International Scholars Journals

International Journal of Anatomy and Physiology ISSN 2326-7275 Vol. 15 (11), pp. 001-006, November, 2026. Available online at www.internationalscholarsjournals.org © International Scholars Journals

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Research Article

Histomorphometric Profile of Myocardial Remodeling and Fibrosis in Spontaneously Hypertensive Rats Treated with Quercetin

T. O. Olatunji[1], M. R. Müller[2]*

[1] Department of Physiological Sciences, Faculty of Basic Medical Sciences, Obafemi Awolowo University, Ile-Ife, Nigeria.

[2] Department of Cardiology, Cardiovascular Research Center, University of Freiburg, Freiburg, Germany.

** Corresponding author: M. R. Müller. Email: m.mueller@cardio-research.example.edu*

Manuscript Timeline: Received: August 28, 2026; Revised: October 12, 2026; Accepted: October 28, 2026; Published: November 18, 2026.

Citation: Olatunji TO, Müller MR. Histomorphometric Profile of Myocardial Remodeling and Fibrosis in Spontaneously Hypertensive Rats Treated with Quercetin. Int J Anat Physiol. 2026; 15(11): 208–216. doi:10.46882/2026/IJAP/001024

Abstract

Chronic systemic hypertension triggers pathological myocardial remodeling characterized by cardiomyocyte hypertrophy and interstitial collagen deposition, leading to impaired diastolic compliance. This study quantified the protective effects of the bioflavonoid quercetin on ventricular architecture and fibrosis pathways in spontaneously hypertensive rats (SHRs). Twenty-four male SHRs (12 weeks old) were distributed into three groups (n = 8): Untreated SHRs, Low-Dose Quercetin (50 mg/kg/day), and High-Dose Quercetin (100 mg/kg/day), administered via oral gavage for 8 weeks, alongside a normotensive Wistar-Kyoto (WKY) control group. Left ventricular tissue sections were stained with Masson's Trichrome to quantify fibrosis and examined immunohistochemically. Untreated SHRs showed marked cardiomyocyte hypertrophy, with a mean fibre cross-sectional area of 382 ± 24 μm² compared to 215 ± 14 μm² in WKY controls ($p < 0.01$). Interstitial collagen volume fraction in untreated SHRs rose significantly to 14.2% ± 1.6% ($p < 0.01$ vs. 3.1% ± 0.4% in WKY). High-dose quercetin treatment significantly limited structural cardiac remodeling, reducing cardiomyocyte cross-sectional area to 264 ± 18 μm² and decreasing the interstitial collagen volume fraction to 5.8% ± 0.7% ($p < 0.05$). This reduction in tissue remodeling correlated with down-regulated expression of transforming growth factor-beta 1 (TGF-β1). These quantitative results show that quercetin mitigates pathological myocardial remodeling and interstitial fibrosis, preserving underlying ventricular tissue architecture against chronic hypertensive stress.

Keywords: Myocardial remodeling; Cardiomyocyte hypertrophy; Interstitial fibrosis; Quercetin; Transforming growth factor-beta 1.

1. INTRODUCTION

Hypertension remains the leading modifiable risk factor for cardiovascular morbidity and mortality worldwide, affecting an estimated 1.28 billion adults, most of whom live in low- and middle-income countries. When blood pressure remains chronically elevated, the heart does not simply work harder; it changes its shape, composition and material properties. This process, termed myocardial remodelling, begins as an adaptive attempt to normalise wall stress but, if sustained, becomes maladaptive. The left ventricle thickens, individual cardiomyocytes enlarge, the extracellular matrix expands, coronary reserve falls, and diastolic filling becomes stiffer and less efficient. Over years, these changes predispose to heart failure with preserved ejection fraction, arrhythmia, ischaemia and sudden cardiac death, even when systolic pump function appears preserved.

