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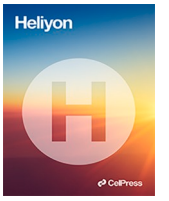

Research article

Nephroprotective effects of Aralia taibaiensis in a high-fat diet-streptozotocin rat model of diabetic nephropathy

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ABSTRACT

Diabetic nephropathy (DN) has emerged as the foremost cause of end-stage renal disease (ESRD) globally. Endoplasmic reticulum (ER) stress plays a critical role in DN progression. Triterpenoid saponin from Aralia taibaiensis (sAT) has been reported to possess anti-diabetic and anti-oxidant effects. The aim of this study was to examine the influence of sAT on DN treatment and elucidate potential underlying mechanisms. A high-fat diet (HFD) and Streptozotocin (STZ) were employed to induce DN in male Sprague Dawley (SD) rats which were subsequently treated with varying concentrations of sAT for 8 weeks. Our findings reveal that different doses of sAT significantly mitigated hyperglycemia, reduced urinary albumin excretion, and decreased plasma creatinine and blood urea nitrogen levels in DN rats. Moreover, sAT administration improved body weight, alleviated renal fibrosis and histopathological changes in the diabetic kidneys. Notably, sAT treatment partially restored increased Bax expression and decreased Bcl-2 expression. Additionally, sAT inhibited ER stress-related proteins, including GRP78, p-PERK, ATF4 and CHOP in kidneys of DN rats. These results suggest that sAT ameliorated experimental diabetic nephropathy, at least in part, through ER stress pathway. These findings provide a scientific basis for the potential development of sAT as a therapeutic agent for DN treatment.

1. Introduction

The type 2 diabetes and its microvascular complications stand as significant contributors to morbidity and mortality worldwide [1]. Among these complications, diabetic nephropathy (DN) stands out as a primary driver of diabetes mellitus (DM) towards end-stage renal disease (ESRD) [2]. DN demands comprehensive treatment, involving dietary adjustments, blood glucose, pressure, and lipid control, alongside kidney protection measures [3]. Current DN drug therapies primarily revolve around ACE inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) to target the renin-angiotensin system (RAS) and glycemic control. Sodium-glucose cotransporter 2 inhibitors (SGLT-2I) or glucagon-like peptide 1 receptor agonists (GLP-1A) are also recommended for DM patients with chronic kidney disease to hinder DN progression to ESRD, although ongoing clinical trials necessitate thorough analysis [4,5]. Despite multiple interventions available for managing DN patients, the ideal solution remains elusive. Hence, there is a pressing need for novel therapeutics capable of preventing and slowing DN progression.

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The endoplasmic reticulum (ER) serves as the principal organelle for newly synthesized protein folding and processing. Pathophysiological stress can result in the accumulation of misfolded and unfolded proteins, activating the unfolded protein response (UPR), a conserved intracellular signaling pathway. Early ER stress aids in restoring normal cellular function, a critical step in disease prevention. However, prolonged or sever ER stress may induce cell injury and apoptosis [6]. Glucose-regulated protein 78 (GRP78), an ER chaperone protein, acts as a central regulator for the UPR signaling network. Under ER stress conditions, GRP78 binds to unfolded or misfolded proteins, subsequently activating protein kinase R-like ER kinase (PERK). PERK, in turn, triggers downstream factors such as activating transcription factor 4 (ATF4) and induces C/EBP homologous protein (CHOP) [7]. CHOP, in the subsequent cascade, regulates the balance between pro- and anti-apoptotic Bcl-2 family members, leading to caspase activation [8]. ER stress has been implicated in pathophysiology of various renal diseases, including DN, with ER stress-induced apoptosis playing a crucial role [9–11]. Consequently, targeting ER stress inhibition has emerged as a promising therapeutic approach for DN treatment.

Aralia taibaiensis (AT), a Chinese medicinal herb widely distributed in the Qinba Mountains of Western China, contains triterpenoid saponin (sAT) among its active components, known for its antioxidant, anti-apoptotic, and antiglycation effects [12–14]. Moreover, sAT has shown antihyperglycemic and hypolipidemic activities in experimental type 2 diabetic rats [13]. However, the effects of sAT on DN and its underlying mechanisms remain poorly defined.

In this study, we aim to explore the impact of sAT on the expression of ER stress signals in high-fat diets (HFD) and low-dose streptozotocin (STZ)-induced model of DN, providing insights into a potential therapy for DN treatment.

