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Lipid-lowering effects of dietary quercetin in Wistar rats challenged with an atherogenic diet

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Abstract

Background: Hyperlipidaemia contributes to cardiovascular disease, and the in- vivo effects of quercetin on lipid metabolism remain unclear.

Aim of the study: To compare the effects of dietary quercetin with simvastatin in male Wistar rats with atherogenic-diet-induced hyperlipidaemia.

Methods: Sixty rats divided into 12 groups (n=5) received standard or high-fat diets. 0.9% normal saline was used as a vehicle for quercetin (50, 75, or 100 mg/kg body weight) or simvastatin (0.6 mg/kg body weight) for 90 days of treatment, prophylactic, or concurrent schedules. Tissues (adipose and pancreas) total cholesterol, triglycerides and total protein, pancreatic lipase, cholecystokinin, hepatic cholesterol-7-alpha-hydroxylase (CYP7A1), 3-hydroxy-3-methylglutaryl-CoA reductase (HMG-CoA reductase) related activity and tissue morphology were assessed.

Results: Quercetin at 100 mg/kg body weight produced the most consistent changes, including significantly ($p<0.05$) higher leves in adipose triglyceride and pancreatic total protein but lower levels of adipose tissue total cholesterol and total protein values compared to high-fat diet group. The concentration also lowered cholecystokinin, CYP7A1 activity and the HMG-CoA/mevalonate ratio and reduced the severity of high-fat-diet-associated lesions.

Conclusions: High-fat-diet-associated tissue lesions may be reduced significantly after quercetin administration. Also, the dietary quercetin, especially at 100 mg/kg body weight, demonstrated lipid-lowering and tissue-preserving potentials.

Introduction

Elevated LDL-cholesterol is an important target in cardiovascular prevention; recent clinical trial evidence shows that lowering LDL-cholesterol can reduce major cardiovascular events [1]. Statins remain established lipid-lowering agents, and contemporary trial analyses indicate that most adverse effects attributed to them are not causally supported, although small risks of selected outcomes remain [2]. Quercetin, a dietary flavonoid, has shown anti-inflammatory and anti-atherosclerotic activity in recent experimental studies, with its effects influenced by gut microbial metabolism [3,4].

Cholecystokinin (CCK) helps coordinate lipid digestion and satiety; recent human intestinal organoid research has identified FFAR1-dependent lipid sensing as an important mechanism of CCK release [5]. 3-Hydroxy-3-methylglutaryl-CoA reductase (HMG-CoA reductase) controls a rate-limiting step in cholesterol biosynthesis and is subject to sterol-dependent feedback regulation [6]. Cholesterol 7 alpha-hydroxylase (CYP7A1) participates in the conversion of hepatic cholesterol to bile acids, and recent experimental work has linked quercetin to regulation of this pathway through mTOR/YY1 signalling [7]. Changes in these processes could influence lipid accumulation in blood and tissues. The lipid profiles in serum, cardiac, hepatic, together with liver morphology, have previously been evaluated. Quercetin

administration at 100 mg/kg body weight induced hypolipidemia following 90 days of treatment under both therapeutic and prophylactic regimens and restored hepatic histoarchitecture, thereby exerting a protective effect on the liver [8]. Lower hepatic cholesterol and triglycerides, together with changes in phospholipids and total protein, as previously suggested, indicate altered hepatic lipid handling by quercetin [8]. Recent experimental studies have associated quercetin with reduced hepatic and cardiac lipotoxicity, inflammation and fibrosis through vitamin D receptor and adiponectin/AdipoR2 signalling [9]. Human evidence is more limited: a randomised crossover trial found that 12 weeks of quercetin reduced intrahepatic fat in patients with nonalcoholic fatty liver disease, with the change partly associated with weight loss [10]. That clinical result supports further investigation but does not establish equivalence between human supplementation and the doses used in this animal study.

We therefore investigated dietary quercetin in atherogenic-diet Wistar rats by measuring adipose tissues and pancreatic lipids; pancreatic CCK and lipase; liver CYP7A1; HMG-CoA reductase-related activity; and tissue morphology in cardic and adipose tissue, with Simvastatin provided as the reference treatment. The molecular structure of quercetin is presented in Fig. 1 [11].