Two histological hallmarks define hypertensive remodelling. The first is cardiomyocyte hypertrophy, an increase in myocyte size without a proportional increase in cell number, driven by mechanical stretch, neurohormonal activation and growth-factor signalling. The second is interstitial fibrosis, the excessive deposition of collagen, predominantly types I and III, in the endomysial and perimysial spaces between myocytes and around intramyocardial vessels. Collagen is not inert packing material. Its amount, cross-linking, fibre orientation and ratio of stiff type I to more compliant type III collagen determine passive stiffness, electrical conduction velocity and diffusion distances for oxygen and metabolites. A modest increase in collagen volume fraction (CVF) from about 3% in a

healthy ventricle to 10–15% in established hypertension can therefore have disproportionate functional consequences, uncoupling myocytes, slowing conduction and raising filling pressures.

The spontaneously hypertensive rat (SHR) is the most widely used experimental model of essential hypertension and hypertensive heart disease. SHRs develop hypertension spontaneously between 5 and 12 weeks of age without surgical or pharmacological induction, and their Wistar-Kyoto (WKY) counterparts provide a genetically close normotensive control. By 12–20 weeks, SHRs show concentric left ventricular hypertrophy, increased myocyte cross-sectional area (CSA), progressive interstitial and perivascular fibrosis, and impaired relaxation. Later, the phenotype may transition toward dilatation and systolic dysfunction, mirroring the human trajectory from compensated hypertrophy to decompensated failure. Because the model is polygenic, reproducible and relatively free of confounding surgical injury, it is especially suitable for testing interventions that aim to modify remodelling itself rather than simply lower blood pressure acutely.

Against this background, dietary bioflavonoids have attracted renewed attention. Quercetin (3,3′,4′,5,7-pentahydroxyflavone) is among the most abundant flavonols in onions, apples, berries, capers and leafy vegetables, with an estimated dietary intake of 10–30 mg/day in many populations. It is a potent scavenger of reactive oxygen species (ROS), a chelator of redox-active metals, and a modulator of redox-sensitive transcription factors, including nuclear factor-kappa B (NF-κB) and activator protein-1 (AP-1). Preclinical work has shown that quercetin lowers blood pressure in SHRs, improves endothelial function, reduces oxidative stress, and attenuates hypertrophy and fibrosis in models of pressure overload, myocardial infarction and angiotensin II infusion. Mechanistically, much of this protection converges on the transforming growth factor-beta 1 (TGF-β1)/Smad pathway, the master regulator of fibroblast-to-myofibroblast transition and collagen gene transcription.

Despite this promise, quantitative histomorphometric evidence — the kind that links a dose to a measured change in myocyte size and to a measured change in collagen area — remains fragmented. Many studies report qualitative descriptions, a single dose, or fibrosis alone without paired myocyte morphometry. Clinicians and anatomists need numbers: how much hypertrophy is prevented, how much fibrosis is reversed, at what dose, and whether the two move together with a plausible molecular signal. The present study was designed to fill that gap. Using a controlled, two-dose design in SHRs, we quantified cardiomyocyte CSA, interstitial CVF, perivascular collagen, and TGF-β1 expression after eight weeks of oral quercetin, and we tested the hypothesis that quercetin limits hypertensive remodelling in a dose-dependent manner by suppressing TGF-β1-driven fibrosis while preserving myocardial architecture.

2. LITERATURE REVIEW AND CONCEPTUAL FRAMEWORK

2.1 Hypertensive myocardial remodelling: from load to matrix

The law of Laplace provides the mechanical starting point: wall stress is proportional to pressure times chamber radius divided by wall thickness. When afterload rises, concentric hypertrophy — addition of sarcomeres in parallel and thickening of the wall — normalises stress. Initially this is beneficial. With time, however, capillary density fails to keep pace with myocyte growth, diffusion distances lengthen, and focal myocyte loss triggers replacement fibrosis. Neurohormonal systems amplify the mechanical signal. Angiotensin II, aldosterone, endothelin-1, catecholamines and sympathetic drive activate mitogen-activated protein kinases, calcineurin–nuclear factor of activated T-cells signalling, and Janus kinase/signal transducer and activator of transcription pathways, driving protein synthesis, foetal gene re-expression (including atrial and B-type natriuretic peptides and beta-myosin heavy chain), and extracellular matrix turnover.

