Quercetin Ameliorates Renal Fibrosis via SIRT5 in Diabetic Nephropathy

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Original Paper

Introduction. Renal fibrosis represents the principal pathological characteristic of diabetic nephropathy (DN). Quercetin, a well-known flavonoid with diverse pharmacological effects, has been studied for its link to preventing DN. Previous studies indicated that SIRT5 might have significant implications in fibrotic diseases. This study investigated whether the protective effects of quercetin on DN was related to SIRT5.

Methods. Three doses of quercetin (30 mg/kg, 60 mg/kg, and 120 mg/kg) were orally administered to streptozotocin-induced diabetic rats over a period of four months. Colorimetric methods were used to measure blood urea nitrogen (BUN), serum creatinine (SCr) and urine creatinine (UCr). Enzyme-linked immunosorbent assay (ELISA) was used to quantify the level of urine microalbumin (Ualb). The ratio of urine microalbumin to urine creatinine (Ualb/UCr) was calculated. Periodic acid-Schiff (PAS) stain and Masson's trichrome stain were used to observe glycogen deposition and collagen accumulation in the renal cortex, respectively. Western blot, ELISA, and immunohistochemical stain were performed to quantify the levels of SIRT5 protein in kidneys of rats.

Results. Diabetic rats exhibited increased levels of SCr, BUN, and Ualb/UCr, accompanied by significant glycogen deposition and collagen accumulation in renal cortex. These changes were associated with an increased level of SIRT5 protein. Following treatment of DN rats with varying doses of quercetin, all kidney function and pathology indices showed varying degrees of reversal, accompanied by a reduction in SIRT5 protein levels.

Conclusion. Quercetin ameliorated renal fibrosis in DN rats via the inhibition of SIRT5, suggesting a novel mechanism of quercetin in the treatment of DN.

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INTRODUCTION

Diabetic nephropathy (DN), recognized as a common microvascular complication of diabetes mellitus (DM), constitutes the primary etiological factor for end-stage kidney disease (ESKD).[1] Hyperglycemia contributes to kidney damage by the accumulation of mesangial matrix and loss of tight junctions between cells, resulting in renal fibrosis.[2-4] Therefore, elucidating the mechanisms of renal fibrosis and exploring effective drugs for

DN have become important issues in the diabetes research.

Sirtuins, a family of evolutionarily conserved NAD^+-dependent deacylases, orchestrate fundamental biological processes including genomic stability maintenance, mitochondrial bioenergetic regulation, and redox homeostasis through dynamic post-translational modifications (lysine malonylation, succinylation, and glutarylation).[5] Among the sirtuin family members, SIRT5 has been implicated in multiple tumors due to its involvement in post-translational modifications.[6] Recently, SIRT5 has emerged as a significant factor in several non-neoplastic diseases, such as lung fibrosis and myocardial fibrosis.[7,8] Notably, recent investigations implicate SIRT5-mediated metabolic reprogramming in the pathogenesis of diabetic renal fibrosis. For example, Chiba *et al.* demonstrated that knocking out SIRT5 in mice enhanced kidney function and improved injury in models of ischemia-induced and cisplatin-induced acute kidney injury.[9] Similarly, Baek J *et al.* reported increased SIRT5 levels in the kidneys of type 2 diabetic mice and in diabetic kidney samples from Southwestern American Indians.[10] However, few studies explored the relationship between SIRT5 and renal fibrosis in DN.

Quercetin, a natural flavonoid, possesses many pharmacological effects and has been used in the treatment of several diseases, especially in chronic metabolic diseases.[11-13] It has also been shown to alleviate kidney damage in diabetic animals, with mechanisms including antioxidant, anti-inflammatory, and regulation of renal lipid accumulation effects.[14,15] However, it remains unclear whether the protective effects of quercetin against DN are mediated through its interaction with SIRT5.

In this study, we investigated the association between SIRT5 and renal fibrosis in DN rats. Furthermore, we investigated whether the beneficial effects of quercetin on DN are associated with its modulation of SIRT5 levels. Overall, this research established a foundation for the application of quercetin in treatment.

