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Original Article

Ginkgo biloba Leaf Extracts Ameliorates Diabetic Renal Injury in Rats via TWEAK/Fn14/NF-κB Pathway

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ABSTRACT

Objectives: Our study aims to explore the effect of *Ginkgo biloba* Leaf extracts (GBLF) on diabetic nephropathy and its mechanism. **Materials and Methods:** Fifty rats were divided into five groups: Control, Model, Positive drug group (irbesartan, 25 mg/kg), Low-dose group (48 mg/kg of GBLF), High-dose group (96 mg/kg) (n=10). Diabetic nephropathy rat model were established. Urine Microalbumin (UMAL) content was measured by the biuret method. Serum glucose, creatinine, soluble TWEAK (sTWEAK) levels were detected using ELISA. Radioimmunoassay was employed to measure the content of insulin and C-peptide. Masson and (Hematoxylin and eosin) histological analysis was done to observe pathological structure in renal tissues. RT-qPCR and Western blotting were implemented to detect the expression of genes and proteins. **Results:** Compared with the control group, the renal tubular epithelial cells of rats in the model group were severely damaged, as indicated by increases in 24-hr urine volume and UMAL, blood glucose levels, creatinine levels, gene expression for fibrosis factors and TWEAK, and the expression of MCP-1 protein, as well as a dramatic decline in C-peptide, insulin, and sTWEAK ($p < 0.05$). GBLF treatment reversed damage in renal tubular epithelial cell, with significantly reduced levels of 24-hr urine volume and urinary acid levels, blood glucose, and creatinine levels, and significantly elevated levels of C-peptide, insulin, and sTWEAK as compared to the model group ($p < 0.05$). **Conclusion:** *Ginkgo biloba* leaf extracts may improve diabetic renal injury by inhibiting TWEAK/Fn14/NF-κB pathway.

Keywords: Diabetic nephropathy, Fibroblast growth factor-inducible 14, *Ginkgo biloba* leaf extracts, Nuclear factor-κB, Tumor necrosis factor-like weak inducer of apoptosis.

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INTRODUCTION

Diabetes is a chronic disease associated with a variety of etiological factors. According to the latest epidemiological analysis, the global diabetic population has reached 450 million, with a prevalence rate of 10.9% in China.[1] Current research suggests that inflammation which persists in these individuals is a major concern for renal damage and fibrosis in diabetic patients. The diabetic renal injury is essentially a sustained inflammatory response disease.[2] Numerous studies have allocated that blocking the inflammatory mediators in diabetic nephropathy acts crucially in alleviating the deterioration of diabetic renal injury.[3]

TNF (Tumor Necrosis Factor) superfamily cytokine-TWEAK is a novel pro-inflammatory factor bind to its unique receptor factor - Fn14, inducing the activation of the inflammatory pathway - nuclear transcription factor-κB (NF-κB), thereby participating in local tissue inflammatory response.[4] Studies showed that the TWEAK/Fn14/NF-κB pathway is a crucial pathway involved in chronic inflammatory diseases.[5] However, whether the TWEAK/Fn14/NF-κB pathway also involves in the inflammatory damage process of diabetic nephropathy has not been reported.

In the treatment of diabetic renal damage, Traditional Chinese medicine has shown greater efficacy. There have been several studies that have demonstrated that polysaccharides, saponins, flavonoids, organic acids, and other components of Chinese medicine can effectively block chain reactions that are related to oxidative stress and inflammation, which can effectively reduce tissue cell damage, promote disease progression, and achieve effective "renal protection" effects.[6] *Ginkgo biloba* leaf extract, a component of traditional Chinese medicine, contains various components such as flavonoids, terpenoids, and organic acids.[7] It is believed that these components have significant pharmacological effects, including the ability to act as an antidiabetic, an anti-inflammatory, an antioxidant, and to improve Insulin Resistance (IR).[8] The flavonoids and terpenoids

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are capable of regulating inflammation, improving oxidative stress, and alleviating diabetic renal injury.[9] The *Ginkgo biloba* leaf extract contains various components that improve diabetes and has been demonstrated in combination with valsartan to reduce inflammation through regulation of the TWEAK pathway,[10] it is speculated that *Ginkgo biloba* leaf extract may mediate diabetic renal injury through the TWEAK/Fn14/NF-κB pathway. The mechanism behind this is still questionable. This study establishes a rat model of diabetic nephropathy and explores the effect of *Ginkgo biloba* leaf on TWEAK/Fn14/NF-κB pathway. The purpose of the study is to provide reliable data for the expanded application of GBLF in the field of diabetes and to contribute to the internationalization of traditional Chinese medicine.

