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The Effectiveness of Brown Rice, Commercial Meal Replacements and Thiazolidinedione on Ratio Firmicutes/Bacteriodetes and PPARγ Expression in Obese Rats

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ABSTRACT

Background: Obesity is a global health problem that continues to increase and is closely related to gut microbiota imbalance and metabolic dysfunction. This study aims to evaluate different interventions for treating obesity in a rat model using both non-pharmacological and pharmacological approaches, including brown rice, meal replacement, and Thiazolidinedione. **Methods:** This study was an *in vivo* laboratory experiment on Sprague Dawley rats with a post-test only controlled group design. A negative control group was given a standard diet, and four experimental groups were subjected to a High-Fat High-Fructose (HFHF) diet during the initial phase. Subsequently, the experimental groups would receive interventions in the form of Brown Rice (BR), Thiazolidinedione (TZD), and Meal Replacement (MR) to assess their respective effects. **Results:** A balanced ratio (~1 or eubiosis) indicated that the number of Firmicutes and Bacteroidetes in the gut microbiota was relatively equal. This study presented that the MR group had a balanced Firmicutes/Bacteroidetes (F/B) ratio compared to other intervention groups. MR group had the highest fiber content among the other groups (5.74±0.22 g, P=0.018). The addition of MR to the diet increased the fiber content in the feed, leading to a decrease in Firmicutes and an increase in Bacteroidetes. The highest PPARγ expression was observed in the TZD group (4.97±2.88, P=0.360). **Conclusions:** The high fiber content contributed to the balance of the F/B ratio in the MR group, while in terms of PPARγ expression, the TZD group remains the most effective due to its direct activation of PPARγ.

Introduction

Obesity has a significant impact on human health and increases the risk of death by 50% from all causes compared to individuals of normal weight (Formica *et al.*, 2020). In the last few decades, there has been an increase in overweight and obesity in Indonesia in all age groups. The World Health Organization (WHO) reported that obesity prevalence worldwide tripled over the period from 1975 to 2016 (Blüher, 2019). Individuals categorized as

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overweight have a body mass index (BMI) >25.0 kg/m², while those categorized as obese have a BMI ≥27.0 kg/m² (World Health Organization, 2016). Obesity is a complex metabolic disorder characterized by the excessive accumulation of body fat resulting from a sustained positive energy balance, where energy intake exceeds energy expenditure (Jin *et al.*, 2023). Causes of obesity are diverse and cannot be ascribed to a single factor, such as excessive eating (Masood and Moorthy, 2023). Several studies revelaed that people who are overweight and obese show dysbiosis, which is characterized by low diversity of gut microbiota (Menni *et al.*, 2018). A well-balanced gut microbiota is typically characterized by high diversity, whereas lack of such diversity is related to health issues like obesity (Turnbaugh *et al.*, 2009). Moreover, gut microbiota dysbiosis is a condition of microbiota imbalance in the intestine that can influence various aspects of health, including the risk of obesity and metabolic complications through immunological, energy, hormonal, and inflammatory mechanisms, indicating the importance of gut microbiota balance for overall health (Valdes *et al.*, 2018). In contrast, the condition where the population of microorganisms in the intestine is balanced and healthy is known as eubiosis (Gomaa, 2020). Gut microbiota plays an essential role in the regulation of energy and obesity. Based on research, genetically obese mice were found to absorb more carbohydrates and proteins through their gut microbiota to provide energy, which contributed to weight gain (Liu *et al.*, 2021). A recent study has suggested a potential relationship between obesity and an imbalance (dysbiosis) in the proportion of the two dominating phyla, namely Firmicutes and Bacteroidetes, called the F/B ratio, where the results showed a significant increase in the Firmicutes phylum and a decrease in the Bacteroidetes phylum in obese mice (Jasirwan *et al.*, 2021).

