Effect of Red Wine on Adipocytokine Expression and Vascular Alterations in Fructose-Fed Rats

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BACKGROUND
Imbalance in adipocytokine secretion is related to the development of metabolic syndrome (MS). In addition, moderate consumption of red wine (RW) decreases the risk of cardiovascular disease. The aim of this study was to evaluate the effects of moderate consumption of RW or ethanol (E) on adiponectin and resistin expression, and vascular alterations in fructose-fed rats (FFRs) as an experimental model of MS.

METHODS
Thirty-day-old male Wistar rats were assigned to control (C), F (10% fructose in drinking water), F+E (4.5 ml/kg), and F+RW (35 ml/kg of Malbec RW containing 4.5 ml/kg E). E and RW were administered during the last 4 weeks of a 10-week period.

RESULTS
RW administration to F rats was able to significantly decrease insulin resistance, mesenteric adipose tissue weight, and systolic blood pressure (SBP) compared to F group. F+E only reduced the SBP (P < 0.05 vs. F). F+RW also reduced aortic NAD(P)H-oxidase activity, NAD(P)H subunits Nox4 expression in mesenteric tissue, plasma thioarbituric acid reactive substances (TBARS), and recovered plasma total antioxidant activity (TAA) compared to F and F+E groups (P < 0.05). Adiponectin expression decreased, whereas resistin, vascular cell adhesion molecules-1 (VCAM-1), and nuclear factor-xB (NF-xB) expression and vascular remodeling in mesenteric arteries were higher in F than in C group (P < 0.05). Only RW was able to partially reverse the aforementioned alterations.

CONCLUSION
In this study, Malbec RW, but not alcohol alone, improved the balance of adipocytokines and attenuated the oxidative stress and vascular inflammation in a model of MS, suggesting that nonalcohol components of RW are responsible for the beneficial effects.

Keywords: adipocytokines; blood pressure; hypertension; metabolic syndrome; resistin; adiponectin; red wine

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Cardiovascular disease is the leading cause of mortality in western countries where metabolic syndrome (MS), characterized by hyperglycemia, hyperlipidemia, and hypertension, is a significant risk factor for cardiovascular disease. Fructose intake has increased dramatically in the past 20 years contributing to the growing worldwide prevalence of MS, obesity, and diabetes. Fructose-fed rats (FFRs) provide a model of dietary-induced insulin resistance, which has been used to assess the pathophysiological mechanisms involved in the metabolic and cardiovascular changes associated with MS.

Oxidative stress has been implicated in the pathogenesis of many cardiovascular diseases. The major sources of reactive oxygen species (ROS) in vascular tissue are membrane-associated NAD(P)H-oxidases, also known as Nox enzymes. Nox4 subunit expression is strongly correlated with an increase of NAD(P)H-oxidase activity. Our group previously reported an enhanced NAD(P)H-oxidase aorta activity and higher plasma lipid peroxidation in FFR implying that this model of MS is characterized by oxidative stress.

Abnormalities in adipose tissue have been observed in FFR, without changes in body weight. Adipose tissue as well as nearby inflammatory cells secrete a variety of bioactive molecules named adipocytokines as tumor necrosis factor-α, plasminogen activator inhibitor-1, interleukin-6, leptin, adiponectin, and resistin. The effects of adipocytokines on vascular function, immune regulation, and adipocyte metabolism make them key factors in the pathogenesis of MS. Previous studies have shown that lowered levels of plasma adiponectin induce insulin resistance and atherosclerosis in an experimental model of obesity. Studies in human aorta endothelial cells show that resistin induces the expression of adhesion molecules such as intercellular cell adhesion molecules and vascular cell adhesion molecules-1 (VCAM-1) via transcription nuclear factor-xB (NF-xB) signals, while adiponectin inhibits the resistin effect over endothelial cells. The exact mechanism by which fat accumulation leads to such adipocytokines imbalance has not been elucidated, but oxidative stress may be implied.

Epidemiological studies have shown a protective effect of moderate red wine (RW) consumption on cardiovascular...
Red Wine and Adipocytokines in Fructose-Fed Rats

Disease, mainly attributed to antioxidant properties of RW polyphenols. Although there is wide evidence showing healthy effects of moderate RW intake, to date there are no studies that evaluate the effect of RW on adipocytokines expression in a model of MS.

