Protective Effects of Rice Bran Water Extract (RBE) on Hepatic Fat Metabolism and Oxidative Damage in Rats Fed A High-Fat Diet

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Background: *RBE is known as nutritious bioactive compounds and is proven to decrease blood lipids, hepatic fat accumulation and oxidative damage. However, the molecular mechanisms of protective effect of RBE has not been clarified.*
Objective: *To investigate the effect and mechanism of RBE on hepatic lipid accumulation and lipid oxidative damage in rats fed a high-fat diet (HFD).*
Material and Method: *Male Sprague-Dawley rats were divided into four groups including 1) control group (C), 2) high-fat diet fed only group (HF), 3) HF co-fed with RBE at the dose of 2,205 mg/kg/day (HFR1 group) and 4) HF co-fed with RBE at the dose of 4,410 mg/kg/day (HFR2 group), respectively. After four weeks, body weight, metabolic and oxidative damage markers were assessed.*
Results: *Body weight, abdominal fat tissue weight, liver weight, and serum lipid levels were reduced in RBE-treated rats compared to HFD alone-fed rats. RBE-fed groups showed significantly lower levels of total-cholesterol, triglyceride and malondialdehyde in the liver tissue. RBE also inhibited hepatic 3-hydroxy-3 methylglutaryl coenzyme A reductase (HMGCR) activity, suppressed expression of hepatic sterol regulatory element binding protein-1 (SREBP-1) and nuclear factor kappa B (NF-kappa B), and up-regulated hepatic adenosine monophosphate-activated protein kinase (AMPK) expression.*
Conclusion: *RBE improves hepatic fat accumulation via the regulation of SREBP-1, AMPK expression and HMGCR activity in HFD induced obese rats. RBE also attenuates the damaging effects of oxidative stress by decreasing lipid peroxidation and NF-kappa B expression in the liver. Thus, RBE may be useful in the management of dyslipidemia and oxidative stress at the onset of obesity.*

Keywords: *Rice bran, Fat metabolism, Non-alcoholic fatty liver disease, Oxidative stress*

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Non-alcoholic fatty liver disease (NAFLD), an excessive triglyceride accumulation within lipid droplets in hepatocytes, is currently the most common chronic liver disease in many countries that may progress to severe liver disease[1]. It is strongly associated with obesity, high-energy diet consumption, and type 2 diabetes[2,3]. De novo lipogenesis can promote triglyceride (TG) accumulation in the liver via the activation of the sterol regulatory element binding protein-1c (SREBP-1c), the key lipogenic transcription factor[4,5]. The increase of de novo cholesterol biosynthesis by stimulation of 3-hydroxy-3 methyl-glutaryl coenzyme A reductase (HMGCR) has been proposed to be a main mechanism for the cholesterol over accumulation in the liver and is now also considered as an important characteristic of NAFLD and non-alcoholic steatohepatitis (NASH)[6-8]. On the contrary, Li et al found that activation of adenosine monophosphate-activated protein kinase (AMPK) suppresses SREBP-2 pathway and SREBP-2 target gene expression, such as the HMGCR gene which is essential for controlling hepatic cholesterogenesis[9].

In addition, malondialdehyde (MDA) was observed in the livers of animals and patients with NAFLD demonstrating the role of oxidative stress

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causing lipid peroxidation which lead to hepatic inflammation and the progression of NAFLD to NASH[10-12]. Moreover, the oxidative stress in hepatocytes and the expression of pro-inflammatory genes, such as tumor necrosis factor-alpha (TNF-alpha) can be promoted by activation of nuclear factor-kappa B (NF-kappa B)[12,13].

Rice bran is an important by-product of rice milling and has phytochemicals and various nutrients. Recent findings show that rice bran improves lipid and glucose metabolism in patients with diabetes mellitus and also decreases oxidative stress in patients and rats with metabolic syndrome[14-16]. However, its exact molecular mechanism is not fully understood. Therefore, the present study was performed to investigate the effects of RBE on hepatic fat mechanism and on hepatic oxidative damage.

Material and Method

RBE preparation

Organic rice bran of Khao Dawk Mali 105 (KDML 105) variety was obtained from the local mill in Surin province, Thailand. Rice bran was extracted as previously described with some modifications[15]. The 2,000 g of stabilized rice bran was extracted with 8,000 mL of distilled water at 70°C for 1 h. After centrifugation at 12,000 xg for 10 min, the supernatant was freeze-dried by using a freeze dryer (Lyophilization System Inc., USA).

