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Effect of *Dangke* consumption on body weight, blood glucose, and total cholesterol in rats subjected to high-fat and fructose diet

Efecto del consumo de *Dangke* sobre el peso corporal, la glucosa en sangre y el colesterol total en ratas sometidas a dieta alta en grasa y fructosa

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SUMMARY

Obesity occurs due to an imbalance in caloric intake, leading to excess fat accumulation in adipose tissue. This condition is associated with hyperglycemia and abnormal lipid levels. Dangke, a traditional Indonesian cheese, contains lactic acid bacteria and bioactive peptides known for their health benefits. This study aims to assess the effects of dangke consumption on body weight, glucose, and total cholesterol levels in rats subjected to a high-fat and fructose diet (HFFD). This research employed an experimental laboratory design. Twenty-four Sprague-Dawley rats, with weights ranging from 100 to 200 g, were divided into six groups, each consisting of four rats. Group 1 (ND) (received a normal diet. Group 2 (HFFD) was provided with a high-fat and fructose diet). Groups 3 and 4, were given the HFFD along with acarbose at a dosage of 0.9 mg/200 g and orlistat at a dosage of 1.08 mg/200 g, respectively. Finally, Groups 5 and 6 were fed the HFFD along with dangke at dosages of 1.8 g/200 g and 3.6 g/200 g, respectively. Results showed that dangke significantly inhibited weight gain and fasting glucose levels ($p<0.05$) compared to the normal diet and HFFD groups. Moreover, dangke consumption reduced total cholesterol levels compared to the HFFD group. In conclusion, dangke consumption demonstrated potential in preventing weight gain, high blood glucose levels, and elevated total cholesterol levels in rats subjected to HFFD.

Keywords: *Dangke, obesity, blood glucose, total cholesterol, functional food*

RESUMEN

La obesidad se produce debido a un desequilibrio en la ingesta calórica, lo que lleva a una acumulación

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excesiva de grasa en el tejido adiposo. Esta condición se asocia con hiperglucemia y niveles anormales de lípidos. Dangke, un queso tradicional de Indonesia, contiene bacterias del ácido láctico y péptidos bioactivos conocidos por sus beneficios para la salud. Este estudio tiene como objetivo evaluar los efectos del consumo de dangke sobre el peso corporal, la glucosa y los niveles de colesterol total en ratas sometidas a una dieta alta en grasas y fructosa (HFFD). Esta investigación empleó un diseño experimental de laboratorio. Veinticuatro ratas Sprague-Dawley, con pesos que oscilaban entre 100 y 200 g, se dividieron en seis grupos, cada uno compuesto por cuatro ratas. El Grupo 1 (ND) recibió una dieta normal. El grupo 2 (HFFD) recibió una dieta rica en grasas y fructosa. Los Grupos 3 y 4, recibieron HFFD junto con acarbosa a dosis de 0,9 mg/200 g y orlistat a dosis de 1,08 mg/200 g, respectivamente. Por último, los grupos 5 y 6 recibieron HFFD junto con dangke en dosis de 1,8 g/200 gy 3,6 g/200 g, respectivamente. Los resultados mostraron que dangke inhibió significativamente el aumento de peso y los niveles de glucosa en ayunas ($p<0,05$) en comparación con los grupos de dieta normal y HFFD. Además, el consumo de dangke redujo los niveles de colesterol total en comparación con el grupo HFFD. En conclusión, el consumo de dangke demostró potencial para prevenir el aumento de peso, los niveles altos de glucosa en sangre y los niveles elevados de colesterol total en ratas sometidas a HFFD.

Palabras clave: *Dangke, obesidad, glucosa en sangre, colesterol total, alimentos funcionales.*

INTRODUCTION

Obesity is a complex, multifactorial, and largely preventable disease, affecting, along with overweight, over a third of the world's population today. Obesity has become a major health issue, with far-reaching consequences for various life-threatening diseases, becoming a significant health problem worldwide over the last few decades reaching epidemic proportions (1). Physiologically, the condition arises from an imbalance in caloric intake, leading to the accumulation of excess fat in adipose tissue (2,3). Obesity greatly increases the risk of chronic disease morbidity — namely disability, depression, cardiovascular disease, certain cancers — and mortality, and type 2 diabetes mellitus due to decreased insulin sensitivity characterized by an increase in fasting serum glucose levels that exceed normal values (4-6). In addition to that, it can cause abnormalities in lipid fractions or dyslipidemia (7). One of the parameters marked in lipid fraction abnormalities is an increase in serum total cholesterol levels that exceed normal limits (8).