The aim of this study was to evaluate in an experimental model of MS the effect of moderate consumption of RW or ethanol (E) on adipocytokines expression in mesenteric adipose tissue. Additionally, we assessed vascular alteration through VCAM-1 expression and lumen/media ratio in vascular mesenteric tissue and oxidative stress.

METHODS

Reagents. Unless otherwise noted, all reagents were purchased from Sigma Chemical (St Louis, MO). All other chemicals were of molecular biology or reagent grade.

Animals, diet, and experimental designs. All procedures were performed according to institutional guidelines for animal experimentation and were approved by the Technical and Science Secretary at the National University of Cuyo School of Medicine. Thirty-day-old male Wistar rats, weighing 90–130 g were housed during the experimental period of 70 days in a room under conditions of controlled temperature (21 ± 2°C) and humidity with a 12 h light/dark cycle.

At the beginning of the study, 40 rats were randomly distributed into two groups: one control group (C; n = 10) and one experimental group (F; n = 30) that received 10% fructose (Saporiti Labs, Buenos Aires, Argentina) solution in drinking water for 10 weeks. After 6 weeks of fructose administration, the experimental group was further divided into three groups (n = 10 each), and for 4 additional weeks received the following treatments, respectively: F; F+E; F received E 4.5 ml/kg administered daily in drinking water diluted in a 10% fructose solution; and F+RW: F received RW 35 ml/kg (containing 4.5 ml E) administered daily in drinking water diluted in a 10% fructose solution. All groups were fed the same standard rat diet (Gepsa-Feeds, Buenos Aires, Argentina) and tap water ad libitum.

The RW (Malbec grape variety 13% ethanol) was provided by the National University of Cuyo School of Agricultural Sciences (Mendoza, Argentina). The phenolic characterization of RW Malbec was evaluated as previously described. Total phenol content expressed as gallic acid was 2.9 g/l of RW. The main phenolic content was (expressed as mg/l): nonflavonoids: 18.2 gallic acid; 2 caffeeic acid; 4.2 cis-caftaric acid, trans-resveratrol: 1.1, flavonoids: 24.1 catechin; 14.2 epicatechin; procyanidin (11.3 B1; 3.1 B3), flavonols: 4.9 quercetin, and anthocyanins (344 malvidin-3-glucoside; 16.2 peonidin-3-glucoside; 60.3 delphinidin-3-glucoside). RW doses were calculated on the basis of the recommended daily consumption of 350 ml for a 70 kg human (5 ml/kg). Using an interspecies dose-conversion factor based on equal body surface (7:1 for conversion from rat to human) and taking into account that liquid consumption of FFRs was 35 ml/day, the dose of RW used was 35 ml/kg per day. RW was administered in the drinking water diluted to 10% fructose and was held in dark bottles changed out daily in order to prevent oxidation of the polyphenols.

Food intake and liquid consumption were recorded throughout the experiment.

At the end of the experimental period, and after overnight fast, the rats were weighed, anesthetized with ketamine (50 mg/kg) and acepromazine (1 mg/kg). Blood was collected from the abdominal aorta into heparinized tubes. Plasma obtained after centrifugation at 1,000 g for 15 min at 4°C was frozen at −70°C until assayed. Arteries and organs from six rats of each group were excised aseptically for the measurement of various parameters described below. The remaining four rats of each group were assigned to histological observations.

Body and mesenteric fat weight. Body weight was measured weekly. At the end of the experimental protocol, mesenteric adipose tissues from six rats of each group were dissected and weighed relative to the total body weight, expressing the ratio as mesenteric fat tissue (mg)/body weight (g).

Biochemical determinations. Plasma glucose, total cholesterol, high-density lipoprotein, and triglyceride concentrations were determined by enzymatic colorimetric methods using commercial kits (GTLab, Buenos Aires, Argentina). Insulin was measured by radioimmunoassay (Coat-A-Count, Siemens, Los Angeles, CA) and insulin resistance was assessed using the homeostasis model assessment (HOMA-IR) originally described by Matthews et al. HOMA-IR was calculated using the following formula: HOMA-IR (mmol/l × μU/ml) = fasting glucose (mmol/l) × fasting insulin (μU/ml)/22.5. The systolic blood pressure (SBP) was monitored indirectly once a week in conscious, prewarmed, slightly restrained rats by the tail-cuff method and recorded on a Grass Model 7 polygraph (Grass Instruments, Quincy, MA).