Animal study

All experimental procedures involving animals were conducted in accordance to Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) and approved by the Animal Ethics Committee of the Faculty of Medicine, Thammasat University, Pathumthani, Thailand (AE 002/2013). Thirty-two male outbred Sprague-Dawley rats, 6 to 8 week old and initial weight about 180 to 220 g were purchased from the National Laboratory Animal Center, Nakhon Pathom, Thailand. Animals were kept on 12: 12 hour light/darkness cycle under environmentally regulated room temperature at 24±1°C and 60% humidity. Rats were singly caged with free access to water and controlled to different dietary regimens. High-fat diet (HFD) were modified from previous report[17]. After seven days of acclimatization, the rats had free access to a standard chow (C group, fat content 13% of energy, n = 8) or HFD alone (HF group, fat content 65% of energy, n = 8) or HFD and co-fed with RBE1 (2,205 mg/kg rat weight, HFR1 group, n = 8) or HFD and co-fed with RBE2 (4,410 mg/kg rat weight, HFR2 group, n = 8). Weight and food intake were monitored once a day. After four weeks, the rats were killed after 16 h overnight fast with an overdose of pentobarbital sodium (intra-peritoneal injection), and blood was collected from a cardiac puncture and serum was prepared and stored at -40°C until further analysis. The liver tissues were removed for the biochemical, histologic, and gene expression analysis as described below.

Determination of serum lipid levels

The concentrations of total-C, TG and high-density lipoprotein-cholesterol (HDL-C) in the serum were analyzed using enzymatic colorimetric method (Fluitest test kits, Analyticon Biotechnologies AG, Germany). Serum low-density lipoprotein-cholesterol (LDL-C) level was determined using the Friedewald equation. The concentrations of non-esterified fatty acid (NEFA) were measured using the enzymatic colorimetric method (NEFA assay kit, Wako, Japan).

Determination of liver total-C and TG contents

Liver lipids were determined as described previously[18]. In brief, 50 mg of liver tissue was homogenized and extracted with 1 mL of isopropanol. After centrifugation (10,000 xg for 15 min at 4°C), total-C and TG contents in the supernatant were determined using the enzymatic colorimetric method (Analyticon Biotechnologies AG, Germany).

The histology of epididymal fat pads and liver tissues

For histologic examination, tissue pieces of epididymal fat pads and right ventral lobe of liver tissues were fixed in 10% neutral buffered formaldehyde, embedded in paraffin, cut, mounted on slides and stained according to standard hematoxylin and eosin (H and E) protocols. The histological changes were imaged under a light microscope (Olympus, Japan). Area of the adipocyte was measured by Axiovision AC (Carl Zeiss, Germany). Mean adipocyte area was calculated from a 100 cells observed/um^2.

Determination of HMGCR activities in the liver

One gram of liver tissue was homogenized and centrifuged at 100,000 xg for 60 min at 4°C for microsomal fraction sedimentation. The microsomes were prepared from freshly liver tissues as described previously[19]. The protein concentrations of the fractions were determined with Folin phenol reagent. The HMGCR activities were measured with a

commercial kit from Sigma-aldrich, USA and expressed as mmol/min/mg protein (Units/mg protein).

Determination of liver oxidative stress markers

MDA levels were used for representative of reactive oxygen species (ROS)-mediated damage. An assay was measured spectrophotometrically at 532 nm as described previously with some modifications[20]. The total protein levels of liver tissues were used for normalization and using 1, 1, 3, 3-tetraethoxypropane (Sigma-Aldrich) as an MDA standard. The total proteins were determined by Bradford protein assay kit (Bio-Rad, USA) according to the manufacturer's instructions. The MDA levels were expressed as nmol/mg of protein.

Liver mRNA extraction, cDNA synthesis, and real-time polymerase chain reaction (real-time PCR)

Total RNA was extracted from liver tissues using TRIzol reagent (Invitrogen, USA), according to the manufacturer's recommendations. Its concentrations were determined by the NanoDrop spectrophotometer (Thermo Scientific, USA). Subsequently, RNA (200 ng) was reverse transcribed into cDNA using the High-capacity cDNA reverse transcription kit (Applied Biosystems, USA) according to the manufacturer's instructions. Quantitative PCR was perfumed using the TaqMan reagent kit and StepOnePlus real-time PCR system (Applied Biosystems). The relative mRNA levels of SREBP-1c (Assay ID Rn01495769_m1), and NF kappa B p65 (Assay ID Rn01502266_m1) were analyzed by the 2-ΔΔCT method. The expression levels of GAPDH (Assay ID Rn99999916_s1) were used for normalization.

