










Red Yeast Rice Mitigates High-Fat Diet Induced-Obesity Related Vascular Dysfunction in Wistar Albino Rats

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Abstract: The red yeast rice methanolic extract (RYR) was suggested to have promising therapeutic effects against vascular endothelial dysfunction. In the present study, the protective effects of RYR at 200 and 400 mg/kg/day were investigated in a specific animal model that exhibits a high-fat diet (HFD)-induced dyslipidemia and vascular endothelium dysfunction. Vascular endothelial reactivity experiments were evaluated using aorta obtained from adult rats in an ex-vivo organ bath setup. Three consecutive weeks of RYR treatment exhibited a significant reduction in body weight (BW), liver weight (LW), and retroperitoneal fat pad weight (RFPW)/BW ratios as compared to HFD only treated rats where a significant body weight gain was observed. RYR treatment also significantly decreased the average daily food intake, waist, lee index, and body mass index compared to rats treated with HFD only. RYR treatment significantly reduced total cholesterol, triglyceride, low-density lipoprotein, and very-low-density lipoprotein levels compared to the HFD group. HFD-induced endothelium dysfunction in the aorta of animals was reversed by RYR treatment, comparable to the HFD group. RYR treatment, specifically at 400 mg/kg/day dose, revealed a significant protective effect on vascular endothelium and an improvement in the lipid panel, hence justifying therapeutic involvement of RYR in dyslipidemia and endothelial dysfunctions.

Keywords: red yeast rice; lipid profile; high-fat diet; endothelial dysfunction.

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1. Introduction

Obesity prevalence has continued to increase and is becoming an economic burden in developed and developing countries due to its link with several other comorbidities. The standard threshold for obesity is a body mass index (BMI) of 30 kg/m², and it was arranged into several classes based on this measurement of weight to the body surface. Obesity etiology includes several genetic predispositions favoring weight gain [1-4]. Environmental causes such

as conveniences in daily life due to modernity lead to an increasingly sedentary lifestyle and high caloric intake [5-7].

Epidemiological data shows that, in general, obese populations are on the rise both globally and within the Gulf Cooperation Council (GCC) countries. For example, in the United States, obesity has been doubled among adults since 1980 [8-10]. Regional trends estimated obesity occurrence in adults was range from 13 to 50% in the Gulf countries [11]. The WHO ranked Saudi Arabia, the United Arab Emirates, and Kuwait within the top 20 highest countries in terms of obesity prevalence.

Of particular interest to our work is endothelial dysfunction, which occurs during obesity and is an underlying mechanism of cardiovascular disorders such as hypertension, coronary artery disease, and atherosclerosis [12,13]. This is because endothelial dysfunction reduces the availability of nitric oxide (NO) and, thus, the ability of vasculature to dilate [14,15]. A High-fat diet was found to cause obesity and inflammatory oxidative stress markers in several experiments [16-19]. Hence, endothelial dysfunction may be an excellent target to reverse or prevent the complications of obesity and HFD due to its link with the events mentioned above, such as oxidative stress.

While most clinically use medications are of synthetic origin, natural compounds and extracts can still exhibit promising therapeutic effects [20]. For example, many natural origin compounds showed an ability to reduce obesity and dyslipidemia biomarkers [21,22]. In this research, we pay attention to red yeast rice (RYR), which is the rice that has been fermented using *Monascus purpureus* mold [23]. Meta-analysis and randomized trials using RYR have repeatedly shown significant beneficial health effects such as reducing total serum cholesterol (TC), low-density lipoprotein (LDL), and triglycerides (TG) [24-27]. RYR was shown to be composed of various molecules pertaining to sterols, unsaturated fatty acids, flavones, and most importantly, monacolin K [28,29]. The latter of which (better known as lovastatin) was found to be an inhibitor of 3-hydroxy-3-methylglutaryl-CoA (HMG CoA) reductase, resulting in reduced cholesterol synthesis and levels in the body [30].

While the activity of RYR against cholesterol and triglyceride levels is well-established, its other beneficial effects are less explored. Furthermore, the therapeutic role of RYR in an animal model of dyslipidemia-mediated endothelial dysfunction has not been reported. Therefore, in the current investigation, we assess the possible therapeutic involvement of RYR on HFD-fed obese rats which exhibited endothelial dysfunction.

2. Materials and Methods

2.1. Chemicals and reagents.

Acetylcholine chloride (a cholinergic agonist), phenylephrine (adrenergic agonist), and kits for the estimation of total cholesterol, triglyceride, and high-density lipoprotein (HDL) in serum were procured from Sigma Aldrich Chemical Co (USA). The chemicals used to make Krebs solution were purchased from E. Merck KGaA (Darmstadt, Germany). All the drugs and extract were prepared as stock, and fresh dilutions were prepared before the relevant experiments.