Currently, it is proposed that the safest method that can be used to reduce the risk of obesity and its comorbidities is to modify lifestyle, including diet and exercise programs (9). Consuming dairy products is included in a healthy diet associated with better diet quality because they contain high levels of calcium and vitamin D (10). Dairy products have been studied to provide possible beneficial physiological effects through the presence of bioactive peptide micro-organisms and macromolecules (11,12) that act as anti-cancer and anti-diabetic agents, reduce the risk of stroke, and may influence adipose tissue function, inflammation, and the gut microbiome (13-16).

Dangke is a traditional type of cheese originating from Indonesia that is made using fresh cow's milk as raw material. *Dangke* is classified as a soft cheese because of its high water content. The *dangke* coagulation process is carried out by heating the milk and adding the papain enzyme to the papaya sap (17). The evidence indicates several beneficial effects in the health sector, such as increasing phosphate and calcium, decreasing bacterial colonies in dental plaque (18), improving the nutritional status of children (19), and increasing the hemoglobin levels of pregnant women with anemia (17). In addition, whey dangke can reduce cholesterol levels (20). However, there is little information regarding the effect of *dangke* on obesity and the risk of complications. Therefore, this study aimed to evaluate the effect of administering *dangke* on body weight, glucose levels, and total cholesterol in rats fed with a high-fat and fructose diet (HFFD).

METHODS

Study design and sample size

This research employed an experimental laboratory design. The study involved twenty-

four healthy and active male Sprague-Dawley rats, aged 6-8 weeks and weighing 100-200 g. Animals were divided into six groups, group 1 was a negative control who received a normal diet (ND), and groups 2-6 were treatment groups. Group three received an Acarbose treatment dose of 0.9 mg/200 g body weight rats (21), and group four received an orlistat treatment dose of 1.08 mg/200 g body weight rats (22). Groups five and six received *dangke* interventions of 1.8 g and 3.6 g/200 g rat body weight (17,18). This research was conducted in the animal laboratory of the Faculty of Medicine, Hasanuddin University, Makassar. Indonesia.

Animal handling and ethical approval

Rats were acclimatized for one week before the beginning of the experiment. The animals received standard rat chow diet and drinking water *ad libitum*, and were housed under controlled conditions of a 12-h light-dark cycle and a temperature range of 26-28°C. The study was approved by the Animal Ethics Committee of the Ethics Commission in the Faculty of Medicine, Hasanuddin University, with letter Number: 125/ UN4.6.4.5.31/ PP36/ 2023.

Diet and medication

The diet employed in the study was a high-fat and fructose combination, comprising regular diet components (AD II Super), along with pork oil, duck egg yolk, and cholic acid in proportions of 70.5 %, 13.5 %, 15 %, and 1 %, respectively. The rats in all groups, except for group 1, received 40 mL of fructose solution (Rose Brand, Indonesia) mixed in drinking water with a ratio of 3:7 (final concentration: 0.2 g/mL). The *dangke* used in this study was obtained from the milk technology laboratory, Faculty of Animal Husbandry, Hasanuddin University, Makassar, Indonesia. The nutritional content of *dangke* consisted of 17.20 % protein, 32.81 % fat, 2.32 % minerals and 45.75 % water content. All rats were fed 10-20 g daily using a 10 % rat body weight formula for four weeks.

Treatment scheme

Sprague-Dawley rats were randomly divided into six groups, each comprising four rats. Group 1 (ND) received a normal diet, and Group 2 (HFFD) received a high-fat and fructose diet. Group 3 was acarbose (receiving HFFD + Acarbose diet of 0.9 mg/200 g of rat body weight). Group 4 was Orlistat (receiving HFFD + Orlistat 1.08 mg/200 g of rat body weight). Group 5 was *dangke* 1.8 (receiving HFFD + *dangke* 1.8 g/200 g of rat body weight). Group 6 was dangke 3.6 (receiving HFFD + *dangke* 3.6 g/200 g of rat body weight). Meanwhile, HFFD, orlistat, acarbose, and *dangke* were administered by oral gavage daily for four weeks.

