Quercetin Ameliorates Cardiovascular, Hepatic, and Metabolic Changes in Diet-Induced Metabolic Syndrome in Rats

Sunil K. Panchal, Hemant Poudyal, and Lindsay Brown

Abstract

Metabolic syndrome is a risk factor for cardiovascular disease and nonalcoholic fatty liver disease (NAFLD). We investigated the responses to the flavonol, quercetin, in male Wistar rats (8–9 wk old) divided into 4 groups. Two groups were given either a corn starch–rich (C) or high-carbohydrate, high-fat (H) diet for 16 wk; the remaining 2 groups were given either a C or H diet for 8 wk followed by supplementation with 0.8 g/kg quercetin in the food for the following 8 wk (CQ and HQ, respectively). The H diet contained ~68% carbohydrates, mainly as fructose and sucrose, and ~24% fat from beef tallow; the C diet contained ~68% carbohydrates as polysaccharides and ~0.7% fat. Compared with the C rats, the H rats had greater body weight and abdominal obesity, dyslipidemia, higher systolic blood pressure, impaired glucose tolerance, cardiovascular remodeling, and NAFLD. The H rats had lower protein expressions of nuclear factor (erythroid-derived 2)-related factor-2 (Nrf2), heme oxygenase-1 (HO-1), and carnitine palmitoyltransferase 1 (CPT1) with greater expression of NF-κB in both the heart and the liver and less expression of caspase-3 in the liver than in C rats. HQ rats had higher expression of Nrf2, HO-1, and CPT1 and lower expression of NF-κB than H rats in both the heart and the liver. HQ rats had less abdominal fat and lower systolic blood pressure along with attenuation of changes in structure and function of the heart and the liver compared with H rats, although body weight and dyslipidemia did not differ between the H and HQ rats.

Thus, quercetin treatment attenuated most of the symptoms of metabolic syndrome, including abdominal obesity, cardiovascular remodeling, and NAFLD, with the most likely mechanisms being decreases in oxidative stress and inflammation. J. Nutr. 142: 1026–1032, 2012.

Introduction

Metabolic syndrome refers to the clustering of insulin resistance, hypertension, central obesity, impaired glucose tolerance, and dyslipidemia (1). Metabolic syndrome increases the risk of cardiovascular disease, nonalcoholic fatty liver disease (NAFLD), and diabetes (2–4). This increased prevalence of cardiovascular disease and NAFLD associated with metabolic syndrome necessitates the discovery of appropriate interventions for these complications. One of the major causes of obesity and NAFLD in Western society is a diet rich in both carbohydrates such as fructose or sucrose and saturated fats from animal sources (5,6). Excess consumption of fat and fructose in the diet leads to disturbances in fatty acid and carbohydrate metabolism (7,8). Excess fructose consumption also leads to increased lipid biosynthesis, because fructose is a lipogenic carbohydrate (9). This is accompanied by reduced fatty acid oxidation and increased storage of fat in the visceral area. Impairment of fatty acid metabolism in the liver leads to hepatic steatosis followed by NAFLD (10).

Quercetin (3,3′,4′,5-pentahydroxyflavone) is an important dietary flavonoid found in red onions, apples, berries, citrus fruits, tea, and red wine (11). Quercetin reduced systolic blood pressure in hypertensive human participants and in animal models of hypertension (12–14), reduced serum TG and cholesterol concentrations in high-fat diet-fed rabbits after 12 wk of treatment (15), and reduced body weight in obese Zucker rats without changing the mean daily food intake, also reducing plasma concentrations of TG, nonesterified fatty acids (NEFA) total plasma concentrations of cholesterol and TG, and improving glucose tolerance (16).

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Abbreviations used: ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; C, corn starch–rich diet-fed rats; CQ, corn starch–rich diet-fed rats treated with quercetin; CPT1, carnitine palmitoyltransferase 1; CV, corn starch–rich diet-fed rats treated with quercetin; H, high-carbohydrate, high-fat diet-fed rats; HQ, high-carbohydrate, high-fat diet-fed rats treated with quercetin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LV, left ventricle; NEFA, nonesterified fatty acids; Nrf2, nuclear factor (erythroid-derived 2)-related factor-2; TG, triglycerides.