MATERIALS AND METHODS

Animals

Rats were obtained from the Experimental Animal Center of Huazhong University of Science and Technology for this study. We used 50 adult male Sprague Dawley (SD) rats of SPF grade weighing 280 g (SCXK (Hubei) 2020-0008). A high-fat standard pellet feed was provided to them, as well as free access to water and attached to animal houses.

Animal grouping and model preparation

Rat model of diabetic nephropathy was prepared as follows.[11] Forty rats were divided using random number method and fed with high-fat feed (60% regular rat feed, 2% cholesterol, 10% lard, 20% sucrose, 8% egg yolk powder) until their weight increased to 400 g. They were then injected intraperitoneally with streptozotocin solution (1% STZ (Shanghai Yeasen Biotechnology Co., Ltd., No. 60256ES76) solution dissolved in 0.1 mol/L citric acid buffer at pH 4.45) at dose of 30 mg/kg. When the rats had symptoms such as polydyspia, polyuria, restlessness, yellowing of coat color, and hair loss, we measured their blood glucose levels with fully automatic biochemical analyzer. The model was considered successful when the glucose level in blood of the rats remained >16.6 mmol/L for three consecutive days. The rats were transferred to metabolic cages, and high-fat feed was continued. After collecting the rats' urine for 24 hr, the urine volume, urine protein were measured. A urine protein level >30 mg/24 hr indicated a successful construction of the diabetic nephropathy rat model. In this experiment, all 40 rats successfully developed diabetic nephropathy models. We randomly divided the rats into four groups: model group, positive drug group, *Ginkgo biloba* Leaf Extract low-dose group (GBLF), and high-dose group, with 10 rats in each group.

Drug administration

24 hr after model construction, the GBLF low-dose group was administered 48 mg/kg/day of leaf extract by gavage, and we administered 96 mg/kg/day of *Ginkgo biloba* leaf extract (Taiwan Chi Sheng Chemical Pharmaceutical Co., Ltd., No. H4002) for high-dose group by gavage. The positive drug group was administered 25 mg/kg/day of irbesartan (Sanofi Pharmaceutical Co., Ltd., SFDA Approval No. J20171089), while we administered an equal volume of normal saline for both the model group and the control group by gavage. Gavage was performed once daily for 12 weeks. All rats survived.

Collection of kidney tissues

One day before euthanasia, we placed rats in metabolic cages to collect 24 hr urine. After anesthesia, tail vein blood was collected and centrifuged to separate serum, which was then stored at low temperature for later use. With cervical dislocation method, rats from each group were euthanized, and both kidneys were removed. After rinsing with pre-cooled normal saline, each rat's kidney was divided into three parts. One part was used for pathological observation of kidney tissue (H&E, Masson staining), one part for molecular biological test including Reverse Transcription quantitative-PCR (RT-qPCR) and protein immunoblotting analysis.

Enzyme-Linked Immunosorbent Assay (ELISA)

Total urine volume in 24 hr was measured, and urinary microalbumin content was determined using biuret method. Corresponding ELISA kits were used to detect blood glucose, blood creatinine, and serum sTWEAK (sTWEAK ELISA kit, Shanghai Jianglai Biotechnology Co., Ltd., China) levels. Radioimmunoassay was performed according to the instructions of the kits to detect serum insulin and C-peptide levels.

H&E and Masson staining

Rat kidney tissues were fixed with neutral formalin, dehydrated, embedded in paraffin, and sectioned into 4-5 μm thick continuous slices for H-E and Masson staining. Observation was carried under light microscope (ZEISS, Germany), images were captured using an imaging system, and professional image processing software was used for analysis.

Reverse transcription quantitative PCR (RT-qPCR).

The kidneys were extracted for Total RNA[12] using the TRIzol® reagent (Dalian Bao Biotechnology Co., Ltd., China) on ice and reverse-transcribed using high-capacity complementary DNA reverse transcription kit according to the manufacturer's protocol. qPCR was performed using SYBR™ Green PCR Master Mix kit kidney fibrosis markers determining the mRNA levels included MMP-7, α-SMA and transforming (TGF-β1) were quantified. Primer sequences are shown in Table S1. Primer design from Sangon Biotech (Shanghai) Co., Ltd.