2. Methods

2.1. Animals and treatment

Male Sprague Dawley rats (160–180 g) were obtained from the Experimental Animal Center of the Fourth Military Medical University. The animal procedures for this study were conducted in accordance with the ARRIVE guidelines and the National Institutes of Health Guidelines for the Care and Use of Laboratory Animals and complied with the Animal Experimentation Ethics Committee of the Fourth Military Medical University. The rats were kept at constant room temperature (22 °C ± 1 °C), 45–55 % relative humidity and freely accessed to food and water under controlled light/dark cycles. After one week of acclimatization, the animals were randomly assigned into the control group and model group. The control group provided ad libitum access to standard rodent chow comprising 10 % fat, 20 % protein, and 70 % carbohydrate, the model group was established by a high fat diet (HFD) comprising 45 % fat, 20 % protein, and 35 % carbohydrate (4.73 kcal/gm, cat no. HF45, Dyets Biotechnology Co., Ltd., Wuxi, China) for 6 weeks, then HFD-fed rats in the model group were given a single intraperitoneal dose of 35 mg/kg streptozotocin (STZ) dissolved in a 0.1 M ice-cold citrate buffer (pH 4.4) and rats in control group were administrated the same volume of sodium citrate buffer. Three days after STZ injection, fasting blood glucose levels were measured from a vein using an Accu-Chek Performa glucometer (Roche Diagnostics, Shanghai, China), rats with plasma glucose level more than 16.7 mM were divided into the DN group, metformin group (Met), sAT low-dosage group (80 mg/kg, sAT-L), sAT medium-dosage group (160 mg/kg, sAT-M), sAT high-dosage group (320 mg/kg, sAT-H) and kept to give the HFD until the end of the study. Drugs were given by gastric gavage once per day for 8 weeks, while rats in control and DN groups were given an equal volume of vehicle. 24 h prior to sacrifice, all rats were individually transferred to metabolic cages for urine collection and urine was stored at 4 °C until analysed. At the end of the experimental protocol, all rats were weighted and sacrificed under anesthesia, kidneys were dissected and rinsed with ice cold normal saline and then weighed, one portion and other samples were soon collected and stored at −80 °C for subsequent experiments, while the remainder was fixed in 10 % neutralized formalin for histology and immunohistochemistry analysis. The experimental design is shown in Fig. 1.

2.2. Serum and urine biochemical parameters analysis

At the end of the study, blood samples were collected from the abdominal aorta. The biochemical parameters in urine and serum were detected by an automatic biochemistry analyser according to the manufacturer's instructions (Nanjing Jiancheng Bioengineering Institute, Nanjing, China) including urine total protein, serum creatinine (SCr) and blood urea nitrogen (BUN).

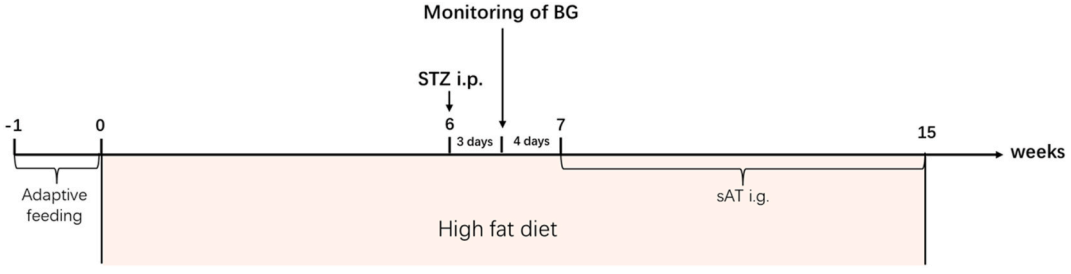

Fig. 1. Experimental design scheme.

2.3. Histopathological examination of the kidneys

The kidney samples were dissected and fixed in 10 % formalin, followed by dehydration and embedding in paraffin. Kidney tissue sections (5 μm) were stained with Masson's trichrome and periodic acid-Schif (PAS) to evaluate the pathological changes of the kidney tissue. The stained specimens inspected were examined under a light microscope (Nikon, Tokyo, Japan) and imaged (× 400).