2.2. Animals.

Healthy male and female Wistar albino rats (150-180 g) were picked up from the Animal care Unit of College of Pharmacy, Prince Sattam Bin Abdulaziz University (PSAU), Kingdom of Saudi Arabia (KSA). The study protocol was approved by the Institutional Animal Ethics Committee, College of Pharmacy, PSAU, KSA. During the acclimation period of one week and during the study, animals were maintained under standard laboratory circumstances, at $25 \pm 2^\circ\text{C}$, under a 12 h light/12 h dark cycle, with food and water *ad libitum*.

2.3. Plant extract preparation.

Red yeast rice raw material (brand: Liew Treatment Centre; batch number: 160000152) was purchased from Kuala Lumpur, Malaysia. The dried red yeast rice powder (500 g) was submitted to extraction with methanol (1.5 L) by maceration at room temperature ($25\text{--}27^\circ\text{C}$) for 2 days. Following filtration, the extract was evaporated using a rotary vacuum evaporator until dryness under reduced pressure. The extract (37.5 g) was then stored in the refrigerator ($2\text{--}4^\circ\text{C}$) for further use, and required concentrations were prepared immediately before use.

2.4. Preparation of high-fat diet.

The method of Xu *et al.* [31] was followed with small adjustments. Briefly, a regular pellet diet, i.e., standard diet (SD), which makes up 73% of the total diet content, was pulverized and combined with the ingredients presented in Table 1. A sufficient amount of water was added to the final blend to make semisolid pellets, which were then appropriately dried in the oven to prevent fungal contamination.

Table 1. Composition of high-fat diet (HFD).

Ingredients	Percentage of HFD
Powdered Normal Pellet Diet (NPD)	73%
Cholesterol	1%
Tallow	10%
Egg yolk powder	10%
Milk powder	6%

2.5. Experimental design.

Rats were randomly distributed into four groups (6 animals in each). Group I rats fed with a standard diet (SD). Group II rats fed with a high-fat diet (HFD). Group III and IV rats were co-administered with HFD and RYR at doses of 200 and 400 mg/kg/day (orally), respectively (Figure 1).

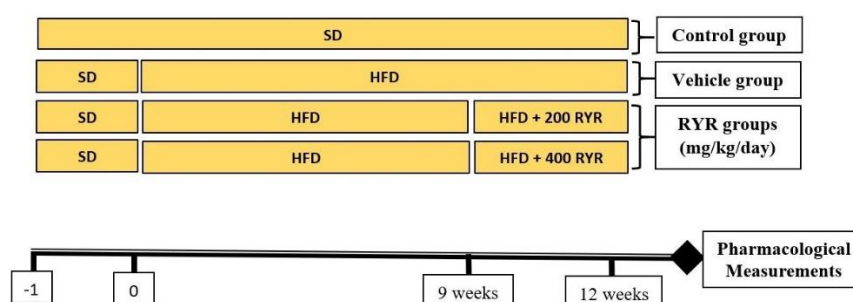


Figure 1. Schematic diagram showing the experimental design of the present study.

2.6. Evaluation of RYR extract effects on animal BW, LW, and RFPW.

To measure the effect of RYR on animal BW, LW, and RFPW, RYR ranged doses (200 and 400 mg/kg/day) were administered to HFD fed rats orally for three weeks (rats were fed HFD for nine weeks preceding RYR administration).

2.7. Effect of RYR on food intake.

Each animal's total food consumption was assessed daily following the method previously reported by Diniz *et al.* [32]. The daily food pellets intake was determined by measuring the amount of food pellets put into the food tray and the amount left in the tray.

2.8. Effect of RYR on different anthropometric indices.

Several anthropometric indices, including BMI, waist circumference, and Lee index of all the rats, were evaluated by the method described earlier [33].

2.9. Effect of RYR on lipid panel.

By penetrating the retro-orbital sinus with a sterile capillary tube, blood samples of all animals were drawn and collected under light ether anesthesia (0.08 ml/L of the volume of a container) in blood collection tubes and then centrifuged (3,000 rpm, 4°C, 20 min) for serum isolation. The isolated serum samples were kept in the refrigerator to be used for lipid analysis, including TC, TG, and HDL levels. VLDL and LDL levels were measured directly using a well-known principle [34]:

$$\begin{aligned} \text{VLDL} &= \text{TGs}/5 \\ \text{LDL} &= \text{TC} - (\text{VLDL} + \text{HDL}) \end{aligned}$$

2.10. Assessment of endothelial dysfunction.

After food deprivation for 16 hours, all animals were killed with a rapid and strong blow to the head. The aortae were carefully isolated, cleaned, transversely cut to obtain rings of 2-3 mm length, and mount in an organ bath contained aerated physiological Krebs solution (37 degrees Celsius), attached to a force sensor connected with data acquisition system (emkaBath2) and IOX2 software for accurate measurement of the tension to study endothelial reactivity. Some changes followed the previously published method of Furchgott and Zawadzki [35]. After mounting, the aortic tissues were stabilized for 45–60 minutes by maintaining a resting force of 2 g and changing the Krebs solution every 15 minutes. Following the equilibrium, contractions were induced using the submaximal concentration of alpha-1 adrenergic agonist; phenylephrine (PE; 1×10^{-6} M). Soon after achieving sustained contractions (usually 15-20 min), Ach (1×10^{-9} – 1×10^{-5} M) was added cumulatively to obtain the inhibitory concentration-response curves (CRCs).

