



Fortified *dadih* increases short-chain fatty acids, reduces leptin levels, and body weight in obese rats

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ABSTRACT

Background: Obesity, a leading global health concern, contributes to oxidative stress and gut dysbiosis. Functional foods like fortified *dadih* may offer a novel approach to manage obesity by enhancing gut health and reducing oxidative stress.

Objective: To assess the impact of *dadih* fortified with red dragon fruit and selenium on cecal short-chain fatty acids (SCFA) and leptin levels in high-fat fructose diet-induced obese rats.

Materials and Methods: A true experimental design was conducted using 20 male Sprague Dawley rats (n = 5 per group) randomly assigned to four groups: healthy control (K-), obese control (K+), *dadih* treatment (1.8 g/200 g BW/day) (P1), and *dadih* enriched with red dragon fruit and selenium (1.8 g/200 g BW/day; sodium selenite 0.4 ppm) (P2). The intervention lasted for 4 weeks. SCFA concentrations were determined using gas chromatography, while leptin levels were quantified via ELISA. Data were analyzed using One-way ANOVA, Kruskal–Wallis tests, and Pearson correlation to assess treatment effects and inter-variable associations.

Results: After HFFD, all groups showed significant weight gain ($p < 0.05$), with the K+ group having the highest body weight (281.2 ± 2.59 g) and the K- group the lowest (219.2 ± 3.42 g). Weight gain was significantly smaller in the K- group (30 g) than in K+, P1, and P2, which had similar gains (92 g). SCFA and leptin levels significantly differed between groups ($p < 0.05$), with K+ showing the highest leptin (9.42 ng/ml) and K- the lowest (1.31 ng/ml). Significant negative correlations were observed between total SCFAs and leptin ($r = -0.545$, $p = 0.002$) and between SCFAs and body weight ($r = -0.909$, $p = 0.000$).

Conclusion: Fortified *dadih* with red dragon fruit and selenium effectively reduced body weight and leptin levels in high-fat fructose diet-induced obese rats. The treatment also enhanced short-chain fatty acid levels, suggesting a beneficial effect on gut health and metabolic markers. These findings indicate the potential of fortified *dadih* as a functional food in obesity management, though further research in humans is necessary to confirm these results.

Keywords: Obesity; *dadih*; short chain fatty acids; leptin; body weight

BACKGROUND

Obesity is a global health issue, with 5 million annual deaths linked to high body mass index (≥ 25 kg/m²) out of 41 million deaths caused by non-communicable diseases (NCDs).¹ In Indonesia, adult obesity prevalence increased from 21.8% in 2018 to 23.4% in 2023.^{2,3} Beyond being a metabolic disorder, obesity also represents a chronic low-grade inflammatory state driven by excessive fat accumulation.⁴ This condition contributes to oxidative stress due to excessive abdominal fat, which releases pro-oxidants and Reactive Oxygen Species (ROS).⁵ Elevated leptin levels in obesity, caused by increased adipocytes, lead to leptin resistance and oxidative stress via NADPH oxidase activation.⁶ Studies show a direct relationship between leptin and oxidative stress markers, such as malondialdehyde (MDA) and glutathione (GSH).⁷

Obesity is also associated with gut dysbiosis, characterized by reduced Short-Chain Fatty Acid (SCFA)-producing bacteria (e.g., *Bacteroides*, *Bifidobacterium*, and *Lactobacillus*).⁸ SCFAs such as acetate, propionate, and butyrate play roles in energy homeostasis and leptin regulation. Dietary interventions that increase SCFA production—through probiotics, prebiotics, or fermented foods—have shown potential to improve metabolic profiles in obesity.⁹