There is a complex relationship between gut microbiota and the peroxisome proliferator-activated receptors-gamma (PPARγ) signaling pathway. PPARγ has an important role in the process of adipogenesis and adipocyte gene expression (Darwish *et al.*, 2022). PPARγ is expressed in white and brown adipose tissue in the colon and spleen. However, its expression is the highest in adipocytes and plays a vital role in regulating adipogenesis, energy balance, and lipid biosynthesis. It also plays a role in lipoprotein metabolism and insulin sensitivity (Janani and Kumari, 2015). In obesity, PPARγ levels decrease, limiting the expansion of adipose tissue and causing a decrease in cytokine production and fibrinosis (Corrales *et al.*, 2018). Changes in the gut microbiota composition can disrupt PPARγ signaling which can lead to metabolic dysfunction and potentially contribute to the pathogenesis of diabetes mellitus (Zhao *et al.*, 2023).

Dietary intervention in reducing weight can be provided by functional foods or commercial food substitutes. Brown rice is a nutrient-dense food produced by removing the outer husk from paddy rice, leaving the grain with its nutrient-rich brown bran layer intact (Turnbaugh *et al.*, 2009). Consuming locally sourced 'Sintanur' brown rice has been proved to reduce the Lee index, fasting blood glucose levels, and HOMA-IR in obese rats by enhancing serum magnesium concentrations (Andarini *et al.*, 2022). This is because brown rice, as a functional food, has a higher fiber content than white rice, with a weight of 100 g, namely the content of brown rice was 22.04 g while white rice was 20.58 g (Sulistyowati *et al.*, 2020). In addition, brown rice takes longer to digest and has a lower glycemic index, making it beneficial for blood sugar management and prolonged satiety (Pirasath *et al.*, 2012). The gut microbiota plays a crucial role in the regulation of type 2 diabetes (T2D). According to Samichah *et al.*, brown rice may beneficially modulate gut microbiota composition, enhance short-chain fatty acid (SCFA) production, and improve metabolic markers due to its higher fiber and magnesium contents and lower glycemic index compared with white rice (Handayani, 2024). Brown rice, which is high in fiber, can change the amount and composition of the gut microbiota as well as improving intestinal dysbiosis in type 2 diabetes mellitus. Brown rice

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also contains gamma oryzanol which is effective in correcting hypercholesterolemia by suppressing cholesterol absorption from the intestine and has the potential to protect against metabolic risk factors in adults who are obese (Kazemzadeh *et al.*, 2014). On the other hand, currently, many diets based on meal replacement products have been developed that are effective in use in the management of obesity (Maston *et al.*, 2020). Meal replacement provides greater control over nutrient composition, allowing for a more specific evaluation of the role of individual components, such as added fiber or fortified micronutrients. One of the meal replacement products in this study contains 15 grams of dietary fiber per serving. (NU Skin, 2020).

As a multifactorial disease, obesity requires comprehensive management strategies that extend beyond lifestyle modification. Current treatment options include dietary interventions, physical exercise, anti-obesity medications, bariatric surgery increasingly being utilized to improve weight-loss outcomes (Baker *et al.*, 2022). Obesity can cause insulin resistance, and many drugs dramatically affect insulin resistance, such as Thiazolidinediones (TZDs), which exhibit anti-inflammatory effects due to activating PPARγ. PPARγ has a significant impact on insulin sensitivity (Singh and Rai, 2019), in obese patients, both diabetic and nondiabetic, and a significant positive correlation was observed between PPARγ expression and BMI, waist circumference (WC), and waist-to-hip ratio (WHR) (Darwish *et al.*, 2022). Therefore, this study aims to evaluate different interventions for treating obesity in a rat model using non-pharmacological and pharmacological approaches, including brown rice, meal replacement, and TZD.

Materials and Methods

Research design

This study used *an in vivo laboratory experiment* on *Sprague Dawley* rats using *Posttest-Only Controlled Group Design*. A randomization method was used to select and group research object in each treatment.

Research objects

This study used *Sprague Dawley* rats, young adults aged 2.5-3 months (70-90 days post-natal), with body weight 200-250 g, and healthy (hair clean, smooth or not falling out), active, responsive cases, with bright eyes, dry nose free from exudate fluid; also normal fecal were small and solid.