Measurement of markers of oxidative stress. The measurement of vascular NAD(P)H-oxidase activity in the aorta was made by the lucigenin-derived chemiluminescence assay as previously described, and the luminescence was measured on a luminometer (Fluoroskan Ascent FL; Thermo Labsystems, Waltham, MA). The results were expressed in arbitrary units (au)/min/mg of aortic tissue.

Thiobarbituric acid reactive substances (TBARS) were determined as previously described. This method is based on the reaction between plasma malondialdehyde, a product of lipid peroxidation, and thiobarbituric acid. Total antioxidant activity (TAA) was measured as previously reported. The assay relies on the ability of antioxidants in the plasma in reducing the preformed radical monocation 2,2′-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS•+) generated by oxidation of 7 mmol/l ABTS with 2.45 mmol/l potassium persulfate. The influences of both the concentration of antioxidant and duration of reaction on the inhibition of the radical cation absorption were taken into account when determining the antioxidant activity and the results were expressed as percent of inhibition of ABTS•+.
Western blot analysis. Adipose and vascular mesenteric tissues were dissected, weighed, and immediately stored at −70°C. Adiponectin and resistin were evaluated in adipose tissue, while Nox4, VCAM-1, and NF-κB protein expression were evaluated in mesenteric vascular homogenates. Samples were homogenized in lysis buffer (containing 2% sodium dodecyl sulfate, 10% glycerol, 5% mercaptoethanol, and 6.25 mmol/l Tris buffer: pH 6.8) for adipose tissue and (10.9% sucrose, 0.037% EDTA, and 0.06% HEPES: pH 7.4) for vascular mesenteric tissue, both with proteinase inhibitors added (100 μg/ml of phenylmethylsulfonyl fluoride and 1 μg/ml soybean trypsin inhibitor). Protein concentrations were quantified in duplicate using the Bradford method with bovine serum protein as reference protein. Twenty micrograms of protein was loaded per lane in sodium dodecyl sulfate–polyacrylamide gel (8–12.5%), electroblotted onto nitrocellulose membranes (Amersham Biosciences, Buckinghamshire, UK), and incubated with an appropriate polyclonal antibody: adiponectin and resistin (1/1,000; Chemicon, Ramona, CA); NF-κB (p65 subunit RelA) (1/500; Chemicon); VCAM-1 and Nox4 (1/500 and 1/1,000, respectively, from Santa Cruz Biotechnology, Santa Cruz, CA). Monoclonal anti-β-actin antibody (1/4,000) was used as an internal standard. Images were digitalized with a Nikon, Kanagawa, Japan). Images were digitalized with a digital camera (GP-KR222 color CCD; Panasonic, Osaka, Japan) and processed with an analysis system Scion Image 4.01 (Scion, Bethesda, MD). The lumen-to-wall media ratio (L/M ratio) was then calculated.

Statistical analysis. Data were expressed as mean ± s.e.m. The statistical significance was assessed by one-way analysis of variance followed by Bonferroni’s Multiple Comparison post-test. GraphPad Prism version 5.00 for Windows (GraphPad Software, San Diego, CA) was used for all statistical analysis. Differences were considered significant at P < 0.05.

RESULTS

Fructose solution intake by F, F+E, and F+RW was higher than water consumption by C group (P < 0.01). All experimental groups (F, F+E, F+RW) ate less food than C group (P < 0.05). The addition of E or RW during the last 4 weeks did not modify the liquid or food intake. At week 6, energy intake (kJ) was higher in F, F+E, and F+RW than C group (P < 0.05). When the E and RW was added to FFRs, the energy intake increased in both F+E and F+RW compared to F (P < 0.01) and C groups (P < 0.001). Although the body weight did not vary among groups, the mesenteric adipose tissue weight was higher in F than C group (P < 0.001). Only RW administration reduced significantly the mesenteric adipose tissue weight (P < 0.01 vs. F; Table 1).

Chronic administration of fructose displays several alterations included in the cluster of risk factors called MS. At the end of the study, FFRs had greater SBP than C group (P < 0.001). Administration of both RW and E to FFR during the last 4 weeks was able to reduce the SBP (P < 0.01), but did not reach the C group values. F and F+E groups had greater fasting levels of glycemia, triglyceridemia, insulinemia, and HOMA_IR index than C (P < 0.001). RW administration to FFRs had the capacity to decrease the insulin levels, HOMA_IR index, and triglycerides compared to F and F+E (P < 0.05). Additionally, F+RW had greater high-density lipoprotein levels than F (P < 0.01). The L/M ratio in vascular mesenteric tissue, decreased in F and F+E compared to C group (P < 0.001). F+RW showed an increase of L/M ratio compared to F and F+E groups (P < 0.01) similar to the C group (Table 2).