2.11. Aorta histological examination.

A small part of the isolated thoracic aortae was fixed in formalin solution and further processed for paraffin embedding. A rotary microtome was used to get aortae tissue sections of 5 µm thickness for histological examinations. The general histological structure, collagen fibers, and elastic fibers of all isolated aortae from rats were examined using various staining

techniques, including hematoxylin and eosin (H&E), van Gieson, and Verhoeff's. Following staining procedures, tissue slices were studied under a light microscope (Hund Wetzlar H600/12, Germany) connected to a digital camera.

2.12. Statistical analysis.

All observed data were presented as mean \pm standard error of the mean (SEM) and considered statistically significant with a *P*-value of <0.05 . Results were evaluated using ANOVA followed by Dunnett's t-test using GraphPad Prism 7.0 (USA).

3. Results and Discussion

3.1. Determination of RYR effect on body and organ weight.

Animals with SD were in the range of 200 g, and it was dramatically and significantly increased by up to 420 g when the food was replaced with HFD.

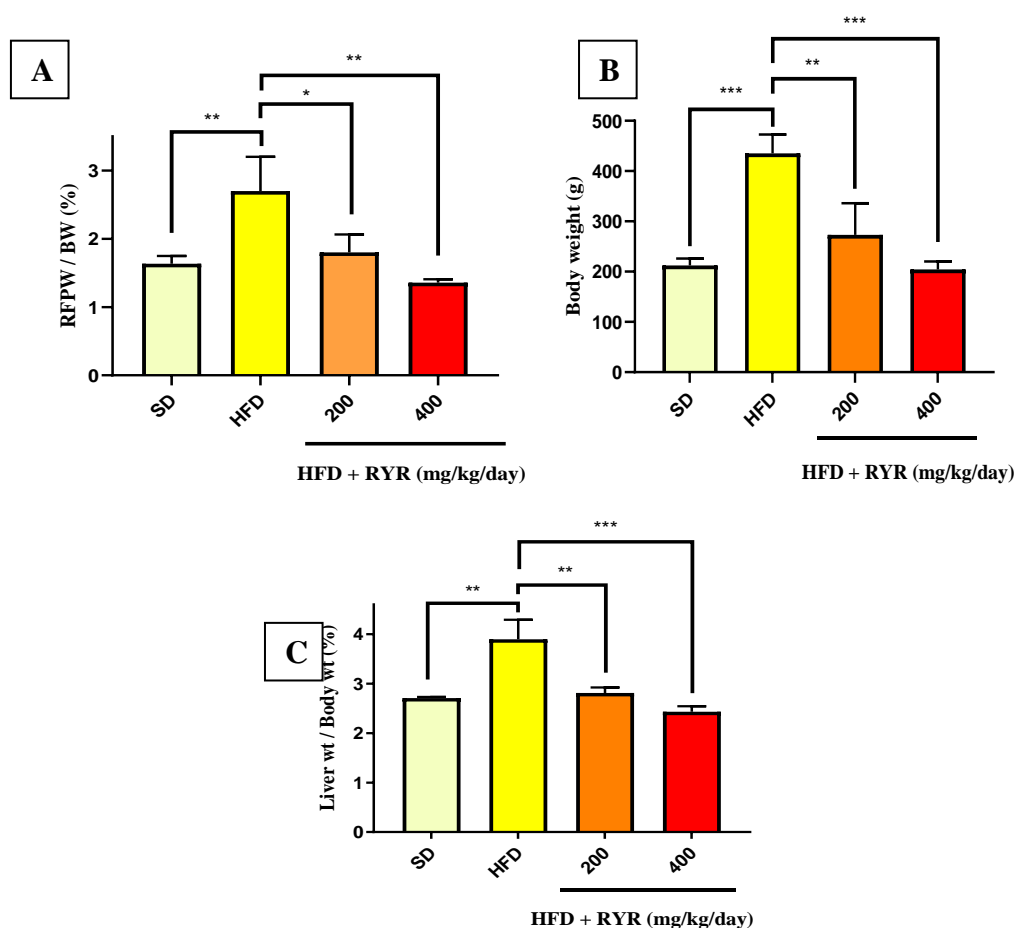


Figure 2. The change in the (A) body weight, (B) liver weight/body weight ratio, (C) retroperitoneal fat pad weight (RFPW)/body weight ratio of the experimental animals. Values represented by the mean \pm SD (n=6), **P* ≤ 0.05 , ***P* ≤ 0.01 , ****P* ≤ 0.001 , represents comparison of HFD with SD (Unpaired t-test) and treated groups (RYR; 200 and 400 mg/kg) with HFD group.