Data collection

This study was conducted over 28 weeks at Animal Development Laboratory (LPHC), Faculty of Medicine, Brawijaya University. About 20 male rats were divided into 5 groups, and the calculation was based on Federer's formula for experimental testing, which was (t-1) (n-1) ≥ 15. The rats were selected according to inclusion criteria and then acclimated for 2 weeks. The acclimation process aimed to allow the rats to adjust to their new environment. The study consisted of two phases: the weight gain phase and the intervention phase. During the weight gain phase, 4 rats were given a standard diet (AIN 93M), while the remaining 16 rats received a high-fat diet + fructose solution for 14 weeks. In the 14th weeks, 4 rats (HFHF group) were sacrificed together with the standard diet group. Then, in the second phase, the remaining 12 rats were divided into intervension groups, including brown rice (BR), commercial meal replacement (MR), and TZD. The intervention phase lasted 12 weeks. The feed composition for the BR group was prepared by mixing 337.5 g of finely ground brown rice into 1 kg of the HFHF diet feed. Moreover, the feed composition for the TZD group involved adding 0.02 g of TZD, dissolved in 14 ml of water, into 1 kg of the HFHF diet feed. The feed composition for this group was the same as the HFHF diet, with the addition of MR Trimshake prepared by mixing 1 kg of HFHF feed with 106.6 g of MR Trimshake; then, it was shaped and weighed to 12 g. Then, MR Jumpstart, Complex, Control, and Lifepack were mixed and dissolved in 12.5 ml of water and administered via gavage daily. The use of brown rice in this study as one of the interventions to treat obesity, which is rich in fiber and has a lower glycemic index, can support dietary regulation, prolong the feeling of

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fullness, regulate blood sugar levels, and help with weight loss. The feed administration for BR groups involved mixing all ingredients until it was well combined andweighed 35 g. Feed intake was then calculated by weighing and recording the remaining feed, and a fructose solution with a caloric content of 1.32 kcal/100 ml/day was administered via gavage, with the remaining liquid recorded. The nutritional composition of 1000 g of feed for each group can be seen in **Table 1**. Body weight and length were measured, and the parameter of obesity in rats was assessed using the Lee Index, where a Lee Index of ≤300 g/cm³ indicates non-obesity, and a Lee Index of >300 g/cm³ indicates obesity. The rats were then sacrificed for dissection using ketamine + xylazine anesthesia. Gut microbiota parameters and PPARγ expression was measured in the laboratory.

Table 1. Nutrient composition of diet.

Variable	Standard diet	HFHF	BR	TZD	MR
Total calories (kcal)	327	435	496	435	439
Energy density (kcal/g)	3.27	4.35	4.96	4.35	4.39
Protein (%)	12.40	11.73	31.20	1.73	11.97
Fat (%)	19.40	82.70	41.36	827.00	82.06
Carbohydrate (%)	68.18	5.54	12.43	5.54	5.96
Fiber (g)	23.2	21.6	43.6	21.6	49.7

***HFHF**: high-fat high-fructose, **BR**: brown rice, **TZD**: thiazolidinediones, **MR**: commercial meal replacement.*

Laboratory data analysis of gut microbiota and PPARγ expression

Gut microbiota was analyzed using the Real Time-Polymerase Chain Reaction (RT-PCR) method with fecal samples conducted at the Biosciences Laboratory, Universitas Brawijaya. Prior to analysis, DNA was isolated from cecal digesta. DNA was extracted from 1.5-2 aliquots of frozen feces using the phenol-chloroform method following the standard procedures. The DNA was finally eluted in 200 µl of elution buffer. The quantity and quality of the DNA were measured using a NanoDrop ND-8000 (Thermo Scientific, USA). After that, samples with DNA concentrations below 20 ng or an A 260/280 ratio of less than 1.8 were subjected to ethanol precipitation for further concentration or purification to fulfill quality standards. Once the purity and concentration met the required standards, RT-PCR measurements were performed. The relative expression levels of Firmicutes and Bacteroidetes were expressed as fold change, representing the ratio of gene expression or microbial abundance changes between the compared groups. A fold change greater than 1 indicated an increase in the expression or abundance of the target, in this case, Firmicutes, compared to the control. Conversely, a fold change less than 1 indicated a decrease.

PPARγ expression was analyzed at the Biomedical Laboratory, Faculty of Medicine, Universitas Brawijaya, using the immunofluorescence method on rat brown adipose tissue (BAT) samples. This method involved measuring PPARγ protein levels and determining the localization of protein expression within the brown adipose tissue (BAT) tissue. In addition, fluorescence intensity was measured using ImageJ software and expressed as mean fluorescence intensity (MFI). Higher MFI values indicated higher levels of PPARγ expression.