Materials and Methods

Animals and ethical approval:

Adult male Wistar rats (n = 60; mean initial body weight = 132.2 g) were acclimatised for 14 days in the animal facility of the Department of Medical Laboratory Science, Ladoke Akintola University of Technology (Osogbo Campus), Osun State, Nigeria. Five animals were housed per cage at 25 ± 3°C and were given unrestricted access to feed and water. The Osun State Health Research Ethics Committee approved the protocol (OSHREC/PRS/2026/842/01/282). All procedures complied with accepted principles for the care and use of laboratory animals [12]. Reporting followed the ARRIVE 2.0 guidelines for animal research [13].

Diet preparation, dosing and experimental arrangement

Standard and atherogenic feeds were produced in 50kg lots according to the formulations in Table 1, which were adapted from Adesiyan et al. [14]. The 60 rats were placed into 12 groups of five as outlined in Table 2. Groups A and L received the standard diet, whereas groups B to K represented the high-fat-diet exposure and treatment schedules. Randomisation and allocation concealment were conducted by Mrs Adeola Temitope Niran-Atiba, a Medical Laboratory Scientist not involved in outcome assessment, to ensure blinding. All experimental procedures and data analyses were conducted with the investigators blinded to group assignments. Quercetin obtained from commercial capsules was prepared in normal saline (50 mg/mL) and delivered by oral cannula at 50, 75 or 100 mg/kg body weight. Simvastatin tablets were given at 0.6 mg/kg as the comparator drug. The administered quercetin doses were below the 2,000 mg/kg acute oral dose reported without mortality in a recent Wistar-rat study [15].

Table 1
Formulation of the standard and atherogenic diets prepared in 50-kg lots.

Component	Weight (kg) Standard diet	Standard diet (%)	Weight (kg) High-fat diet	High-fat diet (%)
Maize	8.97	17.90	8.97	17.75
Soya bean meal	3.74	7.46	3.74	7.40
Brewery dry grain (BDG)	17.50	34.92	17.50	34.64
Wheat bran (WB)	5.00	9.97	5.00	9.89
Rice bran (RB)	12.5	24.94	12.5	24.74
Oyster shell (OS)	1.00	1.99	1.00	1.97
Bone meal (BM)	0.50	0.99	0.50	0.98
Common salt (CS)	0.13	0.25	0.13	0.25
Methionine	0.50	0.99	0.50	0.98
Fish meal	0.50	0.99	0.50	0.98
Groundnut oil	-	-	0.30	0.59
Cholesterol powder	-	-	0.10	0.19

Source: formulation adapted from Adesiyan et al. [14].

Table 2
Experimental Groups According to Diet, Administered Agent, and Exposure Schedule.

Group	Dietary Regimen	Treatment/Agent	Timing / Experimental Period
A	Standard animal feed	No Vehicle	Days 0–90
B	HFD, followed by standard diet	No Vehicle	HFD: days 0–60; standard diet: days 61–90
C	HFD throughout the study	No Vehicle	Days 0–90
D	HFD, followed by standard feed	Simvastatin, 0.6 mg /kg.bw + N/S	HFD: days 0–60; treatment: days 61–90
E	HFD, followed by standard feed	Quercetin, 50 mg /kg.bw + N/S	HFD: days 0–60; treatment: days 61–90
F	HFD, followed by standard feed + treatment	Quercetin, 75 mg /kg.bw + N/S	HFD: days 0–60; treatment: days 61–90
G	HFD, followed by standard feed + treatment	Quercetin, 100 mg /kg.bw + N/S	HFD: days 0–60; treatment: days 61–90
H	Standard feed and prophylactic treatment, followed by HFD	Quercetin, 50 mg /kg.bw + N/S	Prophylactic phase: days 0–60; HFD exposure: days 61–90
I	Standard feed and prophylactic treatment, followed by HFD	Quercetin, 75 mg/ kg.bw + N/S	Prophylactic phase: days 0–60; HFD exposure: days 61–90
J	Standard feed and prophylactic treatment, followed by HFD	Quercetin, 100 mg /kg.bw + N/S	Prophylactic phase: days 0–60; HFD exposure: days 61–90
K	HFD with Quercetin	Quercetin, 100 mg/ kg.bw + N/S	HFD and quercetin administered concurrently, days 0–90
L	Standard feed with Quercetin	Quercetin, 100 mg /kg.bw + N/S	Standard diet and quercetin administered concurrently, days 0–90

HFD: high-fat diet. N/S: normal saline

Collection and preparation of samples

On day 91, the rats were ethically euthanised by cervical dislocation. The liver, adipose and pancreas were excised, rinsed in 1.15% potassium chloride, homogenised in 0.1 M potassium phosphate buffer (pH 7.4; tissue: buffer, 1:4), and centrifuged at 10,000 revolutions per minute for 20 min at low temperature. Post-mitochondrial supernatants were kept at − 80°C until analysis [14].