Table 1 | Body and adipose tissue weight, fluid, food, and energy intake from C, F, F+E, and F+RW rats

<table>
<thead>
<tr>
<th>Groups</th>
<th>C</th>
<th>F</th>
<th>F+E</th>
<th>F+RW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (g)</td>
<td>358 ± 7</td>
<td>369 ± 9</td>
<td>349 ± 7</td>
<td>353 ± 7</td>
</tr>
<tr>
<td>Mesenteric adipose tissue (mg)/body weight (g)a</td>
<td>3.9 ± 0.2</td>
<td>6.5 ± 0.4**</td>
<td>5.5 ± 0.1*</td>
<td>4.5 ± 0.2***,†</td>
</tr>
<tr>
<td>Fluid intake (ml/day)</td>
<td>26.5 ± 1.2</td>
<td>35.5 ± 2.4**</td>
<td>35.1 ± 2.1**</td>
<td>35.2 ± 2.2**</td>
</tr>
<tr>
<td>Food intake (g)</td>
<td>18.3 ± 0.6</td>
<td>16.4 ± 0.4*</td>
<td>15.9 ± 0.5*</td>
<td>15.7 ± 0.6*</td>
</tr>
<tr>
<td>Energy intake (initial to week 6) (kJ)</td>
<td>246.1 ± 9.2</td>
<td>280.3 ± 9.4*</td>
<td>279.1 ± 9.8*</td>
<td>277.4 ± 9.7*</td>
</tr>
<tr>
<td>Energy intake (week 6–10) (kJ)</td>
<td>24.3 ± 8.0</td>
<td>277.6 ± 9.3*</td>
<td>328.8 ± 10.2**,***</td>
<td>327.4 ± 11.7**,***</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± s.e.m., n = 10 in all variables except *n = 6. C, control; E, ethanol; F, fructose; RW, red wine.

*aP < 0.05 (vs. C); **P < 0.01 (vs. C); ***P < 0.05 (vs. F); †P < 0.05 (vs. F+E).
Table 2 | Systolic blood pressure, metabolic variables, and lumen:media ratio in mesenteric arteries from C, F, F+E, and F+RW rats

<table>
<thead>
<tr>
<th>Groups</th>
<th>C</th>
<th>F</th>
<th>F+E</th>
<th>F+RW</th>
</tr>
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<tbody>
<tr>
<td>SBP (mmHg)²</td>
<td>116.2 ± 1.1</td>
<td>132.5 ± 1.2**</td>
<td>123.8 ± 1.2**,***</td>
<td>121.0 ± 1.3**,***</td>
</tr>
<tr>
<td>Plasma glycemía (mmol/l)</td>
<td>5.0 ± 0.4</td>
<td>6.8 ± 0.5*</td>
<td>7.6 ± 0.2**</td>
<td>5.9 ± 0.4†</td>
</tr>
<tr>
<td>Plasma insulin (pmol/l)</td>
<td>69 ± 7</td>
<td>185 ± 18**</td>
<td>154 ± 4**</td>
<td>111 ± 4**,***</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>2.2 ± 0.3</td>
<td>7.6 ± 0.8**</td>
<td>7.4 ± 0.3**</td>
<td>4.2 ± 0.3**,†</td>
</tr>
<tr>
<td>Plasma triglycerides (mmol/l)</td>
<td>0.68 ± 0.02</td>
<td>1.12 ± 0.07**</td>
<td>1.10 ± 0.07**</td>
<td>0.70 ± 0.07**,†</td>
</tr>
<tr>
<td>Plasma high-density lipoprotein (mmol/l)</td>
<td>1.00 ± 0.04</td>
<td>0.92 ± 0.04</td>
<td>1.07 ± 0.02</td>
<td>1.10 ± 0.01***</td>
</tr>
<tr>
<td>Plasma total cholesterol (mmol/l)</td>
<td>1.78 ± 0.04</td>
<td>1.79 ± 0.06</td>
<td>1.76 ± 0.08</td>
<td>1.81 ± 0.08</td>
</tr>
<tr>
<td>L/M ratio in mesenteric arteries³</td>
<td>17.6 ± 0.7</td>
<td>12.5 ± 0.7**</td>
<td>13.8 ± 0.3**</td>
<td>16.3 ± 0.5**</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± s.e.m.; n = 6 in all variables except n = 10, ³n = 4.
C, control; E, ethanol; F, fructose; HOMA-IR, homeostasis model assessment; L/M, lumen to media; RW, red wine; SBP, systolic blood pressure.
*P < 0.05 (vs. C); **P < 0.01 (vs. C); ***P < 0.05 (vs. F); ¹P < 0.05 (vs. F+E); ²P < 0.01 (vs. F); ³P < 0.01 (vs. F+E).