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3 Supplemental Figures 1 and 2 are available from the “Online Supporting Material” link in the online posting of the article and from the same link in the online table of contents at http://jn.nutrition.org.
4 Abbreviations used: ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; C, corn starch–rich diet-fed rats; CQ, corn starch–rich diet-fed rats treated with quercetin; CV, corn starch–rich diet-fed rats treated with quercetin; H, high-carbohydrate, high-fat diet-fed rats; HQ, high-carbohydrate, high-fat diet-fed rats treated with quercetin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LV, left ventricle; NEFA, nonesterified fatty acids; Nrf2, nuclear factor (erythroid-derived 2)-related factor-2.
5 To whom correspondence should be addressed. E-mail: Lindsay.Brown@usq.edu.au.
chol est er, and insulin (16). High-fat, high-cholesterol, and high-
sucrose diet-fed mice treated with quercetin had lower body
weight, visceral fat, blood glucose, plasma insulin, plasma total
cholesterol, plasma TG, plasma NEFA, and plasma TNFα
concentrations with higher plasma adiponectin concentrations.
These mice also had suppressed liver lipid accumulation (17).
In high-fat diet-fed mice, quercetin increased energy expenditure
and reduced plasma concentrations of inflammatory markers
without any changes in food consumption, physical activity,
body weight, or body composition (18). Recent studies have
also shown the protective effects of quercetin in thioacetamide-
and acrylonitrile-induced hepatotoxicity (19,20).

Thus, we characterized the effects of quercetin as a dietary
intervention in a diet-induced rat model of NAFLD and
cardiovascular remodeling as part of metabolic syndrome
induced in rats by feeding a high-carbohydrate, high-fat diet
for 16 wk (21). After treatment with quercetin, the structure and
function of the cardiovascular system were characterized with
echocardiography, isolated Langendorff heart preparation, vas-
cular reactivity studies, and histopathological analysis. The
structure and function of the liver were characterized with
histopathological analysis and measurement of biochemical
variables. Variables for obesity, dyslipidemia, and glucose
tolerance were also measured. The possible mechanisms in-
volved in the action of quercetin were characterized by the
expression of proteins involved in cellular metabolism and stress
regulation.

Methods

Rats, diets, and treatment with quercetin
All experimental protocols were approved by the University of Southern
Queensland Animal Ethics Committee under the guidelines of the
National Health and Medical Research Council of Australia. Male
Wistar rats (8–9 wk old, 333 ± 2 g, n = 40) were obtained from The
University of Queensland Biological Resources facility. Rats were
randomly divided into 4 groups: corn starch–rich diet-fed rats (C; n =
10), corn starch–rich diet-fed rats treated with quercetin (CQ; 0.8 g/kg
food; n = 10; MP Biomedicals), high-carbohydrate, high-fat diet-fed rats
(H; n = 10), and high-carbohydrate, high-fat diet-fed rats treated with
quercetin (HQ; 0.8 g/kg food; n = 10). The compositions of the diets
were previously described in detail (21–23). C and H rats were fed with
corn starch–rich and high-carbohydrate, high-fat diets, respectively, for
16 wk. CQ and HQ rats were fed with corn starch–rich and high-
carbohydrate, high-fat diets, respectively, for the first 8 wk and the
respective diets were supplemented with quercetin (0.8 g/kg food) for a
further 8 wk. All the rats were individually housed under temperature-
controlled, 12-h-light/dark conditions and consumed food and water ad
libitum.

Physiological and metabolic variables
All rats were monitored daily for body weight and food and water
intakes. Abdominal circumference and body length were measured every
4 wk using a standard measuring tape under light anesthesia with Zoletil
(10 mg/kg tiletamine, 10 mg/kg zolazepam, i.p.; Virbac) as previously described
(21).

Echocardiography. Echocardiographic examinations (Phillips iE33,
12MHz transducer) were performed to assess cardiovascular structure
and function in all groups. The examination was performed at the end of
the protocol as previously described (21,22).