Biochemical assays and histopathology

Total cholesterol [16], triglycerides [17] and total protein [18] were determined by established spectrophotometric, precipitation or calculated procedures. MyBioSource ELISA kits (CK-E30986, CK-E31164 and CK-E30867) were used to measure pancreatic lipase, pancreatic CCK and hepatic CYP7A1, respectively, at 450 nm. HMG-CoA reductase activity was estimated indirectly from the HMG-CoA/mevalonate ratio using 0.1% Saline Arsenate solution of liver homogenate [19]. For histology, tissues (heart and pancreas) were fixed in 10% Neutral buffered formalin, dehydrated in graded ethanol, cleared with xylene, embedded in paraffin, sectioned at 4–5 μm and stained with haematoxylin and eosin. Sections were examined at ×100 with a Leica DM750 microscope and CC50 camera [20].

Statistical analysis

Data were analysed in SPSS version 22 and summarized as mean ± SD. Student's t-test and one-way ANOVA with post hoc multiple comparisons were used to assess group differences. $p \leq 0.05$ was considered significant.

RESULTS

The high-fat diet has no significant effect on adipose triglycerides, total cholesterol and total cholesterol in this study compared to negative control ($p > 0.05$). However, adipose lipids (triglycerides and total cholesterol) and total protein in different experimental groups showed significant differences in triglycerides ($p = 0.001$), total cholesterol ($p = 0.001$) and total protein ($p = 0.001$) across the groups (Table 3).

Table 3
Adipose Triglyceride, Total Cholesterol, and Total Protein Concentrations in the Experimental Groups.

Group	Triglycerides (mg/dL)	Total Cholesterol (mg/dL)	Total Protein (g/dL)
A	45.94 ± 15.11	6.70 ± 0.71	1.54 ± 0.59
B	40.83 ± 7.79 [a]	7.88 ± 0.45 [a]	1.67 ± 0.40 [a]
C	37.63 ± 5.38 [Ns a **]	9.47 ± 0.64 [Ns a **]	1.95 ± 0.16 [Ns a **]
D	44.35 ± 8.64 [a]	9.55 ± 0.40 [a]	1.99 ± 0.20 [a]
E	19.81 ± 1.16 [a]	9.30 ± 0.40 [a]	1.25 ± 0.25 [a]
F	37.90 ± 7.01 [a]	11.57 ± 1.98 [a]	2.16 ± 0.26 [a]
G	25.79 ± 1.91 [a]	9.13 ± 0.28 [a]	1.72 ± 0.26 [a]
H	25.65 ± 2.69 [a **]	9.80 ± 0.66 [a **]	1.64 ± 0.17 [a *]
I	25.24 ± 3.33 [a **]	9.55 ± 0.79 [a **]	1.37 ± 0.14 [a *]
J	40.42 ± 2.78 [a **]	10.05 ± 0.69 [a **]	2.20 ± 0.21 [a **]
K	603.65 ± 23.07[b]	14.86 ± 5.01 [a]	0.33 ± 0.07 [a]
L	585.83 ± 18.89[c *]	1.12 ± 0.30[b *]	0.58 ± 0.10[b *]

NS = not significant; S= significant. Groups B and C compared with group A (negative controls).

**= significant. Groups B and C served as positive controls to groups D to L (study groups) where different letters signify level of significance. Different (*) was significant compared to group L.*

Pancreatic levels of triglycerides and total protein varied significantly ($p = 0.05$) across the groups (as shown by ANOVA), Group L demonstrated the lowest level of pancreatic cholesterol ($p > 0.05$) (Table 4).

Table 4
Pancreatic Tissue Triglyceride, Total Cholesterol, and Total Protein Concentrations in the Experimental Groups.