2.4. Immunohistochemistry and immunofluorescence staining

The 5 μm thick paraffin sections of kidneys were processed using a standard immunostaining protocol. The kidney tissue sections were deparaffinized in xylene and hydrated in ethanol, then quenched in 3 % hydrogen peroxide to block endogenous peroxidase for 15 min. The slides were incubated with the primary antibodies, anti-cleaved caspase 3 (1:400, Cell Signaling Technology), *anti*-GRP78 (1:200 , Santa Cruz Biotechnology, Santa Cruz, CA) and anti-CHOP(1:400, Abcam, Waltham, MA, USA) overnight at 4 °C. After washing with PBS for three times, the sections were incubated with horseradish peroxidase-labeled secondary antibodies for 2 h at 37 °C. Immunostaining procedures were conducted according to the manufacturer's methods. For immunofluorescence analysis, the sections were incubated at 4 °C overnight with the TGF-β1 primary antibody. After several PBS rinses, the sections were incubated with Alexa Fluor 488-conjugated secondary antibody for 1 h at room temperature. The sections were examined with a laser scanning confocal microscope (Nikon, Japan).

2.5. Western blotting

Renal tissues were collected with ice-cold RIPA lysis buffer containing the protease inhibitor cocktail, and the protein concentrations were measured by the BCA Protein Assay Kit. An equal amount of protein was separated by 10 % SDS-PAGE gel and then transferred to poly vinylidene fluoride (PVDF) membranes. After blocking with nonfat milk at room temperature for 1 h, membranes were incubated with primary antibodies, including GRP78 (ab21685, Abcam, 1:1000), CHOP (CST#2895, Cell Signaling Technologies, 1:1000), ATF4 (CST#11815, Cell Signaling Technologies, 1:1000), p-PERK (CST#3179, Cell Signaling Technologies, 1:1000), Cleaved Caspase-3 (CST#9661, Cell Signaling Technologies, 1:1000), Bax (CST#2772, Cell Signaling Technologies, 1:1000), Bcl-2 (ab196495, Abcam, 1:1000), β-actin (ab6276; Abcam, 1:5000) and β-tubulin (CST#2128, Cell Signaling Technologies, 1:1000) antibody at 4 °C overnight. After washing, the secondary antibody was added and incubated 1 h at room temperature. The protein bands were visualized by an enhanced chemiluminescence system. Optical densities of the bands were scanned and quantified image-analysis systems (Bio-Rad, USA).

2.6. Statistical analysis

Results were expressed as means ± standard deviation (SD). One-way ANOVA followed by Tukey test was performed by using GraphPad Prism 5.0 (GraphPad Software, La Jolla, CA, USA). $P < 0.05$ was considered to be statistically significant.

