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Research Article

Beneficial effects of red rice bran extract on brown adipose tissue whitening, inflammation, and oxidative stress in mice with obesity induced by a high-fat diet

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ABSTRACT

Red rice bran extract (RRBE) has been demonstrated to have anti-lipid accumulation, antioxidant, and anti-inflammatory effects on the livers of obese animals and/or in macrophages. However, the molecular mechanisms driving these effects have not yet been investigated in brown adipose tissue (BAT). Thus, the present study aimed to investigate the beneficial effects of RRBE on BAT in mice with obesity induced by a high-fat diet (HFD). Six weeks after induction of obesity, the obese mice were fed continuously with HFD, with or without RRBE treatment for 6 weeks. Body weight and food intake were recorded weekly. At the end of the feeding experiment, BAT was collected for determination of expressions of genes associated with liporegulation, inflammation, and oxidative stress, as well as histological examination. Compared with untreated obese mice, RRBE-treated mice had reductions in body weight, food efficiency ratio, and white-like adipocytes in BAT, accompanied by down-regulated expression of nuclear receptor subfamily 1 group H member 3 (NR1H3). Moreover, RRBE decreased the levels of nitric oxide (NO), reactive oxygen species (ROS), and malondialdehyde (MDA) in BAT, which were associated with modulated expressions of target genes for nuclear factor-kappa B and nuclear factor erythroid 2-related factor 2. RRBE produced beneficial effects against HFD-induced abnormalities in BAT by mitigating whitening, inflammation, and oxidative stress.

Keywords:
Red rice bran, Brown adipose tissue, Obesity

1. INTRODUCTION

Obesity, a chronic metabolic disease related to positive energy balance, is an epidemic all over the world[1]. It involves dysregulations in brown adipose tissue (BAT) and white adipose tissue (WAT)[2-3]. BAT is composed of brown adipocytes with small multilocular lipid droplets, and it functions as a thermoregulatory tissue that controls energy expenditure. In contrast, WAT, which contains white adipocytes with large unilocular lipid droplets, accumulates surplus energy in the form of fat within the droplets[2]. It has been recently proposed that dysregulations of metabolic regulators such as uncoupling protein 1 (UCP1) and nuclear receptor subfamily 1 group H member 3 (NR1H3), also known as liver X receptor alpha or LXRα in BAT, plays a role in the pathogenesis of obesity. These dysregulations in BAT may promote formation of WAT-like phenotype termed BAT whitening which contributes to development of other pathological states such as inflammation and oxidative stress[2-6]. Inflammation and oxidative stress in BAT may be mediated by several pathways, especially induction of expression of nuclear factor-kappa B (NF-κB)-mediated proinflammatory gene and impairment of expressions of nuclear factor erythroid 2-related factor 2 (NRF2)-mediated antioxidant enzymes[7-8]. Therefore, the prevention of metabolic dysregulation, inflammation, and oxidative stress in BAT could be important and promising strategies for

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mitigating BAT dysfunction and obesity.

Red-colored rice (*Oryza sativa* Linn.) and its bran extracts contain a variety of phytochemicals such as phenolic compounds and their subclasses which exhibit potent metabolism-improving[9], anti-inflammatory[10-11], and antioxidant properties[12]. Previous study has shown that red rice bran extract (RRBE) attenuated WAT dysfunction in an obese mouse model[9]. In addition, RRBE and red rice polar extract fraction reduced the levels of inflammatory mediators such as nitric oxide (NO), interferon-gamma (IFN-γ), and tumor necrosis factor-alpha (TNF-α) in macrophages[10-11]. Moreover, RRBE has been reported to have higher *in vitro* antioxidant activities and higher contents of phenolic compounds than other colored rice bran extracts[12]. These studies provide evidence of the beneficial effects of RRBE which may be sufficient to attenuate HFD-linked BAT and metabolic dysfunction. However, the mechanism of action of RRBE is not yet clear. Therefore, the purpose of this study was to investigate the effects of RRBE in BAT in a HFD-fed obese mouse model.

2. MATERIALS AND METHODS

2.1. RRBE preparation

Red bran from Red Hawm rice was purchased from Mae Chai Agricultural Cooperative Ltd., Phayao, Thailand. Then, 1,000 g of the rice bran was extracted three times with 6 L of ethanol: water solvent (1:1, v/v) mixture for 3 days at room temperature. The extract was filtered through Whatman filter paper number 1, evaporated in a rotary evaporator, and lyophilized. The resultant extract was designated RRBE, and it was kept refrigerated at -20°C prior to use. The yield of RRBE obtained from the starting rice bran material was 8.50%.