Isolated Langendorff heart preparation. Following terminal anes-
thesia and heparin injection, plasma was collected for biochemical
analyses and isolated rat hearts were perfused for measurement of left
ventricular diastolic stiffness as previously described (21).

Vascular reactivity. Thoracic aortic rings (~4 mm in length; 3–4 rings
from 10 rats/group) were used to obtain cumulative concentration-
response curves for noradrenaline (contraction), sodium nitroprusside
(relaxation), and acetylcholine (relaxation) as in a previous study (21).

Histology of the heart. Two rats from each group were exclusively used
for histology. Hearts were fixed, cut, and stained as previously reported
(21).

Assessment of hepatic structure and function

Histology of liver. Livers (n = 8/group) were isolated and weighed. Two
rats from each group were exclusively used for histology. Liver portions
were isolated from these rats and fixed, cut, and stained as in a previous
study (21).

Liver enzymes in plasma. Plasma activities of alanine transaminase
(ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), and
lactate dehydrogenase (LDH) and the plasma concentrations of albumin,
total bilirubin, ura, and uric acid were determined as previously
described (21).

Western-blot analysis
After perfusion experiments, the heart samples were weighed and
immediately stored at −80°C for protein extraction (n = 4/group).
Similarly, the liver samples were immediately isolated after weighing
the liver (n = 4/group) and were stored at −80°C for protein extraction.
These samples were homogenized and sonicated after adding cell lysis
buffer, followed by centrifugation at 15,000 g for 30 min at 4°C. Supernatants were used to measure the protein concentration in each
sample by the bicineconic acid method (Thermo Scientific). Superna-
tants in equal concentrations from each group were used in Western-blot
analyses to study the expression of carnitine palmitoyltransferase 1
(CPT1), nuclear factor (erythroid-derived 2)-related factor-2 (Nrf2),
heme oxygenase-1 (HO-1) (antibodies from Santa Cruz Biotechnology),
fatty acyl-CoA synthetase (FAS), caspase-3 (antibodies from Cell Signaling Technology), and β-
actin (antibody from Sigma-Aldrich) in the liver and heart. For
quantitative analysis, the expression of proteins was normalized to the
expression of β-actin.

Statistical analysis
Values are presented as mean ± SEM. Results were tested for variance
using Bartlett’s test and variables that were not normally distributed
were transformed (using log 10 function) prior to statistical analyses. All
the groups were tested for effects of diet, treatment, and their interaction
by 2-way ANOVA. When the interaction and/or the main effects were
significant, means were compared using the Newman-Keuls multiple
comparison post test. Mean daily quercetin intakes in CQ and HQ
groups were compared with Student’s t test. P < 0.05 was considered
significant. All statistical analyses were performed using GraphPad Prism
version 5.00 for Windows.

Results

Physiological variables. Body weight was higher in the H rats
than in the C rats at 16 wk. Although body weight was higher in
CQ than in C rats at 16 wk, it did not differ between the H and
HQ rats at 16 wk (Table 1). H rats consumed less food and
water compared with C rats. However, total energy intake was higher in the H rats than in the C rats. HQ rats consumed more food and water than H rats, whereas CQ rats consumed less water and more food compared with C rats. CQ and HQ rats had higher energy intakes compared with C and H rats, respectively (Table 1). Energy efficiency and BMI were higher in the H rats than in the C rats. CQ rats had higher whereas HQ rats had lower energy efficiency compared with C and H rats, respectively. BMI in CQ and HQ rats did not differ from C and H rats, respectively (Table 1). Abdominal circumference was higher in H rats than in C rats. Abdominal circumference was lower in HQ rats compared with H rats, whereas it did not differ between the C and CQ rats (Table 1). Relative to body weight, the daily intake of quercetin was greater in HQ rats (46.4 ± 1.6 mg/kg body weight) compared with HQ rats (48.5 ± 1.1 mg/kg body weight) due to greater food intake ($P < 0.0001$).