Group	Triglycerides (mg/dL)	Total Cholesterol (mg/dL)	Total Protein (g/dL)
A	833.77 ± 53.07	4.52 ± 0.65	0.20 ± 0.07
B	913.20 ± 23.36ns**	5.11 ± 0.20ns	0.25 ± 0.03ns
C	508.25 ± 126.69ns	5.10 ± 0. 08ns	0.11 ± 0.03ns a
D	608.84 ± 103.04[a]	6.87 ± 1.75a	0.26 ± 0.07a
E	683.23 ± 133.36[a]	5.11 ± 0.40[a]	0.24 ± 0.07[a]
F	374.31 ± 130.70[a] *	8.21 ± 3.30[a]	0.14 ± 0.05[a]
G	473.47 ± 127.44[a]	4.52 ± 0.24[a]	0.10 ± 0.03[a]
H	398.20 ± 126.29[a]	5.69 ± 0.41[a]	0.35 ± 0.10[a]
I	856.50 ± 40.20[a] **	6.20 ± 0.45[a]	0.26 ± 0.09[a]
J	777.76 ± 81.81[a]	8.80 ± 3.09[a]	0.53 ± 0.17[a]
K	559.59 ± 44.83[a]	8.92 ± 0.70[a]	0.55 ± 0.15[b]
L	617.50 ± 2.93[a]	2.73 ± 0.69[a]	0.17 ± 0.06[a]

*NS = not significant; S= significant when Groups B and C compared with group A (negative controls). Groups B and C served as positive controls to groups D to L where different letters signify level of significance. **= significant shown significance level compared to F*

Pancreatic lipase ($p > 0.05$), CCK, CYP7A1 and the HMG-CoA/mevalonate ratio varied significantly ($p < 0.05$), using ANOVA. Relative to the high-fat-diet group, the 100 mg/kg prophylactic and concurrent schedules yielded lower activities of enzymes (CCK, pancreatic lipase) but increased CYP7A1 and HMG-CoA/mevalonate ratio (Table 5) compared with Wistar rats in group C.

Table 5
Changes in Selected Lipid Metabolism Biomarkers in Wistar Rats after quercetin exposure.

Group	Pancreatic Lipases (U/L)	Cholecystokinin (pg/mL)	CYP7A1(ng/mL)	HMGCoA/Mevalonate ratio ng/mL)
A	17.24 ± 3.08	54.59 ± 1.33	1.97 + 0.10#	1.41 ± 0.12
B	14.54 ± 1.49 **NS**	54.47 ± 1.38 **NS**	1.86 + 0.10$^{Ns\ ++*}$	1.62 ± 0.64^{Ns**}
C	13.34 ± 1.15 **NS ***	53.07 ± 2.20 **NS ***	1.58 + 0.07^{NS*}	1.14 ± 0.32**Ns ***
D	11.45 ± 2.25 *	51.74 ± 2.78 *	1.60 + 0.15*	1.20 ± 0.29 *
E	13.86 ± 0.94 *	45.96 ± 1.41 *	1.63 + 0.15*	1.63 ± 0.65 **
F	12.67 ± 1.14 *	46.08 ± 1.63 *	1.67 + 0.06*##+	1.18 ± 0.36 *
G	13.10 ± 1.26 *	48.01 ± 1.84 *	1.80 + 0.16##*	1.00 ± 0.45 *
H	11.52 ± 1.12 *	43.49 ± 2.42 **	1.60 + 0.19*	1.41 ± 0.11 *
I	11.74 ± 1.26 *	40.68 ± 1.92 **	1.65 + 0.10*	1.20 ± 0.93 *
J	10.98 ± 2.20 *	42.31 ± 1.35 **	1.70 + 0.18*	1.66 ± 0.49 **
K	12.30 ± 1.62 *	41.90 ± 1.58 **	1.26 + 0.24*##	1.26 ± 0.34 *
L	12.15 ± 0.43 *	39.24 ± 1.01**	1.80 + 0.10*	1.36 ± 0.44 *

NS = not significant; S= significant when Groups B and C are compared with Group A (negative controls). Groups B and C served as positive controls for groups D to L, where (**) signifies the level of significance. ## denotes comparison with group A; + denotes comparisons with group B.