MATERIALS AND METHODS

Materials

The serum creatinine (SCr) kits (C011-2-1) and blood urea nitrogen (BUN) kits (C013-2-1) were purchased from Nanjing Jiancheng Bioengineering Institute (Nanjing, China). The urine microalbumin (Ualb) kit was obtained from Wuhan Xinqidi Biotechnology Co., Ltd. (Wuhan, China). The SIRT5 ELISA kit (hj-C7900) was obtained from Shanghai Lanpai Biotechnology (Shanghai, China). The SIRT5 antibody (EPR23787-116) was obtained from Abcam Technology, Inc (Cambridge, UK), while the β-actin antibody (66009-1-lg) was purchased from Proteintech Group, Inc (Wuhan, China). Quercetin (No. Q4951) with a purity exceeding 95%, determined by HPLC, was supplied by Sigma Technology, Inc (USA).

Experimental animals

Male rats (200 ± 20 g) were provided ad libitum access to standard food and water. Following a 12-hour fasting period, diabetic rats were induced through intraperitoneal administration of 65 mg/kg streptozotocin (STZ). Animals demonstrating sustained hyperglycemia (fasting blood glucose ≥13.88 mmol/l) 48 hours post-induction were randomly stratified into four experimental cohorts: DN control group (untreated diabetic nephropathy model), QL group (low dose of quercetin treatment, 30 mg/kg/d), QM group (medium dose of quercetin treatment, 60 mg/kg/d), and QH group (high dose of quercetin treatment, 120 mg/kg/d). Quercetin dissolved in a 1% sodium carboxymethyl cellulose (CMC-Na) solution was orally administered to the rats. The NS (Normal) and DN groups received an equivalent volume of 1% CMC-Na solution. All rats underwent treatment for a duration of four months, before being sacrificed. The blood and urine samples were collected to detect the levels of BUN, SCr, Ualb and Ucr. The renal cortex was divided into three parts: one for the analysis of SIRT5 protein by western blot; another for the measurement of SIRT5 protein in homogenate using ELISA; and the rest was processed into paraffin sections for various stains.

Enzyme-linked immunosorbent assay (ELISA)

The level of Ualb in the urine samples and the SIRT5 protein in the kidney were determined by ELISA. The two indices were measured as follows: initially, the capture antibody (anti-Ualb or anti-SIRT5) was immobilized in the well of an ELISA plate, followed by the addition of the sample. Subsequently, enzyme-labeled antibodies were used

to bind the detection antibodies. Finally, substrate was added for color development, and both showed a maximum absorption peak at 450 nm.

Kidney function assessment

The levels of SCr and BUN were measured by the colorimetric method. The determination of SCr relied on the catalysis of hydrogen peroxide by a series of enzymes. Hydrogen peroxide reacts with 2,4-(6-triiodo-3-hydroxybenzoicacid) and 4-aminoantipyrine to form a purplish-red compound with a maximum absorption peak at 546 nm. The determination of BUN was based on the hydrolysis of urease, producing ammonia ions and carbon dioxide. In an alkaline environment, ammonia ions combined with a phenolic chromogen to form blue substances with an optical peak at 640 nm.

Western blot analysis

The protein in kidneys was prepared as previously described.[16] Briefly, tissue homogenization was conducted in ice-cold RIPA buffer. A total 30 μg of protein per sample underwent electrophoretic separation on Tris-glycine SDS-PAGE gels at 100 V for 120 min, followed by semi-dry transfer to NC membranes, and blocked with 3% BSA solution for 1h prior to overnight incubation at 4°C with primary antibodies (anti-SIRT5 and β-actin antibodies). Then, membranes were incubated for one hour with species-matched secondary antibodies. Signal densities were then quantified via Image J software.

Immunohistochemical stain

Paraffin sections (4 μm) were dewaxed and rehydrated by conventional methods. Pepsin was applied to the tissues at 30°C for 30 minutes. Then, the sections were blocked with a 2% BSA solution for 10 minutes. Subsequently, the sections were incubated overnight with the primary antibody (diluted 1:100) at 4°C. The following day, the sections were allowed to warm up to 37°C for 40 minutes and were treated with normal goat serum. The cell nucleus was stained with hematoxylin, followed by another round of dewaxing with xylene. Finally, the sections were mounted using neutral balsam and observed under a light microscope.

PAS and Masson's trichrome stain

The sections (4 μm) were treated with a 1% solution of periodic acid, followed by the addition of Schiff's reagent after washing. In PAS stain, the pink areas in the tissue represented glycogen deposition. Masson's trichrome stain was performed with the addition of hematoxylin iron to each dewaxed section, followed by treatment with molybdic acid and dyeing with aniline. After washing, the sections were dyed with fuchsin acid solution and then cleared and mounted. The blue areas in Masson's trichrome stain represented collagen fibers.

Statistical analysis

Statistical analysis was performed by GraphPad Prism Software using one-way ANOVA. Data were shown as mean ± SD. $P < .05$ or $P < .01$ were considered statistically significant.