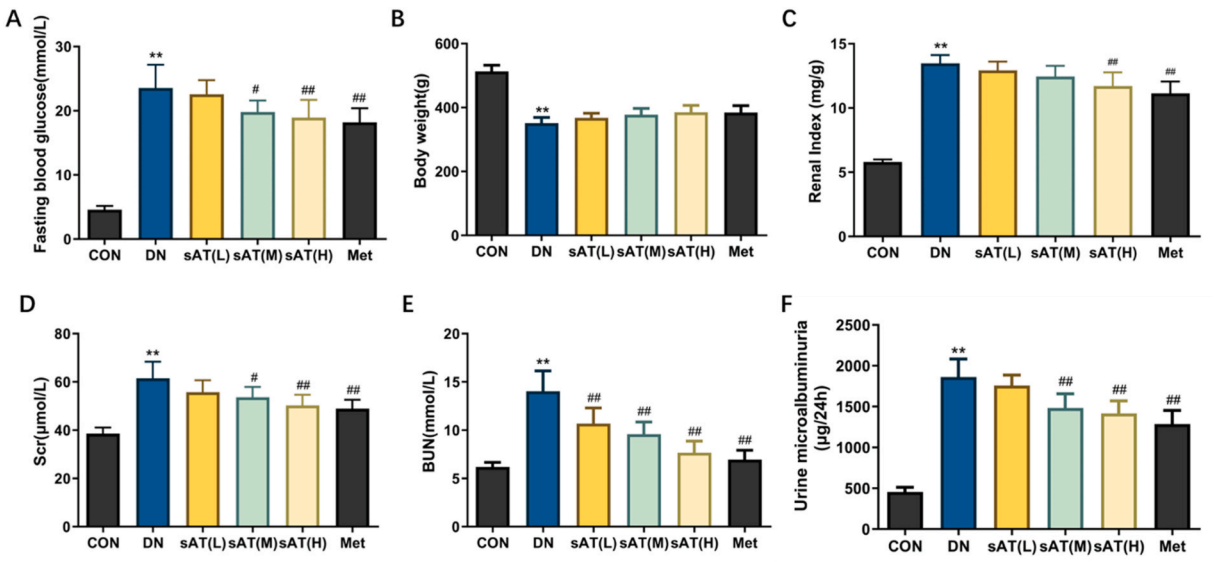

Fig. 2. Physiological parameters in diabetic rats with or without sAT treatment. A. Fasting blood glucose; B. Body weight; C. Renal index; D. Serum creatinine (Scr) levels; E. Blood urea nitrogen (BUN) levels; F. Urine microalbuminuria. $^{**}P < 0.01$ versus normal control group (CON); $^{\#\#}P < 0.01$, $^{\#}P < 0.05$ versus model group (DN). CON: control group; DN: diabetic nephropathy group; sAT (L): DN rats treated with low-dosage sAT; sAT (M): DN rats treated with medium-dosage sAT; sAT(H): DN rats treated with high-dosage sAT; Met: metformin group.

3. Results

3.1. sAT attenuates renal injury in diabetic rats

As shown in Fig. 2, a significant increase in fasting blood glucose was measured in DN rats, after 8 weeks treatment with sAT had a hypoglycemic effect compared with the DN rats (Fig. 2A). DN rats had lower body weights compared to normal control rats (CON). However, sAT treatment had no statistical significance compared with model group (Fig. 2B). The renal index of kidney weight to body weight in DN rats was significantly increased in comparison to the CON group, sAT (320 mg/kg) oral administration to model group significantly ameliorated the kidney index (Fig. 2C). In addition, the levels of BUN, Scr and 24 h urinary protein extraction were measured to reflect the renal function of DN rats. Compared with the normal group, the contents of BUN and Scr in DN group increased significantly and showed severe albuminuria, when treatment with sAT significantly ameliorated these indexes (Fig. 2D–F). These results suggested that sAT attenuates the functional abnormalities in diabetic nephropathy.

3.2. Effects of sAT on renal histopathology

We found that typical glomerular damages appeared in the kidneys of DN rats, including mesangial matrix expansion and the focal thickening of the glomerular basement membrane. After 8 weeks of treatment with sAT, the increased renal lesions were alleviated especially in the groups with sAT 320 mg/kg, marked expansion of ECM in DN rats were greatly improved by sAT treatment (Fig. 3). Also, sAT significantly attenuated renal fibrosis.

3.3. sAT decreased apoptosis in DN rats

Apoptosis participates in the pathogenesis of DN, to investigate the alteration of apoptosis in DN treated with sAT, we analysed apoptosis-related proteins Bax (Fig. 4B and C), Bcl-2 (Fig. 4B and D) and cleaved caspase-3 (Fig. 4A, B and E) by immumohistochemical staining and western blotting. Compared to DN group, sAT and metformin treatment significantly decreased the expression of Cleaved Caspase-3 and Bax (Fig. 4). The results of Cleaved Caspase-3 staining were consistent with that in Western blotting. In addition, we found that the expression of Bcl-2 was markedly decreased in DN group, while this change was prevented by sAT treatment. The above results showed that sAT treatment alter the excessive apoptosis of renal tissues and rescue the renal function.

3.4. Effect of sAT on the expression of TGF-β1

To further examine whether the protective effect of sAT is related to the antifibrotic effects, we measured the expression of TGF-β1 by Immunofluorescence staining. As seen in Fig. 5, the immunofluorescence results showed a significant increase in TGF-β1 of the kidneys of DN rats compared with control group. Attenuated TGF-β1 was found in the kidneys of DN rats treated with sAT.