Collection and analysis of specimens

Throughout the experiment, measures were taken to minimize any discomfort experienced by the rats. After four weeks of treatment, the rats were subjected to a 12-h fasting period before being euthanized using ketamine. Blood samples were collected through the sub-jugular vein as much as 1.5 mL in a non-anticoagulant tube (Tiger-top tube). The sample underwent centrifugation at 300 rpm for 20 min. The serum obtained was collected to analyse glucose and total cholesterol levels.

The rats' body weight was monitored every seven days throughout the experiment. Fasting blood glucose levels were examined according to the guidelines provided by Meril Diagnostic® (Gujarat, India) commercial kits. The total cholesterol levels were determined using enzymatic colorimetry principles with Glory Diagnostic® (Barcelona, Spain). Sample absorbance was measured using Ganesy 150 UV-VIS from Thermo Scientific (Madison, USA).

Statistical Analysis

The statistical analysis was conducted using IBM SPSS Statistics 26 (SPSS Inc, Chicago). The statistical differences among the means were determined using a one-way analysis of variance

(ANOVA), followed by Tukey's Post Hoc test to assess differences in group means. Results were considered statistically significant when the p-value was <0.05.

RESULT

The Effect of *Dangke* Consumption on Rat Body Weight after Four Weeks of Treatment

At the end of the experiment, each group displayed different body weights, with the HFFD group exhibiting the highest weight, followed by the HFFD+Acarbose, HFFD+*dangke* 3.6 g, HFFD+*dangke* 1.8 g, HFFD+Orlistat groups, and the lowest weight was observed in the normal diet treatment. p<0.05 (HFFD) vs. (Normal diet, HFFD+orlistat, HFFD+*Dangke* 1.8 g), #p<0.05 ND vs HFFD, HFFD+orlistat, HFFD+*dangke* 1.8g and 3.6g (Figure 1).

The Effect of *Dangke* Feeding on the Serum Glucose Levels in Rats

The HFFD group exhibited the highest mean glucose level, followed by the normal diet group. These two treatments demonstrated significant differences in their value compared to the HFFD+*dangke* 1.8 g, HFFD+*dangke* 3.6 g, and HFFD+acarbose groups. Meanwhile, the HFFD+*dangke* 1.8 g showed the lowest mean glucose level. *p<0.001 (Normal diet, HFFD) vs. HFFD+*dangke* 1.8g, HFFD+*dangke* 3.6 g, HFFD+acarbose: # p<0.001 Normal diet vs. HFFD (Figure 2).

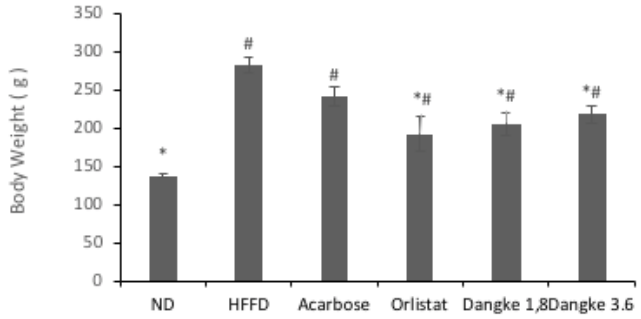

Figure 1. Total weight gain during treatment- Significance values were determined by using a One-Way Anova test, followed by Tukey's Post-Hoc. *p<0.05 (HFFD) vs (Normal diet, HFFD+orlistat, HFFD+*dangke* 1.8 g), #p<0.05 ND vs HFFD, HFFD+orlistat, HFFD+*dangke* 1.8 g and 3.6 g

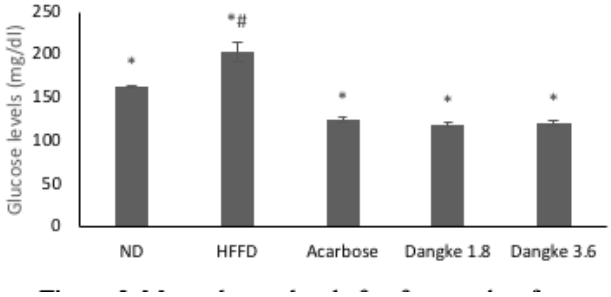

Figure 2. Mean glucose level after four weeks of treatment. The significance value was determined by utilising a One-Way Anova test, followed by Tukey's Post-Hoc. *p<0.001 (Normal diet, HFFD) vs HFFD+*dangke* 1.8 g, HFFD+*dangke* 3.6 g, HFFD+acarbose: # p<0.001 Normal diet vs HFFD.