RESULTS

Quercetin ameliorates renal fibrosis in DN rats

PAS stain is frequently used for semi-quantitative assessment of glycogen levels. Since the mesangial matrix is primarily composed of polysaccharide-associated components, this technique can serve as an indicator of glomerular sclerosis.[17-19] Masson's trichrome stain is a commonly employed method to identify collagen fibers in tissues,[20] where collagen fibers appear blue. Hence, both stain methods are reliable for assessing renal fibrosis. The results of PAS stain demonstrated that glycogen deposition (pink) was obviously higher than that in the NS group. However, glycogen deposition decreased in quercetin-treated rats, particularly in the QM and QH groups (Figure 1A). Similarly, Masson's trichrome stain results indicated that collagen fibers (blue) were more abundant in the DN group than the NS group. And they were reduced to different degrees in the quercetin treatment groups (Figure 1B). These findings suggest that quercetin can improve kidney fibrosis in DN rats.

Quercetin improves kidney function in DN rats

Previous studies have established that SCr, BUN and Ualb/Ucr can be used to evaluate kidney function.[21] Our results demonstrated that the levels of SCr, BUN and Ualb/UCr in the DN group were higher than those in the NS group. The results suggest that the rat model of DN complicated by type 1 diabetes were constructed successfully. Following quercetin treatment, the levels of SCr,

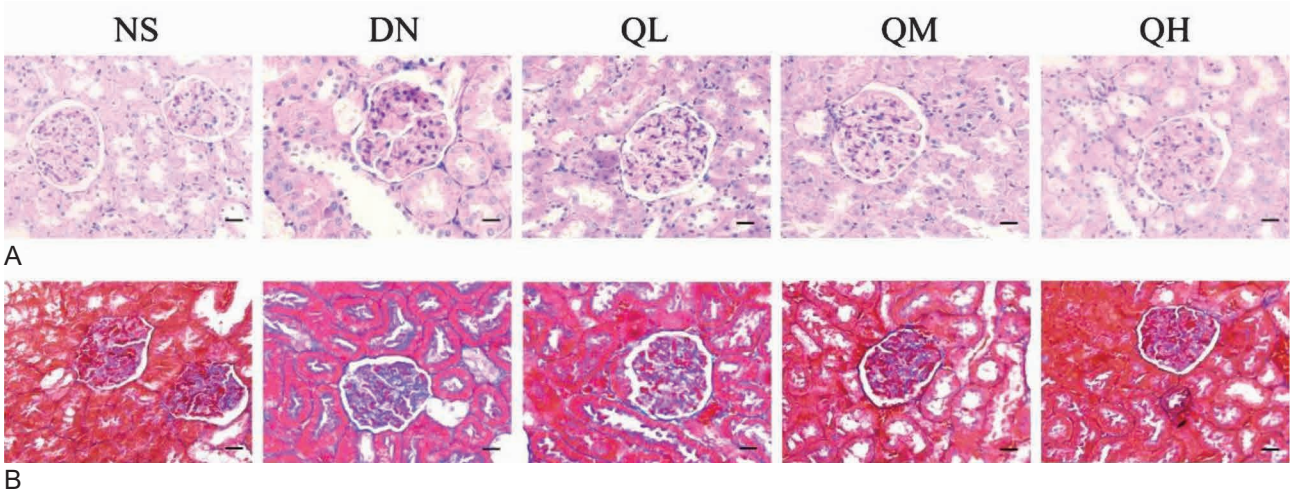

Figure 1. Quercetin reduces renal fibrosis of DN rats. (A) Periodic acid-Schiff (PAS) stain for glycogen deposition (scale bar, 50 μm). (B) Masson's trichrome stain for collagen fibres accumulation (scale bar, 50 μm). NS: Normal rats; DN: diabetic nephropathy rats, QL: DN rats treated with low dose of quercetin, 30 mg/kg/d; QM: DN rats treated with medium dose of quercetin, 60 mg/kg/d; QH: DN rats treated with high dose of quercetin, 120 mg/kg/d.

BUN, and Ualb/UCr were markedly reduced in both QM and QH groups (Table 1). These findings indicate that kidney function was compromised in DN rats, and that quercetin can improve kidney function in this context.