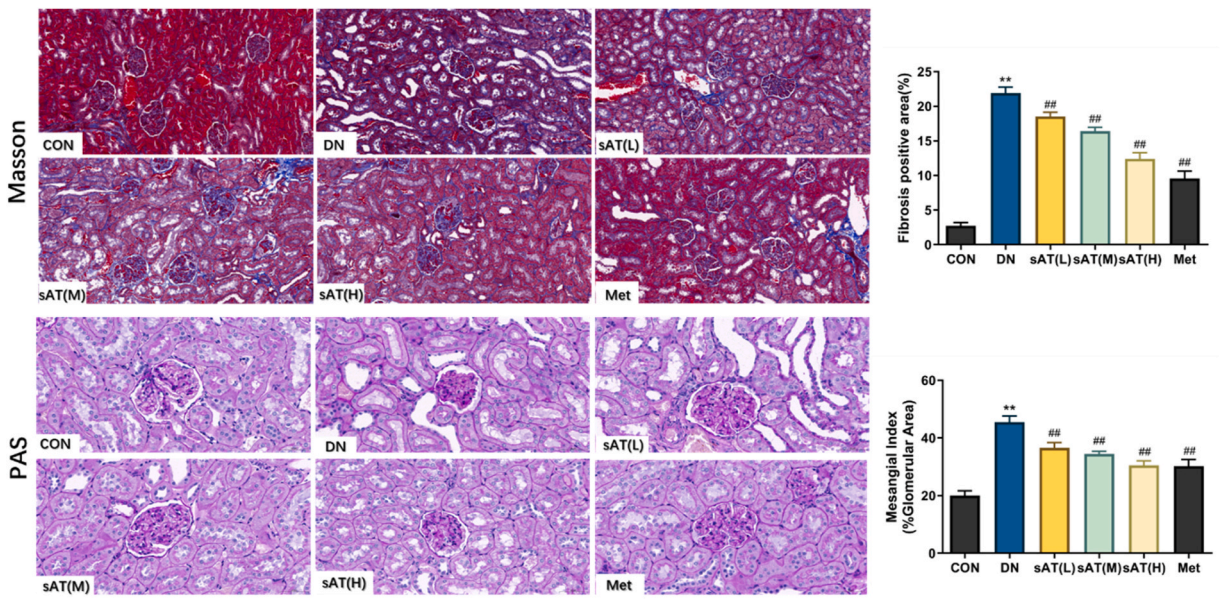

Fig. 3. Histopathological changes in the kidneys of diabetic rats with or without sAT treatment. Representative images of Masson's trichrome and PAS staining from each group.

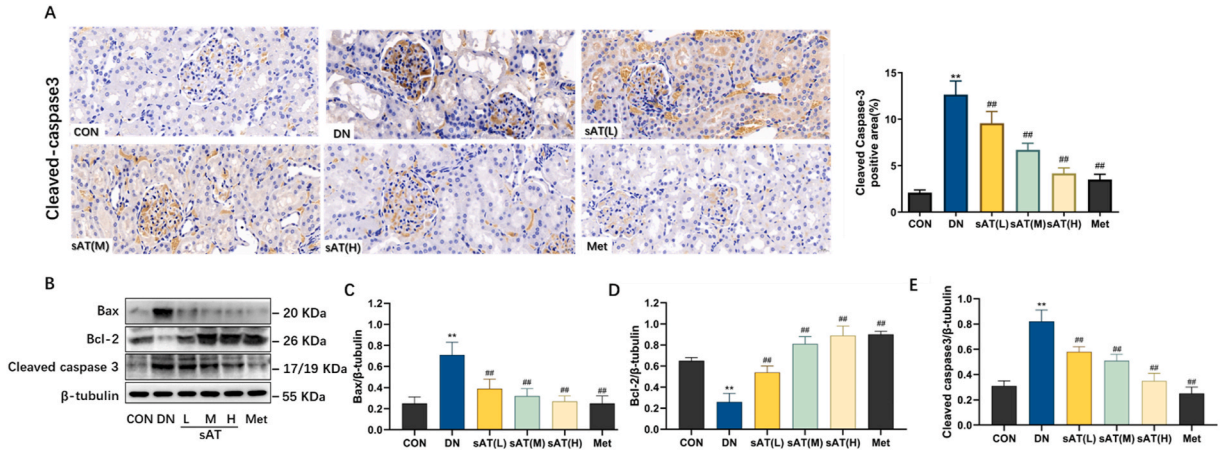

Fig. 4. Effects of sAT on cleaved caspase-3, Bax and Bcl-2 proteins expression levels in renal tissues of DN rats. A. The kidney tissues removed from each groups were immunohistochemically stained with anti-cleaved caspase-3. B. The protein levels of Bax, Bcl-2 and cleaved caspase-3 were detected by western blotting; C-E. Quantitative analysis of Bax, Bcl-2 and cleaved caspase-3 were normalized to the expression of β-tubulin. $^{**}P <$ 0.01 versus normal control group (CON); $^{\#\#}P < 0.01$ versus model group (DN). CON: ontrol group; DN: diabetic nephropathy group; sAT (L): DN rats treated with low-dosage sAT; sAT (M): DN rats treated with medium-dosage sAT; sAT(H): DN rats treated with high-dosage sAT; Met: metformin group.