Dadih, a traditional fermented buffalo milk from West Sumatra, contains lactic acid bacteria (LAB) with probiotic potential.¹⁰ Previous studies indicate that fortified *dadih* can improve glucose metabolism and SCFA levels.¹¹ However, its sour taste limits consumer preference, necessitating flavor improvements. Adding red dragon fruit (*Hylocereus polyrhizus*) can enhance flavor while providing fructan oligosaccharides with prebiotic properties, increasing beneficial LAB abundance and SCFA production.^{12,13} Higher dragon fruit concentrations in yogurt also raise LAB content, supporting gut health.¹⁴ Selenium, an antioxidant micronutrient, may further enhance the health benefits of fermented products by boosting glutathione peroxidase (GPx) activity, modulating gut microbiota, and potentially improving leptin sensitivity.^{15–18} However, no previous study has investigated the combined supplementation of *dadih*, red dragon fruit, and

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selenium in an obesity model, particularly focusing on their effects on cecal SCFA and leptin levels. Therefore, this study aimed to evaluate the impact of *dadih* fortified with red dragon fruit and selenium on cecal SCFA and leptin levels in high-fat fructose diet-induced obese rats.

MATERIALS AND METHODS

This study employed a true experimental design with a post-test-only control group with simple randomization. After a one-week acclimatization period under controlled conditions (23 °C, 12-hour light/dark cycle, daily cage cleaning), twenty male Sprague Dawley rats (*Rattus norvegicus*), aged 8 weeks and weighing 150–200 g, were fed a high-fat fructose diet (HFFD) for 4 weeks, except the healthy control group (K⁻). The rats were then randomly allocated using simple randomization into four groups (n = 5/group): K⁻ (healthy control), K⁺ (obese control), P1 (*dadih*), and P2 (*dadih* with red dragon fruit and selenium). Group assignments were concealed from laboratory analysts measuring SCFA and leptin to minimize selection and measurement bias. Body weight was recorded every week from acclimatization until the end of the intervention.

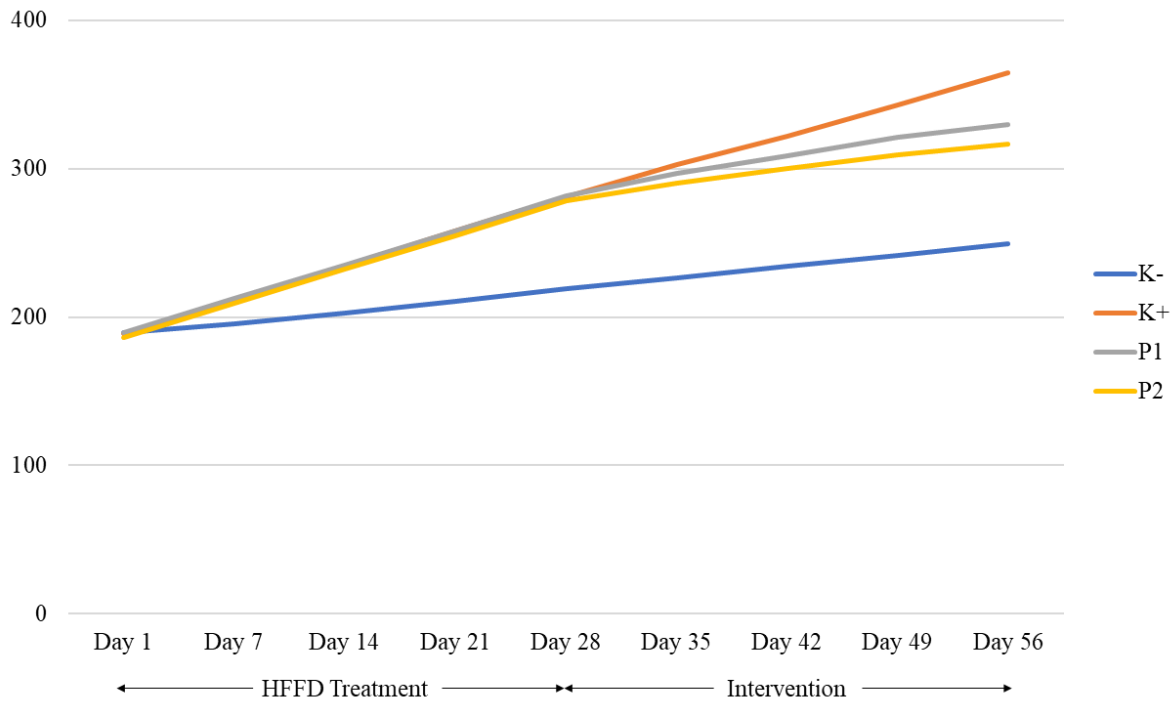
Dadih was prepared using buffalo milk sourced from buffalo farms in Agam, West Sumatera, and red dragon fruit (*Hylocereus polyrhizus*) from local plantations. Selenium was provided as commercially available sodium selenite (Na₂SeO₃). The preparation of *dadih* with red dragon fruit followed the method of previous study with modifications. 100 mL of buffalo milk was pasteurized at 72°C for 15 seconds, then cooled to 30°C, and added with red dragon fruit juice (10%) and selenium (0.4 ppm). The buffalo milk and red dragon fruit mixture were poured into bamboo containers and sealed with banana leaves. The 10% concentration of red dragon fruit was selected based on a previous study reporting higher preference compared to 10% orange juice or no fruit addition.¹⁹ The selenium dose of 0.4 ppm was adopted from prior findings in buffalo milk yoghurt showing no adverse sensory effects compared to 0.2 and 0.6 ppm.²⁰ The buffalo milk and red dragon fruit mixture were poured into bamboo containers and sealed with banana leaves. The fortified *dadih* was then incubated at room temperature for 48 hours to allow the growth of lactic acid bacteria.¹¹ After 48 hours, the fortified *dadih* was placed in an icebox and transported to the PSPG PAU Universitas Gadjah Mada. Subsequently, it was stored at -18°C. During the intervention, rats in the P1 and P2 groups received *dadih* supplementation at a dose of 1.8 g/200 g body weight/day for 4 weeks. The P1 group was given plain *dadih*, while the P2 group received fortified *dadih* containing red dragon fruit (10%) and sodium selenite (0.4 ppm).