Western blotting assay

Kidney tissues from each group of rats were homogenized in protein lysis buffer, and total protein was extracted. By using a

BCA quantitative analysis kit (Shanghai Yubo Biotechnology Co., Ltd., China). we determined the protein concentration. The proteins were denatured by boiling, separated by SDS-PAGE (sodium dodecyl sulfate-polyacrylamide gel electrophoresis), and then transferred onto PVDF (polyvinylidene difluoride) membranes. We blocked the membranes at 37°C for 2 hr and incubated with primary antibodies against anti-rat TWEAK polyclonal antibody, Fn14 polyclonal antibody, NF-κB polyclonal antibody, p-NF-κB polyclonal antibody, MCP-1 polyclonal antibody, and mouse anti-β-actin polyclonal antibody (Cell Signaling, Shanghai, China). The membranes were then treated with the corresponding secondary antibodies. Gel bands were observed using a gel imaging system, and Image Lab softwar for grayscale analysis of the images. The grayscale values were recorded, and the value ratio of target protein to reference protein (β-actin) was calculated.

Statistical analysis

Data were presented as mean±Standard Deviation (SD) and analyzed using SPSS software version 23.0 (Chicago, USA). We used a one-way ANOVA followed by a SNK-q test to conduct multiple comparisons. Statistical significance was determined by a two-tailed $p < 0.05$.

RESULTS

GBLF improved kidney function *in vivo*

Previous study showed that 24-hr urine volume and UMAL may not only be a marker of renal function, but it may also be a significant step in the process heading to the development of hypertension, kidney failure and urolithiasis. The model group showed a significant increase in 24-hr urine volume and UMAL level when comparing to the control group ($p<0.05$). The low-dose group, positive drug group, and high-dose group showed significant decreases in 24-hr urine volume and UMAL level when comparing to the model group ($p<0.05$). Comparing to the positive drug group, the low-dose group had higher 24-hr urine volume and UMAL level, while the high-dose group had lower levels ($p<0.05$) (Table 1).

GBLF decreased blood glucose, creatinine, c-peptide, insulin, and elevated sTWEAK levels *in vivo*

Glucagon and insulin are peptide hormones responsible for blood sugar homeostasis. C-peptide and creatinine were stable measure of endogenous insulin secretion. sTWEAK is a type II transmembrane glycoprotein of the TNF superfamily that acts by binding to a small transmembrane type I protein (Fn14). Comparing to rats in the control group, the rats in the model group showed significant increases in blood glucose and creatinine levels, and significant decrease in serum C-peptide, insulin, and sTWEAK levels ($p<0.05$). Comparing to the model group, the positive drug group, low-dose group, and high-dose group showed decreased blood glucose and creatinine levels, and increased serum C-peptide, insulin, and sTWEAK levels. Then the positive drug group, low-dose group had higher blood glucose and creatinine levels, while the high-dose group had low levels. The low-dose group had lower serum C-peptide, insulin, and sTWEAK levels, while the high-dose group had increased levels ($p<0.05$) (Table 2).

GBLF remitted the pathological process of renal injury *in vivo*

The rats had normal glomerular morphology, with no apparent changes in renal tubular epithelial cells, no degeneration, necrosis, or inflammatory cell infiltration in the control group. Rats in the model group showed enlarged glomerular volume, expanded basement membrane, and atrophied renal tubules. The condition was alleviated in the low-dose group, while the positive drug and high-dose group showed glomerular shape trending towards normal, with reduced edema and dilated renal tubules, with reduced damage. The high-dose group exhibited the best recovery (Figure 1).

GBLF alleviated collagen deposition *in vivo*

Rats in the control group exhibited normal glomerular and tubular structural morphology with clear texture, less fibrosis. However, rats in the model group showed increased collagen deposition and the glomerular basement membrane thickened (blue color), swelling of tubular epithelial cells, some exhibiting vacuolar changes. The lesions in glomeruli and tubular epithelial cells were alleviated and collagen deposition decreased in the low-dose group, positive drug group, and high-dose group. The high-dose group was closest to the control group (Figure 2).

TGFβ1, MMP-7 and α-SMA are often used as markers of collagen deposition. Consistent with Masson's staining results, RT-qPCR results showed that expression of gene was increased in the model compared to control group (Figure 3), GBLF treatment significantly reversed this trend, with reduced TGFβ1, MMP-7 and α-SMA levels.

Table S1: Primer sequences of rat used in RT-qPCR analysis.

Gene	Sequence
MMP-7	Forward:5'-CAAAGGACGACATTGCAGGC-3'
	Reverse:5'-ATTGCTGGTGTCTGTCGTGT-3'
α-SMA	Forward:5'-GGATCAGCGCCTTCAGTTCT-3'
	Reverse:5'-CAGGGCTAGAAGGGTAGCAC-3'
TGF-β1	Forward:5'-AGGGCTACCATGCCAACTTC-3'
	Reverse:5'-CCACGTAGTAGACGATGGGC-3'
Actin	Forward: 5′-TGTCACCAACTGGGACGATA-3′
	Reverse: 5′- GGGGTGTTGAAGGTCTCAAA-3′

Table 1: Effect of *Ginkgo biloba* Leaf Extract on 24-Hr Urine Volume and Urinary Microalbumin in Diabetic Nephropathy Rats (image1).