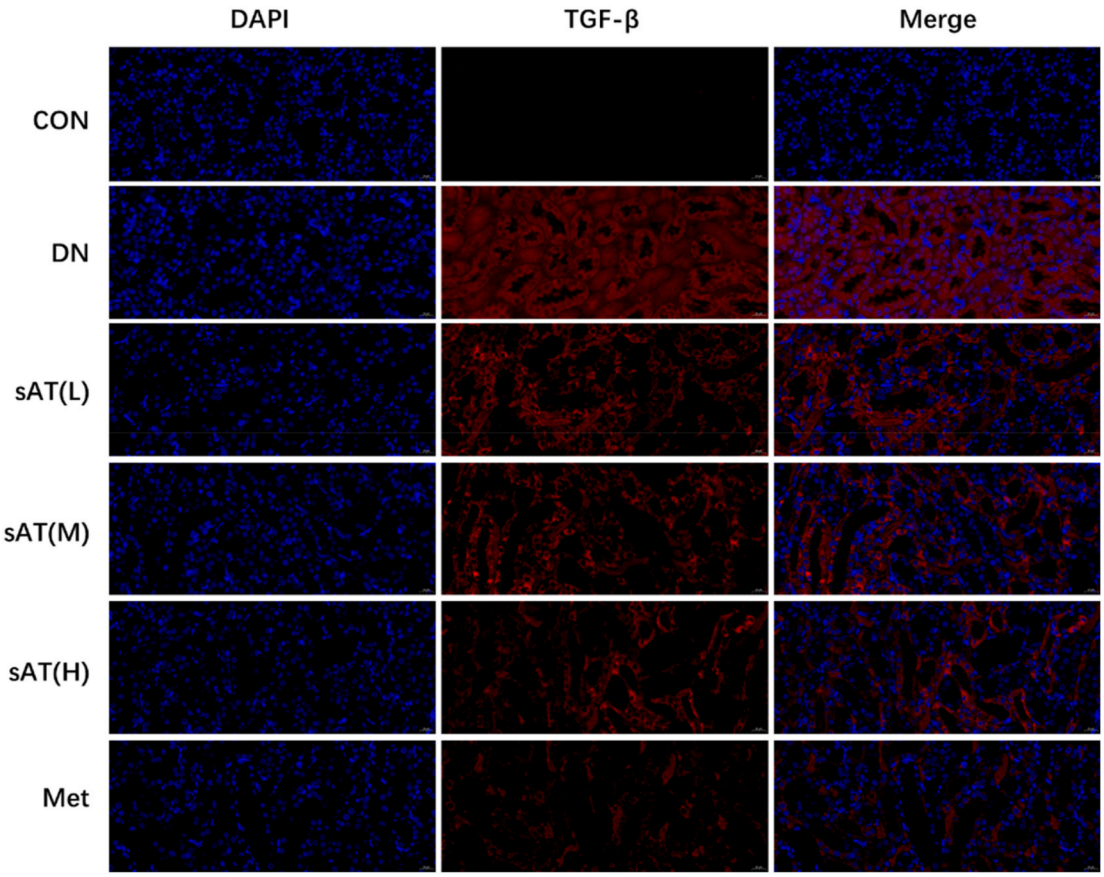

Fig. 5. Immunofuorescence staining for TGF-β1 expression in each group.