Data analysis was conducted using SPSS 25. The normality test was performed using the Shapiro-Wilk test and all data were confirmed to be normally distributed. Differences in body weight before and after intervention were analyzed using the Paired T-test. The difference in cecal SCFA and leptin levels after treatment in each group was analyzed using One-way ANOVA, followed by Post Hoc tests. The correlation between SCFA, leptin, and body weight was analyzed using Pearson correlation. This study used a significance level of p<0.05 for analysis. The Health Research Ethics Commission of the Faculty of Medicine, Diponegoro University, Semarang, granted ethical clearance for this research, with approval number 090/EC-H/KEPK/FK-UNDIP/IX/2024.

RESULTS

Body Weight

The rat's body weight was weighed weekly from before acclimatization until the end of the intervention (Figure 1). After the acclimatization process for one week, rats were weighed to obtain body weight before receiving HFFD feed. After that, randomization was carried out and divided into six groups. Rats in the K⁻ group only received standard feed, while the other groups (K⁺, P1, and P2) received HFFD feed for 4 weeks. Initially, all groups had no significant differences in the mean body weight (p = 0.313). However, after HFFD feeding, all groups exhibited a significant increase in body weight (p < 0.05). The K⁺ group had the highest mean body weight (281.2 ± 2.59 g), whereas the K⁻ group showed the lowest (219.2 ± 3.42 g). Groups P1 and P2, representing intervention groups, showed similar mean body weights (281.4 ± 3.36 g and 278.4 ± 3.36 g, respectively) to the K⁺ group, significantly higher than the K⁻ group.