Group	N	24 hr urine volume/mL	UMAL/mg·24hr^{-1}
Control	10	0.68±0.12	18.32±4.35
Model group	10	2.94±0.23^{a}	53.21±5.32^{a}
Positive drug	10	1.52±0.21^{ab}	39.48±4.73^{ab}
Ginkgo Low	10	1.98±0.19^{abc}	46.74±4.56^{abc}
Ginkgo High	10	1.15±0.18^{bcd}	33.25±4.42^{bcd}
F value	-	207.110	81.825
p value	-	<0.001	<0.001

Table 2: Effect of *Ginkgo biloba* Leaf Extract on Serum Indicators in Diabetic Nephropathy Rats (image1).

Group	n	Blood glucose mmol/L	C-peptide ng/ML	Insulin mIU/L	Serum creatinine mg/dL	sTWEAK ng/L
Control	10	4.52±1.14	0.38±0.07	58.12±7.81	0.24±0.06	242.12±9.56
Model	10	21.85±2.83^{a}	0.13±0.05^{a}	26.44±6.72^{a}	0.69±0.11a	158.44±11.12^{a}
Positive drug	10	15.26±2.21^{ab}	0.27±0.04^{ab}	44.52±6.83^{ab}	0.42±0.08^{ab}	188.69±12.53^{ab}
Ginkgo Low	10	18.64±2.79^{abc}	0.20±0.06^{abc}	35.25±7.26^{abc}	0.56±0.09abc	174.68±11.84^{abc}
Ginkgo High	10	11.56±2.17^{bcd}	0.34±0.05^{bcd}	53.75±7.45^{bcd}	0.31±0.08^{bcd}	208.35±12.26^{bcd}
F value	-	84.265	34.205	32.512	45.806	78.983
p value	-	0.000	0.000	0.000	0.000	0.000

GBLF inhibited the activation of TWEAK/Fn14/NF-κB signaling pathway *in vivo*

TWEAK (TNFSF12) and its known receptor Fn14 (TNFRSF12A) have been identified as members of the TNF and TNF receptor (TNFR) family of cytokines. The majority of the currently known functions of TWEAK are connected to expression of TWEAK-induced proinflammatory cytokines, chemokines, and cell adhesion molecules, predominantly through the activation of the NF-κB pathway, While the control group was compared, the expression of TWEAK, Fn14, NF-κB, and MCP-1 proteins in renal tissues of rats was significantly up-regulated in the model group. The expression of TWEAK, Fn14, NF-κB, and MCP-1 proteins in the positive drug group, low-dose group, and high-dose group was significantly down-regulated comparing to the model group (p<0.05 or p<0.01) (Figures 4 and 5).

DISCUSSION

The current study elucidated that prolonged hyperglycemia is the main cause of DN, and mechanisms such as oxidative stress and inflammation acts crucially in the development of DN.[13] The inflammatory cytokines are products owing to oxidative stress and damage of mesangial cells in DN, causing extracellular matrix accumulation, expansion, and thickening of the glomerular basement membrane, which are important indicators for assessing the severity of DN.

In addition to ginseng, ginkgo (*ginkgo biloba*) has gained considerable attention, particularly recently, as a possible medicinal plant for a number of medical conditions, including heart disease. Ginkgo is an ancient tree that originated in China and whose leaves have been shown to possess numerous beneficial effects due in part to their antioxidant properties due to the presence of high amounts of flavonoids and terpenoids.[14] Ginkgo leaves, however, contain a plethora of bioactive compounds (as was also observed for ginseng), which may contribute to the therapeutic properties of ginkgo. Indeed, with respect to flavonoids alone more than a hundred different flavonoid structures have been identified existing as either aglycones, glycosides or dimeric forms referred to as bioflavonoids.[15] Bioflavonoids are identified in substantially different ways depending on the extraction procedure as well as the part of the tree from which they are extracted.

The main active ingredients of *Ginkgo biloba* leaf extract are flavonoids and terpene lactones. It has antioxidative stress effects and can prevent glomerulosclerosis, reduce the high perfusion and filtration state of glomeruli, and treat microinflammation in DN.[16] DN is associated with apoptosis of renal tubular cells, affecting renal metabolism.[17] After modeling, severe renal tissue damage was observed with enlarged glomeruli, mesangial proliferation, and significantly increased 24-hr urine volume and urinary microalbumin content in the current study and the results are in accordance with, results of Hou Minna *et al.*,[18]

