighing 150–200 g were acclimatized for seven days. The rats were maintained at room temperature (23 °C) with 12 h of light. The rat cages were cleaned daily, and the body weights of the rats were measured every week, starting from the acclimatization process and ending the study. Until the conclusion of the trial, rats were fed a regular diet of 15 g/day and given access to unlimited amounts of drinking water. In Limited II, the typical diet consisted of 15% crude protein, 3-7% crude fat, 12% moisture, 6% crude fiber, 7% ash, 0,5% phosphorus, 0,9–1,1% calcium, and vitamins.

The large sample used in this study refers to the WHO requirement for a large minimum animal sample of herbal medicine with five animals for each treatment group. To avoid sample dropout, a reserve rat was used to make the total sample size 30. Randomization was performed consisting of a group of healthy rats (KS), a group of obese rats given standard feed (K-), a group of obese rats given L-Bio 0,018 g/200 g BB of rats (K+), a group of rats administered the intervention with Dangke 1,8 g/200 g BB of rats (P1), and a group of rats that received the intervention with Dangke 3,6 g/200 g BB of rats (P2). Each rat consisted of six rats, one of which was used as the reserve. Rats were fed a high-fat, high-sugar diet for 28 days with a composition of 21% lard, 34% sugar, and Dangke for 28 days at doses according to the treatment group.

The dose was calculated according to the human (70 kg) dose conversion to rats (200 g). Dough consumption is usually a single meal (50 g/day); therefore, the total dose twice a day is 100 g and the animal conversion factor is 0,018). Therefore, the lowest dough dose is 1,8 g/200 gBB/day and the highest dose was by marking it to 3,6 g/200 gBB/ day.

Dangkes were prepared by heating 1 litre of buffalo milk at 80°C. For 15 seconds, add 0,3% papaya sap was added to thicken the milk. The milk and papain mixture was stirred until syneresis (separation of curd and whey) occurred. The curd was then filtered, formed using coconut shells, and pressed until it reached the solid state.

TNF-α was measured in the serum using an ELISA KIT reader at a wavelength of 450 nm and was expressed in pg/ml. Serum intake was measured through the retroorbital sinus. SOD activity was measured in the liver tissue using an ELISA Kit and expressed as a percentage.

The data normality test was performed using the Shapiro-Wilk test (sample number <50). The variations in serum TNF-α levels following the Dangke intervention in the treatment group, control + group, control group, and regular group were analyzed using the Kruskal-Wallis test if the data were not normally distributed, the Mann Whitney test was used, or one-way ANOVA if the distribution was normal (p>0,05) and homogeneous (p>0,05), and the Bonferroni post hoc test was used. The same was also performed for the analysis of Liver SOD levels. Moreover, correlation analysis between serum TNF-α levels and liver SOD was performed using the Pearson correlative test if the data were normally distributed and the Spearman correlation test if the data were not normally distributed. Data were considered significantly correlated if p<0,005. The Ethics Committee (No.001/EC-H/KEPK/FK-UNDIP/I/2024) approved the experimental procedures of the Faculty of Medicine at Diponegoro University.

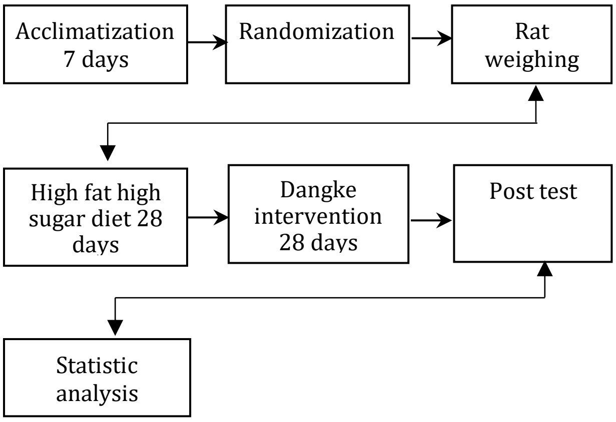

Figure 1. Research flow chart

Result and Discussion

Compared to obese rats fed high-fat and high-sugar diets, obese rats fed low (P1) and high (P2) doses together with L-Bio (K+) for 28 days had lower TNF-α levels and increased liver SOD levels (Table 1). In this study, there was a significant difference in TNF-α levels between the healthy and obese rats (p<0,05).