The Effect of *Dangke* Feeding on the Total Cholesterol Level in Rats

The HFFD treatment group displayed the highest mean total cholesterol level, which differed significantly from the HFFD+*dangke* 1.8 g and HFFD+*dangke* 3.6 g groups. However, the groups receiving *dangke* and orlistat treatments showed no significant difference compared to the normal diet group. *p<0.05 HFFD vs. HFFD+dangke 1.8g, HFFD+*dangke* 3.6 g (Figure 3).

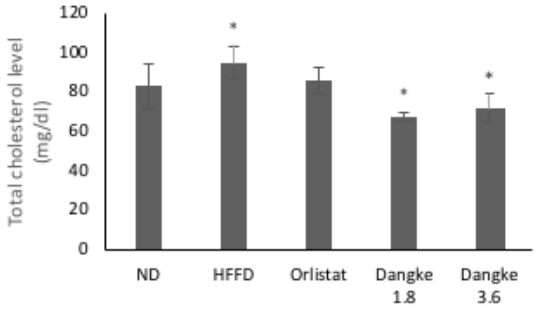

Figure 3. Mean total cholesterol levels four weeks after treatment. The significance level was determined by utilizing a One-Way Anova test, followed by Tukey's Post-Hoc *p<0.05 HFFD vs. HFFD+*dangke* 1.8 g, HFFD+*dangke* 3.6 g.

DISCUSSION

Preventive trials *dangke* in reducing the risk of metabolic syndrome are carried out to find a breakthrough in controlling this disease. *Dangke* is a dairy product rich in probiotic bacteria, essential amino acids, and other nutrients that have a positive impact on health. Probiotic bacteria have been widely associated with improvements in metabolic syndrome conditions through improvements in glucose and lipid profiles (23). The diet employed in the current study demonstrated a notable increase in the risk of metabolic syndrome based on the tested parameters. These results are in agreement with findings from prior research which demonstrated that HFFD induces insulin resistance and gut microbiota dysbiosis and accentuates dyslipidaemia in Watanabe rabbits; that when subjected to HFFD, might become a potential diet-induced MetS animal model with two main features, dyslipidaemia and insulin resistance (24); and in male C57BL/6 mice fed high-fat high-fructose diet (HFD) for 60 days, to induce Non-alcoholic fatty liver disease (NAFLD) and -steatohepatitis (NASH) that imply a state of excessive fat built-up in livers with/or without inflammation (25). Our present results indicated that 4-week treatment period, the group fed with HFFD showed a 70 % rise in body weight, leading to a notable decline in the movement performance of the rats. In fact, it has been reported that the decrease in metabolic ability among obese individuals displays an inverse relationship with weight loss, decreased contractile function, and movement (26). In contrast, rats treated with *dangke* 1.8 g and 3.6 g and orlistat experienced an increase in body weight of 14 %, 30 %, and 15 %, respectively. The lowest weight gain was observed in the normal diet group at 0.9 %. Orlistat is a medication used in the management of obesity. Orlistat acts by reversibly inhibiting gastric and pancreatic lipases. The inactivation of lipases prevents the hydrolysis of triglycerides, and thus free fatty acids are not absorbed (27). *Dangke* is believed to exert its effects on weight control by increasing energy metabolism and muscle contraction, thereby regulating weight gain through its lactic acid bacteria (LAB) and bioactive peptides. The findings are in line with a previous study (28), which suggests that milk

on daily consumption does not lead to weight gain and may even decrease the risk of type 2 diabetes mellitus.

Our data show that feeding rats with *dangke* could successfully inhibit the rise in glucose levels. Indeed, *dangke* consumption in the HFFD-fed group demonstrated an anti-hyperglycaemic effect when compared to both the normal diet and HFFD groups ($p<0.05$). According to Mozaffarian, the consumption of dairy products can reduce the risk of type 2 diabetes mellitus (28). Furthermore, previously it was shown that fermented *dangke* has the effect of anti-hyperglycemia, since reduced fasting blood glucose in rats treated with propylthiouracil and a high-fat diet after the administration of *dangke* cheese at 1.5 g/200 g body weight of rats for 14 days.