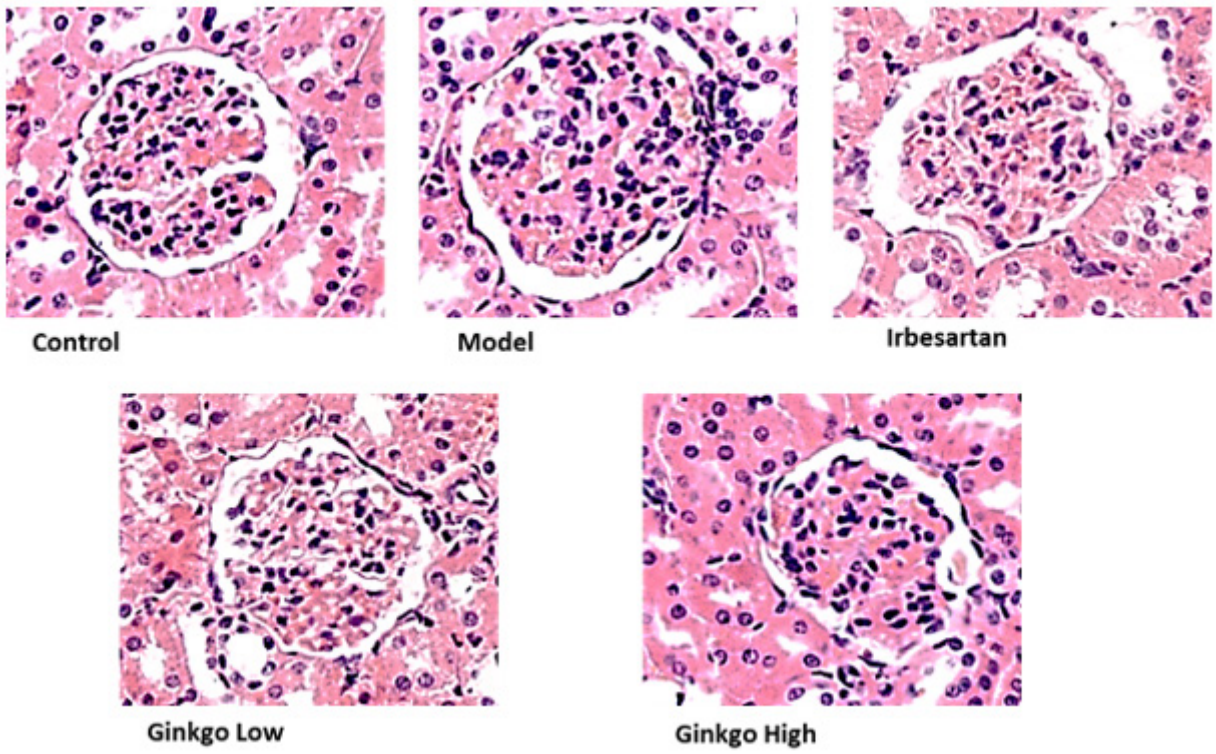

Figure 1: Observation of Renal Pathological Morphological Changes in Rats from Each Group by H&E Staining (×200).