Table 1. Results of TNF-α and SOD liver levels after dangke intervention in obese rats

Treatment Group	n	TNF-α levels (pg/ml)	SOD liver levels (%)
KS	6	6,49 ± 0,14	82,79 ± 3,06
K-	6	18,90 ± 0,23	24,59 ± 3,88
K+	6	8,59 ± 0,20	62,56 ± 4,06
P1	6	8,88 ± 0,18	61,47 ± 4,71
P2	6	7,33 ± 0,22	73,49 ± 4,07
p-value		0,000*	0,000*

Note: KS, healthy control; K-, obese control; K+, obese control with L-Bio 0,018 g/200 g BB, P1, low-dose Dangke (1,8 g/200 g BB); P2, high-dose Dangke (3,6 g/200 g BB); p*, one-way ANOVA.

Table 2. Bonferroni further test results of Dangke intervention

	KS	K-	K+	P1	P2
TNF-α					
KS	-	0,000*	0,000*	0,000*	0,000*
K-	0,000*	-	0,000*	0,000*	0,000*
K+	0,000*	0,000*	-	0,188	0,000*
P1	0,000*	0,000*	0,188	-	0,000*
P2	0,000*	0,000*	0,000*	0,000*	-
SOD liver					
KS	-	0,000*	0,000*	0,000*	0,005*
K-	0,000*	-	0,000*	0,000*	0,000*
K+	0,000*	0,000*	-	1,000	0,001*
P1	0,000*	0,000*	1,000	-	0,000*
P2	0,005*	0,000*	0,001*	0,000*	-

Note: *Significantly different with the p-value <0,05 on bonferroni's further test

According to Table 1, K- was a group of obese rats who were given a high-fat high-sugar diet has the highest TNF-α ratio Based on previous research (Collins et al., 2016), on the third day of intervention, a diet high in fat and sugar can increase TNF-α and IL-6 levels. Hypoxia in adipose tissue induced by a high-fat diet can result in adipocyte death. This can decrease T cells, release pro-inflammatory cytokines, including IL-6, IL-12, and TNF-α, and boost M1 macrophages that penetrate the adipose tissue. M2 macrophages and regulators (Maulana and Ridwan 2021).

Table 1 shows that group P2's TNF-α levels were lower than those in group P1. This indicates that the optimal dose of Dangke for lowering TNF-α levels in obese rats was found to be 3,6 g/200 gBB, out of the two doses used in this investigation. TNF-α levels were lower in the K+ group than in the P1 group, suggesting that feeding obese rats dangerous was a more effective way to lower TNF-α levels than L-BIO. This result agrees with the findings of Yuan et al. (2021). Administration of lactic acid-containing yoghurt to obese rats significantly lowered the levels of pro-inflammatory cytokines such as TNF-α, IL-6, and MCP1 in both their serum and visceral adipose tissue.

As shown in Table 2, the post-hoc Bonferroni test findings showed that there was no significant difference in TNF-α levels between the K+ and P1 groups (p= 0,188). These results indicate that the administration of L-Bio at a dose of 0,018 g/200 g BB and a low dose of 1,8 g/200 gBB had the same ability to lower TNF-α levels in obese rats. It has been reported that administering obese rat yoghurt containing lactic acid bacteria dramatically reduced the levels of pro-inflammatory cytokines in the serum and visceral adipose tissue, including TNF-α, IL-6, and MCP1 (Toshimitsu et al., 2016).

Probiotics have been shown to reduce inflammation because of their capacity to modify microbiota. Dysbiosis of the microbiota affects the intestinal epithelial barrier and leads to endotoxemia related to lipopolysaccharide (LPS), which in turn stimulates the immune system and produces cytokines (Neyrinck et al., 2016).