**Metabolic variables.** Higher basal blood glucose concentrations and AUC in the H rats compared with C rats were normalized in HQ rats and there was no effect of quercetin in CQ rats on basal blood glucose concentrations and AUC (Table 1). Plasma concentrations of total cholesterol, TG, and NEFA were higher in the H rats than in C rats. CQ rats did not differ in plasma total cholesterol concentrations from C rats, whereas plasma concentrations of TG and NEFA were higher in the CQ rats than in the C rats (Table 1). H and HQ rats did not differ in plasma concentrations of total cholesterol and NEFA, whereas plasma TG concentrations were higher in HQ rats than in H rats (Table 1). Abdominal fat pad weights (retroperitoneal, epididymal, and omental) were higher in H rats compared with C rats and were normalized in HQ rats, but lower in the CQ rats than in the C rats (Table 1).

**Cardiovascular structure and function.** The LV (left ventricle) of the heart from H rats had more infiltration of inflammatory cells (Supplemental Fig. 1C) along with hypertrophy and more collagen deposition (Supplemental Fig. 1G) than C rats (Supplemental Fig. 1A,E). These changes were attenuated in the LV of the HQ rats (Supplemental Fig. 1D,H). Systolic blood pressure was higher in H rats compared with C rats at 16 wk. It was normalized in HQ rats, whereas it was lower in CQ rats than in C rats (Table 2). The left ventricular internal diameter during systole and diastole and the systolic volume were higher in H rats than in C rats, whereas these variables were normalized in HQ rats and did not differ between the C and CQ rats (Table 2). Left ventricular posterior wall thickness during diastole was higher in H rats compared with C rats and it did not differ in the CQ and HQ rats compared with the C and H rats, respectively. Relative wall thickness did not differ between the C and H rats, whereas it was higher in both CQ and HQ rats compared with C and H rats, respectively (Table 2). Indicators of ventricular function (fractional shortening, ejection fraction, and the ratio of early mitral inflow velocity to late mitral inflow velocity) were lower in H rats than in C rats, indicating impaired ventricular function (Table 2). These indicators of ventricular function were normalized with quercetin supplementation in HQ rats (Table 2). The estimated LV mass was higher in H rats compared with C rats and did not differ between H and HQ rats, whereas it was higher in CQ rats than in C rats. The actual LV wet weight (with septum) did not differ between the groups. The right ventricular wet weight did not differ between the C and H rats, whereas it was higher in the CQ and HQ rats compared with the C and H rats (Table 2). The left ventricular diastolic stiffness constant was higher in H rats compared with C rats and it was lower in HQ rats than in H rats, whereas it did not differ between the C and CQ rats (Table 2). Vascular responses, including noradrenaline-induced contraction and sodium nitroprusside- and acetylcholine-induced relaxation, were impaired in H rats compared with C rats (Fig. 1A–C). Noradrenaline-

### TABLE 1 Physiological and metabolic variables in rats fed C or H diets for 8 wk and those diets or CQ or HQ diets for an additional 8 wk