2.2. HFD-induced obesity mouse model and BAT collection

All mouse studies were approved by the Institutional Animal Care and Use Committee of University of Phayao, Phayao, Thailand (59 01 04 0037). Four-week-old male Institute of Cancer Research (ICR) mice were purchased from Nomura Siam International Co. Ltd., Bangkok, Thailand. After the acclimatization period, the mice were randomly divided into two groups: low-fat diet (LFD; 10% kcal from fat, Research Diets Inc., USA) group (n=6) and high-fat diet (HFD; 45% kcal from fat, Research Diets Inc.) group (n=12). After 6 weeks, half of the mice in the HFD group were treated with 500 mg/kg/day of RRBE (HFD+RRBE) for the next 6 weeks. The remaining mice in the HFD group and all mice in the LFD group were maintained on HFD and LFD, respectively, throughout the 12-week experimental period. Mice in both LFD and HFD groups were treated with distilled water from Weeks 6 to 12. Distilled water or RRBE was administered once daily using an oral gavage. The HFD-fed mice were considered obese by the statistically significant increase in their absolute body weight and body weight gain compared with LFD-fed mice. A preliminary study showed that treatment of obese mice with RRBE at a dose of 500 mg/kg/day resulted in better reduction of glucose intolerance and dyslipidemia, when compared to obese mice treated with a lower dose of RRBE (250 mg/kg/day). The 500 mg/kg dose of RRBE was therefore selected for use in this study. Body weight and food intake were recorded weekly, and food efficiency ratio (FER) was calculated as follows:

$$\text{FER} = \frac{\textbf{Average daily body weight gain (g)}}{\textbf{Average daily feed intake}} \times 100$$

Following 6 weeks of treatment, all mice were sacrificed after isoflurane inhalation, and BAT was rapidly isolated from the interscapular region of each mouse, washed with normal saline, weighed, and divided into two parts. One part of the collected tissue was fixed in 10% neutral-buffered formalin at room temperature for histological analysis, while the remaining part was snap-frozen in liquid nitrogen and stored at -80°C. The frozen samples were used for analysis of gene expression, NO level, and oxidative stress indexes. The experimental design of this study is shown in Figure 1.

2.3. Histological analysis

Following tissue fixation, BAT specimens were randomly selected from each group, embedded in paraffin, sectioned to 5-μm thickness, and stained with hematoxylin and eosin (H&E). The morphology of BAT was examined under an Olympus BX53-P polarizing light microscope, and images were captured with an Olympus DP21 digital microscope camera (Olympus Corporation, Japan). Five randomly selected microscopic fields at 40×magnification per section from each group (n=3/group) were selected for blinded histopathological analyses. Brown adipocyte was characterized by adipocyte containing multiple small lipid droplets, while white adipocyte was characterized by adipocyte containing a single large lipid droplet. Multilocular adipocyte area, unilocular adipocyte area, and unilocular adipocyte size were determined using AxioVision AC software (Carl Zeiss, Germany). Both multilocular and unilocular adipocyte areas were presented as percentage of total adipocyte area, as previously described[13], with minor modifications.

2.4. Measurements of NO and oxidative stress parameters

The levels of NO and reactive oxygen species (ROS) in BAT were measured using the fluorescence dyes 4, 5-diaminofluorescein diacetate (DAF-2DA) and

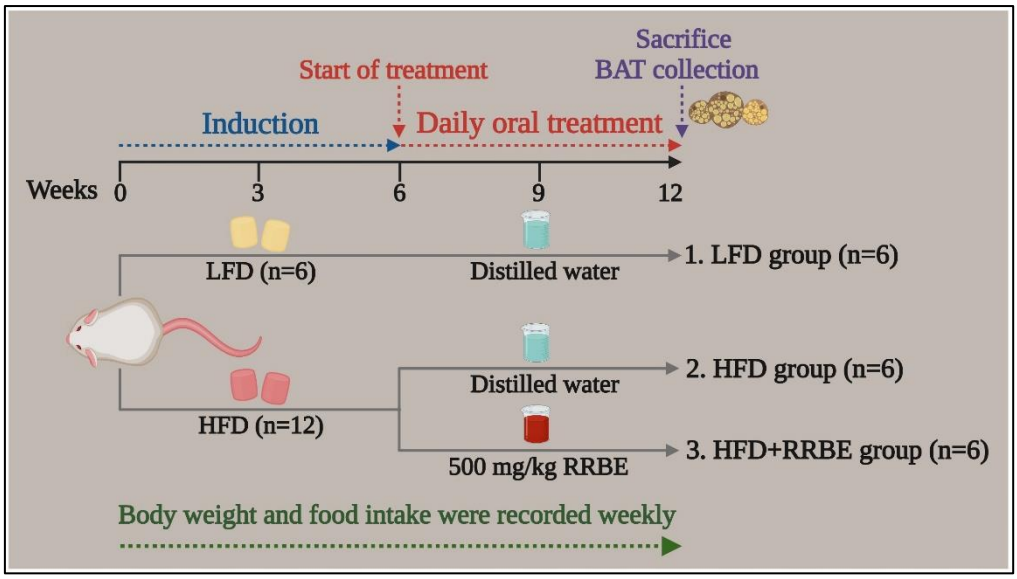

Figure 1. The experimental design. Abbreviations: LFD-low-fat diet, HFD-high-fat diet, HFD+RRBE- high-fat diet+red rice bran extract, BAT-brown fat tissue.