Consumption of foods with probiotic strains can help in the process of intestinal colonization and restore disturbed intestinal microflora, thereby reducing physiological dysfunction in the human body (Kober et al., 2024). Superoxide dismutase (SOD) activity in the liver tissues was measured using colorimetric and SOD activity assay kits. Using a homogenizer, the liver tissue was combined to create a supernatant, and the absorbance was measured using a microplate reader at a wavelength of 450 nm.

As shown in Table 1, there were significant differences in the SOD levels in the liver tissue between healthy and obese rats (p<0,05). P2 was an obese group of rats who were intervened with Dangke at a dose of 3,6 g/200 gBB had the highest rate of liver SOD when compared to the obese K- group of rats who had an intervened high-fat high-sugar diet. The probiotic administration of Lactobacillus and Bifidobacterium can be used as effective complementaries to enhance antioxidant defenses by reducing ROS, inhibiting pro-oxidative enzymes, and synthesizing antioxidants (Zhao et al., 2023). Lactobacillus probiotics can produce functional products such as exopolysaccharides (EPS) that reduce oxidative damage or activate the expression of host transcription factors involved in cellular oxidative stress modulation (B. Li et al., 2018).

As shown in Table 1, Liver SOD levels in group P1 were lower than those in group P2 were. This shows that Dangke at a dose of 3,6 g/200 gBB was the best dose among the two doses of dangke in this study for reducing Liver SOD levels in obese rats. In the K+ group, Liver SOD levels were lower than those in the P2 group and higher than those in the P1 group, indicating that Dangke was more effective in reducing SOD levels than L-bio in obese rats. This may be because the dose contained in the P2 rat group is greater than that of L-Bio, where the dose for the P2 rat group is 3,6 g/200 gBB while L-Bio is 0,018 g/200 gBB. This could be a dose-response effect of the administration of Dangke and L-Bio on liver SOD levels in obese rats.

Subsequently, the homogeneity significance values showed the same variants with a significance value of p=0,668 (p>0,05) so a post-hoc Bonferroni test was performed to determine the difference in tnf-a rates between groups. Based on the Table 2, the liver SOD levels of the K+ group and P2 group did not significantly differ from one another, according to the post hoc Bonferroni test results in the above Table 2 (p=1,000). These results indicate that the commercial product L-Bio has the same ability to induce SOD levels. Liver in obese rats. This may be because the antioxidants in Dangke were the same as those in L-Bio. According to previous studies (Safitri, 2023), feeding rodent kefir made from cow's milk can prevent the rats' SOD activity from declining because kefir contains acidic bacteria. Lactate from cow milk kefir functions as an antioxidant, reducing the amount of superoxide anion (SOD) enzyme while also boosting antioxidant activity to combat free radicals.

The human body collects Reactive Oxygen Species (ROS) as a result of physiological and metabolic activities. ROS may trigger severe damage to lipids, proteins, and DNA, resulting in additional damage to tissues and organ failure. Further research shows that ten weeks of oral LAB therapy significantly lowered the level of lipid peroxidation in the serum and liver of rats experiencing oxidative stress (Lin et al., 2018).

The correlation between TNF-α and Liver SOD levels was analyzed using Spearman's correlation test because the data were not normally distributed. Table 3 presents the statistical results.

Table 3. Relationship between liver TNF and SOD levels in obese rats

Variable	average ± SD	p	R
TNF-α (pg/ml)	10,04 ± 4,5	0,000	-0,925
SOD Liver (%)	60,98 ± 20,47		

As shown in Table 3, there was a significant relationship between the TNF-α and SOD levels (p<0,05). Obesity is closely related to an increase in body weight, which causes excess fat accumulation, and is believed to be pathogenic in degenerative diseases. Obesity is frequently linked to low-grade systemic inflammation in the adipose tissue. This disorder is caused by the activity of the innate immune system in the adipose tissue, which promotes oxidative stress and inflammation. This leads to a systemic acute-phase response and reduction in the body's antioxidant capacity (Marseglia et al., 2014).