<table>
<thead>
<tr>
<th>Variables</th>
<th>C</th>
<th>CQ</th>
<th>H</th>
<th>HQ</th>
<th>D</th>
<th>Q</th>
<th>D×Q</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physiological variables</strong></td>
<td></td>
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<tr>
<td>Initial body weight, g</td>
<td>334 ± 1</td>
<td>332 ± 1</td>
<td>334 ± 1</td>
<td>331 ± 2</td>
<td>0.71</td>
<td>0.07</td>
<td>0.71</td>
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<tr>
<td>Final body weight, g</td>
<td>406 ± 5</td>
<td>441 ± 12</td>
<td>499 ± 9</td>
<td>488 ± 13</td>
<td>0.0001</td>
<td>0.11</td>
<td>0.09</td>
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<tr>
<td>Water intake, mL/d</td>
<td>31.4 ± 1</td>
<td>24.8 ± 1</td>
<td>19.6 ± 0.6</td>
<td>23.4 ± 0.7</td>
<td>&lt;0.0001</td>
<td>0.13</td>
<td>&lt;0.0001</td>
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<tr>
<td>Food intake, g/d</td>
<td>30.4 ± 0.7</td>
<td>34.0 ± 0.4</td>
<td>22.1 ± 0.5</td>
<td>28.2 ± 0.5</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.026</td>
<td></td>
</tr>
<tr>
<td>Energy intake, kJ/d</td>
<td>349 ± 10</td>
<td>382 ± 6</td>
<td>462 ± 9</td>
<td>592 ± 11</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
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<tr>
<td>Energy efficiency, kJ/g</td>
<td>0.19 ± 0.01</td>
<td>0.28 ± 0.03</td>
<td>0.36 ± 0.02</td>
<td>0.28 ± 0.02</td>
<td>0.0003</td>
<td>0.82</td>
<td>0.0003</td>
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<tr>
<td>BMD, g/cm²</td>
<td>0.65 ± 0.01</td>
<td>0.66 ± 0.01</td>
<td>0.74 ± 0.01</td>
<td>0.75 ± 0.01</td>
<td>&lt;0.0001</td>
<td>0.32</td>
<td>1.00</td>
<td></td>
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<tr>
<td>Abdominal circumference, cm</td>
<td>19.6 ± 0.4</td>
<td>19.0 ± 0.4</td>
<td>23.3 ± 0.4</td>
<td>20.9 ± 0.2</td>
<td>&lt;0.0001</td>
<td>0.0002</td>
<td>0.017</td>
<td></td>
</tr>
<tr>
<td><strong>Metabolic variables</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Basal blood glucose, mmol/L</td>
<td>4.0 ± 0.1</td>
<td>3.9 ± 0.1</td>
<td>5.0 ± 0.1</td>
<td>4.2 ± 0.2</td>
<td>&lt;0.0001</td>
<td>0.02</td>
<td>0.012</td>
<td></td>
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<tr>
<td>Blood glucose AUC, mmol/L/min</td>
<td>680 ± 13</td>
<td>656 ± 8</td>
<td>771 ± 10</td>
<td>641 ± 24</td>
<td>0.016</td>
<td>&lt;0.0001</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Plasma total cholesterol, mmol/L</td>
<td>1.4 ± 0.1</td>
<td>1.4 ± 0.1</td>
<td>2.0 ± 0.1</td>
<td>1.8 ± 0.1</td>
<td>&lt;0.0001</td>
<td>0.32</td>
<td>0.32</td>
<td></td>
</tr>
<tr>
<td>Plasma TG, mmol/L</td>
<td>0.4 ± 0.1</td>
<td>1.0 ± 0.1</td>
<td>0.8 ± 0.1</td>
<td>1.3 ± 0.2</td>
<td>0.012</td>
<td>0.0002</td>
<td>0.71</td>
<td></td>
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<tr>
<td>Plasma NEFA, mmol/L</td>
<td>1.2 ± 0.3</td>
<td>2.9 ± 0.5</td>
<td>3.6 ± 0.7</td>
<td>3.4 ± 0.7</td>
<td>0.016</td>
<td>0.20</td>
<td>0.11</td>
<td></td>
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<tr>
<td>Retroperitoneal fat, mg/mn tibial length</td>
<td>213 ± 9</td>
<td>135 ± 7</td>
<td>357 ± 21</td>
<td>220 ± 11</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.031</td>
<td></td>
</tr>
<tr>
<td>Epididymal fat, mg/mn tibial length</td>
<td>129 ± 11</td>
<td>87 ± 3</td>
<td>225 ± 14</td>
<td>141 ± 4</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.029</td>
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<tr>
<td>Omental fat, mg/mn tibial length</td>
<td>93 ± 6</td>
<td>68 ± 4</td>
<td>194 ± 12</td>
<td>103 ± 4</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Total abdominal fat, mg/mn tibial length</td>
<td>435 ± 24</td>
<td>290 ± 9</td>
<td>775 ± 46</td>
<td>465 ± 14</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.005</td>
<td></td>
</tr>
</tbody>
</table>

1 Values are mean ± SEM, n = 10. Means in a row with superscripts without a common letter differ, P < 0.05. C, corn starch–rich diet-fed rats; CQ, corn starch–rich diet-fed rats treated with quercetin; D, effects of diet; D×Q, interaction between the effects of diet and quercetin; H, high-carbohydrate, high-fat diet-fed rats; HQ, high-carbohydrate, high-fat diet-fed rats treated with quercetin; NEFA, nonesterified fatty acids; Q, effects of quercetin.
induced contraction and acetylcholine-induced relaxation were normalized in HQ rats, whereas these responses did not differ between the C and CQ rats (Fig. 1A,C). The HQ rats had a greater sodium nitroprusside-induced relaxation response compared with H rats, whereas CQ rats had a lower response to sodium nitroprusside compared with C rats (Fig. 1B).