K-: Healthy control, K+: Positive control (Obese Rat), P1: Treatment 1 (*dadih*), P2: Treatment 2 (fortified *dadih*). The data presented in the graph are mean values

Figure 1. Body Weight Development of Rats in Different Treatment Groups

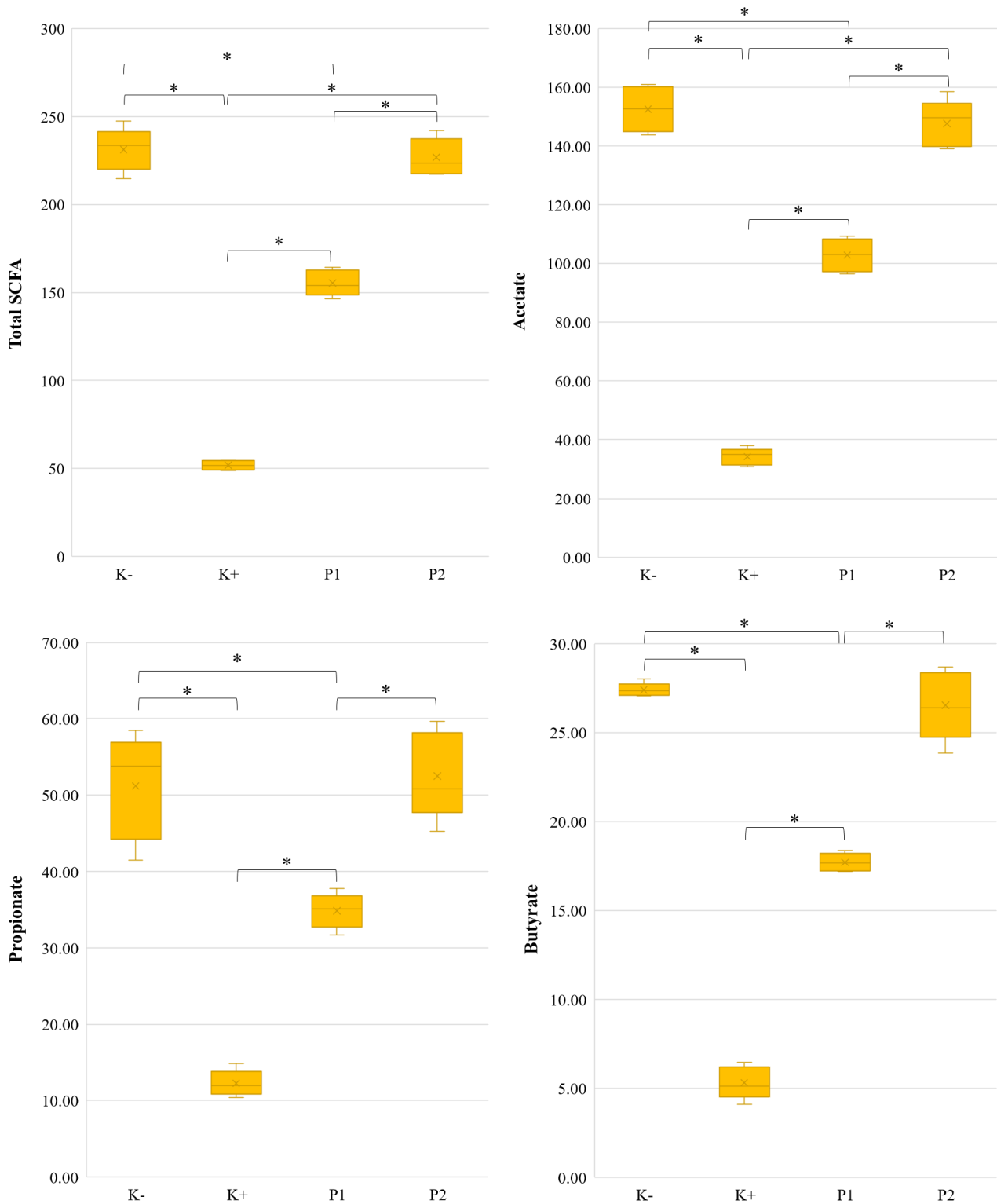
After receiving HFFD for 4 weeks, the K- and K+ groups received standard feed for 4 weeks, while the intervention groups (P1 and P2) received the *dadih* and fortified *dadih*. Before the intervention, the mean body weight of the K- group was significantly lower (219.2 ± 3.42 g) compared to the other groups (K+, P1, and P2), which all had similar weights (281.2 ± 2.59 g, 281.4 ± 3.36 g, and 278.4 ± 3.36 g, respectively). This difference was statistically significant, as indicated by the one-way ANOVA ($p < 0.05$). After the intervention, significant weight increases were observed in all groups, as reflected by the paired t-tests ($p < 0.05$ for all groups). However, the extent of the weight gain varied between groups. The K+ group showed the most significant in body weight (83.2 ± 1.09 g), followed by the P1 group (48.4 ± 1.14 g), the P2 group (38.2 ± 1.09 g), and finally the K- group, which had the smallest weight gain (30.2 ± 1.3 g).