The correlation results in Table 3 show that there is a negative correlation (-0,925) between TNF-α and Liver SOD, which means that if there is a decrease in inflammation, such as TNF-α, the antioxidant defense system, such as SOD, will experience an increase and vice versa; if there is an increase in inflammation, the antioxidant defense system will increase. Will experience a decline. This is in line with the theory, which states that under conditions of obesity, there is an increase in the number of macrophages that have higher pro-inflammatory properties compared to M2, which acts as an anti-inflammatory agent, resulting in increased production of inflammatory cytokines, such as TNF-α (Saltiel & Olefsky, 2017).

In addition, under obese conditions, there is an increase in mitochondrial oxygen consumption, which causes mitochondrial dysfunction and ROS production. Under normal conditions, the body neutralizes ROS through the antioxidant defense systems SOD, CAT, and GSH. However, when pathological conditions, such as obesity, occur, there is a decrease in antioxidant sources, where the activity of the SOD enzyme decreases drastically, increasing ROS production in excess of the antioxidant defense system, which causes oxidative stress and worsens inflammatory conditions (Mardhotillah et al., 2024).

Conclusion

Dangke administration at low and high doses significantly reduced serum TNF-α levels and increased liver SOD. Dangke at a dose of 3,6 g/200 gBB (P2) was the best dose for reducing serum TNF-α levels and increasing liver SOD levels when compared to L-Bio at a dose of 0,018 g/gBB (K+). However, Dangke administration at a dose of 1,8 g/200 g BB (P1) and L-Bio administration at a dose of 0,018 g/200 g BB (K+) had the same effect of reducing serum TNF-α and increasing liver SOD. TNF-α and SOD are inversely related; when the inflammatory response increases, SOD activity decreases, and vice versa.

Considering the potential of Dangke in reducing inflammation and oxidative stress, further research is needed on its efficacy and other components contained in Dangke as a potential therapy for obesity.

Acknowledgements

We are grateful to the Center for Food and Nutrition Studies Laboratory at the Yogyakarta Gadjah Mada University.

References

Ali Redha, A., Perna, S., Riva, A., Petrangolini, G., Peroni, G., Nichetti, M., Iannello, G., Naso, M., Faliva, M. A., & Rondanelli, M. (2021). Novel insights on the anti-obesity potential of the miracle tree, Moringa oleifera: a systematic review. *Journal of Functional Foods*, *84*, 104600. https://doi.org/10.1016/j.jff.2021.104600

Ayuningtyas, D., Kusuma, D., Amir, V., Tjandrarini, D. H., & Andarwati, P. (2022). Disparities in Obesity Rates among Adults: Analysis of 514 Districts in Indonesia. *Nutrients*, *14*(16), 3332. https://doi.org/10.3390/nu14163332

Burhan, H., Priyambada, S. A., Taufik, E., & Arief, I. I. (2017). Potential of Lactic Acid Bacteria Isolated from Dangke and Indonesian Beef as Hypocholesterolaemic Agent. *Media Peternakan*, *40*(2), 136–142. https://doi.org/10.5398/medpet.2017.40.2.136

Collins, K. H., Paul, H. A., Hart, D. A., Reimer, R. A., Smith, I. C., Rios, J. L., Seerattan, R. A., & Herzog, W. (2016). A High-Fat High-Sucrose Diet Rapidly Alters Muscle Integrity, Inflammation and Gut Microbiota in Male Rats. *Scientific Reports*, *6*(1), 37278. https://doi.org/10.1038/srep37278

Djabir, Y. Y., & Yustisia, I. (2023). Efek pemberian dangke terhadap kadar kolesterol dan trigliserida darah tikus pemodelan hiperkolesterolemia dan hipertrigliseridemia. *Farmasi dan Farmakologi*, *2*, 43–46. https://doi.org/10.20956/mff.v27i2.25302