Western blot analysis

The total protein of the liver tissues was isolated using the cell lysis buffer (Cell Signaling Technology, USA) according to the manufacturer's instructions. The extracted total protein concentrations were determined by Bradford protein assay kit (Bio-Rad). Equal amounts of sample proteins (50 μg) were electrophoresed on 7% sodium dodecyl sulfatepolyacrylamide gel and electroblotted to nitrocellulose membrane (Bio-Rad). The membranes were blocked by a mixture of Odyssey blocking buffer (LI-COR Bioscience, USA) in the dark at room temperature for 1 h. The blocked membranes were then incubated with a primary anti-SREBP-1 antibody, anti-AMPK alpha Santa Cruz Biotechnology, USA), anti-NF-kappa B p65 antibody, and anti-GAPDH antibody (Cell Signaling Technology) overnight at 4°C. The membranes were washed with Tris-buffer saline containing 0.1% Tween-20 and incubated with the DyLight 680 conjugated antibodies (Cell Signaling Technology) for 1 h in the dark at room temperature. After washing, the densities of bands were determined using the Odyssey Fc imaging system (LI-COR Bioscience). The protein levels of GAPDH were used for normalization.

Statistical analysis

The results were expressed as means $\pm$ the standard error of the mean (SEM). Multiple comparisons were analyzed by one way analysis of variance (ANOVA) and least significant difference's (LSD) post hoc test. The statistical analysis was performed using computer-based software SPSS version 16 (SPSS Inc., USA). The level of statistical significance was identically set at $p<0.05$.

Results

Effects of RBE on HFD-induced changes in body weight, organ weight, and histology of epididymal fat tissue and liver tissue

The average initial body weight of each group did not differ prior to treatment. Food and energy intakes were not significantly different among the HF-fed groups (Fig. 1A and B, respectively). However, the energy intakes were significantly higher in all HF groups as compared to the C group. After four weeks, the HF group had a higher final body weight, adipocyte size, relative weights of omental fat tissue, epididymal fat tissue, and liver than those of the C group (Fig. 1C, 2C, 2A, 2B, and 2D, respectively). As illustrated in Fig. 2E and F, sections from the HF-fed animals showed a marked hypertrophied adipocyte and hepatocyte lipid vacuoles (arrow) when compared to the C group and RBE-treated groups. These parameters (body weight, organ weight and histology of epididymal fat tissue and liver tissue) were significantly reduced by the RBE treatments.

Effects of RBE on HFD-induced TG over accumulation in the liver

Compared with the controls, the rats fed an HFD only exhibited a marked increase in liver TG contents and SREBP-1 expression levels, whereas the AMPK alpha protein levels had decreased in the liver (Fig. 3A, C, D, and B, respectively). In contrast to the HF group, both RBE1 and RBE2 treatments significantly improved the contents of liver TG and SREBP-1 and AMPK alpha expression levels.

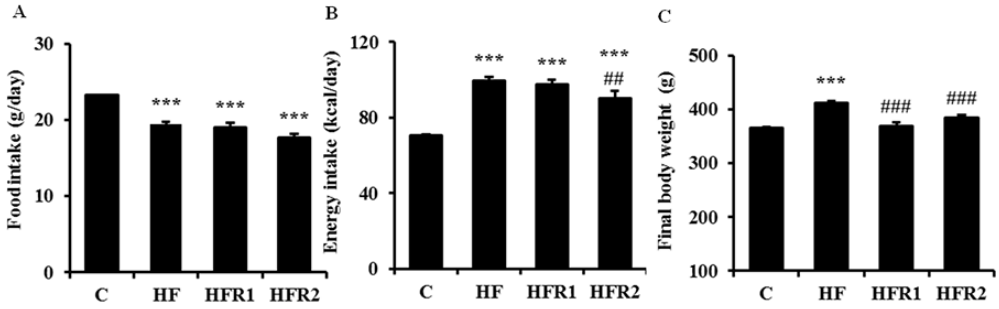

Fig. 1 Effect of RBE on food intake (A), energy intake (B), and final body weight (C) in HFD-fed rats results are expressed as mean ± SEM (n = 8) *** $p<0.001$ versus C group; ### $p<0.001$ versus HF group.