Upon RYR treatment using 200 or 400 mg/kg/day along with HFD, the mean of animals' weight was around 280 and 200 gm, respectively (Figure 2A).

Animals with SD had a liver weight that is around 2.75%, and it was significantly increased by up to 3.9% when the food was replaced with HFD. However, in the animals given 200 or 400 mg/kg/day, the liver weight was around 3.95 and 2.4 %, respectively (Figure 2B).

Each bar represents the mean for each group. Animals with SD were having RFPW, which is around 1.6%. It was dramatically and significantly increased by up to 4.6% when the food was replaced with HFD. However, in the animals given 200 or 400 mg/kg/day, the RFPW levels were 1.8 and 1.4 %, respectively (Figure 2C).

3.2. Evaluation of RYR effect on food intake.

Food pellets intake was assessed by measuring the amount of food pellets placed into the food tray and subtracting the amount left in the tray. Statistically, no significant difference was reported between the average daily food intakes for treatment groups, with an average ranging around 20 g per day (Figure 3).

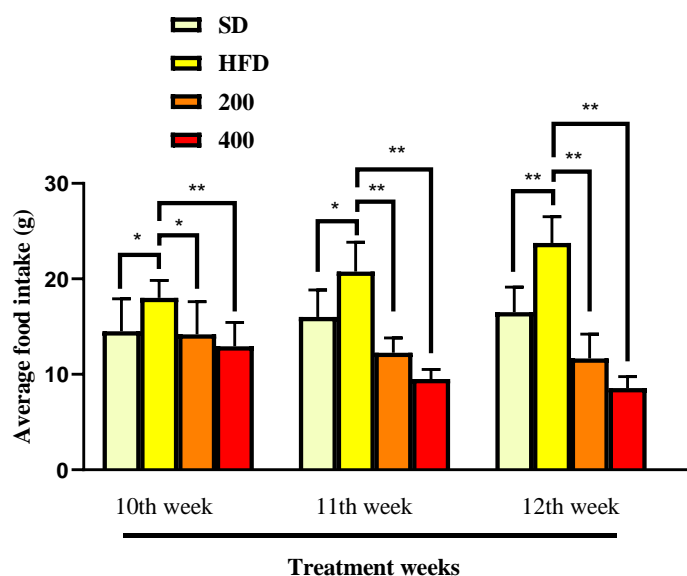


Figure 3. The average daily feed intake of all the animals. Values represented by the mean \pm SD (n=6), *P \leq 0.05, **P \leq 0.01, represent a comparison of HFD with SD (Unpaired t-test) and treated groups (RYR; 200 and 400 mg/kg) with HFD group.

3.3. Determination of RYR effect on waist, Lee index, and BMI.

The waist size was measured in centimeters to verify the validity of the obesity model used (Figure 4A). For the SD animals, the waist size was in the range of 15 cm. Upon HFD feeding, animals experienced an increase in the waist for up to 20 cm. However, when the animals received 200 or 400 mg/kg/day of RYR and HFD, they have shown a decrease in the waist size ranging in 16 and 14 cm, respectively, compared to the HFD animals without any RYR treatment.

The same effect was seen when Lee's index and body mass index (BMI) were evaluated (Figure 5A and 5B). Lee index for the SD animals was around 0.28 g/cm, which significantly increased to 0.36 upon receiving HFD.

When the animals received 200 or 400 mg of RYR along with HFD, Lee index was attenuated to the baseline levels seen in the SD animals in the range of 0.28 g/cm for both treatments. However, no statistical differences between the two treatments favor any concentration for its positive effects.

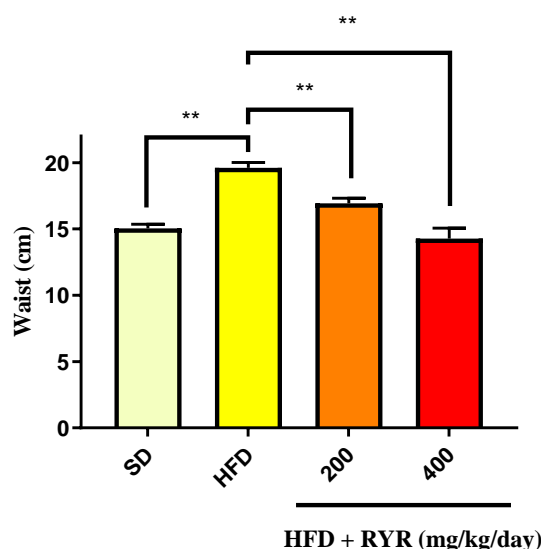


Figure 4. Effect of RYR treatment on waist size in High fat diet-induced obese rats. Values represented by the mean \pm SD (n=6), $**P \leq 0.01$, represent a comparison of HFD with SD (Unpaired t-test) and treated groups (RYR; 200 and 400 mg/kg) with HFD group.