Etical considerations

The permission to conduct it was granted by the Ethics Committee, Faculty of Health Sciences, Universitas Brawijaya (2020 / UN10.F17.10.4 / TU/ 2023).

Data analysis

The data obtained are presented as Mean±SD. Additionally, data on feed intake (g), energy intake, protein, fat, carbohydrate, fiber, and PPARγ expression were not normally distributed and

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homogeneous; therefore, the Kruskal-Wallis test was used to determine differences between groups. However, data such as body weight, body length, and Lee index were normally distributed and were analyzed using One-Way ANOVA. In general, a significant difference was considered when P-value<0.05, followed by a Tukey Post Hoc test. Furthermore, the analysis was performed using IBM SPSS Statistics 26 for Windows.

Results

Characteristics of research objects

This study was an *in vivo* experimental investigation conducted in the laboratory using 20 male Sprague Dawley rats that were divided into standard diet, HFHF, BR, MR, and TZD groups with the intervention phase over 12 weeks. Sample selection within the population was performed using randomization to ensure that the samples represented the entire population and could be generalized. The first phase showed a significant difference between the standard and HFHF groups (P=0.001). The HFHF diet intervention resulted in a higher average body weight in rats compared to those on a standard diet (**Table.2**).

By week 14, all groups of rats on the HFHF diet experienced increased body weight, as shown in **Table 2**. The mean body weight in each group exhibited weight gain, reaching an obese state before the intervention. Average total energy intake over 14 weeks is presented in **Figure 1**.

Table 2. Anthropometry characteristics.

Anthropometry	Groups		P-value
	Standard	HFHF	
Body weigh (g)	255.55±19.32	344.70±44.39	0.001[a]
Lee index (g/cm^3)	293.45±12.92	308.98±6.98	0.023[b]

[a]: *Independet-t test;* [b]: *Mann-Whitney test.*

Dietary intake

In this study, there were two stages of treatment: weight gain phase and intervention phase. Food intake during the intervention phase is documented in **Table 3**. Also, the average dietary intake for the rats was calculated by subtracting the remaining food after 24 hours. The average total energy intake includes energy from feed plus energy derived from a fructose solution beverage over 14 weeks. Based on statistical tests, there was a significant difference in food intake among the standard and HFHF groups (P<0.001).

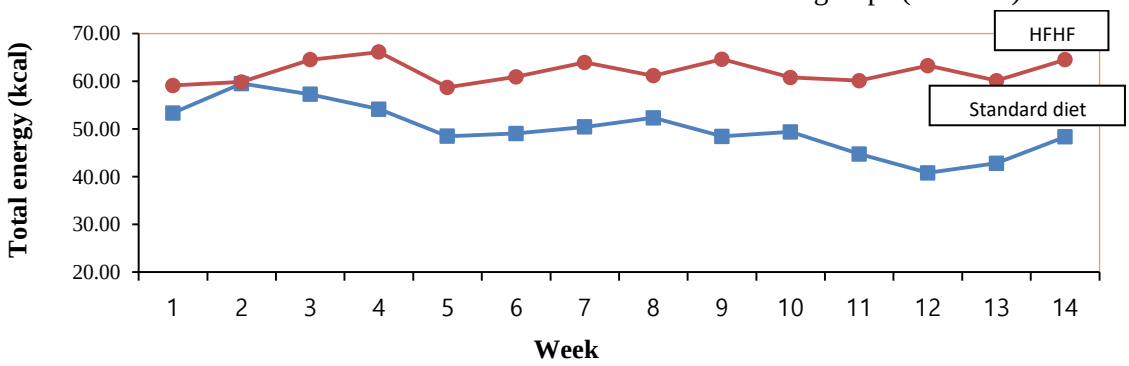

Figure 1. Average total energy intake over 14 weeks.

Table 3. Food intake during the weight gain phase.