A prior study demonstrated that rat consumption of *dangke* at 1.5 g/200 g body weight was more effective in reducing fasting blood glucose levels comparable to that of rats treated with acarbose, a drug known to lower blood sugar by preventing the breakdown of starch into sugar (29). In line with the present findings, administration of *dangke* at 1.8 g/200 g body weight effectively inhibited the increase in glucose levels, even though it did not was a significant difference when compared to the acarbose group.

The HFFD treatment group displayed the highest mean total cholesterol level, which differed significantly from the groups administered with *dangke* (1.8 g and 3.6 g) ($p<0.05$). These findings are in accordance with the research of Fadhilah et al., which demonstrated that *dangke* contains lactic acid bacteria that are capable to ferment sugar or carbohydrates to produce large amounts of lactic acid and reduce cholesterol levels (30). Similarly, Sulmiyati et al., also stated that administering whey *dangke* can reduce total cholesterol levels in the research subjects, specifically broiler chicken (20). Among the doses tested, 1.8 g of *dangke* proved to be the most effective in preventing an increase in total cholesterol levels, outperforming the 3.6 g dose and the control drug Orlistat.

The hypoglycemia and anti-hypercholesterol activity of *dangke* is obtained from fermentation-derived bioactive peptides by enhancing insulin uptake and inhibiting key enzymes involved in glucose metabolism (31,32). Recent findings (32) have isolated several types of amino acids contained in *dangke* as potential bioactive peptides such as arginine 3.6 %, histidine 2.3 %, isoleucine 5.1 %, leucine 9.2 %, lysine 7.3 %, methionine 4.1 %, and tryptophan 1.3 %. Bioactive peptides play a role in improving dyslipidaemia by interfering with micelle solubility and absorption of dietary cholesterol, altering enterohepatic bile acid circulation, and promoting cholesterol catabolism, as well as regulating lipogenic proteins and genes. Typically, this peptide remains encrypted within its parent protein sequence and is released either during maturation or through processes like chemical, microbial, or enzymatic hydrolysis (31). Furthermore, it can bind bile acids, which then can inhibit the reabsorption of bile acids in the ileum, can attach to starch and prevent it from being digested, thereby lowering blood cholesterol levels (33,34).

Additionally, *dangke* contains probiotic bacteria (30,35-37). The highest count of lactic acid bacteria contained in *dangke* was observed after three days of fermentation, with a total colony of 0.912 x 108 CFU/mL (29). Probiotic bacteria are living microorganisms that can improve the nutritional status of their host if given in the right dose (38). Probiotic bacteria have a positive impact on weight loss (39) and also exhibit anti-hyperglycemic effects through their antioxidant activity, which helps prevent oxidative damage, inhibits lipid peroxidation, elevate the levels of antioxidants such as glutathione, superoxide dismutase, and glutathione peroxidase; additionally, probiotic bacteria can enhance the bioavailability of gliclazide, as well as inhibit and or delay intestinal glucose absorption (40). Based on a meta-analysis (41), probiotic bacteria demonstrated a significant reduction in serum total cholesterol levels. Probiotic bacteria intake can lead to elevated levels of short-chain fatty acids (SCFA), particularly propionate, which effectively inhibits hydroxymethylglutaryl coenzyme A reductase (HMG CoA reductase) in the liver. This is a rate-limiting step of the cholesterol synthesis pathway, leading to increased cholesterol metabolism (42).

A limitation of this study is that we did not measure all parameters associated with metabolic

syndrome conditions. In addition, the duration of the treatment seems to be still short enough for conditioning metabolic syndrome in experimental animals. However, our findings have revealed some of the advantages that *dangke* has in preventing or reducing the risk of metabolic syndrome.

CONCLUSION

Dangke consumption has been shown to effectively inhibit the increase in body weight, fasting blood glucose levels, and total cholesterol levels in rats subjected to high-fat and fructose diets. These findings serve as valuable reference points for future clinical research trials on the effects of *dangke* consumption on body weight, glucose levels, and total cholesterol levels using human subjects. However, carrying out similar studies with diverse parameters is necessary to uncover the potential influence that *dangke* may have on human metabolic processes.

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