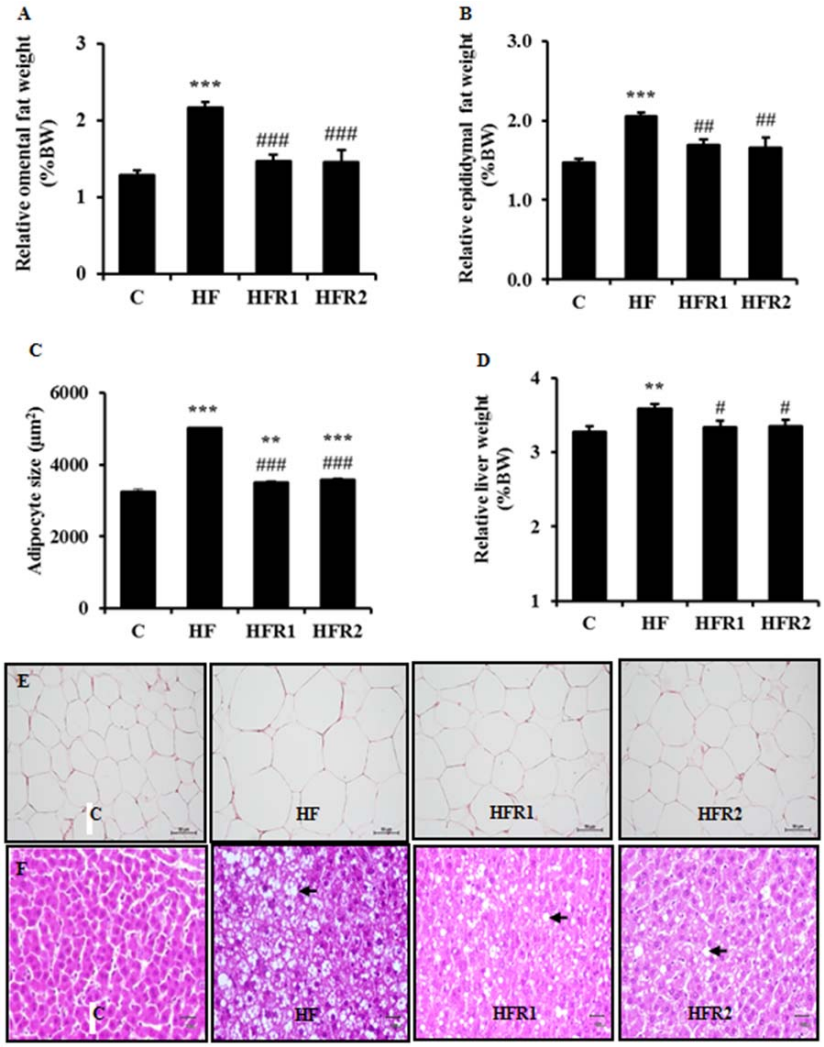

Fig. 2 Effect of RBE on omental fat tissue weight (A), epididymal fat tissue weight (B), epididymal adipocyete size (C), liver weight (D), and histology of epididymal fat tissue (E) and liver (F) (H and E, 400x; scale bar = 100 μm) in HFD-fed rats.
BW = body weight; Results are expressed as mean ± SEM, (n = 8 for organ weight and n = 3 for histological analysis). ** $p<0.01$, *** $p<0.001$ versus C group; # $p<0.05$, ## $p<0.01$, ### $p<0.001$ versus HF group.

