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Shen-Qi-Yan-Shen Formula attenuates diabetic renal lipid deposition by down-regulating proteoglycan expression

[La fórmula Shen-Qi-Yan-Shen atenúa la deposición lipídica renal diabética al regular a la baja la expresión de proteoglicanos]

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Abstract: Diabetic nephropathy (DN) is characterized by renal lipid accumulation, often driven by proteoglycan (PG) interactions with lipoproteins. To investigate the effects of Shen-Qi-Yan-Shen Formula (SQYSF) on DN. Db/db mice were used as an experimental model and divided into different groups: db/m normal control, db/db model, SQYSF-treated, captopril-treated, and SQYSF + captopril-treated groups. Mice were treated with saline, SQYSF, captopril, or SQYSF + captopril for 12 weeks. SQYSF significantly reduced blood glucose, lipid levels, and markers of renal damage (blood urea nitrogen, serum creatinine, urinary albumin) in db/db mice compared to controls. SQYSF downregulated the expression of proteoglycan (PG), apolipoprotein B (apoB), and LDL-receptor in the kidney, suggesting a mechanism that involves reduced lipid accumulation. The protective effects of SQYSF were enhanced when combined with captopril. SQYSF may prevent lipid deposition by modulating PG expression, suggesting its potential as an innovative therapeutic agent for DN.

Keywords: Shen-Qi-Yan-Shen Formula (SQYSF); Diabetic nephropathy; Lipid deposition; Proteoglycan; Low-density lipoprotein

Resumen: La nefropatía diabética (DN) se caracteriza por la acumulación lipídica renal, a menudo impulsada por interacciones de proteoglicanos (PG) con lipoproteínas. Este estudio investiga los efectos de la fórmula Shen-Qi-Yan-Shen (SQYSF) sobre la DN. Se utilizaron ratones Db/db como modelo experimental y se dividieron en diferentes grupos: grupo control normal db/m, grupo modelo db/db, grupo tratado con SQYSF, grupo tratado con captopril y grupo tratado con SQYSF + captopril. Los ratones fueron tratados con solución salina, SQYSF, captopril o SQYSF + captopril durante 12 semanas. La SQYSF redujo significativamente los niveles de glucosa en sangre, lípidos y marcadores de daño renal (nitrógeno ureico en sangre, creatinina sérica, albúmina urinaria) en ratones db/db en comparación con los controles. La SQYSF reguló a la baja la expresión de proteoglicanos (PG), apolipoproteína B (apoB) y el receptor de LDL en el riñón, sugiriendo un mecanismo que involucra la reducción de la acumulación lipídica. Los efectos protectores de la SQYSF se potenciaron cuando se combinó con captopril. La SQYSF puede prevenir la deposición lipídica al modular la expresión de PG, sugiriendo su potencial como un agente terapéutico innovador para la DN.

Palabras clave: Fórmula Shen-Qi-Yan-Shen (SQYSF); Nefropatía diabética; Deposición lipídica; Proteoglicano; Lipoproteína de baja densidad.