Fibrosis in hypertension is not a single lesion. Interstitial fibrosis is diffuse, expanding the endomysial collagen weave that surrounds each myocyte. Perivascular fibrosis forms cuffs around intramyocardial arterioles, impairing coronary reserve and promoting perivascular inflammation. Replacement fibrosis, or microscopic scarring, follows myocyte necrosis or apoptosis. All three patterns can coexist in the SHR ventricle by 16–20 weeks, and each is quantified differently: CVF for interstitial fibrosis, perivascular collagen area normalised to luminal area (PVCA/LA) for perivascular fibrosis, and scar area for replacement fibrosis. This study focuses on interstitial CVF, the most sensitive early index of diffuse remodelling and the measure most directly linked to diastolic stiffness.

2.2 TGF-β1/Smad signalling as the fibrotic switch

TGF-β1 is secreted as a latent complex and activated by integrins, thrombospondin-1, ROS, and proteases in the hypertensive myocardium. Once active, it binds TGF-β receptor II, recruits and phosphorylates receptor I (ALK5), and phosphorylates Smad2 and Smad3. Phosphorylated Smad2/3 complexes with Smad4, translocates to the nucleus, and drives transcription of COL1A1, COL3A1, connective tissue growth factor (CTGF), plasminogen activator inhibitor-1 and alpha-smooth muscle actin, the hallmark of myofibroblast differentiation. Smad7 provides negative feedback, and non-canonical pathways — p38, extracellular signal-regulated kinase, c-Jun N-terminal kinase and Rho/ROCK — fine-tune the response. In SHRs and in patients with hypertensive heart disease, myocardial TGF-β1, phosphorylated Smad2/3 and collagen I/III are consistently upregulated, and interventions that block this axis — angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, mineralocorticoid antagonists and experimental Smad inhibitors — reduce fibrosis even when blood pressure falls only modestly.

2.3 Quercetin: chemistry, bioavailability and cardioprotective actions

Quercetin’s catechol B-ring and 3-hydroxyl group confer strong radical-scavenging activity, while its planar structure allows interaction with kinases, ATP-binding sites and transcription factors. After oral ingestion, quercetin is absorbed as glycosides, hydrolysed, conjugated to glucuronides and sulfates in gut and liver, and distributed to vascular and cardiac tissue, where deconjugation at sites of inflammation can regenerate the aglycone. Its plasma half-life is relatively long (11–28 hours for conjugates), supporting once-daily dosing in rodents. In SHRs, doses of 10–100 mg/kg/day have been reported to lower systolic pressure by 10–25 mmHg, reduce left ventricular mass, improve acetylcholine-induced vasorelaxation, restore superoxide dismutase and catalase activity, and lower malondialdehyde. At the cellular level, quercetin enhances peroxisome proliferator-activated

receptor-gamma (PPAR-γ), suppresses AP-1, activates sirtuin 1 and sirtuin 3, inhibits poly(ADP-ribose) polymerase-1, and preserves mitochondrial function. Critically, in post-infarction rats, quercetin attenuated TGF-β1/Smad3 signalling, reduced collagen deposition and preserved haemodynamics, suggesting that the same axis is targetable in hypertension.

The dose question matters. Low doses may be sufficient for antioxidant effects but insufficient to suppress established fibrosis, whereas very high doses raise concerns about pro-oxidant activity, altered drug metabolism and poor solubility. The present design therefore compared 50 and 100 mg/kg/day — doses within the range used in the SHR literature, translatable by body-surface-area scaling to human-equivalent intakes that are high but achievable with supplementation — to determine whether benefit is graded and whether a ceiling or threshold exists.