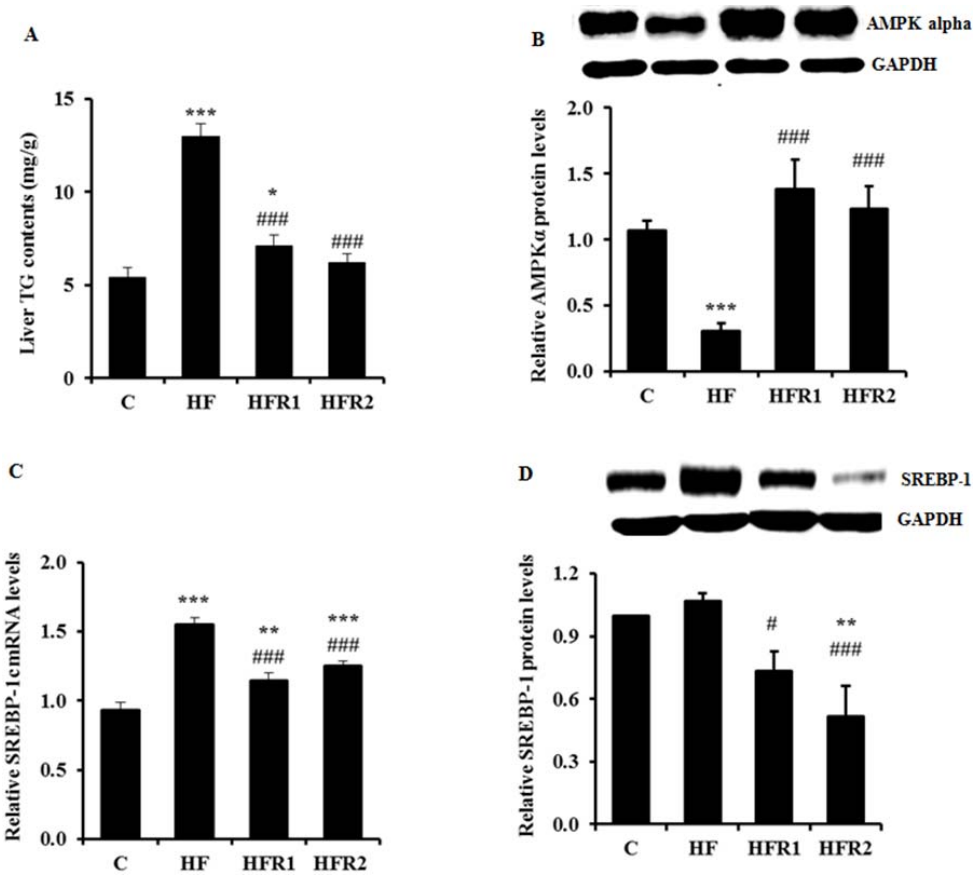

Fig. 3 Effect of RBE on TG contents (A), AMPK alpha protein expression (B), SREBP-1c mRNA expression (C), and SREBP-1 protein expression (D) in the livers of HFD-fed rats results are expressed as mean ± SEM (n = 8 for TG assay and n = 6 for gene expression). * $p<0.05$, ** $p<0.01$, *** $p<0.001$ versus C group; $^{\#}$ $p<0.05$, $^{\#\#\#}$ $p<0.001$ versus HF group.

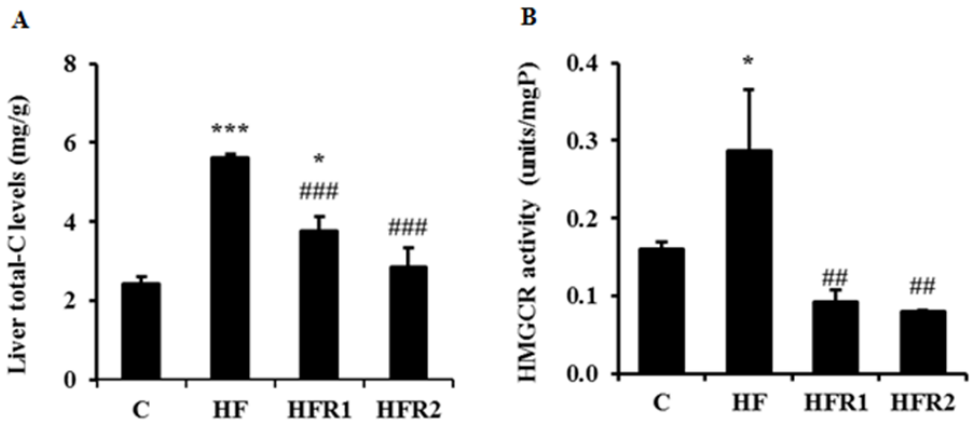

Fig. 4 Effect of RBE on total-C contents (A) and HMGCR activities (B) in the livers of HFD-fed rats. Results are expressed as mean ± SEM (n = 8 for cholesterol assay and n = 3 for HMGCR activities). * $p<0.05$, *** $p<0.001$ versus C group; $^{\#\#}$ $p<0.01$, $^{\#\#\#}$ $p<0.001$ versus HF group.