**Hepatic structure and function.** Liver from H rats had more infiltration of inflammatory cells (Supplemental Fig. 2C) than C rats (Supplemental Fig. 2A) along with presence of fat vacuoles (Supplemental Fig. 2G) and portal fibrosis (Supplemental Fig. 2K), which were absent in the liver from C rats (Supplemental Fig. 2E,I). The wet weight of the liver was higher in H rats than in C rats and normalized in HQ rats, whereas it was lower in CQ rats than in C rats (Table 3). Plasma activities of ALT, AST, ALP, and LDH were higher in H rats compared with C rats. Plasma activities of ALT and ALP were normalized in HQ rats, whereas they were lower in CQ rats than in C rats. Plasma AST and LDH activities did not differ between C and CQ rats. Plasma AST activities did not differ between the H and HQ rats, whereas plasma LDH activity was normalized in HQ rats (Table 3). Although plasma total bilirubin concentrations did not differ between the C and H rats, they were lower in HQ rats compared with H rats. Plasma urea and plasma uric acid concentrations were lower and higher, respectively, in H rats than in C rats. The HQ rats had higher plasma urea concentrations compared with H rats, although not normalized, whereas plasma uric acid concentrations were normalized in HQ rats (Table 3).

**Expression of regulatory proteins in the liver and the heart.** In the liver from H rats, the protein expression of Nrf2, HO-1, CPT1, and caspase-3 was lower whereas NF-κB expression was higher compared with C rats. In HQ rats, the expression of Nrf2, CPT1, and caspase-3 in the liver was normalized, whereas the expression of HO-1 was higher compared with H rats. NF-κB expression in the liver was lower in both CQ and HQ rats compared with C and H rats, respectively. Hepatic expression of Nrf2 and CPT1 did not differ between C and HQ rats, whereas hepatic expression of HO-1 and caspase-3 were higher in CQ rats than in C rats. Hepatic expression of NF-κB was lower in CQ rats but was higher in C rats (Fig. 2A,C). In the heart from H rats, expression of Nrf2, HO-1, and CPT1 was lower, whereas expression of NF-κB was higher in C rats compared with CQ rats. The expression of HO-1 and CPT1, whereas the expression of NF-κB was lower in the heart compared with H rats. Cardiac expression of Nrf2, HO-1, and CPT1 did not differ between the C and CQ rats, whereas cardiac expression of NF-κB was lower in CQ rats than in C rats. Caspase-3 expression in the heart did not differ between the groups (Fig. 2B,D).

**Discussion**

Flavonoids are secondary plant metabolites that are useful, e.g., for protection of plants against fungal infection (25–27); quercetin is one of the most common flavonoids in the human diet. Because quercetin is abundant in plant-based products in the diet, it is important to determine whether quercetin can reduce human health challenges such as obesity, metabolic syndrome, and NAFLD. Hence, we have characterized the effects of quercetin in an appropriate animal model of diet-induced metabolic syndrome and associated complications (21,28). This rodent model mimics most of the complications associated with human metabolic syndrome (21).

Obesity is a chronic condition characterized by excess fat deposition in the abdomen, including retroperitoneal, epididymal, and omental fat pads. Excess fat deposition increases morbidity and mortality through health complications, including oxidative stress, chronic low-grade inflammation, dyslipidemia, type 2 diabetes, cardiovascular disease, NAFLD, and some cancers (29–36). In this study, we have targeted NAFLD, obesity, and cardiovascular disease with quercetin using an appropriate rat model of metabolic syndrome (21). Using the same model, we showed that rutin, a glycoside of quercetin,
Our recent study with chia seeds has demonstrated a link between lipid trafficking away from the abdomen and attenuation of metabolic syndrome in a diet-induced rat model. The hepatic changes in metabolic syndrome.