Histopathological findings

Histopathological findings of the cardiac section across different experimental groups are shown in Fig. 2. Groups A and B show predominantly regular myocardial fibres with elongated, centrally located nuclei and preserved fibre alignment. Groups E, H and J exhibit largely preserved myocardial architecture. Group C (continuous HFD) shows wavy and irregularly arranged myocardial fibres, widened interstitial spaces, increased interstitial cellularity, and occasional small or pale-appearing nuclei. Groups D, F, G and I exhibit relatively mild myocardial alterations, including focal attenuation or loss of visible cross-striations and apparent reduction in fibre calibre. Group K (HFD with concurrent quercetin, 100 mg/kg) shows myocardial fibre disorganisation and separation, with widened interstitial gaps. The quercetin alone treatment (Group L) exhibits mild myocardial histoarchitectural alterations. Figure 3 shows the pancreatic section of rats in Group C (continuous HFD), Group D (simvastatin), Group I (prophylactic quercetin followed by HFD) and Group K (HFD with concurrent quercetin, 100 mg/kg). Rats in Group C

(continuous HFD) show vascular congestion and widened interlobular spaces, with preserved exocrine acinar and endocrine islet architecture. The simvastatin Group D treatment exhibits vascular congestion and widened interlobular spaces, while the acinar and islet structures remain identifiable. Group I (prophylactic quercetin followed by HFD) shows vascular congestion with preserved pancreatic parenchymal architecture. Group K (HFD with concurrent quercetin, 100 mg/kg) exhibits essentially preserved pancreatic architecture, with identifiable acinar cells containing discernible zymogen granules and preserved islet-cell morphology.

Discussion

Over view of recent research showed that high-fat regimen produced a dyslipidaemic state, reflected by higher cholesterol and triglyceride concentrations in tissues as indicated by Degrave et al. [21] that hypercholesterolemia caused early cardiac lipid overload and redox-inflammatory imbalance, which could lead to impaired left ventricular (LV) function. This mechanism is similar to what had been previously reported in tissues [8,14]. Intervention of quercetin administration further confirmed the cardioprotective effects in ameliorating cardiac lipid overload by reversing high-fat diet-induced cardiac lipid droplet accumulation by inhibition of cardiomyocyte hypertrophy, reduced ventricular stiffness and normal ventricular function [22]. Earlier reports by Adesiyan et al. [8] also showed that 100 mg/kg body weight of quercetin demonstrated increased serum HDL-C and decreased atherogenic lipoproteins (LDL cholesterol) following exposure to a high-fat diet and reductions in triglycerides, total cholesterol and total protein increase are dose-dependent. Higher HDL-C in some quercetin-treated groups may reflect altered cholesterol transport, but HDL-C concentration alone does not indicate improved HDL function. This response is consistent with recent high-fat-fed rat experiments in which quercetin improved lipid profiles [15,23]. The reductions in atherogenic lipids observed in several schedules in the present study support a lipid-modulating effect, although the magnitude and direction of individual outcomes varied across groups. Similar variation appears in other models: Kábelová et al. [24] reported lower serum and hepatic triglycerides after quercetin supplementation, without reducing total cholesterol. A recent study using ApoE-deficient mice showed that quercetin increased ABCA1/ABCG expression and biliary cholesterol excretion while reducing atherosclerotic lesions [25]. These observations provide a mechanistic comparison, rather than evidence that the same transport pathways were activated in the present rats, because transporter expression and cholesterol efflux were not measured here.

Consumption of high-fat diet though not significant in this study caused elevation in the adipose tissue concentrations of total cholesterol and total protein and decreased triglyceride when compared to the negative control. A similar report affirmed that increased dietary cholesterol selectively increases visceral fat adipocyte size free cholesterol and macrophage content [26]. Administration of quercetin either for treatment (E, F, G) or as prophylaxis (H, I, J), did not have positive effects on concentration of total cholesterol in adipose tissue. Only concurrent administration of quercetin of 100 mg/kg body weight reduced the concentration of total cholesterol. How quercetin induces cholesterol reduction and metabolic consequences are poorly understood in this study but study by Akan et al. [27] reported that

quercetin supplementation significantly reduce adipose tissue cholesterol accumulation via downregulation of SREBP-1 and upregulation of UCP1-mediated browning.