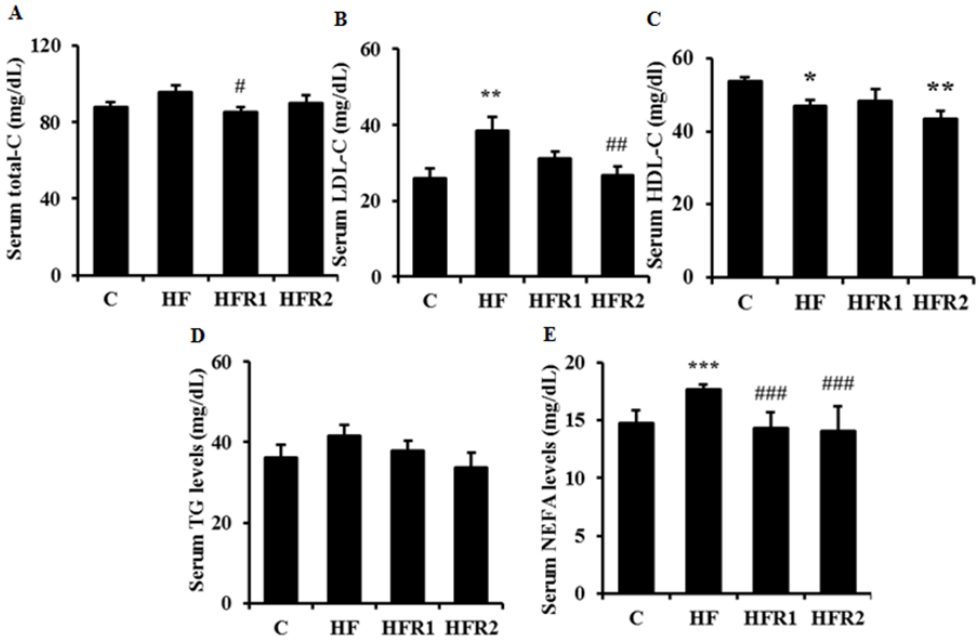

Fig. 5 Effect of RBE on total-C (A), LDL-C (B), HDL-C (C), TG (D), and NEFA levels (E) in the serum of HFD-fed rats. Results are expressed as mean ± SEM (n = 8) * $p<0.05$, ** $p<0.01$, ***$p<0.001$versus C group; $^{\#}$ $p<0.05$, $^{\#\#}$ $p<0.01$, $^{\#\#\#}$ $p<0.001$ versus HF group.

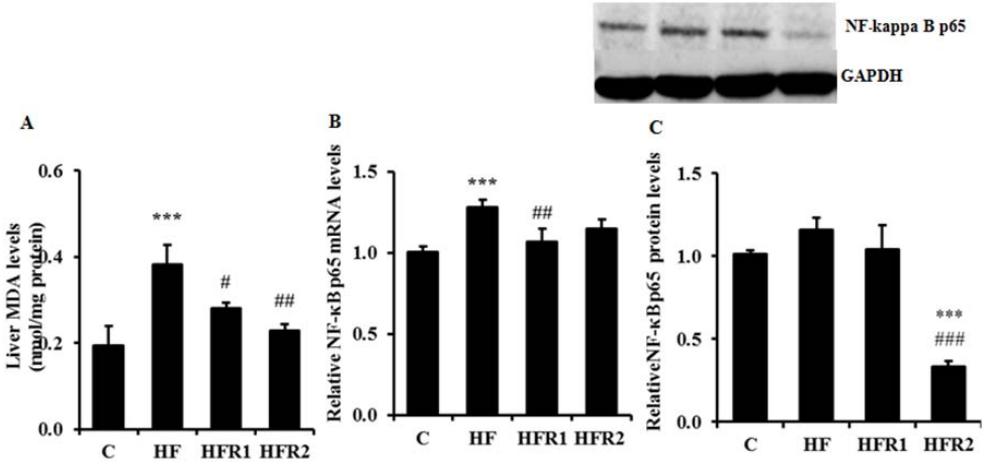

Fig. 6 Effect of RBE on MDA levels (A), and NF-kappa B p65 mRNA expression (B), and NF-kappa B p65 protein expression (C) in the livers of HFD-fed rats. Results are expressed as mean ± SEM, (n = 8 for MDA assay and n = 6 for gene expression). *** $p<0.001$ versus C group; $^{\#}$ $p<0.05$, $^{\#\#}$ $p<0.01$, $^{\#\#\#}$ $p<0.001$ versus HF group.

Effects of RBE on HFD-induced cholesterol over accumulation in the liver

The total-C levels and HMGCR activity were significantly higher in the livers of rats fed an HFD as compared to control group (Fig. 4A and B, respectively). However, supplements with both doses of RBE showed significantly decreased the cholesterol accumulation and HMGCR activity in the livers of the rats.

Effects of RBE on HFD induced-oxidative damage and NF-kappaB p65 expression in the liver

The HF group showed a significant increase in liver MDA levels as compared to control group (Fig. 6A). Both the HFR1 and the HFR2 groups showed a significant reduction in the levels of MDA in the liver. The hepatic tissues from the HF group, when compared with the C group, showed a significant increase in

the mRNA levels and tended to have increased levels of the protein NF-kappa B p65 (Fig. 6B and C, respectively). HFR1 group showed a significant decrease in the mRNA levels whereas the HFR2 group showed significant decrease in the protein levels of NF-kappa B p65.