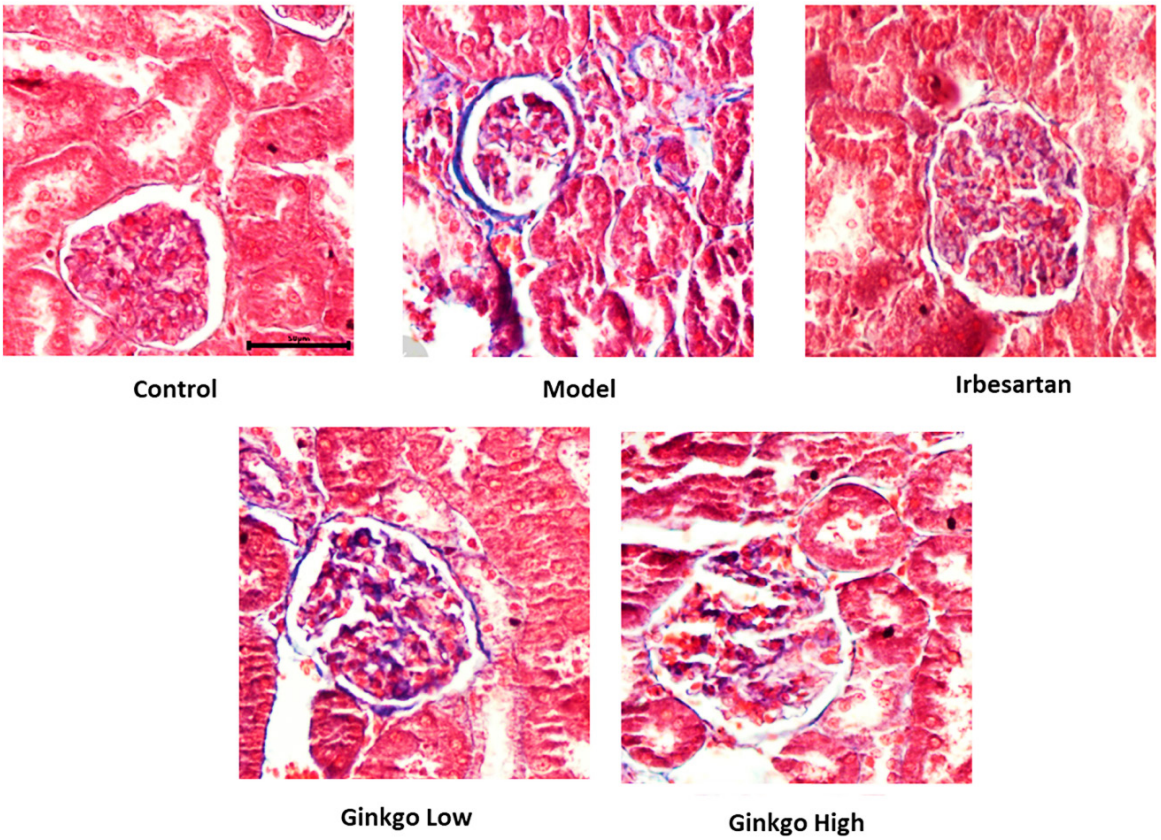

Figure 2: Observation of Renal collagen deposition Changes in Rats from Each Group by Masson Staining (×200).

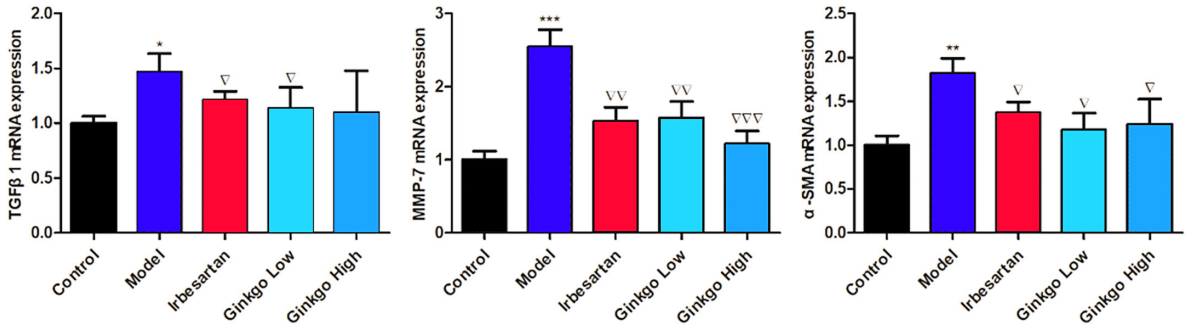

Figure 3: The TGFβ1, MMP-7 and α-SMA mRNA expressions were detected by qRT-PCR.

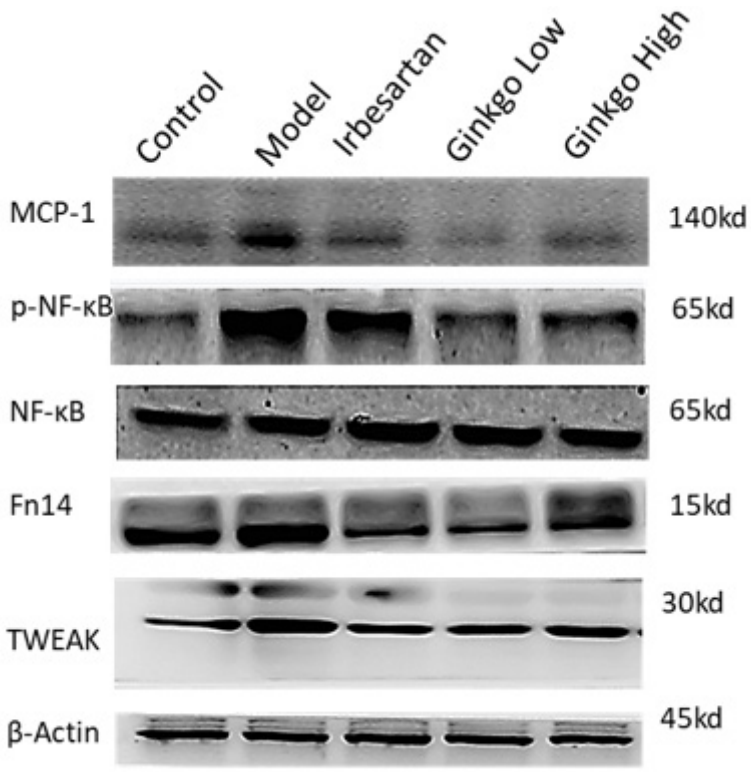

Figure 4: TWEAK, Fn14, NF-κB, and MCP-1 expression were detected by Western Blot Analysis.

indicating successful modeling. Both of high-dose and low-dose groups showed alleviated renal tissue damage, gradual recovery of glomeruli and mesangium, significant reduction in 24-hr urine volume and urinary microalbumin content, indicating that GBLF can improve glomerular filtration function, inhibit renal injury, and prevent the development of DN.