Moreover, quercetin induced a significant increase in triglycerides in concurrent group K and L as observed in this study. Compared to group L, Prophylactic treatment groups (H, I, J) from 50–100 mg/kg body weight of quercetin administration reduced the adipocyte triglycerides concentration. The triglycerides-lowering effect of quercetin is better than simvastatin as observed in this study. Evidence from previous studies has documented the quercetin supplement-induced attenuation of high-fat diet-induced obesity, insulin resistance, and inflammation in adipose tissue [28], and inhibits body weight gain and adipogenesis via metalloproteinases in mice fed a high-fat diet where adiponectin, an adipose-derived hormone with insulin-sensitizing and cardioprotective actions via AMPK/PPARα activation, enhances fatty acid oxidation and reduces triglyceride accumulation [29]. Its increase following quercetin treatment suggests improved adipose function and protection against high-fat diet-induced cardiac lipid overload. This observation could also be due to the combined effects of reduced cholecystokinin and inhibition of pancreatic lipase activity as later disscussed. The mechanism involved in triglyceride reduction might be the regulatory effect of quercetin on apo C-II for the effective activation of extracellular lipoprotein lipase leading to the increased degradation of adipocyte TG or reduced absorption of dietary fat. Meanwhile, lipids such as triglycerides are stored in adipose tissues. Adipose tissue undergoes hyperplasia (increase in the number of adipocytes) and hypertrophy (increase in the size of each adipocyte) allowing adipose tissue to expand in times of nutrient excess [30], and this is expected to have been regulated by the action quercetin in this study.

Pancreatic lipase and CCK tended to be lower after quercetin administration. Recent enzyme experiments demonstrated reversible, noncompetitive inhibition of pancreatic lipase by quercetin, while an extract containing quercetin and rutin also reduced fat absorption in vivo [31]. This offers a possible explanation for altered lipid handling, but the pancreatic ELISA measurements in the present study do not demonstrate direct inhibition of intestinal lipase activity. Similarly, the recent identification of lipid-sensing pathways controlling CCK release [5] does not establish that the lower pancreatic CCK values observed here caused reduced cholesterol absorption.

Interpretation of the cholesterol-metabolism biomarkers also requires care. A higher HMG-CoA/mevalonate ratio is an indirect indicator of lower HMG-CoA reductase activity under the original assay method [19]; the inconsistent ratio changes across the present groups therefore do not establish uniform enzyme inhibition. Yang et al.[7] showed that quercetin can promote CYP7A1-mediated cholesterol-to-bile-acid conversion through mTOR/YY1 regulation. Additional studies have also linked quercetin-driven changes in gut microbiota to CYP8B1-dependent bile-acid metabolism [32]. These studies support bile-acid regulation as a candidate mechanism, but the CYP7A1 concentrations measured by ELISA here do not directly demonstrate increased catalytic activity or bile-acid flux.

Cardiac histopathological findings across the experimental groups are presented in Fig. 2. Groups A (standard-diet control) and B (HFD withdrawal) exhibited predominantly regular myocardial fibres with

elongated, centrally located nuclei and generally preserved fibre alignment. Groups E, H, and J also exhibited largely preserved myocardial architecture, with no conspicuous evidence of extensive myofibre disruption. In contrast, Group C (continuous HFD administration) showed wavy and irregularly arranged myocardial fibres, widened interstitial spaces, increased interstitial cellularity, and occasional small or pale-appearing nuclei. These changes are suggestive of myocardial structural injury, potentially involving myofibre degeneration and interstitial expansion. Groups D, F, G, and I exhibited comparatively mild myocardial alterations, characterised by focal attenuation or loss of visible cross-striations and apparent reduction in myofibre calibre. These findings suggest mild myocardial structural changes. Group K (HFD with concurrent quercetin, 100 mg/kg) exhibited more conspicuous myocardial disorganisation, with fragmented or separated fibres, sparse visible nuclei in affected areas, and widened interstitial gaps. These features are consistent with myocardial fibre degeneration and interstitial expansion. Group L (quercetin alone) also showed mild histoarchitectural alterations. The observed findings across the quercetin-treated groups did not demonstrate a consistent dose-dependent pattern, as some groups retained essentially normal architecture whereas others exhibited mild structural changes. Collectively, the findings suggest that continuous HFD exposure was associated with the most prominent cardiac alterations, while the apparent myocardial response varied across the treatment regimens. The relatively conspicuous changes in Group K also indicate that concurrent quercetin administration did not uniformly prevent HFD-associated myocardial alterations under the conditions examined. Histology seemed to follow the biochemical reports in this study. Studies have documented that Wistar rats on a high-fat diet were accompanied by hepatic steatosis and degeneration and disrupted cardiac architecture [8]. Changes were also observed in other high-fat-diet experiments [33,34]. Treatment with quercetin and prophylactic exposure improved the appearance of cardiac tissue (Fig. 2). Histological findings showed disrupted cardiac architecture and pancreatic vascular congestion in selected high-fat-diet groups. Recent studies have likewise reported hepatic and cardiac injury during experimental metabolic syndrome and improvement after quercetin exposure [9,14].