Figure 1 | NAD(P)H-oxidase activity and expression. (a) NAD(P)H-oxidase aorta activity and (b) Nox4 protein expression in vascular mesenteric tissue from C, F, F+E, and F+RW rats. Bar graph represents mean ± s.e.m., (n = 6). Symbols indicate *P < 0.05 and **P < 0.01 (vs. C); filled circle: P < 0.05 and two filled circles: P < 0.01 (vs. C); filled square: P < 0.05 and two filled squares: P < 0.01 (vs. F+E); C, control; E, ethanol; F, fructose; RW, red wine.

Aortic NAD(P)H-oxidase activity, Nox4 expression in vascular mesenteric tissue (Figure 1a,b, respectively) and plasma TBARS levels were higher, while plasma TAA was lower in F and F+E than the C group (P < 0.05; Figure 2a,b, respectively). RW administration to F group significantly lowered aortic NAD(P)H-oxidase activity, vascular Nox4 expression, and plasma TBARS levels, while increased the plasma TAA in comparison with F and F+E (P < 0.05).

When the adipocytokines expression was examined in mesenteric adipose tissue by western blotting, lower adiponectin expression and greater resistin expression was observed in F and F+E groups than in C group (P < 0.01 and P < 0.05, respectively). The administration of RW to F group significantly increased adiponectin and decreased resistin expression (P < 0.05 vs. F and F+E groups; Figure 3a,b).

Protein expression of VCAM-1 was also higher in F and F+E groups than in C group (P < 0.01). This increase was reversed in F+RW group (P < 0.05 vs. F+E and P < 0.01 vs. F; Figure 4a). To explore the main transcriptional regulator of VCAM-1, NF-κB (NF-κB p65) protein was examined in vascular mesenteric tissue homogenates (Figure 4b). In agreement with the pattern observed for VCAM-1 expression, we observed an enhancement of NF-κB protein expression in F and F+E groups (P < 0.01 vs. C group). The increased expression of NF-κB was attenuated when RW was administrated to FFRs (P < 0.01 vs. F and F+E).

**DISCUSSION**

In this study, we found that moderate consumption of RW prevents the imbalance of adiponectin and resistin expression in adipose tissue. RW also attenuates VCAM-1 expression, vascular remodeling, and oxidative status. All these effects could be associated with actions of RW nonalcoholic compounds on the mechanisms of oxidative stress enhanced in FFRs.
According to previous studies, fructose-fed animals develop insulin resistance, hypertriglyceridemia, increased SBP, and oxidative stress. The decrease of insulin sensitivity and the hypertriglyceridemic effect of a high-fructose diet have been widely studied. In this study, RW administration to FFRs reversed the development of insulin resistance, hypertriglyceridemia, and also lowered the SBP. It has been shown in diabetic type 2 patients that moderated RW consumption for 2 weeks decreased the insulin resistance state. Conversely, E administration to FFR only decreased the SBP. Similar results in SBP without changes in ROS production were found in FFR treated with E alone. The vascular effect of alcohol could be attributed to the involvement of extracellular and intracellular Ca2+ mobilization of vascular smooth muscle cells.