Quercetin decreases the level of SIRT5 protein in DN rats

In this study, we assessed the levels of SIRT5 protein by Western blot and ELISA in rat kidneys. Compared with the NS group, protein levels (Figure 2A-B) of SIRT5 were significantly elevated in the DN group. Meanwhile, the results of immunohistochemical stain also showed that the stain of SIRT5 (brown) proteins were darker and denser than that of DN group (Figure 2C). After four months of quercetin treatment, the levels of SIRT5 protein in the kidneys of DN rats were reduced to different degrees. Furthermore, stain of SIRT5 protein became lighter and less intense in quercetin treatment groups. These findings suggest that quercetin has a considerable inhibitory effect on the expression of SIRT5 protein in the kidneys of DN rats.

DISCUSSION

It has been known that renal fibrosis is the major feature of DN. In this process, extracellular matrix such as collagen and laminin accumulated in the kidney which resulted in renal fibrosis and ultimately renal failure of DN.[22] In this study, STZ-induced DN rats were used to assess the effects of quercetin. A high dose of STZ (65 mg/kg) was administered to induce extensive β-cell destruction in the islets, thus establishing a type 1 diabetes model.[23] In the present study, we used PAS and Masson's trichrome stain to observe the renal fibrosis. PAS stain is frequently used for the assessment of glycogen levels. The mesangial matrix in the kidneys was primarily composed of polysaccharide-associated components. Consequently, this technique serves as an indicator of renal fibrosis.[17-19] Masson's trichrome stain is a common method to identify collagen fibers in

Table 1. Quercetin improves the kidney function of DN rats

Group	n	SCr (μmol/l)	BUN (mmol/l)	Ualb/Ucr (mg/mmol)
NS	8	47.13 ± 3.25	5.26 ± 0.46	30.05 ± 1.88
DN	8	61.77 ± 3.52**	12.61 ± 1.32**	117.50 ± 12.30**
QL	8	59.56 ± 3.08	10.44 ± 0.66	113.70 ± 8.59
QM	8	50.61 ± 3.30#	8.71 ± 1.11#	90.29 ± 11.09#
QH	8	47.43 ± 1.14##	8.13 ± 0.93#	57.57 ± 6.87#

Data were presented as mean ± S.D. **$P < 0.01$ vs. NS group, #$P < 0.05$, ##$P < 0.01$ vs. DN group. SCr, serum creatinine; BUN, blood urea nitrogen; Ualb, Urine microalbumin; Ucr, urine creatinine.

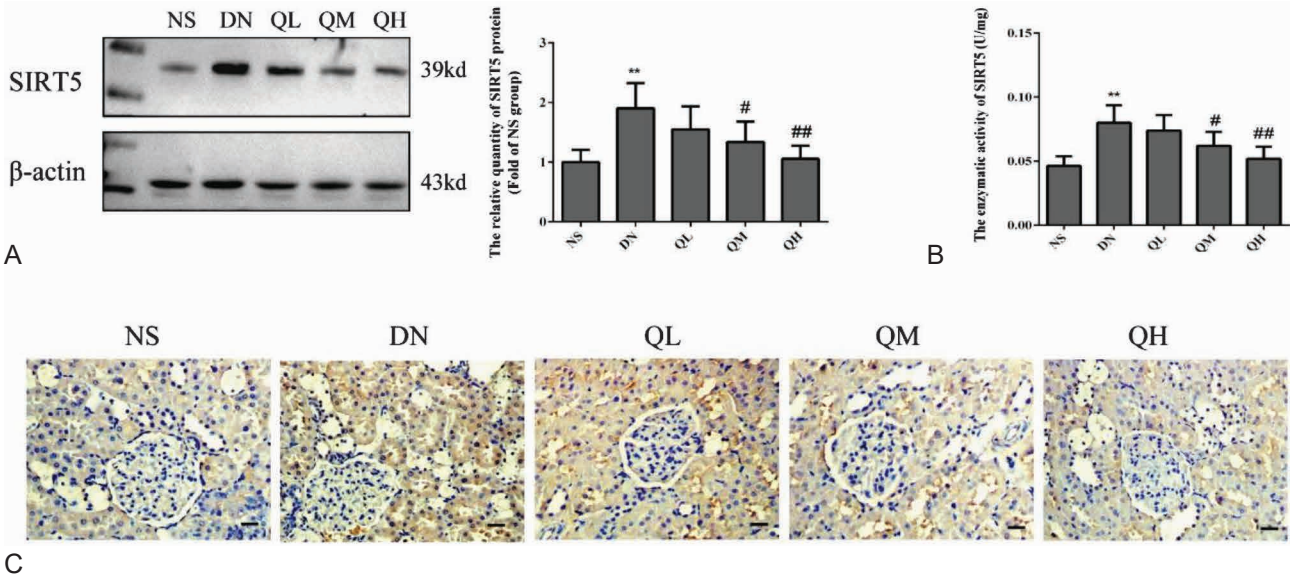

Figure 2. The effects of quercetin on SIRT5. (A) The SIRT5 proteins in kidneys by Western blot and its densitometric analysis of bands. (B) The levels of SIRT5 protein in kidneys by ELISA. $^{**}P < 0.01$ vs. NS group, $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ vs. DN group. (C) The SIRT5 proteins in kidneys by immunohistochemical stain (scale bar, 50 μm).