2′,7′-dichlorodihydrofluorescein diacetate (DCFH-DA), respectively, in line with previous protocols[14-15], with a few modifications. In essence, 30 mg of each tissue sample was homogenized in phosphate buffer using a tissue homogenizer, and the homogenate was centrifuged to obtain supernatant. These supernatants were incubated with DAF-2DA and DCFH-DA solutions for determination of NO and ROS levels, respectively. These results were calculated as percentage values of the LFD group. The assay of MDA, a biomarker of oxidative damage to lipids, was performed as described previously[16], with some modifications. In this assay, BAT supernatants and tetraethoxypropane standard were heated with trichloroacetic and thiobarbituric acid solutions (Sigma-Aldrich, USA), cooled with tap water, and centrifuged to obtain clear supernatants for absorbance measurements. Total protein levels were determined using the Bradford assay (Bio-Rad, USA). The MDA results were calculated in terms of nmol/mg protein.

2.5. Quantitative real-time polymerase chain reaction (qRT-PCR)

Total RNA was isolated from each BAT sample using TRIzol reagent (Ambion by Life Technologies, USA) according to the standard protocol, and its concentration was determined spectrophotometrically using NanoDrop spectrophotometer (Thermo Fisher Scientific Inc., USA). Then, cDNA was synthesized from the isolated RNA using High-Capacity cDNA Reverse Transcription kit (Applied Biosystems™, Thermo Fisher Scientific Inc., USA). The cDNA was applied as template for qRT-PCR using TaqMan gene expression assays (Applied Biosystems™). The reaction was run on a qRT-PCR machine (CFX96 Touch™ system, Bio-Rad), and the result was calculated as fold change in target mRNA expression using the $2^{-\Delta\Delta Ct}$ method. The expression levels which were calculated relative to the LFD group, were normalized to GAPDH mRNA.

2.6. Statistical analysis

All results are expressed as mean±S.E.M. Data were analyzed using the SPSS version 26.0 statistical package for Windows (IBM Corp., USA). Descriptive data were compared using one-way ANOVA, followed by Turkey's test. Repeated measures two-way ANOVA was used to compare absolute body weight and percentage changes in body weight at weeks 6 and 12 in each group. Values of $p<0.05$ were considered statistically significant.

3. RESULTS

3.1. RRBE mitigated characteristic features of obesity

At baseline (week 0), there were no significant differences in body weights amongst the three groups of mice (Table 1). However, absolute body weight and percent weight change after 6 weeks of obesity induction were significantly increased in all HFD-fed mice, when compared to LFD-fed mice (Table 1). At the end of 12 weeks study period, absolute body weight and percent changes in body weight remained significantly greater in HFD group than in the LFD group, but these significant differences were not observed in HFD+RRBE group (Table 1). Repeated measures ANOVA revealed that obese mice treated with RRBE had significant decreases in both absolute body weight and percentage of body weight change at week 12, when compared to the absolute body weight and percentage of body weight change at week 6 (Table 1). FER of LFD-fed and RRBE-treated groups was significantly lower than those in the HFD-fed

Table 1. Absolute body weight, percent body weight change, food intake, FER, and BAT weight of the experimental groups.

Parameters	LFD	HFD	HFD+RRBE
Absolute body weight (g)			
Week 0	29.93 ± 0.51[a]	30.11 ± 0.31[a]	30.07 ± 0.47[a]
Week 6	42.16 ± 0.68[b]	47.26 ± 1.18[a]	49.37 ± 1.07[a]
Week 12	42.46 ± 0.52[b]	47.39 ± 0.77[a]	44.89 ± 1.13[a,b,*]
Percent body weight change (% change from baseline)			
Week 6	42.14 ± 2.49[b]	56.42 ± 4.59[a]	60.06 ± 3.39[a]
Week 12	40.44 ± 3.03[b]	56.43 ± 1.76[a]	49.00 ± 2.85[a,b,*]
Food intake (g/mouse/day)	4.50 ± 0.00[a]	3.89 ± 0.04[b]	3.99 ± 0.07[b]
FER (%)	305.19 ±17.03[b]	409.91 ±19.68[a]	336.13 ± 30.83[a,b]
BAT weight (g)	0.30 ± 0.02[a]	0.28 ± 0.03[a]	0.26 ± 0.03[a]

Data are expressed as mean±SEM (n=6). Different low-case letters indicate statistically significant differences (p<0.05) between the groups. Asterisks (*) indicate significant difference (p<0.05) between the 6-week and 12-week experimental periods. Abbreviations: LFD-low-fat diet, HFD-high-fat diet, HFD+RRBE- high-fat diet+red rice bran extract, FER-food efficiency ratio, BAT-brown fat tissue.