Food intake	Groups		P-value
	Standard	HFHF	
Energy from feed (kcal)	49.95±1.50	62.00±15.49	0.047[b]
Total energy (kcal)	49.95±1.50	106.57±19.64	0.000[a]

[a]: *Independet-t test;* [b]: *Mann-Whitney test.*

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The next phase was the intervention phase, which lasted for 12 weeks. In this phase, the 12 rats receiving the HFHF diet were further divided into BR, TZD, and MR. **Table 4** indicates that rats' nutritional intake in the BR, TZD, and MR diet groups differed significantly in each analyzed nutrient.

Table 4. Food intake during intervention phase.

Nutritional intake	Intervention groups			P-value
	BR	TZD	MR	
Energy(kcal)	87.85±10.37^{c}	71.69±7.92^{b}	54.25±2.27^{a}	0.010
Protein(g)	5.65±0.89^{b}	1.70±0.20^{a}	1.51±0.05^{a}	0.018
Fat(g)	3.32±0.52^{a}	5.32±0.64^{b}	4.62±0.17^{b}	0.015
Carbohydrate(g)	5.95±0.37^{c}	4.10±0.78^{b}	1.59±0.10^{a}	0.007
Fiber (g)	6.36±1.01^{b}	2.87±0.34^{a}	5.74±0.22^{b}	0.018

Kruskal-Wallis test, there is a significant difference if P<0.05. The post hoc test shows significant differences between groups marked by different letters (a,b,c), ***BR****: brown rice,* ***TZD****: thiazolidinediones,* ***MR****: commercial meal replacement*

Anthropometry

Anthropometric measurements were conducted from the early stages of the study. In this research, anthropometric measurements included body weight and body length, with obesity assessed using the Lee index on the experimental animals. After a 14-week weight gain phase, rats on the HFHF diet exhibited a Lee index value of more than 300 g/cm³, as shown in **Table 2**, fulfilling the criteria for being classified as an obesity model. Rats in the HFHF group had the highest body weight (344.70±44.39 g), attributed to higher intake of food, calories, protein, fat, and carbohydrates in this group. These findings are in agreement with those reported by Deal *et al.*, who demonstrated that consumption of a high-fat diet resulted in adverse metabolic effects, characterized by increased body weight and adipose tissue mass, reduced glucose tolerance, and elevated fasting insulin concentrations (Deal *et al.*, 2020) . This may be attributed to the higher fat content in the HFHF group. Fat is not directly oxidized or converted into heat (thermogenesis) but rather stored in adipose tissue.

Anthropometric measurements were repeated after the intervention phase at week 26. Differences in body weight and Lee index among the experimental groups are shown in **Table 5**. The results indicated no significant differences in weight loss among the groups. However, the TZD group had a lower Lee index compared to the other diets (288.27±8.92 g/cm³). Statistical analysis revealed significant differences in the Lee Index among all groups (P=0.035), and subsequent post hoc tests showed that the Lee index for TZD was significantly lower than that of the BR group but not significantly different from MR.

Gut microbiota analysis

The F/B ratio results indicate that the HFHF group had the highest ratio, while the MR group had the lowest ratio F/B of 1. It was not significantly different from BR and TZD intervention groups, which showed a balanced gut microbiota (**Figure 2**). The dietary fiber content in MR group was 49.7 g, with an average daily intake of 5.47±0.22 g; MR group has the highest fiber content among the other groups. Adding meal replacement to the diet increased the fiber content in the feed, leading to a decrease in Firmicutes and an increase in Bacteroidetes.

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Table 5. Anthropometry after intervention period.

Variable	Groups			P-value
	BR	TZD	MR	
Body weight (g)	300.42±46.40	341.60±20.18	336.50±44.06	0.334
Lee index (g/cm^3)	306.47±8.02^b	288.27±8.92^a	290.95±2.81^a	0.035

Kruskal-Wallis test, there is a significant difference if P<0.05. The post hoc test shows significant differences between groups marked by different letters (a,b), ***BR****: brown rice,* ***TZD****: thiazolidinediones,* ***MR****: commercial meal replacement.*