The effect of RW on body weight reduction had been assessed. Monteiro et al. found a reduction of body weight in normal male rats treated with RW or E, but only RW decreased the adiposity size associated with an increase of the adipose tissue aromatase expression. A similar effect of RW on adipose tissue reduction was observed in male Zucker rats fed a high-fat diet. We did not observe significant differences in body weight among groups, although the F group consumed fewer calories during the last 4 weeks than F+E and F+RW. Moreover, we observed higher mesenteric adipose tissue weight in F rats consistent with previous data reports, and only RW administration to F group had lowered visceral adiposity. It is important to note that both E and RW reduced body weight but only RW reduced adipose tissue suggesting that nonalcohol content of RW is responsible. It has been reported that polyphenols such as catechin reduces body weight in obese mice and increases the metabolic rate and fat oxidation levels in humans. Resveratrol inhibited preadipocyte proliferation and adipogenic differentiation through sirtuin-1-pathway, an important regulator on energy homeostasis, and also influences adipose tissue mass and function in human adipocytes. Moreover, in a rat model of obesity, RW polyphenols corrected vascular alterations, especially endothelial dysfunction, by increasing NO availability resulting from enhanced NO production and reduced ROS release via decreased expression of NAD(P)H-oxidase membrane subunit, Nox1. Consistent with previous studies, the present results demonstrate that RW administration reduced aortic NAD(P)H-oxidase activity and Nox4 expression in mesenteric tissue. RW also decreased plasma TBARS and enhanced the TAA in FFRs. Furthermore, in this study RW attenuated the expression of VCAM-1 and NF-кB, and decreased L/M ratio in mesenteric tissue. Conversely, ethanol alone did not modify the oxidative and vascular inflammation status, although it did reduce the SBP. This highlights the importance of the role of inflammation and oxidative stress on vascular damage. Previous studies have shown the key role of NAD(P)H-oxidase in the vascular oxidative stress, vascular smooth muscle cells...
proliferation, endothelial dysfunction, and development of hypertension.\textsuperscript{4,5,20} Moreover, Nyby et al.\textsuperscript{33} have shown that increased ROS production by NAD(P)H-oxidase was associated with vascular inflammation assessed through VCAM-1 mRNA expression and vascular dysfunction in FFR. On the other hand, Sarr et al.\textsuperscript{34} showed that RW polyphenols prevented endothelial dysfunction, vascular ROS production, and NAD(P)H-oxidase expression in rats infused with angiotensin II–induced hypertension.

Activation of the vascular endothelium constitutes the initiating event in vascular inflammation and the development of vascular disease. Once activated, endothelium expresses cellular adhesion molecules and cytokines that work in concert to recruit circulating inflammatory cell into vessel wall. Increased production of ROS promotes endothelial inflammatory activation. Moreover, oxidative stress promotes vascular remodeling in human and animal experimental studies.\textsuperscript{35} All this effects are attributed mainly through activation of NF-κB pathway, playing a key role in the development of vascular dysfunction. The corresponding gene products mediate important biological functions such as immune and inflammatory reactions, smooth muscle cell proliferation, and angiogenesis.\textsuperscript{36} A limitation of this study could be that we cannot answer whether the decreased L/M ratio and VCAM-1 expression is possibly an improvement in vascular function.

Also, some adipocytokines play a key role in vascular inflammation and vascular function.\textsuperscript{37} Adiponectin inhibits the expression of adhesion molecules, such as VCAM-1, the tumor necrosis factor-α that promotes monocyte adhesion to endothelial cells, and also inhibits the proliferation and migration of smooth muscle cells.\textsuperscript{10} Contrarily, resistin has the opposite effect of adiponectin. Resistin induces the production of proinflammatory cytokines by endothelial cells and by macrophages, and promotes migratory activity of vascular smooth muscle via activation of the NF-κB pathway,\textsuperscript{38} suggesting that the balance of adipocytokines concentration may determine the inflammatory vascular status. In this study, F rats increased resistin expression and decreased adiponectin expression compared to the control group. Only RW administration partially reversed the imbalance of adipocytokine expression. Excess of ROS and visceral adiposity appears to be associated with an adipocytokine imbalance and vascular inflammation. Recent studies have shown that polyphenols from RW such as resveratrol have anti-inflammatory effects on adipocytokine expression and secretion in human adipose tissue in vitro through the sirtuin-1-pathway.\textsuperscript{39} Resveratrol also modulated adipocytokines expression and improved insulin sensitivity in adipocytes via suppression of extracellular receptor–activated kinase and NF-κB activation.\textsuperscript{40} On the other hand, procyanidins from grape seed also attenuated the expression of inflammatory molecules and enhanced adiponectin expression in white adipose tissue in rats fed a high-fat diet.\textsuperscript{41} Our results suggest that RW attenuated oxidative stress and decreased the adipose tissue, thus reducing imbalance of adipocytokines and markers of vascular inflammation.

In summary, consumption of RW counters oxidative stress, the imbalance of adipocytokines, VCAM-1 expression, and vascular remodeling, supporting the hypothesis that RW has other nonethanol-related beneficial effects that may be linked with antioxidant properties of its nonalcoholic constituents. Further research is necessary for understanding the molecular mechanisms of RW or its constituents on adipocytokines imbalance in this pathological condition, focusing on the regulation of adipocytokine expression and its mechanisms of action.

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original contributions


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