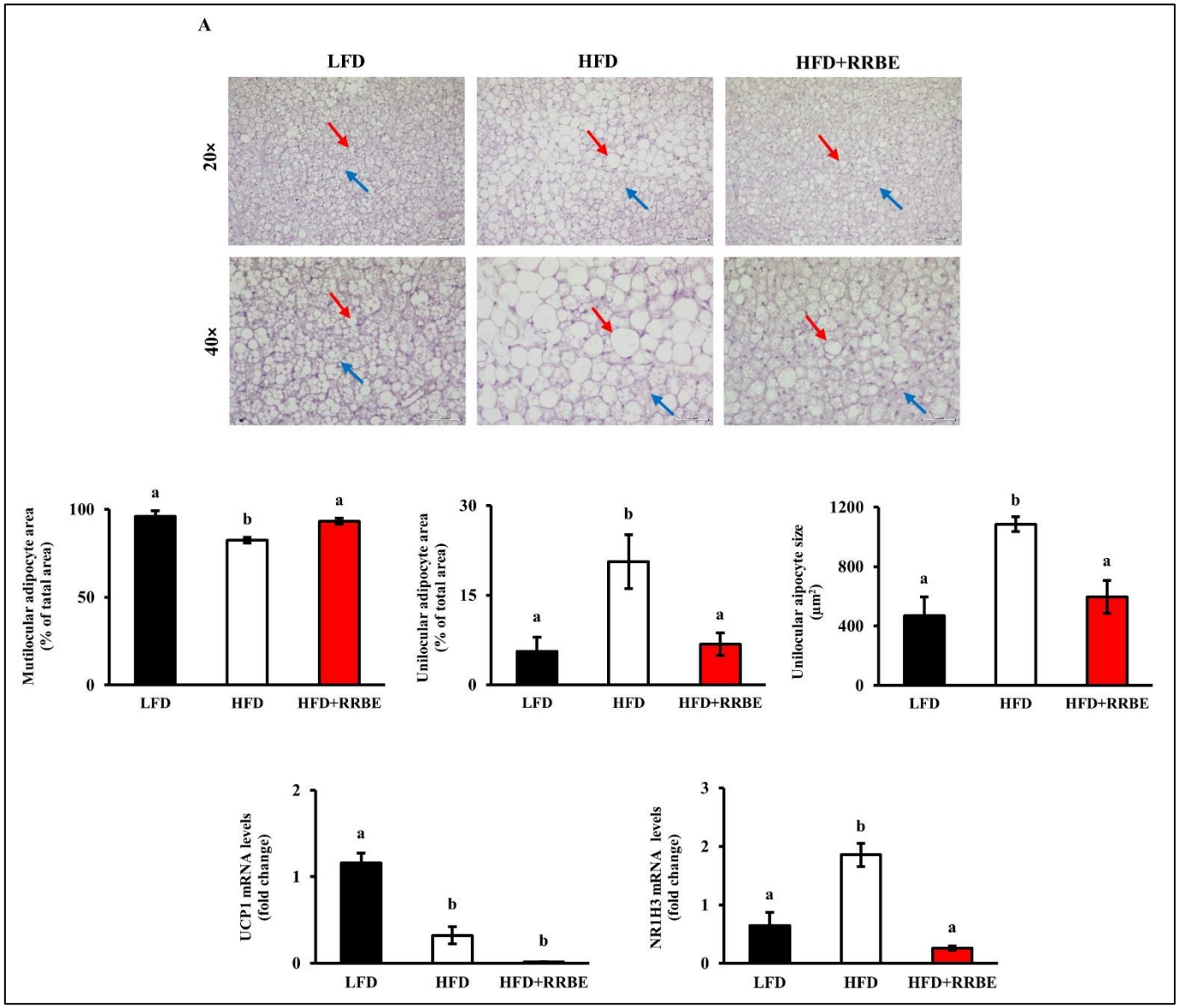

Figure 2. Histology (A), multilocular adipocyte area (B), unilocular adipocyte area (C), unilocular adipocyte size (D), UCP1 mRNA (E), and NR1H3 mRNA (F) levels of BAT of the experimental groups. Blue arrows indicate brown adipocytes with small multilocular lipid droplets. Red arrows indicate white adipocytes with large unilocular lipid droplets. Data are mean±SEM (n=3-4). Different low-case letters above each bar indicate statistically significant differences (p<0.05). Abbreviations: LFD-low-fat diet, HFD-high-fat diet, HFD+RRBE- high-fat diet+red rice bran extract, BAT-brown fat tissue, UCP1- uncoupling protein 1, NR1H3-nuclear receptor subfamily 1 group H member 3.

group, while food intake was not significantly different between the HFD and HFD+RRBE groups (Table 1). In addition, BAT weight was not significantly different between the three groups of mice (Table 1).