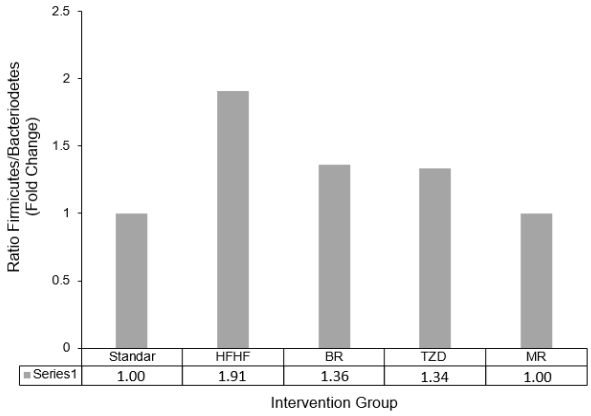

Figure 2. Ratio Firmicutes/Bacteroidetes (F/B).

Analysis of PPARγ expression

Table 5 shows that the expression of PPARγ did not exhibit significant differences among the treatment groups (P=0.360). The highest PPARγ expression was observed in the TZD group (4.97±2.88), while the lowest expression was found in the standard group (2.76±1.42).

Discussion

Dietary intake

The dietary intake results in **Table 3** indicate that the HFHF group had a significantly higher intake than standard groups (P<0.001). HFHF can increase appetite by influencing hormones that regulate hunger, such as ghrelin and leptin. Chronic consumption of a high-fat diet has been linked to reduced satiety signaling mediated by cholecystokinin (CCK) and glucagon-like peptide 1 (GLP-1), potentially leading to disturbances in appetite regulation involving ghrelin and leptin, the key hormones responsible for stimulating hunger and promoting satiety, respectively (Moris *et al.*, 2022). The HFHF diet can also affect body metabolism, increasing energy consumption and higher caloric needs. Rats may eat more to meet these energy demands. Additionally, high-fat and fructose diets can alter the gut microbiota's composition, affecting the signals that regulate hunger and satiety. Furthermore, high-fat and high-fructose diets are highly palatable and may encourage animals to consume more food, resulting in greater energy (Song *et al.*, 2021). The standard diet typically contains a more balanced nutrient composition with lower fat, which can optimize nutrient absorption. A more balanced diet composition can aid in the optimal absorption of nutrients, potentially reducing weight gain. Standard diets generally provide adequate protein to meet the body's needs, while high-fat diets often contain lower protein levels. Protein intake contributes to greater satiety by increasing appetite-suppressing hormones and reducing ghrelin levels, thereby helping to decrease energy intake and support weight management (Moon and Koh, 2020).

Table 6. PPARγ analysis.

Variable	Groups					P-value
	Standard	HFHF	BR	TZD	MR	
PPARγ expression	2.76±1.42	3.45±1.65	3.37±0.40	4.97±2.88	4.43±3.10	0.360

Kruskal-Wallis statistical test; there is a significant difference if P<0.05, indicating significant difference between groups, ***HFHF:*** *high-fat high-fructose,* ***BR****: brown rice,* ***TZD****: thiazolidinediones,* ***MR****: commercial meal replacement*.

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During the intervention phase, each treatment group exhibited distinct nutritional advantages. The BR group had the highest intake of energy, protein, carbohydrates, and fiber compared to the other groups, highlighting its potential as a nutrient-rich dietary intervention. Furthermore, the MR group was characterized by its high fiber content in the diet composition. The use of MR was also associated with better control of food intake and hunger, which commonly occurs during energy restriction, potentially through ketosis or limited stimulation, although the exact mechanism remains unclear (Edwards-Hampton and Ard, 2024). The TZD group had the highest fat intake but lower carbohydrate and fiber consumption.

Anthropometry

Anthropometric measurements are a series of quantitative assessments used to evaluate body composition, including muscle, bone, and fat tissue. Accurate assessment of nutritional status is critical for determining obesity in experimental rats. Body composition analysis complements anthropometric measurements by providing quantitative estimates of fat mass, visceral adiposity, and fat-free mass (Fitri *et al.*, 2024). The accumulation of fat in adipose tissue leads to a greater increase in body weight in the HFHF diet group compared to the standard groups (**Table 2**). Fructose consumption also causes the rats to develop metabolic syndrome, including obesity, hypertension, and hyperglycemia (Mamikutty *et al.*, 2014). After the intervention phase, no significant differences were observed in body weight parameters (P=0.334). However, Lee index parameters showed significant differences between the groups (P=0.035).**Table 4** shows the lowest average Lee index observed in the TZD group.