Post hoc analysis revealed that the mean differences in weight gain (Δ) between the groups were statistically significant ($p < 0.05$). The K+ group had significantly more significant weight gain than all other groups, while the weight gain in the K- group was the smallest among all groups. P1 and P2 groups had moderate weight gains, with P1 showing a significantly higher increase than P2.

Short Chain Fatty Acids Levels

SCFA concentration of rat cecum was measured after the intervention of fortified *dadih* for 28 days. The differences in rat cecum SCFA levels after intervention consisting of acetate, propionate, and butyrate between groups of experimental animals can be seen in Figure 2.

Based on the One Way ANOVA test, significant differences were observed in the total SCFA, acetate, propionate, and butyrate levels among the treatment groups (K-, K+, P1, and P2) ($p < 0.05$). Post Hoc Bonferroni test results indicated significant differences in total SCFA levels between groups K-, K+, P1, and P2. Significant differences were found between groups K+, P1, and P2 for acetate levels compared to K-. The Post Hoc Tamhane test revealed significant differences in propionate levels between groups K+ and compared to K-, P1, and P2. No significant differences were found between P1 and P3 compared to K-. Significant differences were observed among groups K-, K+, P1, and P2 regarding butyrate levels, although no significant differences were found between P1 and P2.



K-: Healthy control, K+: Positive control (Obese Rat), P1: Treatment 1 (*dadih*), P2: Treatment 2 (fortified *dadih*). Data are presented as mean \pm SD. Statistical analysis for acetate and total SCFA was performed using one-way ANOVA followed by Bonferroni post hoc tests, while propionate and butyrate were analyzed using one-way ANOVA followed by Tamhane post hoc tests. Significant differences ($p < 0.050$) are indicated by *.

Figure 2. SCFA Levels of Rats After the Intervention.

Leptin Levels

Leptin levels were measured after the intervention of fortified curd for 28 days. Table 3 presents the difference in leptin levels after the intervention.

Table 1. Leptin Level Post-intervention

| Group | Leptin Median (Min-Max) ng/ml |
|---------|---------------------------------|
| K- | 1.31 (1.29 – 1.34) ^a |
| K+ | 9.42 (9.26 – 9.48) ^b |
| P1 | 3 (2.98 – 3.01) ^c |
| P2 | 3.3 (3.17 – 3.32) ^d |
| p-value | 0.000 |

K-: Healthy control, K+: Positive control (Obese Rat), P1: Treatment 1 (*dadih*), P2: Treatment 2 (fortified *dadih*), $p =$ Kruskal Wallis, $p^1 =$ One Way ANOVA. Superscript letters (a, b, c, d) indicate significant differences ($p < 0,05$) between groups.

The leptin level in the K group is 1.31 ng/ml, ranging from 1.29 to 1.34 ng/ml, indicating the lowest leptin levels among the groups. In contrast, the K+ group shows a significantly higher leptin level of 9.42 ng/ml, ranging from 9.26 to 9.48 ng/ml, highlighting the impact of obesity on leptin levels. The treatment groups, P1 and P2, exhibit leptin levels of 3 ng/ml (range: 2.98–3.01 ng/ml) and 3.3 ng/ml (range: 3.17–3.32 ng/ml), respectively. These levels are lower than the K+ group but higher than the K- group, suggesting that both treatments effectively reduced leptin levels compared to the positive control group. The statistical analysis using the Kruskal-Wallis test shows a significant difference ($p = 0.000$) in leptin levels among the groups. Post hoc analysis further indicates distinct differences between the groups, denoted by the different superscript letters (a, b, c, d) associated with each group's leptin levels.