Discussion

The present study examined the protective effect of RBE from Khao Dawk Mali variety on hepatic lipid accumulation and lipid oxidative damage in rats fed a high-fat diet (HFD). Our results found that high fat diet developed visceral obesity, dyslipidemia, hepatic fat accumulation, lipid oxidative damage and altered NF-kappa B expression in liver tissue. Rice bran water extract ingestion caused a significant decrease in body weight and intra-abdominal fat deposition, serum levels of total-C and NEFA without affecting the serum LDL-C, TG and HDL-C levels which are similar to the previous observation[16]. RBE improved hepatic fat accumulation and also attenuated the damaging effects of oxidative stress.

The mechanism of NAFLD remains largely unknown. The present study is consistent with the earlier study revealed that it is associated with obesity and high fat diet ingestion[2,3]. NAFLD is characterized by abnormal lipid metabolism in the liver, including elevated de novo lipogenesis, increased cholesterogenesis, or decreased fat oxidation leading to dyslipidemia[1,2,4,6]. Metabolic stimuli, including hyperinsulinemia, hyperglycemia, and high NEFA levels, stimulate TG synthesis in the liver via activation of various lipogenic transcription factors, such as SREBP-1c [4,5]. It is now recognized that SREBP-1c plays a primary regulatory role via its capacity to up-regulate a number of lipogenic enzymes, such as fatty acid synthase (FAS) and acetyl-CoA carboxylase (ACC). In addition, the activation of HMGCR is an essential regulatory step in the de novo synthesis of cholesterol. Previous studies reported that increased HMGCR activity and expression have led to hepatic cholesterol over accumulation in humans and rodents with MS[7,8]. AMPK regulates lipogenesis and cholesterogenesis by inactivating SREBP-1c and HMGCR pathways, respectively and also inhibits the activities of ACC, further leading to FA oxidation[9]. The impairment of AMPK activation has been observed in the livers of rodents with MS and NAFLD, suggesting that stimulation of the AMPK pathway could represent a possible mechanism to prevent hepatic fat accumulation[21]. In the present study, rats fed an HFD only exhibited abdominal obesity, excessive accumulation of TG and total-C in the liver and hyperlipidemia. These findings were associated with an increased expression of SREBP-1 and activity of HMGCR, but down-regulated protein expression of AMPKalpha in the livers. Our present data are concordant with those of previous studies[5,7,21]. Along with the decrease in obesity and hyperlipidemia, treatment of HF-fed rats with RBE effectively decreased intracellular lipid vacuoles, as well as the levels of TG and total-C in the livers. These were accompanied by improving HMGCR activity, and the expression of SREBP-1 and AMPK alpha genes. Thus, present findings suggest that RBE suppresses hepatic fat synthesis, thereby reduces the hypercholesterolemia and hypertriglyceridemia under diet-induced obesity conditions. These are similar to those obtained by Wang et al[16], who reported that an inhibition of hepatic HMGCR activity by treatment with aqueous enzymatic extract from rice bran may be beneficial in the improvement of dyslipidemia in high-energy diet-fed rats. Furthermore, Boonloh et al[22] showed that KDML 105 rice bran protein decreased the expression of lipogenic genes SREBP-1 and FAS in the liver tissues of high-energy diet-fed rats.

The present study found that HF-fed rats treated with RBE showed a significant decrease in MDA levels when compared with the HFD-only rats. We also found that the RBE treatment could decrease the expression of hepatic NF-kappa B p65. A recent study revealed that treatment with NF-kappa B inhibitor was found to attenuate the increase in oxidative stress and formation of MDA in the hepatocytes[13]. Thus, the anti-oxidative damage activity of RBE is believed to be a result of the inhibition of the NF-kappa B p65 gene expression. However, further studies are needed to examine the antioxidant mechanisms of RBE. In accordance with our results, previous study has revealed that decreased levels of MDA in the plasma and erythrocytes of mice fed rice bran and phytic acid[23]. Moreover, the plasma levels of oxidative damage markers, including MDA and protein carbonyl, in hypertensive rats were significantly reduced by treatment with KDML 105 rice bran peptides[24].

Conclusion

The results of this study indicate that RBE form KDML105 has a lipid lowering effect by inhibiting hepatic TG and cholesterol synthesis through the regulation of SREBP-1c and AMPK alpha expressions, and HMGCR activity in HFD-induced obese rats. In

addition, RBE may also attenuate the damaging effects of oxidative stress by decreasing lipid peroxidation and NF-kappa B expression in the liver. Thus, RBE may be useful in the management of hepatic fat metabolism and oxidative stress at the onset of obesity. Further studies will be needed to examine the bioactive constituents of RBE.