For the BMI (Figure 5B), SD animals had 4.4 g/cm² that increased up to 6.5 g/cm² upon receiving HFD. When the 200 and 400 mg/kg/day of RYR was given to animals along with HFD, the BMI was reduced to 4.5 g/cm² and 4.1 g/cm², respectively.

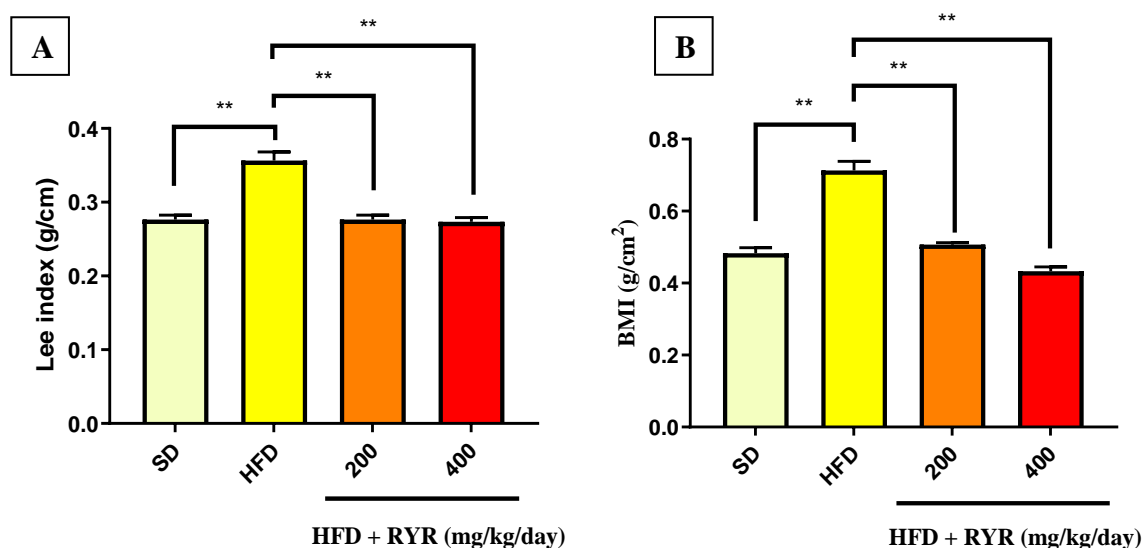


Figure 5. Effect of RYR treatment on (A) Lee index; and (B) Body mass index (BMI) on High fat diet-induced obese rats. Values represented by the mean \pm SD (n=6), $**P \leq 0.01$, represent a comparison of HFD with SD (Unpaired t-test) and treated groups (RYR; 200 and 400 mg/kg) with HFD group.

To visually explore the changes in various animal groups' fat levels, a representative image of retroperitoneal fat of various treated animal groups was shown. Animals with SD had moderate fat levels. HFD animals had an excessive amount of fats compared to the SD animals (Figure 6).