TZD are a class of drugs specifically designed to treat insulin resistance, a major factor contributing to the increase in type 2 diabetes mellitus and a significant cause of the rise in atherosclerotic cardiovascular disease (Lebovitz, 2019). Glucagon-like peptide 1 (GLP-1) receptor agonists and dipeptidyl peptidase 4 (DPP-4) inhibitors work by enhancing insulin secretion and reducing hyperglucagonemia, which collectively lowers hyperglycemia (Sánchez-Garrido *et al.*, 2017). GLP-1 receptor agonists also contribute to weight loss and a reduction in systolic blood pressure (Zaccardi *et al.*, 2016). Sodium-glucose cotransporter 2 (SGLT-2) inhibitors lower blood glucose by increasing renal glucose excretion, with the secondary benefit of reducing glucose toxicity. These inhibitors enhance hepatic glucose production, glucagon secretion, ketogenesis, and lipid oxidation (Liu *et al.*, 2023).

Significant side effects of these inhibitors include weight loss, reduction in blood pressure, and decreased insulin resistance. Weight loss reduces hepatic triglycerides, peripheral and visceral adipose tissue mass, and plasma triglycerides (Lebovitz, 2019). GLP-1 receptor agonists and SGLT-2 inhibitors secondarily reduce insulin resistance in patients, comparable to their effects in promoting weight loss (Pereira and Eriksson, 2019). The primary effect of TZDs is to markedly alleviate insulin resistance and metabolic syndrome and reduce insulin requirements (Lebovitz, 2019). However, treatments for obesity are limited by their side effects. While several solutions are available for individuals with obesity and diabetes, effective treatments for those who are obese but do not have diabetes are still lacking or suboptimal.

Gut microbiota analysis

Figure 2 illustrates the F/B ratio across various intervention groups: Standard, HFHF, BR, TZD, and MR. The F/B ratio is a critical indicator in obesity research, as changes in gut microbiota composition - particularly an increase in Firmicutes and a decrease in Bacteroidetes - are often associated with enhanced energy absorption and obesity. The F/B ratio in the BR (1.36) and TZD (1.33) groups decreased compared to HFHF, but was still higher than the Standard group. This decrease indicates a partial restoration of gut microbiota composition. The MR (1.00), indicating eubiosis, had an F/B ratio similar to the brown rice intervention group, potentially reducing the dominance of Firmicutes and restoring the

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benefits of the Standard diet. This suggests that meal replacement can help contribute to stabilizing the F/B ratio. Individuals with an F/B ratio ≥ 1 were 23% more likely to be overweight than those with an F/B ratio < 1 (Koliada *et al.*, 2017). According to Susmiati, the composition of intestinal microbiota in individuals is influenced by internal factors such as genotype and age and external factors such as diet, prebiotics, antibiotics, and physical activity. Disruption of the intestinal microbiota balance is often associated with inflammatory processes and metabolic disorders, including obesity. One suggested method for reducing obesity risk is to alter intestinal microbiota composition by addressing internal and external factors, particularly diet. Studies in obese rats have found significant changes in intestinal microbiota composition, which may explain some obesity risk factors (Susmiati, 2019).

Obese individuals have been found to exhibit a reduction in Bacteroidetes and an increase in Firmicutes, along with a rise in the relative abundance of conditionally pathogenic bacteria like *Atopobium sp*. and *Proteobacteria* in the gut. This is accompanied by a decrease in antimicrobial peptides and secreted mucins, resulting in heightened intestinal permeability (Lee *et al.*, 2017). Recent studies suggest that diets containing dietary fiber have the potential to prevent obesity (Deehan and Walter, 2016). First, the physicochemical properties of dietary fiber, such as viscosity and fermentability, provide protective effects against obesity. Viscous fiber can slow gastric emptying and prolong small intestine transit time, converting consumed nutrients into more absorbable components (Zhang *et al.*, 2022). Second, dietary fiber supports energy homeostasis and prevents obesity by increasing the abundance and diversity of beneficial gut microbiota associated with obesity (Chen *et al.*, 2018). This contributes to a reduction in F/B ratio at the phylum level and increases the relative abundance of the genus Roseburia (Wang *et al.*, 2018). Third, dietary fiber can be fermented by gut microbiota to produce short-chain fatty acids (SCFAs) (Makki *et al.*, 2018), which play a crucial role in maintaining health, regulating energy metabolism, preventing certain diseases by lowering intestinal lumen pH, inhibiting pathogenic or harmful gut bacteria, reducing lipopolysaccharides (LPS), and other metabolites detrimental to metabolic health (Alexander *et al.*, 2019).