tissues.[20] After four months, renal fibrosis was observed by these two stains in rats that were intraperitoneally injected with STZ. Concurrently, kidney function indicators, such as SCr, BUN, and Ualb/Ucr, were significantly elevated, suggesting the development of kidney failure and successful establishment of a rat model of DN in type 1 diabetes.

Sirtuins are a group NAD (+) -dependent protein deacetylases, which play an important role in cell aging and cell metabolism.[24] SIRT5 participates in mitochondrial metabolism, cell lifespan, inflammatory response, and cell apoptosis through the activation of pathways involving cytochrome C.[25] Consequently, SIRT5 has emerged as an important target for the treatment of cancer and metabolic diseases.[26] Studies have pointed out that the upregulation of SIRT5 is implicated in fibrotic diseases, including myocardial and pulmonary fibrosis.[7,8] Additionally, SIRT5 has been shown to be involved in kidney diseases.[10,27] In our research, we observed that SIRT5 protein was enhanced in the kidneys of STZ-induced DN rats, along with renal fibrosis and decreased kidney function. This suggests a close association between SIRT5 and DN in type 1 diabetes. Baek J *et al* pointed out that SIRT5 also increased in the kidneys of type 2 diabetic mice,[10] suggesting that the upregulation of SIRT5 may be a common feature of renal fibrosis in DN, similar to myocardial and pulmonary fibrosis.

Quercetin is a flavonoid abundantly found in the human diet and functional foods. It exerts beneficial effects on various diseases, including osteoporosis, cancers, and pulmonary and cardiovascular problems.[28] Previous studies showed that quercetin had the favorable anti-diabetic effects in the *in vitro* and *in vivo* experiments.[29] In our present study, we found that quercetin reduced glycogen deposition and collagen fiber accumulation in the kidneys of DN rats. Additionally, the treatment with quercetin resulted in varying degrees of improvement in kidney function. These findings highlighted the favorable effect of quercetin on DN, and the amelioration of renal function may be due to the alleviation of renal fibrosis. Our findings were consistent with those of Liu T, *et al.* and Wang Q, *et al.*, who observed that quercetin ameliorated renal fibrosis through mitophagy protection or inhibition of the AREG/EGFR signaling pathway.[30,31] In our study, quercetin decreased the level of SIRT5 protein in DN rats, along with the remissions of renal fibrosis and improvement in the kidney function to different degrees. Quercetin's effect on SIRT5 in renal fibrosis was very similar to myocardial fibrosis, in which it was also found that quercetin could increase the expression of SIRT5, thereby

improving heart function through the regulation of mitochondrial energy metabolism.[32] Abnormal mitochondrial energy metabolism is also present in DN. As a result, the effects of quercetin on SIRT5 are unlikely to be tissue-specific, and the improvement of quercetin on kidney function can be closely related to the downregulation of SIRT5 expression.

As a summary, this study demonstrates that quercetin inhibits the level of SIRT5 protein in the kidneys of DN rats, thus ameliorating renal fibrosis and improving kidney function. Our study presents a new mechanism for quercetin in the prevention of DN and provides a new theoretical basis for the use of quercetin against DN.

AUTHORS' CONTRIBUTIONS

Ma GY and Xu Z equally contributed to this work. Ma GY performed the most of experiments, Xu Z analyzed and interpreted the data. Dong BZ checked the manuscript for the first submission. Zhang YY, Cheng X, Chen JQ and Sun W helped to raise rats. Wang JY designed and wrote the manuscript.

ETHICAL APPROVAL

Animal experiments and surgical processes were conducted in strict compliance with Guide for the Care and Use of Laboratory Animals. This research had been approved by the Animal Experiment Ethics Committee of Xuzhou Medical University (Ethical Approval Number: 201904S01). Surgical procedures were performed under anesthesia with sodium pentobarbital to minimize animal discomfort.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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