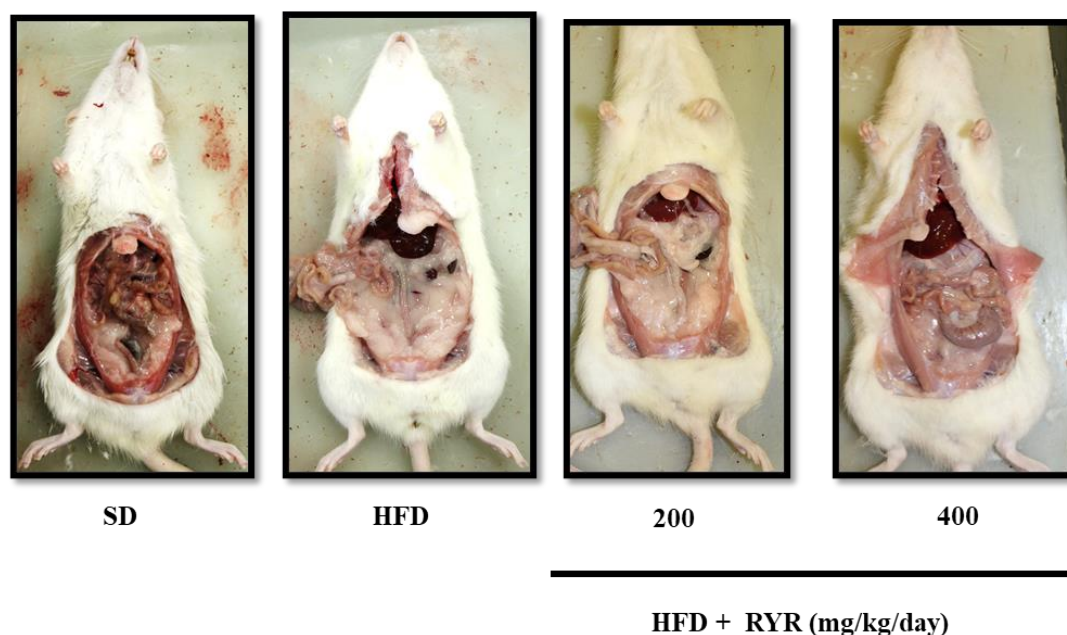


Figure 6. Ventral view of dissected rats after 3 weeks treatment. Photographs of the representative of retroperitoneal fat of rats of each group; SD, HFD, HFD + RYR 200 or 400 mg/kg/day) after 3 weeks treatment (at the end of the study). SD: Standard diet; HFD: High-fat diet; RYR: Red yeast rice.

3.4. Effect of RYR on lipid profile.

Based on the experimental setup that has been used, animals were divided into four different treatment groups. The first group was fed SD; the second group was fed HFD; the third and fourth groups received HFD and the suggested dose of RYR of 200 or 400 mg/kg/day, consecutively. Various parameters were selected to be compared between treatment groups, Cholesterol, Triglycerides, and Lipoproteins in the blood. Group fed SD have shown normal levels of Cholesterol, Triglycerides, and Lipoproteins based on the range of normal levels available in the literature for this type of experiment. Groups treated with HFD exhibited a statistically significant increase in cholesterol, triglycerides, VLDL, and LDL. The only parameter that demonstrated a statistically significant decrease was HDL as compared to the SD fed group (Table 2).

Table 2. Effect of RYR on lipid profile.

Groups	Cholesterol (mg/dL)	Triglycerides (mg/dL)	HDL-C (mg/dL)	VLDL-C (mg/dL)	LDL-C (mg/dL)
SD	152.95±10.45	22.91±2.72	83.98±3.84	4.76±0.41	64.20±9.55
HFD	375.26±16.30***	85.41±5.99***	47.91±1.28***	17.08±1.19***	310.27±17.46***
HFD + RYR 200 mg/kg/day	355.91±14.71 ^{ns}	52.08±3.10***	57.16±1.86 ^{ns}	10.42±0.62***	288.33±13.81 ^{ns}
HFD + RYR 400 mg/kg/day	265.32±13.34***	43.05±3.30***	59.11±3.24 ^{ns}	8.61±0.66***	197.59±15.07***

Values represented by the mean ± SD (n=6), ***P ≤ 0.001, represent a comparison of HFD with SD (Unpaired t-test) and treated groups (RYR; 200 and 400 mg/kg) with HFD group.

Next, the RYR treated groups were investigated for the same parameters' levels. The group that received 200 mg RYR has shown a significant reduction level of triglycerides as compared to the HFD group. However, there was also a significant margin in the levels between the RYR 200 mg treated group and the SD group. The same effect was seen in the VLDL parameter, where the animals treated with RYR 200 mg produced a substantial reduction

compared to the HFD group, but the reduced value was still significantly higher than the SD group. The other parameters, including cholesterol, HDL, and LDL, did not significantly change as compared to the HFD group.

Finally, the 400 mg RYR treated group was investigated. The levels of all parameters except HDL produced a significant reduction in levels compared to the correspondent parameter levels from the HFD group. But this reduction was not sufficient to be close to the baseline normal levels seen in the SD group. HDL levels were not affected by any RYR treatment in the experiment.

3.5. Effect of RYR on endothelial dysfunction.

Different groups of animals were treated with SD, HFD, and HFD, along with RYR (400 mg/kg). After 16 h treatment, the thoracic aorta's endothelial reactivity was evaluated by determining the concentration of the vasoactive substances such as acetylcholine (Ach) in the endothelium. The more Ach concentration released, the healthier the endothelium. The normal healthy aorta, when they induced vasoconstriction by phenylephrine (PE) up to 20 % increased the Ach concentration. On the other hand, the unhealthy aorta had significant low vasoconstriction up to 90 % of the original aorta activity. Upon treatment of HFD with RYR, the loss of vasoconstriction seen in the diseased animals were restored, resulting in around 30 % vasoconstriction in HFD rats treated with RYR at a dose of 400 mg/kg/day and showed endothelium-dependent vasodilatation, whereas RYR at low dose exhibited smaller relaxation compared to the higher dose (Figure 7).