Analysis of PPARγ expression

The group receiving the anti-obesity drug TZD showed a higher PPARγ expression, with a value of 4.97±2.88, potentially indicating the drug's effect in enhancing PPARγ expression (**Table** 5). However, no significant difference was observed between this group and the others.

Although no significant differences were observed in this study, several previous studies have indicated that high-fat and fructose diets can increase PPARγ expression which regulates lipid and glucose metabolism. Peroxisome Proliferator-Activated Receptor Gamma (PPARγ) expression plays a crucial role in regulating lipid and glucose metabolism (Chyau *et al.*, 2020). Activation of PPARγ can enhance insulin sensitivity, which is essential for managing type 2 diabetes. Studying PPARγ expression is important for developing more effective therapeutic strategies to combat obesity. PPARγ expression can also be measured to evaluate the effectiveness of drugs that activate PPARγ, such as pioglitazone and telmisartan, in reducing body weight and addressing obesity. PPARγ plays a critical role in obesity pathophysiology, making its expression a valuable target for therapeutic research. Measuring PPARγ expression can help evaluate the effectiveness of pharmacological, which exert their effects through PPARγ activation (Wu *et al.*, 2021).

Inflammation in adipose tissue in individuals with obesity leads to insulin resistance, thereby contributing to obesity (Singh and Rai, 2019). TZDs reduce insulin resistance directly through the activation of PPARγ receptors, which facilitate the differentiation of mesenchymal stem cells into adipocytes, promote lipogenesis in peripheral adipocytes, reduce triglycerides in the liver and peripheral tissues, decrease visceral adipocyte activity, and increase adiponectin (Lebovitz, 2019).

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TZDs are synthetic PPARγ activators designed to enhance insulin sensitivity in patients with type 2 diabetes mellitus. PPARγ, as a key regulator of adipogenesis in brown and beige adipose tissues, mediates the effects of TZDs on these adipose tissues (Pan *et al.*, 2023).

It is well known that gut microbiota has a complex relationship with PPARγ. Research has shown that gut microbiota can influence PPARγ activity in various metabolic organs. For example, SCFAs, the most abundant type of metabolite produced by anaerobic fermentation of dietary fiber by gut microbiota, are PPARγ agonists (Oh *et al.*, 2019). SCFAs, particularly butyrate and propionate, are major bacterial metabolites in the intestine and act as ligands for PPARγ, activating PPARγ transcriptional activity (Kyriachenko *et al.*, 2019).

This study was limited to the sample size. Thus, further studies with larger sample sizes should be carried out to validate the findings. This research primarily focused on short-term effects of MR intervention. Although this study is promising, the long-term impact of MR on gut microbiota, metabolic health, and the sustainability of its benefits remains unclear. Future research should explore the prolonged effects of MR consumption, including potential adaptations in gut microbiota and metabolic regulation over time.

Conclusion

The results of this study demonstrated that MR groups showed improvements in gut microbiota, with an F/B ratio approaching balance due to high fiber content. However, regarding PPARγ expression, the TZD group that directly activates PPARγ remained the most effective obesity management strategy compared to the MR and BR groups.

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Authors' contributions

Sulistyowati E: Conceptualization, methodology, laboratory analysis; Nuraissa P: Methodology, data collection and laboratory analysis, manuscript writing; Handayani A: Methodology, data collection and laboratory analysis, manuscript writing; Sasharini S: Supervision, manuscript review; Rahmawati W: Supervision, manuscript review; Rudijanto A: Supervision, manuscript review and Handayani D: Conceptualization, supervision, manuscript review. All authors reviewed and approved the final manuscript.

Conflict of interests

The authors declared no conflict of interests.

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