3.2. RRBE attenuated characteristic features of whitening and NR1H3 expression in BAT without changes in UCP1 expression

Compared with control BAT, histologic examination of BAT from HFD-fed mice revealed a whitened appearance, with high deposition of single large lipid droplets displacing the normal browning adipocytes (Figure 2A). This was associated with a significant decline in multilocular adipocyte area (Figure 2B), as well as significant enhancements in area and size of unilocular adipocytes (Figure 2C and Figure 2D, respectively). However, in comparison with untreated HFD-fed mice, treatment with RRBE led to significant decreases in unilocular adipocyte area and unilocular adipocyte size. Moreover, RRBE increased multilocular adipocyte area in BAT, although the increase was not statistically significant. Results from qRT-PCR assays showed that UCP1 mRNA levels were significantly down-regulated (Figure 2E), while NR1H3 mRNA levels were significantly up-regulated (Figure 2F) in BAT from of HFD-fed mice, when compared to the corresponding expression in LFD-fed mice. There was no significant difference in UCP1 mRNA level between the RRBE-treated HFD and untreated HFD groups, but significant decrease in NR1H3 mRNA levels were observed in the treated group.

3.3. RRBE suppressed elevations of pro-inflammatory markers in BAT

Compared with the LFD group, the HFD group showed increased expression levels of NF-κB p65, TNF-α, and MCP-1 (monocyte chemoattractant protein-1), which were reversed by RRBE treatment as shown in Figures 3A, 3B, and 3C, respectively. Consistent with qRT-PCR data on expression levels of inflammatory genes, NO level in HFD+RRBE group was significantly reduced, when compared to the corresponding level in mice treated with HFD alone, as shown in Figure 3D.

3.4. RRBE reduced levels of oxidative stress markers in BAT

Compared with mice fed LFD, mice fed HFD had significantly increased BAT levels of ROS and MDA, as shown in Figure 4A and Figure 4B, respectively. In addition, mice fed HFD had up-regulated mRNA levels of NRF2 and SOD2 (superoxide dismutase 2) in BAT, as presented in Figure 4C and Figure 4D, respectively. In contrast, RRBE treatment significantly reduced HFD-induced ROS production and up-regulations of expressions of NRF2 and SOD2 genes in BAT, when compared with the untreated HFD group. Moreover, MDA level was