Fabersani, E., Marquez, A., Russo, M., Ross, R., Torres, S., Fontana, C., Puglisi, E., Medina, R., & Gauffin-Cano, P. (2021). Lactic Acid Bacteria Strains Differently Modulate Gut Microbiota and Metabolic and Immunological Parameters in High-Fat Diet-Fed Mice. *Frontiers in Nutrition*, *8*, 718564. https://doi.org/10.3389/fnut.2021.718564

Fadhillah, A. N., Hafsani, & Nur, F. (2015). *Penurunan Kadar Kolesterol Oleh Bakteri Asam Laktat Asal Dangke Secara In Vitro*. 174–180. https://doi.org/10.24252/psb.v1i1.2135

Gan, Y., Tang, M., Tan, F., Zhou, X., Fan, L., Xie, Y., & Zhao, X. (2020). Anti-obesity effect of *Lactobacillus plantarum* CQPC01 by modulating lipid metabolism in high-fat diet-induced C57BL/6 mice. *Journal of Food Biochemistry*, *44*(12). https://doi.org/10.1111/jfbc.13491

Jeong, S. (2023). Gut microbiota's impact on obesity. *Clinical and Experimental Pediatrics*, *66*(7), 294–295. https://doi.org/10.3345/cep.2023.00458

Kober, A. K. M. H., Saha, S., Ayyash, M., Namai, F., Nishiyama, K., Yoda, K., Villena, J., & Kitazawa, H. (2024). Insights into the Anti-Adipogenic and Anti-Inflammatory Potentialities of Probiotics against Obesity. *Nutrients*, *16*(9), 1373. https://doi.org/10.3390/nu16091373

Kobi, J. B. B. S., Matias, A. M., Gasparini, P. V. F., Torezani-Sales, S., Madureira, A. R., da Silva, D. S., Correa, C. R., Garcia, J. L., Haese, D., Nogueira, B. V., De Assis, A. L. E. M., Lima-Leopoldo, A. P., & Leopoldo, A. S. (2023). High-fat, high-sucrose, and combined high-fat/high-sucrose diets effects in oxidative stress and inflammation in male rats under presence or absence of obesity. *Physiological Reports*, *11*(7), e15635. https://doi.org/10.14814/phy2.15635

Lasker, S., Rahman, M. M., Parvez, F., Zamila, M., Miah, P., Nahar, K., Kabir, F., Sharmin, S. B., Subhan, N., Ahsan, G. U., & Alam, M. A. (2019). High-fat diet-induced metabolic syndrome and oxidative stress in obese rats are ameliorated by yogurt supplementation. *Scientific Reports*, *9*(1), 20026. https://doi.org/10.1038/s41598-019-56538-0

Li, B., Evivie, S. E., Lu, J., Jiao, Y., Wang, C., Li, Z., Liu, F., & Huo, G. (2018). *Lactobacillus helveticus* KLDS1.8701 alleviates d - galactose-induced aging by regulating Nrf-2 and gut microbiota in mice. *Food & Function*, *9*(12), 6586–6598. https://doi.org/10.1039/C8FO01768A

Li, H., Liu, F., Lu, J., Shi, J., Guan, J., Yan, F., Li, B., & Huo, G. (2020). Probiotic Mixture of Lactobacillus plantarum Strains Improves Lipid Metabolism and Gut Microbiota Structure in High Fat Diet-Fed Mice. *Frontiers in Microbiology*, *11*, 512. https://doi.org/10.3389/fmicb.2020.00512

Lin, X., & Li, H. (2021). Obesity: Epidemiology, Pathophysiology, and Therapeutics. *Frontiers in Endocrinology*, *12*, 706978. https://doi.org/10.3389/fendo.2021.706978

Lin, X., Xia, Y., Wang, G., Yang, Y., Xiong, Z., Lv, F., Zhou, W., & Ai, L. (2018). Lactic Acid Bacteria With Antioxidant Activities Alleviating Oxidized Oil Induced Hepatic Injury in Mice. *Frontiers in Microbiology*, *9*, 2684. https://doi.org/10.3389/fmicb.2018.02684