INTRODUCTION

Diabetic nephropathy (DN) is a major complication of type 2 diabetes mellitus (T2DM), significantly affecting the microvascular domain and simultaneously contributing to the development of end-stage renal disease (ESRD) (Cheng *et al*., 2020). The pathogenesis of DN is intricate, with modern medicine recognizing lipid deposition in the kidney as an independent and major determinant in DN development (Chen *et al*., 2019). The combination of the extracellular matrix small molecule proteoglycan (PG) and low-density lipoprotein (LDL) is primarily responsible for lipoprotein deposition in tissues (She *et al*., 2016, Nahon *et al*., 2018). Traditional Chinese Medicine (TCM) views PG as closely related to "Jin Ye" (津液) (refers to the intrinsic fluids and normal secretions of various organs, such as gastric juice, intestinal fluids, saliva, and synovial fluid. It also encompasses metabolic by-products like urine, sweat, and tears) (Guoying *et al*., 2024). Early clinical observations indicated that treating DN based on the "Tan Yu Hu Jie" (痰淤互结) theory, which describes the Interconnection of Phlegm and Stasis (Phlegm is caused by the dysfunction of fluid transformation, leading to the accumulation of damp and turbid fluids in certain areas, resulting in pathological changes. Blood stasis refers to the stagnation of blood, where blood accumulates in the body and fails to circulate properly, obstructing meridians and organs) within the body, yielded promising results (Bilian *et al*., 2024). However, the underlying scientific explanation for this effectiveness remains elusive. Therefore, investigating the impact of TCM on deterring DN through the PG pathway is of considerable importance in guiding treatment strategies (Khramova *et al*., 2021). Chinese Herbal Medicine (CHM) is extensively applied in China to address diabetes and its associated complexities, including DN (Hu *et al*., 2018, Li *et al*., 2018a, Li *et al*., 2018b). The Shen-Qi-Yan-Shen Formula (SQYSF) is a CHM solution designed to address diabetic renal injuries. Our previous clinical studies demonstrated SQYSF's remarkable efficacy in ameliorating proteinuria and improving estimated glomerular filtration rate (eGFR) in patients with DN. Nevertheless, the precise mechanisms underlying SQYSF's therapeutic actions in DN remain largely unknown. This study delves into the target proteins modulated by SQYSF in the management of DN, meticulously scrutinizing the intricate molecular pathways involved in the progression of DN.

MATERIALS AND METHODS

Herbal formulation and components

This research involved the utilization of a blend known as SQYSF, which was composed of seven botanical components, namely red ginseng (*Panax ginseng*), astragalus root (*Astragalus membranaceus*), raw rhubarb (*Rheum palmatum*), epimedii (*Epimedium brevicornum*), ligusticum wallichii (Chuanxiong Rhizoma), rehmannia root (*Rehmannia glutinosa*), vinegar-processed carapax trionycis (*Pelodiscus sinensis*). The SQYSF powder was meticulously formulated and standardized at the Chongqing Institute of Traditional Chinese Medicine. The development of this herbal formula adhered to the procedures outlined in the 2010 version of the Pharmacopoeia of the People's Republic of China.

Animals and experimental design

Male C57BLKS/J db/db mice aged 8 weeks (n=36) were sourced from the Chongqing Medical University Laboratory Animal Center (Chongqing, China). A control group of db/m mice (n=9) was also included. The mice were housed under controlled conditions, maintained at a humidity of (55 ± 15)% and a temperature of (23 ± 2)℃, following a 12-h light/dark cycle (Teijeiro *et al*., 2021). Standard laboratory food and water were provided to the mice *ad libitum*. The db/db mice were randomly categorized into four distinct groups (n=9 each): SQYSF group: received SQYSF via intragastric gavage at a dosage of 3.6 g/kg/day (Ying *et al*., 2019); Captopril group: administered captopril via intragastric gavage at a dosage of 12.5 mg/kg/day (Guimarães *et al*., 2023); Combined group: received a combination of both captopril (12.5 mg/kg/day) and SQYSF (3.6 g/kg/day) via intragastric gavage, and the final group was administered saline (10 mL/kg). After 12 weeks of treatment, blood and tissue samples were collected for subsequent analysis. The effective dose of SQYSF for mice was determined to be 3.6 g/kg/day, based on a standardized conversion formula from a previous clinical study.

Assessment of urinary albumin excretion and renal function

Mice were housed in specialized metabolic cages

(Fengshi Inc., Suzhou, Jiangsu, China) to collect 24-hour urine samples for volume assessment. Urinary albumin levels were quantified using an enzyme-linked immunosorbent assay (ELISA) kit (Bethyl Laboratories Inc., Montgomery, Texas, USA) following the manufacturer's instructions. Blood samples were obtained via intracardiac puncture and centrifuged at 3000 rpm for 15 min to isolate the serum. Serum samples were then used to assess renal biochemical parameters. Blood urea nitrogen (BUN) and serum creatinine levels were determined using an automatic analyzer, specifically the Hitachi 747 model (Hitachi Co., Ltd., Tokyo, Japan).