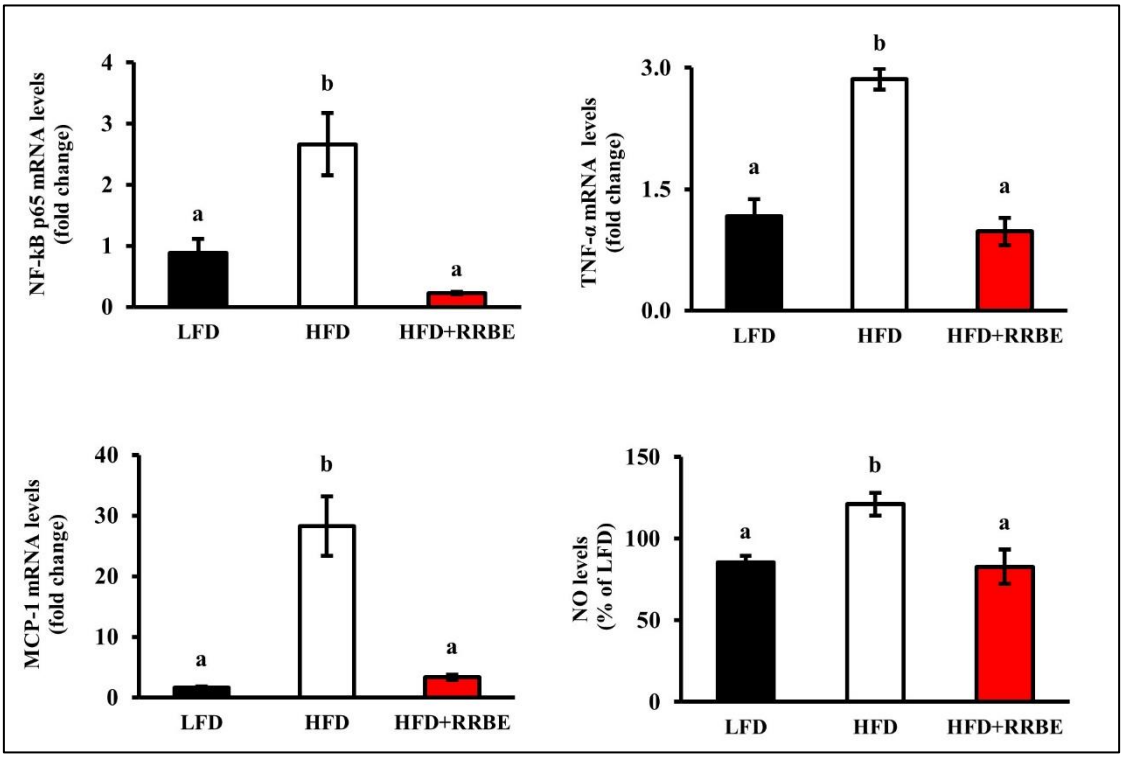

Figure 3. mRNA levels of NF-κB p65 (A), TNF-α (B), and MCP-1 (C), and NO levels (D) in BAT of the experimental groups. Data are mean±SEM (n=4-6). Different low-case letters above each bar indicate statistically significant differences (p<0.05). Abbreviations: LFD-low-fat diet, HFD-high-fat diet, HFD+RRBE- high-fat diet+red rice bran extract, BAT-brown fat tissue, NF-κB p65-nuclear factor-kappa B p65, TNF-α-tumor necrosis factor-alpha, MCP-1-monocyte chemoattractant protein-1, NO-nitric oxide.

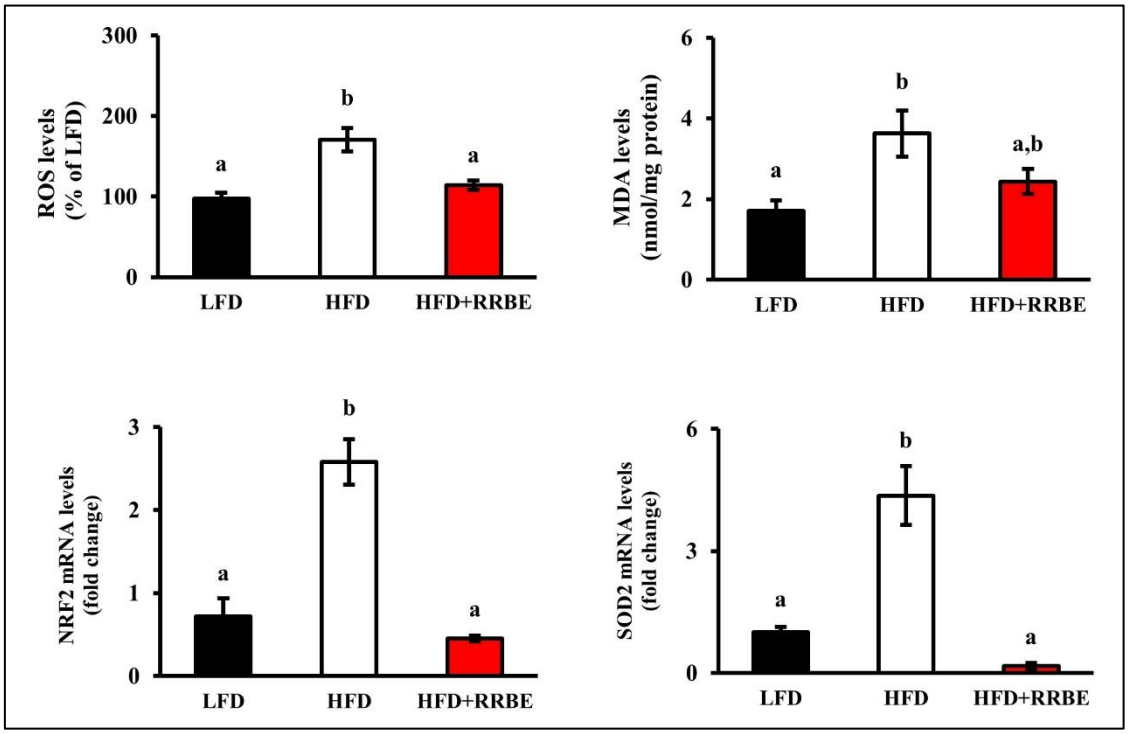

Figure 4. Levels of ROS (A), MDA (B), NRF2 mRNA (C), and SOD2 mRNA (D) in BAT of the experimental groups. Data are mean ± SEM (n=4-6). Different low-case letters above each bar indicate statistically significant differences (p<0.05). Abbreviations: LFD-low-fat diet, HFD-high-fat diet, HFD+RRBE-high-fat diet+red rice bran extract, BAT-brown fat tissue, ROS-reactive oxygen species, MDA-malondialdehyde, NRF2-nuclear factor erythroid 2-related factor 2, SOD2- superoxide dismutase 2.

also reduced in RRBE-treated group, relative to the HFD group, although the decrease was not statistically significant.