Mardhotillah, H., Nur Afifah, D., & Pramono, A. (2024). Effect of isocaloric fructose restriction and moringa leaf capsule (Moringa oleifera) on anthropometric values in obese group aged 19-50 years. *SAGO : Gizi Dan Kesehatan*, *5*(2), 419–426. http://dx.doi.org/10.30867/sago.v5i2.1655

Marseglia, L., Manti, S., D'Angelo, G., Nicotera, A., Parisi, E., Di Rosa, G., Gitto, E., & Arrigo, T. (2014). Oxidative Stress in Obesity: A Critical Component in Human Diseases. *International Journal of Molecular Sciences*, *16*(1), 378–400. https://doi.org/10.3390/ijms16010378

Maulana, H., & Ridwan, A. (2021). High-Fat Diets-Induced Metabolic Disorders to Study Molecular Mechanism of Hyperlipidemia in Rats. *3BIO: Journal of Biological Science, Technology and Management*, *3*(2), 38–50. https://doi.org/10.5614/3bio.2021.3.2.5

Mutia, A., Jumiyati, J., & Kusdalinah, K. (2022). Pola makan dan aktivitas fisik terhadap kejadian obesitas remaja pada masa pandemi COVID-19. *Journal of Nutrition College*, *11*(1), 26–34. https://doi.org/10.14710/jnc.v11i1.32070

Neyrinck, A. M., Schüppel, V. L., Lockett, T., Haller, D., & Delzenne, N. M. (2016). Microbiome and metabolic disorders related to obesity: Which lessons to learn from experimental models? *Trends in Food Science & Technology*, *57*, 256–264. https://doi.org/10.1016/j.tifs.2016.08.012

Safitri, D. N. (2023). The Effect of Kefir (Cow's Milk) Administration to Prevent Reduction of SOD (Superoxide Dismutase) Activity in Pregnant White Rats (Rattus norvegicus) Placenta with Cigarette Smoke Exposure. *Jurnal Aisyah : Jurnal Ilmu Kesehatan*, *8*(4), 1770–1780. https://doi.org/10.30604/jika.v8i4.2488

Saltiel, A. R., & Olefsky, J. M. (2017). Inflammatory mechanisms linking obesity and metabolic disease. *Journal of Clinical Investigation*, *127*(1), 1–4. https://doi.org/10.1172/JCI92035

Toshimitsu, T., Mochizuki, J., Ikegami, S., & Itou, H. (2016). Identification of a Lactobacillus plantarum strain that ameliorates chronic inflammation and metabolic disorders in obese and type 2 diabetic mice. *Journal of Dairy Science*, *99*(2), 933–946. https://doi.org/10.3168/jds.2015-9916

Vetrani, C., Di Nisio, A., Paschou, S. A., Barrea, L., Muscogiuri, G., Graziadio, C., Savastano, S., Colao, A., & on behalf of the Obesity Programs of Nutrition, Education, Research and Assessment (OPERA) Group. (2022). From Gut Microbiota through Low-Grade Inflammation to Obesity: Key Players and Potential Targets. *Nutrients*, *14*(10), 2103. https://doi.org/10.3390/nu14102103

Yuan, M., Singer, M. R., & Moore, L. L. (2021). Yogurt Consumption Is Associated with Lower Levels of Chronic Inflammation in the Framingham Offspring Study. *Nutrients*, *13*(2), 506. https://doi.org/10.3390/nu13020506

Zhang, J., Mu, J., Li, X., & Zhao, X. (2022). Relationship between probiotics and obesity: A review of recent research. *Food Science and Technology*, *42*, e30322. https://doi.org/10.1590/fst.30322

Zhao, T., Wang, H., Liu, Z., Liu, Y., DeJi, Li, B., & Huang, X. (2023). Recent Perspective of Lactobacillus in Reducing Oxidative Stress to Prevent Disease. *Antioxidants*, *12*(3), 769. https://doi.org/10.3390/antiox12030769