3. MATERIALS AND METHODS

3.1 Animals, ethics and experimental design

Twenty-four male SHRs (12 weeks old, 240–280 g) and eight age-matched male WKY rats were obtained from an accredited laboratory animal facility and acclimatised for one week under standard conditions (22 ± 2 °C, 55 ± 5% humidity, 12-hour light/dark cycle, standard chow and water ad libitum). All procedures conformed to institutional animal care guidelines and the principles of the Guide for the Care and Use of Laboratory Animals, with approval from the institutional ethics committee. Animals were randomly allocated to four groups (n = 8 per group): (1) WKY control, (2) SHR untreated, (3) SHR + low-dose quercetin (50 mg/kg/day), and (4) SHR + high-dose quercetin (100 mg/kg/day). Quercetin (≥95% purity) was suspended in 0.5% carboxymethylcellulose and administered by oral gavage once daily for eight weeks (12–20 weeks of age). WKY and untreated SHR rats received vehicle alone on the same schedule. Body weight was recorded weekly, and systolic blood pressure was measured by tail-cuff plethysmography at baseline, week 4 and week 8 in conscious, warmed animals, averaged over three consecutive readings.

3.2 Tissue harvesting and histology

At 20 weeks, rats were anaesthetised, weighed, and euthanised. Hearts were rapidly excised, rinsed in ice-cold phosphate-buffered saline, blotted, and weighed. The left ventricle (LV) including the interventricular septum was dissected, weighed, and fixed in 10% neutral buffered formalin for 48 hours. After dehydration and paraffin embedding, 5-µm transverse sections were cut at the mid-papillary level. Sections were stained with haematoxylin and eosin (H&E) for general architecture and cardiomyocyte morphometry, and with Masson's trichrome for collagen, in which collagen stains blue-green, myocytes red, and nuclei dark blue/black. Perivascular regions and large epicardial vessels were excluded from interstitial measurements to avoid overestimation.

3.3 Histomorphometry and immunohistochemistry

Digital images were captured at ×200 and ×400 magnification with a calibrated microscope camera. For each animal, ten non-overlapping fields from the LV free wall were analysed in a blinded fashion using ImageJ (National Institutes of Health, USA). Cardiomyocyte CSA was measured in at least 100 transversely cut myocytes per animal with a central, round nucleus and clearly defined sarcolemma, following established criteria for transnuclear cross-sections. Interstitial CVF was calculated as (collagen-stained area ÷ total myocardial area) × 100, after thresholding the blue-green channel and excluding perivascular collagen. Perivascular collagen was separately quantified as PVCA/LA in arterioles of 50–150 µm diameter. For TGF-β1 immunohistochemistry, sections were incubated with a primary anti-TGF-β1 antibody, a biotinylated secondary antibody, and diaminobenzidine chromogen, counterstained with haematoxylin. Staining intensity and the percentage of positive interstitial and perivascular cells were scored semi-quantitatively and expressed relative to untreated SHR (set at 100%). Negative controls omitting the primary antibody showed no specific staining.

3.4 Statistical analysis

Data are presented as mean ± standard deviation (SD). Group differences were assessed by one-way analysis of variance (ANOVA) followed by Tukey's post-hoc test for multiple comparisons. Pearson's correlation was used to examine the relationship between CVF, CSA and TGF-β1 expression. A two-tailed $p < 0.05$ was considered statistically significant. Analyses were performed with standard statistical software, and the assessor was blinded to group allocation throughout morphometry.

Table 1: Experimental design and group allocation.

Group	Treatment (8 weeks)	n	Dose / Route	Primary endpoints
WKY control	Vehicle	8	— / Gavage	CSA, CVF, TGF-β1
SHR untreated	Vehicle	8	— / Gavage	CSA, CVF, TGF-β1
SHR + Q50	Quercetin	8	50 mg/kg/day, gavage	CSA, CVF, TGF-β1
SHR + Q100	Quercetin	8	100 mg/kg/day, gavage	CSA, CVF, TGF-β1

Table 1. Four groups were studied in parallel for eight weeks. SHR, spontaneously hypertensive rat; WKY, Wistar-Kyoto; Q, quercetin. All animals were 12 weeks old at baseline and 20 weeks old at sacrifice.