The Correlation Between Variables

The correlation analysis between SCFA concentrations and body weight and leptin levels aims to determine the relationship between increased SCFA levels, reductions in leptin levels, and changes in body weight following the intervention. The results of the Spearman correlation test between SCFA concentrations, body weight, and leptin levels are presented in Table 3.

Table 2. SCFA Correlation with Body Weight and Leptin

| | Leptin | | Body Weight | |
|-------------|----------|----------|-------------|----------|
| | <i>r</i> | <i>p</i> | <i>r</i> | <i>p</i> |
| Total SCFA | -0.545 | 0.002* | -0.909 | 0.000* |
| Acetate | -0.56 | 0.001* | -0.901 | 0.000* |
| Propionate | -0.538 | 0.002* | -0.874 | 0.000* |
| Butyrate | -0.57 | 0.001* | -0.911 | 0.000* |
| Body Weight | 0.582 | 0.001* | - | - |

$p =$ Spearman, $*p < 0,05 =$ Significant difference

A significant negative correlation was observed between total SCFA levels and leptin ($r = -0.545$, $p = 0.002$), indicating that higher SCFA concentrations were associated with lower leptin levels. When examining individual SCFAs, acetate ($r = -0.56$, $p = 0.001$), propionate ($r = -0.538$, $p = 0.002$), and butyrate ($r = -0.57$, $p = 0.001$) all showed significant negative correlations with leptin, further supporting this relationship. Conversely, body weight exhibited a significant positive correlation with leptin ($r = 0.582$, $p = 0.001$), suggesting that leptin levels increase as body weight rises.

Regarding the relationship between SCFAs and body weight, total SCFAs were strongly and negatively correlated with body weight ($r = -0.909$, $p = 0.000$), indicating that higher SCFA levels were associated with lower body weight. Similarly, acetate ($r = -0.901$, $p = 0.000$), propionate ($r = -0.874$, $p = 0.000$), and butyrate ($r = -0.911$, $p = 0.000$) each showed strong negative correlations with body weight.

DISCUSSION

The administration of a high-fat, high-fructose diet (HFFD) has consistently been shown to increase body weight in rodent models, largely through alterations in energy metabolism, enhanced lipogenesis, and

the development of leptin resistance triggered by excessive fat and fructose intake.²¹ Previous studies have reported significant increases in caloric intake and body weight within just one week of HFFD feeding,²¹ while others observed an 11.94% increase in body weight compared to normal diet controls, accompanied by a markedly higher lipid profile.²² These findings are consistent with the present study, where the HFFD control group (K+) exhibited significant weight gain compared to the healthy control (K-). In contrast, groups receiving *dadih* supplemented with red dragon fruit (P1) or red dragon fruit plus selenium (P2) showed attenuated weight gain. This aligns with prior evidence that red dragon fruit reduces fat mass and improves lipid profiles in animal models of diet-induced obesity.²³ Selenium has also been reported to prevent weight gain by suppressing adipogenesis and modulating PPAR γ activity, thereby limiting the formation of new adipocytes.²⁴⁻²⁷