In conclusion, quercetin was effective against the symptoms of metabolic syndrome in a diet-induced rat model. The trafficking of fat away from the abdomen did not lower body weight and body composition (18). This suggests that the abdominal fat has been moved to other fat storage areas or has been converted to muscle mass.

Although dyslipidemia was not attenuated with quercetin, the other symptoms of metabolic syndrome were attenuated, including systolic blood pressure, glucose tolerance, and visceral obesity. Quercetin abolished hepatic steatosis, prevented the infiltration of inflammatory cells in the liver, and reduced the portal fibrosis along with improvements in liver function. Along with these changes were cardioprotective effects, including reduced collagen deposition, less infiltration of inflammatory cells, inhibition of cardiomyocyte hypertrophy, reduced ventricular stiffness, lower ventricular dimensions, and a return toward normal ventricular function.

The presence of inflammation and oxidative stress leads to cellular injury leading to organ dysfunction (37,38). One of the major defense systems against stress-related injury is the Nrf2 system (39). Nrf2 is the transcription factor present in inactive forms in the cell. Once activated, Nrf2 translocates to the nucleus and activates the antioxidant response elements (39). This, in turn, gives rise to proteins and enzymes, such as HO-1, which reduce the cellular stress (39). This suggests that the activators of Nrf2 system can protect organ systems. Similarly, the role of NF-κB has been established in the activation of inflammation (40).

In obesity, oxidative stress and inflammation induce organ dysfunction (31). Our results showed that the high-carbohydrate, high-fat diet upregulated the hepatic and cardiac expression of NF-κB, whereas the hepatic and cardiac expression of Nrf2 was downregulated, clearly indicating the presence of inflammation and oxidative stress in both the liver and the heart. The hepatic and cardiac expression of NF-κB was downregulated by quercetin, confirming its antiinflammatory role. Similarly, quercetin supplementation upregulated the expression of Nrf2, resulting in activation of antioxidant response elements, followed by upregulation of HO-1, and hence the reduction of oxidative stress. Thus, attenuation of hepatic and cardiac changes by quercetin could be mediated through its antioxidative and antiinflammatory actions.

Quercetin also upregulated the expression of CPT1, a regulator of fatty acid oxidation, in the liver and the heart. This change could attenuate NAFLD, thereby leading to attenuation of steatosis through higher fatty acid oxidation in the liver. Caspase-3 expression was also higher in the liver, but not in the heart, with quercetin as with rutin (24). Greater expression of caspase-3 indicates higher levels of apoptosis, possibly leading to the removal of steatotic cells from the liver. These results explain the role of quercetin in the attenuation of hepatic changes in metabolic syndrome.

In this study, 0.8 g/kg food of quercetin was used to provide a daily dose of ~50 mg/kg body weight. This dose corresponds to ~1 g/d quercetin in a 70-kg human based on scaling equation (41) or ~0.6 g/d based on body surface area comparisons between rats and humans (42). Although the mean daily human intake of quercetin is not known, the total intake of polyphenols is ~1 g/d, with two-thirds being flavonoids, including quercetin and rutin (43). This suggests that the dose of quercetin used in this study is realistic in humans.

In conclusion, quercetin was effective against the symptoms of metabolic syndrome in a diet-induced rat model. The trafficking of fat away from the abdomen did not lower body weight and body composition (18). This study also showed that the lipid components in plasma were higher with quercetin treatment consistent with the trafficking of fat by the circulation. The lack of difference in the body weights of quercetin-treated and untreated rats may suggest that the abdominal fat has been moved to other fat storage areas or has been converted to muscle mass.
TABLE 3  Hepatic structure and function in rats fed C or H diets for 8 wk and those diets or CQ or HQ diets for an additional 8 wk