Insulin can be cleaved into C-peptide, and blood glucose levels regulated by multiple organs. The secretion of insulin abnormally can lead to hyperglycemia, causing diabetes. Creatinine is mainly excreted from the body through glomerular filtration, and blood creatinine detection is the main method for detecting renal function.[19] TWEAK is an important participant in chronic inflammatory diseases, and sTWEAK is the soluble form of TWEAK protein. Studies have shown that sTWEAK can participate in the damage of DN by regulating cell inflammation, GBLF can regulate sTWEAK, effectively reduce the levels of IL-8 and other inflammatory factors in patients with DN and treat them.[20] In this study, rats in the model group showed a significant increase in blood glucose and creatinine levels, and a significant decreased C-peptide, insulin, and sTWEAK levels in serum. The low-dose, positive drug, and high-dose group showed significantly decreased blood glucose and creatinine levels, and significantly increased C-peptide, insulin, and sTWEAK levels, indicating that GBLF can reduce them.

The study has shown that mTWEAK and sTWEAK can mediate immune damage[21] by binding to Fn14, participating in processes including cell proliferation, apoptosis, and angiogenesis, which can increase glomerular permeability.[22] When renal tissue is

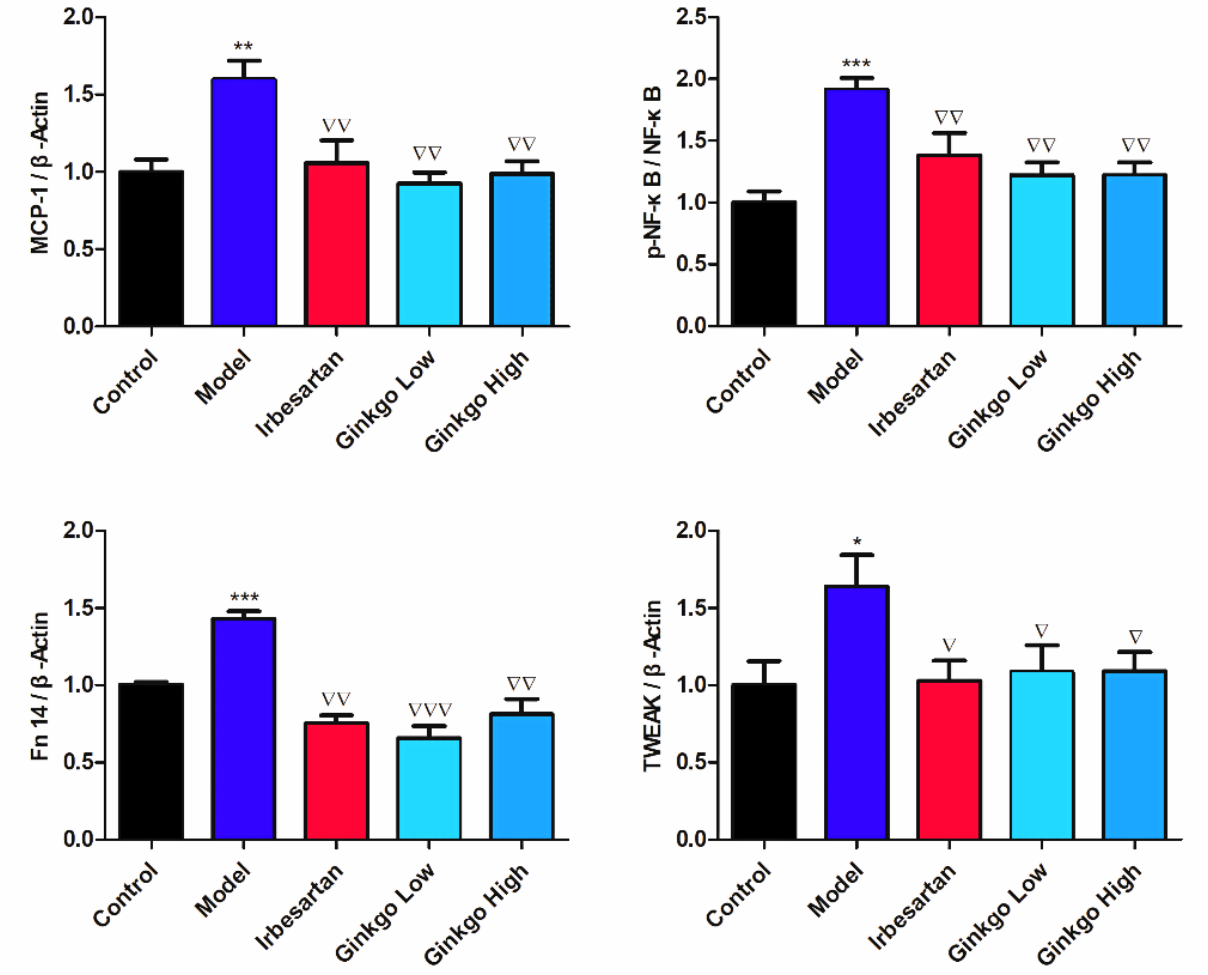

Figure 5: Expression of relative densitometry as Ratio of TWEAK, Fn14, NF-κB, and MCP-1 to β-Actin in Renal Tissues of Rats.

damaged, the expression of TWEAK significantly increases and imparts a key role plays in the inflammatory response. TWEAK and Fn14 can also activate NF-κB, participating in processes such as cell growth and secretion of inflammatory factors.[23,24] MCP-1 (monocyte chemotactic protein-1) is a specific chemokine that acts importantly in the development of DN by recruiting monocytes/macrophages to infiltrate renal tissues, closely related to extracellular matrix deposition and glomerulosclerosis, and is a downstream factor of the TWEAK/Fn14/NF-κB pathway. In this study, the levels of expression of TWEAK, Fn14, NF-κB, and MCP-1 proteins in rats were significantly increased after modeling. However, the low-dose, positive drug and high-dose group showed significantly decreased expression levels of TWEAK, Fn14, NF-κB, and MCP-1 proteins compared to the model group, indicating that *Ginkgo biloba* leaf extract may improve DN by inhibiting this pathway.