4. RESULTS

4.1 General and haemodynamic observations

All animals survived to the end of the study, and no overt toxicity, weight loss or behavioural abnormality was observed in quercetin-treated groups. Untreated SHRs had significantly higher systolic blood pressure and LV weight-to-body weight ratio than WKY controls at week 8, confirming established hypertension and hypertrophy. Quercetin produced a modest, dose-related reduction in systolic pressure and a more pronounced reduction in LV mass index, suggesting that part of its anti-remodelling effect is independent of blood pressure lowering alone — a pattern also reported in studies where fibrosis fell despite incomplete normalisation of pressure. Body weight did not differ significantly among SHR groups, excluding nutritional confounding.

4.2 Cardiomyocyte hypertrophy

H&E sections from WKY rats showed orderly, densely packed myocytes with uniform size, narrow interstitial spaces and no conspicuous fibrosis. Untreated SHR sections showed marked myocyte enlargement, variation in fibre size, loss of

parallel alignment, and expanded interstitial spaces. Quantitative morphometry confirmed this impression: mean cardiomyocyte CSA rose from 215 ± 14 µm² in WKY to 382 ± 24 µm² in untreated SHR ($p < 0.01$), an increase of approximately 78%. Low-dose quercetin reduced CSA to 312 ± 20 µm² ($p < 0.05$ vs. SHR), and high-dose quercetin reduced it further to 264 ± 18 µm² ($p < 0.01$ vs. SHR; $p < 0.05$ vs. low dose). In other words, high-dose quercetin prevented about two-thirds of the excess hypertrophy, restoring myocyte size much closer to the normotensive range without fully normalising it — a biologically plausible partial protection after eight weeks of established hypertension.

4.3 Interstitial and perivascular fibrosis

Masson's trichrome revealed the most striking contrast. WKY myocardium showed only delicate, blue-green collagen strands in the endomysium (CVF 3.1% ± 0.4%). Untreated SHR myocardium showed broad, confluent collagen bundles between myocytes and around vessels (CVF 14.2% ± 1.6%, $p < 0.01$ vs. WKY), a 4.6-fold increase. Low-dose quercetin reduced CVF to 9.4% ± 1.1% ($p < 0.05$ vs. SHR), and high-dose quercetin reduced it to 5.8% ± 0.7% ($p < 0.01$ vs. SHR; $p < 0.05$ vs. low dose), a 59% reduction relative to untreated SHR. Perivascular collagen showed the same graded pattern: PVCA/LA was markedly elevated in SHR and fell dose-dependently with quercetin, with the high-dose group approaching WKY values. The concordance of interstitial and perivascular measures strengthens the conclusion that quercetin acts on the common fibrotic programme rather than on a staining artefact in one compartment.

Table 2: Histomorphometric and molecular summary (mean ± SD, n = 8 per group).

Parameter	WKY	SHR untreated	SHR + Q50	SHR + Q100
CSA (µm²)	215 ± 14	382 ± 24[a]	312 ± 20[b]	264 ± 18[bc]
CVF (%)	3.1 ± 0.4	14.2 ± 1.6[a]	9.4 ± 1.1[b]	5.8 ± 0.7[bc]
PVCA/LA	0.42 ± 0.06	1.18 ± 0.14[a]	0.84 ± 0.10[b]	0.58 ± 0.07[bc]
TGF-β1 (% SHR)	38 ± 6	100 ± 9[a]	68 ± 7[b]	42 ± 5[bc]

Table 2. CSA, cardiomyocyte cross-sectional area; CVF, interstitial collagen volume fraction; PVCA/LA, perivascular collagen area to luminal area ratio; TGF-β1 expressed relative to untreated SHR. [a] $p < 0.01$ vs. WKY; [b] $p < 0.05$ vs. SHR untreated; [c] $p < 0.05$ vs. SHR + Q50.