4. DISCUSSION

Whitening of BAT, the conversion of multilocular brown adipocytes with thermogenic, fat-burning properties to unilocular white-like adipocytes with lipid-storage properties, is known to play an important role in reducing BAT content and activity in the context of obesity[2,17]. The inactivation of UCP1 and/or activation of NR1H3 pathways are considered to be mechanisms through which obesity may induce whitening and lipid accumulation in BAT, as evidenced from studies on knockout mouse and obese mouse models[3,6,18]. During activation, BAT-specific UCP1 increases heat production by uncoupling mitochondrial fat oxidation from ATP synthesis, resulting in energy expenditure[18], whereas NR1H3 stimulates lipogenesis by up-regulating its downstream lipogenic genes[6]. Consistent with previous findings[3], the present study has demonstrated that HFD intake is sufficient to induce obesity and formation of white-like adipocytes in BAT, as indicated by increased unilocular adipocyte area and size, accompanied by lowered expression of UCP1 and enhanced expression of NR1H3. Our previously published data also showed that HFD intake induced abdominal fat accumulation, hypertriglyceridemia, and hypercholesterolemia in mice, accompanied by signs of fatty liver[9,19]. Our present and previous results indicate the development of BAT whitening and metabolic dysfunction in obesity. In contrast, the induced increases in expressions of WAT-like phenotype and NR1H3 in BAT were reduced by RRBE intervention, without increasing the expression of UCP1 gene. This was associated with reductions in FER and body weight. During the induction of brown adipocytes, peroxisome proliferator-activated receptor gamma (PPARγ) is one of the key transcription factors that control brown adipocyte function via up-regulation of expression of UCP-1[20]. According to our previous result, PPARγ expression in WAT of obese mice was unaffected by RRBE treatment[9], which might be the reason for an insignificant expression of UCP-1 mRNA in BAT of RRBE-treated mice. Thus, we infer that the inhibition of BAT whitening by RRBE treatment may be not through the transcription of UCP-1gene but rather other mechanisms involving the induction of the brown adipocyte phenotype. Detailed mechanisms behind this effect of RRBE still need further analysis. Our previous study demonstrated the presence of phenolic compounds in RRBE at a concentration of 327 mg/g, as well as phenolic subtypes such as proanthocyanidins (72 mg/g) which exerted anti-hypertrophic and anti-hyperlipidemic effects by decreasing lipogenic gene expression in WAT and livers of obese mice[9,19]. These data are consistent with previous results derived from the same rice variety enriched in phenolic compounds (246 mg/g) and proanthocyanidins (203 mg/g), associated with its antioxidant effects on lung cancer cells[12]. Furthermore, it has been

demonstrated that rice bran phenolics produced anti-lipogenic effect by repressing LXRα nuclear translocation[21]. A class of polyphenolic flavonoids such as proanthocyanidins also improves thermogenic capacity and mitochondrial function in BAT from obese rats[22]. Hence, observations indicate that RRBE may down-regulate NR1H3 expression and inhibit lipid accumulation and whitening of BAT, thereby attenuating obesity-linked BAT dysfunction. The presence of phenolic compounds and proanthocyanidins in RRBE could be contributory to its beneficial effects on BAT.

In the obese condition, pro-inflammatory state in BAT occurs via activation of various inflammatory signaling pathways, including NF-κB pathway[7,23]. This results in the up-regulation of several inflammatory genes or mediators such as TNF-α, iNOS, and MCP-1, leading to oxidative stress and whitening of BAT. For instance, excessive NO production suppressed lipolysis in brown adipocytes, whereas genetic ablation of iNOS improved brown-like phenotype and reduced body weight in *ob/ob* mice. In agreement with previous study[7], it was found that HFD-fed mice had increased gene expression levels of NF-κB, TNF-α, and MCP-1 in BAT, along with an increase in NO levels, indicating that consumption of HFD induced pro-inflammatory state in mouse BAT. Interestingly, these increases were reversed by treatment with RRBE. Consistent with these data, *in vitro* studies showed that RRBE and red rice polar extract fraction rich in phenolics and proanthocyanidins, attenuated the production of NO, IFN-γ and TNF in macrophages by inhibiting the stimulator of interferon genes or NF-κB pathway[10-11]. Moreover, a recent study showed that treatments with rice bran phenolic compounds inactivated the NF-κB pathway, resulting in the attenuation of inflammation in the livers of ethanol-fed animals[24]. The present study has demonstrated that RRBE exerted anti-inflammatory properties in BAT by down-regulating NF-κB target gene expression and decreasing NO production. These properties could be attributed to the phenolic compounds in RRBE.

Oxidative stress is another pathological factor that affects BAT[25]. It results from as imbalance between the generation of ROS and the capacity of antioxidants to scavenge them[26]. This causes oxidative damage to cellular components, including lipids, and eventually leads to the formation of MDA. Transcription factor NRF2 is an oxidative stress sensor which responds to changes in intracellular ROS levels by activating antioxidant defense pathways through the induction of antioxidant-specific genes such as SOD2 and catalase, leading ultimately to counteraction of oxidative stress[8]. As expected, signs of oxidative stress were found in BAT of HFD-fed mice, along with the transcriptional up-regulations of NRF2 and SOD2 genes. These upregulations may have occurred to compensate for increased oxidative stress in BAT. A similar result was obtained in a previous investigation by Alcalá et al[25]. Interestingly, the induction of oxidative stress and antioxidant gene expression caused by HFD