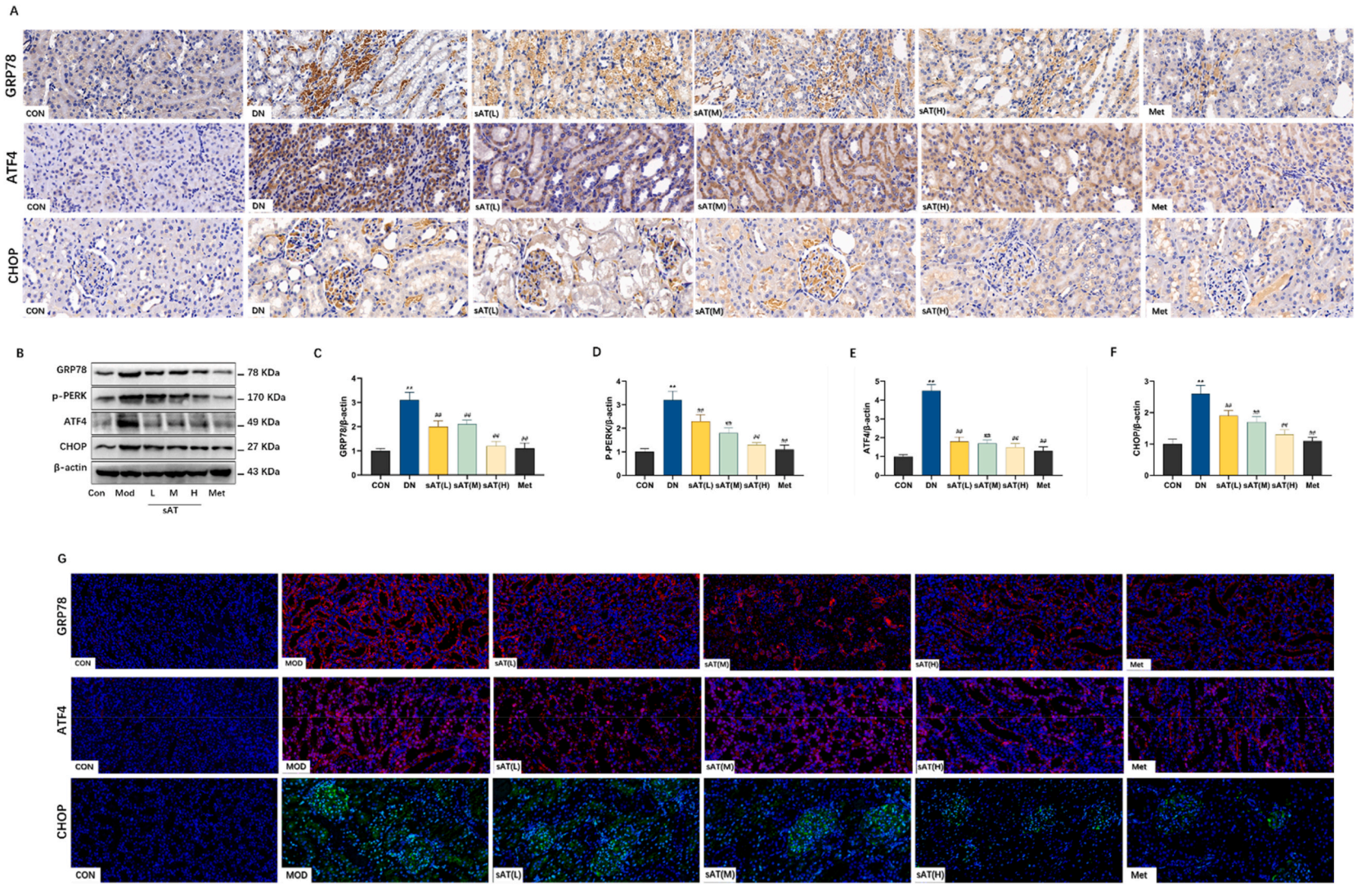

Fig. 6. sAT treatment inhibits diabetes-induced elevated ER stress in kidney. Representative images of immunohistochemical (A) and immunofluorescence (G) staining of GRP78, ATF4 and CHOP in kidney from each group. Western blotting and quantification of GRP78 (B,C), p-PERK (B,D), ATF4 (B,E) and CHOP (B,F) in different groups. $^{**}P < 0.01$ versus normal control group (CON); $^{\#\#}P < 0.01$, $^{\#}P < 0.05$ versus model group (DN).

3.5. sAT reduces ER stress in kidneys of DN rats

Immunohistochemistry, immunofluorescence and western blotting were used to determine the expression of the ER stress-associated proteins GRP78, p-PERK, ATF4 and CHOP. As seen in Fig. 6, compared with those in DN rats, the expressions of GRP78 (Fig. 6A, B and C), P-PERK (Fig. 6B and D), ATF4 (Fig. 6A, B and E) and CHOP (Fig. 6A, B and F) were significantly increased in the kidney from DN group, indicating that STZ did induce ER stress, whereas these increases were reversed by sAT treatment (Fig. 6). Taken together, our finding suggested that sAT treatment could inhibit ER stress in the kidney of DN rats.

4. Discussion

Diabetic nephropathy (DN), the primary cause of end-stage renal disease, poses a global health challenge that remains unresolved. The pathogenesis of DN is multifactorial, with interconnected factors influencing each other. Natural products offer the advantage of exerting multi-target effects and can be utilized in the treatment of diabetes and its associated complications. Previous reports have highlighted the antihyperglycemic, hypolipidemic, and antioxidant activities of triterpenoid saponin from Aralia taibaiensis (sAT) [15]. In this study, our aim was to investigate the protective effects of sAT on kidney injury in high-fat diet (HFD) and low-dose streptozotocin (STZ)-induced DN rats.