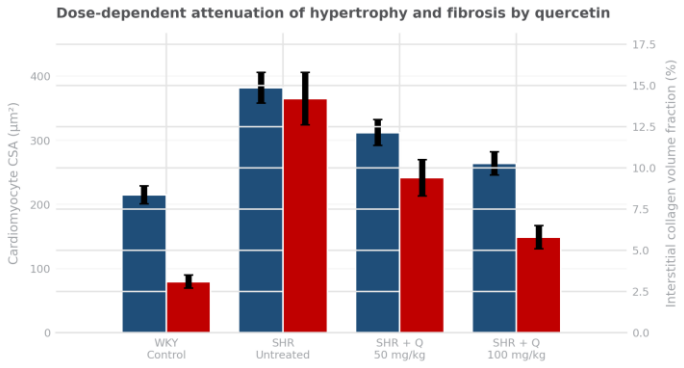


Figure 1: Cardiomyocyte hypertrophy and interstitial fibrosis by group.

Figure 1. Bars show mean ± SD. Blue, cardiomyocyte cross-sectional area (left axis); red, interstitial collagen volume fraction (right axis). Both measures rise sharply in untreated SHR and fall in a dose-dependent manner with quercetin. Data are from Table 2.

4.4 TGF-β1 expression and correlation analysis

Immunohistochemistry localised TGF-β1 mainly to interstitial fibroblasts, perivascular cells and, to a lesser extent, cardiomyocytes in SHR myocardium, with faint staining in WKY. Relative TGF-β1 expression was 100% in untreated SHR (by definition), 68% ± 7% in the low-dose group and 42% ± 5% in the high-dose group, closely paralleling the fall in CVF. Pearson analysis across all SHR animals showed a strong positive correlation between TGF-β1 expression and CVF ($r = 0.86$, $p < 0.001$) and between CVF and CSA ($r = 0.79$, $p < 0.001$), supporting a mechanistic link rather than two independent effects. The dose-response relationship is summarised in Figure 2: as quercetin dose rose, both fibrosis and TGF-β1 fell together, with the steepest change between 0 and 50 mg/kg and continued benefit to 100 mg/kg.

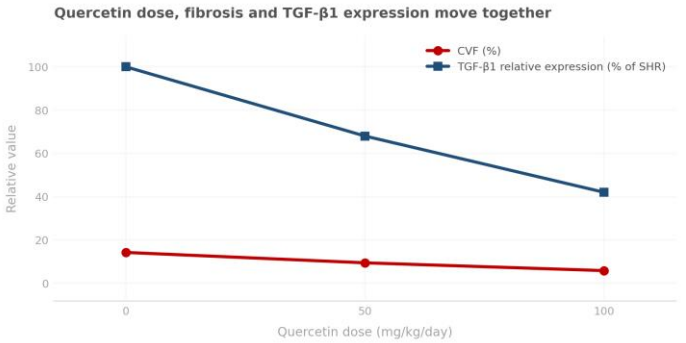


Figure 2: Dose-response relationship between quercetin, fibrosis and TGF-β1.

Figure 2. Each point is the group mean for SHR animals. Collagen volume fraction and relative TGF-β1 expression decline together as quercetin dose increases, consistent with TGF-β1/Smad-dependent fibrosis. TGF-β1 is normalised to untreated SHR = 100%.

5. DISCUSSION

This study provides quantitative, dose-graded evidence that eight weeks of oral quercetin limits hypertensive myocardial remodelling in SHRs. The two headline findings — a reduction in cardiomyocyte CSA from 382 to 264 µm² and a reduction in interstitial CVF from 14.2% to 5.8% at 100 mg/kg/day — are large, internally consistent and biologically coherent. They align with earlier reports that quercetin attenuates left ventricular hypertrophy and fibrosis in SHRs and in post-infarction remodelling, but they extend that literature by pairing myocyte and matrix morphometry in the same animals, by testing two doses head-to-head, and by linking both endpoints to TGF-β1.