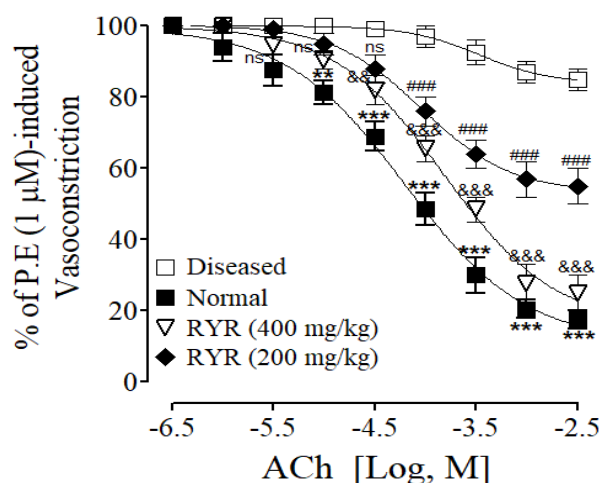


Figure 7. Effect of RYR on vascular endothelium; ■ SD (Normal); □ HFD (Diseased); ♦ HFD + RYR (200 mg/kg/day); ▽ HFD + RYR (400 mg/kg/day). ns $p > 0.05$, *, **, && $p < 0.01$ and ***, &&& $p < 0.001$ (Two-way ANOVA, followed by Bonferroni post-tests).

3.6. Effect of RYR on histopathological changes.

Using Hematoxylin and Eosin, histological staining of isolated rat aorta at 30x and 35x magnification shows that samples from rats with SD represent the ideal collagen-elastic ratio. In comparison, samples from rats with HFD have shown poor elasticity accompanied by a significant reduction in the collagen-elastic ratio. However, samples from rats with HFD treated with RYR (400 mg/kg/day) show little improvement in elastic fiber, but there was no improvement in collagen-elastic ratio. In addition, many degeneration areas are present in the area of elastic fibers (Arrow at photo 7A x30). Van Gieson and Verhoeff stains were used to

further differentiate between collagen fibers and elastic fibers in all treatment samples (Figure 8).

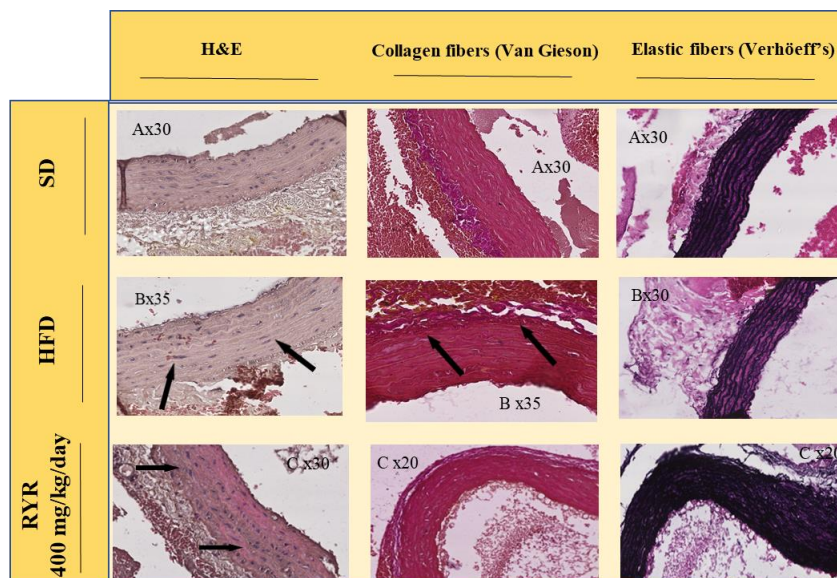


Figure 8. Effect of RZR on histology of isolated rat aorta. Histological sections of the aortae of all animals were stained with hematoxylin and eosin (H & E) stains to study general structure. Whereas to investigate, collagen and elastic fibers sections were stained with van Gieson and Verhoeff's stains, respectively (x 30).

3. Results and Discussion

The vascular endothelium is an active organ that is regulating normal vascular tone and maintaining vascular homeostasis. The role of endothelial dysfunction in the development of atherosclerosis and plaque progression is well established [36]. Endothelial dysfunction ends up with reduced vasodilatation, specifically nitric oxide and/or an increase in endothelium-derived contracting factors [37]. A difference between vasodilation and vasoconstriction leads to functional characteristics of endothelial dysfunction. Pathophysiology of endothelial dysfunction includes multiple cardiovascular risk factors such as oxidative stress, hypercholesterolemia, hypertension, hyperglycemia, aging, and smoking [38,39]. It is well-established that obesity is strongly correlated with an elevated risk of cardiovascular, hypertension, and diabetes complications. However, there are limited medicinal treatment agents that can interfere with obesity-related complications, specifically cardiovascular complications. This research was planned to explore the possible positive effects of red yeast extract (RZR) in the major complications of obesity, specifically vascular endothelial dysfunction and dyslipidemia. Based on several studies and experiments, we used two doses of RZR that achieved the best results in our experimental settings, 200 and 400 mg/kg/day. These doses were used in rats receiving HFD (which induced obesity-related complications like dyslipidemia and vascular endothelial dysfunction) [40].