What is already known on this topics?

Rice bran water extract (RBE) from Khao Dawk Mali 105: KDML 105) (Oryza sativa Linn) decreased blood TG level and abdominal fat weight, improved pre-diabetic state, reduced fat cell size and liver steatosis in rats fed with high fat diet (HF). Also, RBE had antihyperlipidemic and antioxidant effect in animal model. Though many health benefits have been found from rice bran, little is known about the effect of RBE on the hepatic fat metabolism and oxidative damage.

What this study adds?

To our knowledge, this is the first report which aims to find the mechanism at the molecular level of RBE in the improvement of fat accumulation and lipid oxidative damage in liver of rat fed a high fat diet at the onset of obesity.

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Potential conflicts of interest

None.

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ผลเชิงป้องกันของสารสกัดชั้นน้ำรำข้าวต่อเมทาบอลิซึมของไขมัน และความเสียหายจากภาวะเครียดออกซิเดชันในตับของหนูที่ได้รับอาหารไขมันสูง

สุรัสวดี สมนึก, สุรัตน์ โคมินทร์, ณรงค์ศักดิ์ มั่นคง, วสันต์ ภาคลักษณ์, นุชสิริ เลิศวุฒิโสภณ

ภูมิหลัง: *สารสกัดชั้นน้ำรำข้าวขาวดอกมะลิ 105 (RBE) นั้นมีสารสำคัญหลายชนิด และสามารถลดความผิดปกติของไขมันในเลือด แต่ความผิดปกติที่เกิดจากกระบวนการเมทาบอลิซึมของไขมันและจากภาวะเครียดออกซิเดชันในระดับโมเลกุล ยังคงไม่ได้รับการศึกษา*

วัตถุประสงค์: *เพื่อศึกษาผลของสารสกัดชั้นน้ำของรำข้าวขาวดอกมะลิ 105 ต่อการสะสมไขมัน และการทำลายไขมัน จากภาวะเครียดออกซิเดชันในหนูทดลองที่ได้รับอาหารไขมันสูง*

วัสดุและวิธีการ: *หนูขาวเพศผู้พันธุ์ Sprague-Dawley ถูกแบ่งออกเป็น 4 กลุ่มได้แก่ กลุ่มที่ได้รับอาหารหนูปกติ (C), กลุ่มที่ได้รับอาหารไขมันสูง (HF), กลุ่มที่ได้รับอาหารไขมันสูงร่วมกับสารสกัดชั้นน้ำรำข้าวที่ขนาด 2,205 มก./กก./วัน (HFR1) และกลุ่มที่ได้รับอาหารไขมันสูงร่วมกับสารสกัดชั้นน้ำรำข้าวที่ขนาด 4,410 มก./กก./วัน (HFR2) ทำการทดลองไปจนครบ 4 สัปดาห์ หลังจากนั้นทำการวัดตัวบ่งชี้ด้านเมทาบอลิซึมของไขมันและความเสียหายจากการทำลายไขมันในภาวะเครียดออกซิเดชั่นจากตับ*

ผลการศึกษา: *สารสกัดชั้นน้ำของรำข้าวสามารถลดน้ำหนักตัว, น้ำหนักของเนื้อเยื่อไขมันในช่องท่อง, น้ำหนักของตับ ลดระดับไขมันผิดปกติในเลือดและสามารถลดระดับโคเลสเตอรอล ไตรกลีเซอร์ไรด์ และมาลอนไดดีไฮด์ (malondialdehyde) ยับยั้งการทำงานของเอ็นไซม์ที่ใช้ในการสังเคราะห์โคเลสเตอรอล (HMGCR), ลดการแสดงออกของจีน SREBP-1 และจีน NF-kappa B นอกจากนั้นสารสกัดรำข้าวนี้ยังเพิ่มการแสดงออกของจีน AMPK ในตับ*

สรุป: *สารสกัดชั้นน้ำของรำข้าวขาวดอกมะลิ 105 สามารถเป็นสารป้องกันความผิดปกติทางเมทาบอลิซึมของไขมันและความเสียหายจากการทำลายไขมันของภาวะเครียดออกซิเดชันในระดับโมเลกุลได้ โดยมีกลไกการออกฤทธิ์ ผ่านการปรับแต่งกระบวนการแสดงออกของจีน SREBP-1, NF-kappa B และ AMPK ในตับ และควบคุมสมดุลทางพลังงาน*