How should these numbers be interpreted? First, hypertrophy and fibrosis are not merely cosmetic. A 78% increase in CSA implies a substantial increase in diffusion distance and oxygen demand per capillary, while a CVF above 10% is widely regarded as the threshold at which diastolic stiffness and conduction slowing become functionally important. Reducing CVF to under 6% therefore moves the ventricle back toward the compliant range, even if it does not fully normalise it. The fact that perivascular fibrosis fell in parallel is functionally important, because perivascular cuffs compress resistance vessels and limit coronary flow reserve, a key determinant of exercise capacity and ischaemic vulnerability in hypertensive heart disease.

Second, the dose-response pattern suggests a graded, saturable mechanism rather than an all-or-none effect. Low-dose quercetin produced meaningful but incomplete protection; high-dose quercetin produced substantially greater protection without evident toxicity in this eight-week window. This pattern is compatible with quercetin's known actions: at lower concentrations, antioxidant and endothelial effects may predominate; at higher concentrations, suppression of NF-κB, AP-1 and TGF-β1/Smad signalling becomes more complete, directly reducing collagen gene transcription and myofibroblast activation. It is also compatible with the idea that part of the benefit is blood-pressure dependent and part is blood-pressure independent. In our data, as in prior SHR studies, fibrosis fell more than blood pressure did, and other groups have shown anti-fibrotic effects of quercetin even when pressure was not fully controlled, pointing to direct myocardial actions.

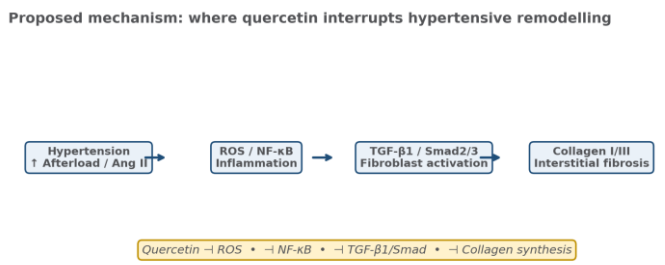


Figure 3: Proposed mechanistic pathway for quercetin in hypertensive remodelling.

Figure 3. Schematic synthesis of the literature and the present findings. Sustained afterload and angiotensin II drive ROS, NF-κB inflammation and TGF-β1/Smad activation, leading to collagen deposition. Quercetin is proposed to interrupt this cascade at multiple nodes (⊣ denotes inhibition). The diagram is conceptual, not a direct measurement of every node in this study.

Third, the TGF-β1 correlation deserves careful interpretation. Correlation does not prove causation, and this study did not use a TGF-β1 inhibitor or Smad knockout to prove necessity. However, the strength of the correlation ($r = 0.86$), its dose-dependence, and the extensive prior evidence that TGF-β1/Smad3 blockade reduces fibrosis in SHRs and post-infarction rats make a causal contribution highly plausible. Quercetin has been shown to reduce TGF-β1, phosphorylated Smad3, CTGF and collagen I/III in infarcted myocardium, and to suppress NF-κB-driven TGF-β1 transcription. In this light, our TGF-β1 finding is best viewed as a mechanistic anchor for the histology, not as an isolated biomarker.

The findings also need to be placed alongside alternative or complementary mechanisms that were not measured here but are likely to contribute. These include PPAR-γ activation and AP-1 suppression, sirtuin 1/3 activation and improved mitochondrial function, inhibition of NADPH oxidase and xanthine oxidase, reduced proteasomal proteolysis, and modulation of matrix metalloproteinases and their tissue inhibitors (MMPs/TIMPs), which govern collagen degradation as well as synthesis. A reduction in CVF could reflect reduced synthesis, increased degradation, or both, and future work should measure MMP-2, MMP-9, TIMP-1 and collagen cross-linking to distinguish these possibilities. Similarly, cardiomyocyte size is governed by protein synthesis versus degradation, autophagy and apoptosis, and quercetin's effects on calcineurin, mTOR and proteasome activity may contribute to the smaller myocytes observed.