The first step was to investigate in-vivo model validity. Based on the HFD animals' bodyweight compared to the SD animals, our data demonstrated a significant variance in adiposity between the SD and HFD groups (Figure 2). To further investigate model validity, LW to BW, RFPW to BW, waist, Lee index, and BMI were evaluated in all animals feeding patterns with or without RZR treatment.

As expected, animals that received HFD showed a significant increase in all parameters, suggesting that these animals showed classical signs of obesity compared to those that received SD. These findings are consistent with similar findings previously reported in the literature

using animals receiving the same formula of HFD [31]. On the other hand, significant reductions were observed in BW, LW/BW, RFPW/BW, waist, Lee index, and BMI in the animals that received RYR treatment of 200 or 400 mg/kg/day along with the HFD. There was no statistical difference between the effects of the two concentrations in all parameters. These results suggest that RYR had a positive protective effect against obesity, which in turn suggested having a role in lowering obesity-related complications such as dyslipidemia, diabetes, and hypertension.

The feeding pattern and amount of ingestion of all groups during treatment weeks were monitored and showed a consistent food amount. This suggests that bulging and overeating did not have any effect on the obesity-related results (Figure 5). These numerical results are consistent with the rats' visual examination upon an exploration of retroperitoneal fat of various treated animal groups (Figure 6). Animals with SD have shown the least amount of fat and a minor increase in the fat in animals treated with 200 or 400 mg/kg/day along with the HFD. Finally, HFD animals exhibited the highest fat content, which represents a clear sign of obesity. It is worth mentioning that the selection of the animals for the exploration was made randomly.

It is very well known that HFD can produce significant negative effects on the lipid panel [41]. These effects are suggested to be mediated through increased lipids absorption from the gastrointestinal tract (GIT) and a reduction of cholesterol metabolism. Animals that received HFD have shown several obesity-related dyslipidemia characteristics, such as a marked elevation in serum TC, TG, VLDL, and LDL levels. On the contrary, HFD-fed animals have been shown significantly lower HDL levels as compared to the SD animals. Lipid profile from animals with SD was considered the baseline values.

Based on our results, animals treated with 400 mg/kg/day RYR and HFD have shown significantly lower levels of TC, TG, VLDL, and LDL, along with a significant increase in HDL level as compared to the HFD group. However, these values were also statistically different from baseline levels, suggesting partial positive effects on the lipid profile when using the 400 mg of RYR. Moreover, 200 mg RYR treatment has shown a limited positive effect since it did not induce a significant change in TC, HDL, and LDL levels. These results suggest that RYR can significantly improve the lipid profile in HFD treated animals.

Another aspect that has been investigated is the relationship between obesity due to HFD and the vascular endothelium, specifically, the aortic vascular endothelial dysfunction. This parameter is essential since it is highly associated with the excessive deposition of adipose tissue, which in turn affects vascularity since the major function of the endothelium is to form the interface between the circulating blood and the vascular wall.

Literature has clearly shown an association between the increase in blood cholesterol levels with atherosclerotic and angiographically smooth coronary arteries relaxation [42], which is mainly dependent on the vascular endothelium. Based on that, we have selected one of the vasoactive substances, acetylcholine, which regulates systemic vascular resistance.

Our findings suggest that animals treated with RYR for 400 mg/kg/day and the HFD did not show the endothelial dysfunction signs, which was very clear in the HFD-animals. This is represented by the significant increase in acetylcholine-induced vasorelaxation in the animals that received RYR as compared to the HFD animals. The levels of protection against endothelial dysfunction were great at the 400 mg/kg/day and very close to the SD animals' baseline values. However, the 200 mg/kg/day provided partial protection, which suggests a dose-dependent vascular endothelial protection.

Moreover, the aorta's vascular histology in all categories was investigated since it is highly suggested that obesity can induce physical histological changes in vascular endothelium tissues [43]. Our results suggest that the aortic tissues, which are typical vascular endothelium tissues of the HFD animals, have shown fat accumulation signs. These signs include an increase in adipocytes, a reduction in the elastic fiber layers, and an increase in the collagen-elastic ratio demonstrated by an increase in collagen layer compared to aortic tissues of the SD animals. These findings are associated with many reports in the literature that linked the increase of the body mass index (BMI) to reduce aortic tissue elasticity, which is an important indicator of the cardiovascular complication of obesity [44]. However, pharmacological intervention, specifically when using 400 mg/kg/day, resulted in significant protection against the complication caused by HFD-induced obesity, such as aortic stiffness. This resulted in an overall lowering of endothelium degradation signs, such as collagen-elastic ratio.

4. Conclusions

The present study results conclude the antidyslipidemic and endothelial protective effects of RYR as evident by improved lipid profile and vascular endothelial function. Hence, it justifies the therapeutic role of RYR in the treatment of hyperlipidemia and related cardiovascular conditions. However, more systematic studies are still needed to isolate and identify pure active compounds of RYR to confirm their beneficial role.

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Conflicts of Interest

The authors declare no conflict of interest.

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