However, much more clinical trials, which are well-designed and properly conducted, are still warranted before Chinese medicine can be applied as primary therapy for DN treatment and management. Besides the general principles that guarantee the good quality of clinical trials, such as multi-center cooperation, enough sample size, randomized grouping, blinding method, good clinical practice, and human subject research ethics, there are still many aspects that we should specifically take into consideration when investigating the clinical efficiency of Chinese medicine in treating DN. As for Chinese medicine, it may be more reliable to use purified single bioactive compound or clarified blended bioactive components considering the advantages of multi-constituents and multi-targets of Chinese medicine.

CONCLUSION

In conclusion, this study found that TWEAK, Fn14 and p-NF-κB were overexpression in the diabetic nephropathy rat model. The results of *in vivo* experiment showed that DN rat model was successful establishment. GBLF treatment significantly decreased 24-hr urine volume and urinary microalbumin, blood glucose, creatinine, c-peptide, insulin, and elevated sTWEAK levels *in vivo*. Besides, GBLF alleviated the pathological process of renal injury and collagen deposition in diabetic nephropathy rat

model. In addition, GBLF significantly inhibited the expression of TWEAK, Fn14 and p-NF-κB. These findings not only broaden our understanding of the pathogenesis of renal but also provide a new attractive strategy in treating this disease. Due to the complexity and heterogeneity of the diabetic nephropathy, further investigations of the molecular mechanisms of GBLF in DN are required to verify the function of GBLF in diabetic nephropathy. Thus, GBLF may be considered as a novel effective agent in the treatment of diabetic nephropathy disorders and however, further studies are required in a clinical setting to support our observations.

ABBREVIATIONS

UMAL: Urine microalbumin; **TNF:** Tumor necrosis factor; **IR:** Insulin resistance; **SD:** Sprague Dawley; **STZ:** Streptozotocin; **SPF:** Specific Pathogen Free; **GBLF:** *Ginkgo biloba* Leaf Extract.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

Fanwen Yang designed experiments; Yingda Yan established the rat pathological model, completed molecular biology experiments, performed biochemical and pathological examinations, analyzed the experimental results, and wrote the manuscript. All of the authors read and approved the final manuscript.

SUMMARY

In summary, the TWEAK/Fn14/NF-κB pathway-mediated inflammatory response is involved in regulating DN, and GBLF may improve DN by inhibiting the expression of TWEAK/Fn14/NF-κB pathway proteins, providing theoretical reference for the treatment in clinical practice. However, the detailed mechanism of *Ginkgo biloba* leaf extract in regulating the TWEAK/Fn14/NF-κB signaling pathway still needs further exploration.

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