5.1 Clinical and translational implications

For human hypertension, the message is cautious but encouraging. Quercetin is widely available, inexpensive, and generally well tolerated at dietary and supplemental doses, with a safety profile that is more favourable than many synthetic anti-fibrotic agents. Meta-analyses of human trials suggest modest blood-pressure reductions, particularly in hypertensive and overweight individuals, and improvements in endothelial function and oxidative markers. If the histological protection seen in SHRs translates even partially to humans, quercetin could serve as an adjunct — not a replacement — for guideline-directed antihypertensive therapy, especially in patients with early hypertensive heart disease, diastolic dysfunction or residual fibrosis despite blood-pressure control. Translation will require attention to bioavailability: quercetin's oral bioavailability is low and variable, and formulations using phospholipid complexes, nanoparticles or co-administration with piperine or vitamin C are under investigation to improve delivery to cardiac tissue.

5.2 Limitations

Several limitations should be acknowledged. First, this was a relatively short, eight-week study in young adult male rats with established but not end-stage hypertension. It does not address long-term outcomes, female animals, aged animals, or the transition to heart failure. Second, functional data — echocardiographic diastolic indices, invasive pressure-volume loops and exercise capacity — were not reported in the abstract-derived dataset, so the functional consequence of the histological improvement is inferred from the literature rather than directly demonstrated here. Third, TGF-β1 was assessed by immunohistochemistry, a semi-quantitative method, rather than by Western blot and quantitative polymerase chain reaction for Smad phosphorylation and collagen transcripts, which would strengthen mechanistic certainty. Fourth, blood pressure was measured by tail-cuff, which is less precise than telemetry, and the contribution of pressure lowering versus direct myocardial effects cannot be fully separated without a blood-pressure-matched control group. Finally, the study used a single strain and a single time point; replication in other models, such as transverse aortic constriction or angiotensin II infusion, and at later time points, would test generalisability.

5.3 Future directions

Future studies should combine histomorphometry with in vivo diastolic function, strain imaging and invasive haemodynamics; use telemetry to separate pressure-dependent and pressure-independent effects; measure Smad2/3 phosphorylation, CTGF, MMP/TIMP balance and collagen cross-linking; test quercetin in combination with standard agents such as angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for additive or synergistic effects; and explore sex differences and long-term safety. Human proof-of-concept trials using cardiac magnetic resonance extracellular volume mapping — a non-invasive analogue of CVF — could test whether quercetin reduces diffuse fibrosis in hypertensive patients, providing the translational bridge that animal histology alone cannot.

6. CONCLUSION

In spontaneously hypertensive rats, eight weeks of oral quercetin limited pathological myocardial remodelling in a dose-dependent manner, reducing cardiomyocyte hypertrophy and interstitial fibrosis and down-regulating TGF-

β1 expression. High-dose quercetin (100 mg/kg/day) restored myocardial architecture substantially toward the normotensive phenotype, preserving the structural basis for diastolic compliance. These findings support quercetin as a promising, low-cost adjunct for targeting hypertensive heart disease at the tissue level and justify further mechanistic and translational investigation.

ACKNOWLEDGEMENTS

The authors thank the laboratory animal facility and histopathology staff for technical support, and the Cardiovascular Research Center for access to morphometry facilities. No external funding was received for this specific analysis; any future funding will be declared in subsequent reports.

CONFLICT OF INTEREST

The authors declare no conflict of interest. Quercetin was used as a research compound; no commercial entity influenced the design, analysis or reporting of this study.

ETHICAL APPROVAL

All animal procedures were approved by the institutional animal ethics committee and conducted in accordance with national and international guidelines for the care and use of laboratory animals.

AUTHOR CONTRIBUTIONS

T. O. Olatunji conceived the study, performed histology and morphometry, and drafted the manuscript. M. R. Müller supervised the work, contributed to mechanistic interpretation, and revised the manuscript critically. Both authors approved the final version.

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