<table>
<thead>
<tr>
<th>Variables</th>
<th>C</th>
<th>CQ</th>
<th>H</th>
<th>HQ</th>
<th>F value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver wet weight, mg/mm² tibial length</td>
<td>267 ± 13⁶</td>
<td>229 ± 8⁵</td>
<td>298 ± 11⁴</td>
<td>261 ± 8⁶</td>
<td>0.004</td>
<td>0.0008</td>
</tr>
<tr>
<td>Plasma ALT activity, U/L</td>
<td>35 ± 3⁶</td>
<td>22 ± 2⁵</td>
<td>58 ± 4³</td>
<td>42 ± 3⁶</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Plasma AST activity, U/L</td>
<td>79 ± 3⁶</td>
<td>72 ± 5⁶</td>
<td>109 ± 9⁶</td>
<td>129 ± 11⁴</td>
<td>&lt;0.0001</td>
<td>0.43</td>
</tr>
<tr>
<td>Plasma ALP activity, U/L</td>
<td>172 ± 12⁶</td>
<td>116 ± 9⁶</td>
<td>247 ± 19³</td>
<td>158 ± 16⁶</td>
<td>0.0003</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Plasma LDH activity, U/L</td>
<td>252 ± 27⁶</td>
<td>211 ± 25⁵</td>
<td>459 ± 37⁹</td>
<td>283 ± 18³</td>
<td>&lt;0.0001</td>
<td>0.0004</td>
</tr>
<tr>
<td>Plasma albumin, g/L</td>
<td>28.0 ± 0.6</td>
<td>28.1 ± 0.4</td>
<td>28.7 ± 0.3</td>
<td>29.0 ± 0.5</td>
<td>0.09</td>
<td>0.67</td>
</tr>
<tr>
<td>Plasma total bilirubin, µmol/L</td>
<td>2.2 ± 0.1³</td>
<td>1.9 ± 0.1³</td>
<td>2.5 ± 0.1³</td>
<td>1.5 ± 0.2³</td>
<td>0.71</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Plasma urea, mmol/L</td>
<td>5.8 ± 0.2³</td>
<td>5.1 ± 0.2³</td>
<td>3.0 ± 0.3³</td>
<td>3.8 ± 0.2³</td>
<td>&lt;0.0001</td>
<td>0.83</td>
</tr>
<tr>
<td>Plasma uric acid, µmol/L</td>
<td>37 ± 3⁶</td>
<td>38 ± 3⁶</td>
<td>60 ± 9³</td>
<td>37 ± 4³</td>
<td>0.048</td>
<td>0.048</td>
</tr>
</tbody>
</table>

1 Values are mean ± SEM, n = 8–10. Means in a row with superscripts without a common letter differ, P < 0.05. ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; C, corn starch–rich diet-fed rats; CQ, corn starch–rich diet-fed rats treated with quercetin; D, effects of diet; D×Q, interaction between the effects of diet and quercetin; H, high-carbohydrate, high-fat diet-fed rats; HQ, high-carbohydrate, high-fat diet-fed rats treated with quercetin; LDH, lactate dehydrogenase; Q, effects of quercetin.

weight and blood lipids, while the cardiovascular and liver complications of metabolic syndrome were attenuated. Quercetin supplementation attenuated the changes in expression of markers for oxidative stress and inflammation in the liver and the heart such as Nrf2, HO-1, and NF-κB along with higher fatty acid oxidation. Livers had greater expression of caspase-3, an apoptotic marker, indicating the attenuation of steatosis. Thus, quercetin can be considered as a nutraceutical with potential for the treatment of metabolic syndrome; clinical trials of this relatively safe natural compound should be undertaken.

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Literature Cited


FIGURE 2  Expression of Nrf2, HO-1, NF-κB, CPT1, and cleaved caspase-3 (Cl. cas 3) in the liver (A, C) and the heart (B, D) from rats fed C or H diets for 8 wk and those diets or CQ or HQ diets for an additional 8 wk. Values are mean ± SEM, n = 4. Means without a common letter differ, P < 0.05. C, corn starch–rich diet-fed rats; CQ, corn starch–rich diet-fed rats treated with quercetin; H, high-carbohydrate, high-fat diet-fed rats; HQ, high-carbohydrate, high-fat diet-fed rats treated with quercetin; NF-κB, nuclear factor (erythroid-derived 2)-related factor-2.