Pancreatic histopathological findings in selected experimental groups (C, D, I and K) are presented in Fig. 3. Groups C (continuous HFD), D (simvastatin), and I (prophylactic quercetin followed by HFD) exhibited vascular congestion, characterised by the presence of erythrocytes and/or eosinophilic intravascular material within vascular lumina. Groups C and D additionally showed widened interlobular spaces, potentially reflecting interstitial expansion. However, the exocrine pancreatic acini and endocrine islets of Langerhans appeared structurally preserved in the examined sections, without conspicuous acinar disruption or overt islet-cell loss. Group K (HFD with concurrent quercetin, 100 mg/kg) exhibited essentially preserved pancreatic architecture, with identifiable acinar cells containing discernible zymogen granules and preserved islet-cell morphology. No conspicuous structural abnormalities were evident in the examined field. Overall, the pancreatic findings were comparatively limited, consisting primarily of vascular congestion in Groups C, D, and I and interlobular-space widening in Groups C and D. The preservation of acinar and islet architecture across the examined groups suggests an absence of overt pancreatic parenchymal destruction in the sampled sections. In the selected pancreatic section, concurrent treatment at 100 mg/kg body weight produced an almost normal appearance. Because

lesions remained in some groups, the protective response appears to have varied with both the organ examined and the exposure schedule. This could make the interpretation of the pancreatic results require caution since total pancreatic cholesterol was not significantly different among groups. Although some groups show differences in triglycerides and protein, together with vascular congestion in selected sections, the findings are compatible with the known vulnerability of pancreatic tissue to injury associated with lipid excess [35,36]. The pancreatic observations should be interpreted alongside the absence of a significant overall difference in pancreatic cholesterol. Quercetin has also been documented to reduce inflammatory injury and improve mitochondrial function in a separate rat model of acute pancreatitis [37], but that model has a different initiating insult and cannot establish the mechanism of protection against dietary lipid excess here. Taken together, the contemporary literature supports further testing of quercetin while reinforcing the need to distinguish biochemical associations from demonstrated mechanisms and clinical efficacy. In a high-fat-fed rat model, Rasheed et al. [38] observed pancreatic degeneration and inflammation that were reduced by concurrent quercetin administration. Treatment and prophylactic exposure in the present study improved tissue appearance in some groups, while lesions persisted in others (Figs. 2–3), indicating that the response depended on the organ and exposure schedule.

Conclusions

Dietary quercetin improved several measures of lipid status in this Wistar-rat model, with the 100 mg/kg body-weight treatment and prophylactic schedules showing the most consistent benefits. Tissue responses varied across organs and exposure schedules. Changes in CCK, the HMG-CoA/mevalonate ratio and CYP7A1 concentration identify possible pathways for further investigation, but do not establish direct enzyme inhibition, increased bile-acid synthesis or superiority to simvastatin. The findings support additional investigation of quercetin as a nutraceutical candidate in experimental dyslipidemia.

Declarations

Author Contributions

A.A.A. conceived the study, curated the data, conducted the laboratory analyses, and prepared the original manuscript draft. A.F.A. contributed the laboratory analyses and data curation. M.O.A. and T.O.A. performed and reviewed the statistical analyses. A.M. conducted the histological analyses and contributed to data visualisation. A.S.A. contributed to the study conceptualisation and supervision. All authors contributed to the manuscript review and editing and approved the final version of the manuscript.

Consent for Publication

Not applicable. The manuscript contains no person’s data, images, or videos.

Conflict of Interest

The authors declare no financial or personal relationships that could have influenced this work.

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Declaration of generative AI use

OpenAI ChatGPT assisted with language revision, reorganisation of manuscript text, and document formatting. All authors reviewed the scientific statements, interpretation of the data, and conclusions, approved the final content, and retain full responsibility for the submitted manuscript.

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Data availability statement

The individual-animal biochemical datasets are designated as Supplementary Materials S1–S4. Quercetin/simvastatin preparation details are designated as S5. These materials relate to the 60 animals and the 90-day protocol described in this article.

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