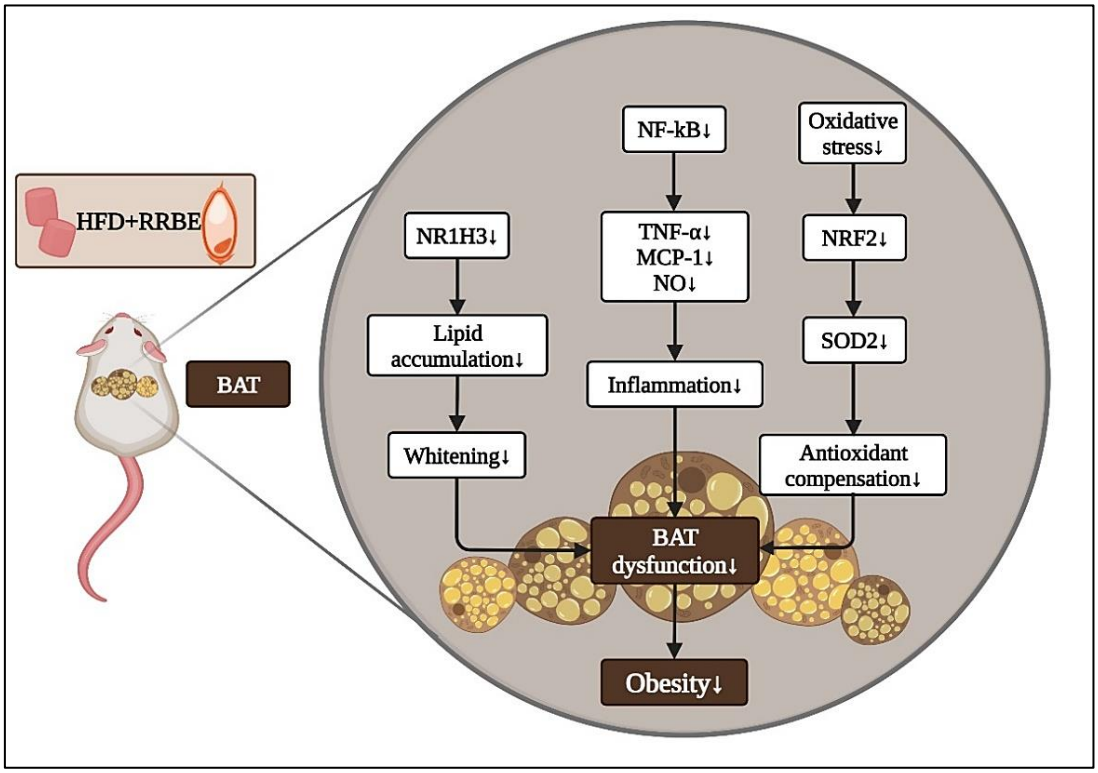

Figure 5. Schematic summary of the mechanism of action of RRBE on HFD-induced pathological conditions, including whitening, inflammation, and oxidative stress, in BAT of obese mouse model. Abbreviations: HFD+RRBE-high-fat diet+red rice bran extract, BAT-brown fat tissue, NR1H3-nuclear receptor subfamily 1 group H member 3, NF-κB p65-nuclear factor-kappa B p65, TNF-α-tumor necrosis factor-alpha, MCP-1-monocyte chemoattractant protein-1, NO-nitric oxide, NRF2-nuclear factor erythroid 2-related factor 2, SOD2- superoxide dismutase 2.

were reversed to normal control levels by treatment with RRBE. Consistent with these findings, Surarit et al.[12] reported that RRBE protected lung cancer cells against oxidative stress by restoring the activities of SOD and catalase. These data clearly demonstrate that RRBE mitigated obesity-induced oxidative stress in BAT through the modulation of NRF2-regulated antioxidant gene expression. The high contents of phenolics and proanthocyanidins in RRBE may have contributed to its antioxidant effects in BAT, since these phytochemicals are well-known for their antioxidant properties.

5. CONCLUSION

This study has demonstrated for the first time that RRBE has the potential to inhibit the pathological processes in the BAT of HFD-fed mice by suppressing whitening, inflammation, and oxidative stress through the regulation of the expressions of the target genes of NR1H3, NF-κB, and NRF2 (Figure 5). However, further in-depth studies are required to determine specific phytochemicals in RRBE and their direct effects on BAT and obesity.

Conflict of interest
None to declare.

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Ethics approval
The animal study protocol was approved by the Institutional Animal Care and Use Committee of University of Phayao, Thailand (Approval No. 59 01 04 0037).

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Author contribution
We declare that this research was done by the names of authors in this article and all liabilities for all claims relating to the content of this article will be borne by the authors. Nattanida Jantarach and Narongsuk Munkong conceived and designed the study. Nattanida Jantarach, Wirinya Mueangchang, and Jatuporn Prathumtet collected and analysed the data and wrote the manuscript. Nattanida Jantarach, Wirinya Mueangchang, and Narongsuk Munkong aided in analysing and writing of the manuscript. All authors approved the manuscript for publication.

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