Short-chain fatty acids (SCFAs), the primary metabolites produced by gut microbial fermentation of undigested carbohydrates, play an important role in host energy regulation. Approximately 95% of SCFAs are absorbed by colonocytes, while the remaining fraction is excreted in feces.²⁸ In this study, SCFA concentrations were highest in K- and lowest in K+, consistent with meta-analyses showing that obese individuals tend to have higher fecal SCFA levels than lean individuals, potentially reflecting both increased production and impaired utilization.²⁹⁻³¹ Previous research has shown that traditional fermented milk such as *dadih* can partially restore microbial fermentation capacity and increase SCFA production in obese animals.³² The improvement observed in P1 in the present study is in line with these reports. The additional enhancement seen in P2 can be attributed to the synergistic effects of red dragon fruit and selenium: red dragon fruit provides soluble fiber and polyphenols that serve as substrates for beneficial bacteria, increasing acetate, propionate, and butyrate production, while selenium, even in inorganic selenite form, can interact with gut microbiota to improve fermentation and boost SCFA output.^{16,33} SCFAs, particularly acetate, are known to influence host metabolism by activating AMPK pathways, modulating lipid and glucose metabolism, and stimulating gut hormone secretion.^{34,35}

Leptin, secreted by adipose tissue, is a key regulator of appetite and energy homeostasis. In obesity, hyperleptinemia often develops alongside leptin resistance, blunting satiety signals and promoting excess energy intake.³⁶⁻³⁸ In the present study, K+ animals displayed elevated leptin levels relative to K-, consistent with these mechanisms. Both P1 and P2 groups showed significant reductions in leptin compared to K+, supporting findings that red dragon fruit can lower leptin levels while reducing fat mass and improving lipid profiles.³⁹⁻⁴¹ Selenium further contributes via its antioxidant and anti-inflammatory properties, which can reduce oxidative stress and inflammation in adipose tissue, thereby improving leptin sensitivity.⁴²⁻⁴⁴ Mechanistically, this may involve suppression of pro-inflammatory gene expression and enhancement of antioxidant enzyme activity.³⁹

The superior performance of P2 compared to P1 suggests potential additive or synergistic effects between *dadih*, dragon fruit, and selenium. *Dadih* provides lactic acid bacteria that enhance microbial fermentation, dragon fruit supplies oligosaccharides and antioxidants, and selenium supports both microbial activity and host antioxidant defenses. Together, these components could more effectively improve metabolic outcomes than individual interventions alone.

The correlation analysis in this study revealed negative associations between SCFA concentrations and both body weight and leptin levels, consistent with earlier research.^{36,45-47} SCFAs can influence appetite regulation and energy metabolism via activation of free fatty acid receptors FFAR2/3 on enteroendocrine cells, stimulating the release of anorexigenic hormones such as GLP-1 and PYY.^{9,48} This hormonal modulation improves insulin sensitivity, suppresses food intake, and enhances energy expenditure.^{28,49} Acetate, for instance, has been shown to promote weight loss by increasing lipid oxidation and reducing fat accumulation, while propionate and butyrate exert complementary effects on glucose metabolism and hepatic lipid regulation.^{28,49}

STRENGTHS AND LIMITATIONS

This study is among the first to examine the effects of fortified *dadih* with red dragon fruit and selenium on obesity-related outcomes, using a controlled experimental design that strengthens the validity of its findings and provides insight into the interplay between SCFA and leptin. However, the relatively small sample size, use of only male rats, and reliance on an animal model limit the generalizability of the results to humans. The study also assessed only cecal SCFA and leptin levels without evaluating gut microbiota composition or other metabolic markers, while the use of sodium selenite and the short intervention period further constrain the

interpretation of long-term and translational effects. Future studies in larger and more diverse populations, including human clinical trials, are warranted to confirm these findings.

CONCLUSIONS

In conclusion, this study demonstrated that fortified *dadih* containing red dragon fruit and selenium significantly improved metabolic parameters in obese rats by reducing body weight and leptin levels while enhancing short-chain fatty acid concentrations. These findings highlight the potential of fortified *dadih* as a functional food candidate for obesity management. However, as the study was conducted in an animal model with a relatively short intervention period, the results should be interpreted with caution. Further studies with longer duration, larger sample sizes, and especially well-designed human clinical trials are required to validate these effects and determine their applicability to human health.

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

DECLARATION USE AI

The authors declared that Generative AI was not used in the creation of this manuscript.

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