Prolonged hyperglycemia is known to impair kidney function and structure [16,17]. Early pathological changes in DN include kidney enlargement, thickening of glomerular and tubular basement membranes, and increased urine albumin excretion rate [18]. Decreased glomerular filtration capacity leads to elevated blood urea nitrogen (BUN) and serum creatinine (Scr) levels, indicative of renal dysfunction. Our results demonstrated that sAT effectively lowered blood glucose levels, improved renal index and urinary albumin excretion, reversed renal function deterioration, and ameliorated renal histopathology, consistent with previous reports of sAT's potent antidiabetic activity [19]. Renal pathomorphological alterations directly reflect the extent of pathological damage, crucial for evaluating treatment efficacy. Additionally, increased TGF-β1 expression in DN leads to glomerulosclerosis and renal interstitial fibrosis. We observed improvements in kidney injury and suppressed TGF-β1 expression following sAT administration. Apoptosis, the programmed cell death, plays a significant role in DN pathogenesis. The balance between pro- and anti-apoptotic Bcl-2 family proteins, as indicated by the Bax/Bcl-2 ratio, regulates apoptosis. Increased Bax expression promotes cell apoptosis, while increased Bcl-2 inhibits it [20]. Caspase-3 is a critical effector protease in apoptosis [21]. Our investigation of sAT's effect on kidney apoptosis revealed a significant decrease in Bax expression and cleaved caspase-3 levels, alongside increased Bcl-2 expression following sAT treatment, indicating sAT's ability to attenuate renal cell apoptosis in DN rats.

Oxidative stress and ER stress are interconnected phenomena involved in DN pathophysiology. Previous studies have associated sAT's cardioprotective effect with its antioxidant activity [22], prompting our evaluation of sAT's inhibitory role on ER stress in DN. The endoplasmic reticulum (ER) plays a pivotal role in protein synthesis, folding, and modification within cells. In conditions characterized by proteinuria and hyperglycemia, such as in patients with diabetic nephropathy (DN), elevated glucose levels and tubular protein deposition can trigger the generation of reactive oxygen species (ROS), leading to increased ER stress due to the heightened demand for membrane protein synthesis in the kidneys [23]. This ER stress can be further exacerbated by inflammatory responses, hypoxia, oxidative stress, and the accumulation of advanced glycation end products (AGEs) in DN [24]. Ultimately, prolonged ER stress can contribute to renal cell apoptosis and the progression of renal fibrosis [25]. Among the regulators of the unfolded protein response (UPR), glucose-regulated protein 78 (GRP78) acts as a central mediator in ER stress activation [26]. Additionally, studies have identified C/EBP homologous protein (CHOP) as a critical mediator of ER stress-induced apoptosis in DN. Upon ER stress, the activation of protein kinase RNA-like ER kinase (PERK) leads to the downstream induction of activating transcription factor 4 (ATF4), which in turn upregulates the expression of CHOP, thereby promoting apoptosis by increasing the Bax/Bcl-2 ratio [27,28]. In our study, we observed a significant increase in the expression of ER stress-related markers including GRP78, phosphorylated PERK (p-PERK), ATF4, and CHOP in DN rats. Treatment with sAT not only attenuated the imbalance in Bax/Bcl-2 ratio and caspase-3 activation but also suppressed the expression of ER stress-associated proteins, thereby reducing renal damage in DN rats. Thus, our findings provide novel insights into the renoprotective mechanisms of sAT, highlighting its ability to mitigate ER stress, which may offer therapeutic benefits in the management of DN. Furthermore, other herbal remedies, such as astragaloside IV, curcumins, and resveratrol, have also been shown to alleviate diabetic kidney damage by suppressing ER stress [29,30]. These findings collectively suggest that herbal remedies may confer renoprotective benefits through ER stress modulation, presenting a promising strategy for DN treatment.

5. Conclusions

In conclusion, our study demonstrates that sAT can alleviate both structural and functional abnormalities in a rat model of DN, potentially through the inhibition of ER stress-induced cell apoptosis. These findings suggest that sAT may offer therapeutic benefits for both the prevention and treatment of DN.

Funding

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Ethics statement

The animal care and experimental procedures were performed in accordance with the guidelines of the NIH and approved by Animal Care and Use Committee of the Fourth Military Medical University.

Data availability statement

The datasets generated during and/or analysed during the current study are available from the corresponding author upon reasonable request.

CRediT authorship contribution statement

Jia Cui: Writing – original draft, Software. **Mingming Wang:** Writing – original draft, Software. **Meiyou Liu:** Project administration, Investigation. **Na Jia:** Project administration, Investigation. **Meina Zhao:** Validation, Data curation. **Yan Weng:** Validation, Data curation. **Wei Zhang:** Writing – review & editing. **Lei Wang:** Conceptualization. **Jingwen Wang:** Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Jia Cui reports financial support was provided by The National Natural Science Foundation of China. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e31775.

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