Assessment of blood lipid and blood glucose levels

Fasting blood glucose (FBG, 20181205147, Shanghai Rongsheng Biotech Co., Ltd, Shanghai, China), hemoglobin A1c (HbA1c, BPE20512, ShangHai Lengton Bioscience Co.,LTD, Shanghai, China), total cholesterol (TC, A111-1, Nanjing Jiancheng Bioengineering Institute, Nanjing, China), triglycerides (TG, A110-2, Nanjing Jiancheng Bioengineering Institute, Nanjing, China), LDL-c (A113-1, Nanjing Jiancheng Bioengineering Institute, Nanjing, China), and HDL-c (A112-1, Nanjing Jiancheng Bioengineering Institute, Nanjing, China) levels were assessed using an automated biochemical analyzer (SynergyTM HTX, Bio Tek, New Jersey, USA).

Western blot analysis

In this experiment, 20 μg portions of kidney homogenates were separated on a 12% polyacrylamide gel (Cell Signaling Technology Co., Boston, MA, USA) and transferred to a polyvinylidene difluoride membrane. After electron transfer, the blots were subjected to a 1-hour blocking step at room temperature with a blocking buffer containing 20 mM Tris, 137 mM NaCl, 0.1% Tween 20, and 5% skim milk (pH 7.6). The blots were then incubated overnight with primary antibodies specific to PG, apoB, and LDL-receptor (LDL-R) (Cell Signaling Technology Co., Boston, MA, USA) at a 1:1000 dilution in the same blocking buffer. Following multiple washes with a buffer containing 20 mM Tris-HCl, 137 mM NaCl, and 0.1% Tween 20 (pH 7.6), the blots were incubated with 1:2000 diluted anti-rabbit IgG HRP-linked secondary antibody (Cell Signaling Technology Co., Boston, MA, USA) for 1 h at room temperature. After further washing, the immunoreactive proteins were visualized and quantified by densitometric analysis using Image J software developed by Wayne Rasband from the National Institutes of Health located in Stapleton, NY, USA.

Statistical analysis

Data are presented as the average with standard deviation (SD). Statistical analyses were conducted using SPSS version 20.0. Statistical analysis involved the use of an Independent Samples t-test or one-way analysis of variance (ANOVA). The multiple comparisons are analyzed using ANOVA, followed by Tukey Honestly Significantly Difference (HSD) tests. To compare pairs, t-tests were performed. Statistical significance was set at p values<0.05.

RESULTS

SQYSF alleviated proteinuria and renal functional damage in db/db mice with T2DM

On the 12th week, 24-h urinary protein (24 h UP) levels were analyzed in db/m, db/db, and db/db mice treated with SQYSF and/or captopril. In contrast to db/m mice, db/db mice exhibited a significant increase in 24-h UP levels. Notably, SQYSF administration significantly reduced proteinuria in db/db mice (Figure No. 1A). Mice in the db/db group exhibited heightened levels of BUN and serum creatinine compared to the db/m group. Notably, db/db mice treated with either SQYSF or captopril demonstrated a pronounced effect on lowering BUN and serum creatinine levels than that received saline treatment. Furthermore, the combined administration of SQYSF and captopril had a more pronounced effect on reducing BUN and serum creatinine levels than SQYSF or captopril alone (Figure No. 1B).

SQYSF down-regulated blood lipid and FBG levels in db/db mice with T2DM

Blood glucose and lipid levels were assessed using an automated analyzer. At week 12, FBG, HbA1c, TC, TG, LDL-c, and HDL-c protein levels were markedly elevated in the kidneys of saline-treated db/db mice compared to the db/m group. Both SQYSF and captopril significantly reduced FBG, HbA1c, TG, LDL-c, and HDL-c protein levels in db/db mice. Notably, the SQYSF + captopril group exhibited lower protein expression levels compared to the

SQYSF or captopril groups alone. While there was no significant difference in TC expression across all groups, except for the db/m group (Figure No. 2). These findings suggest that SQYSF's kidney-protective effect in db/db mice is linked to its impact on lipid metabolism.

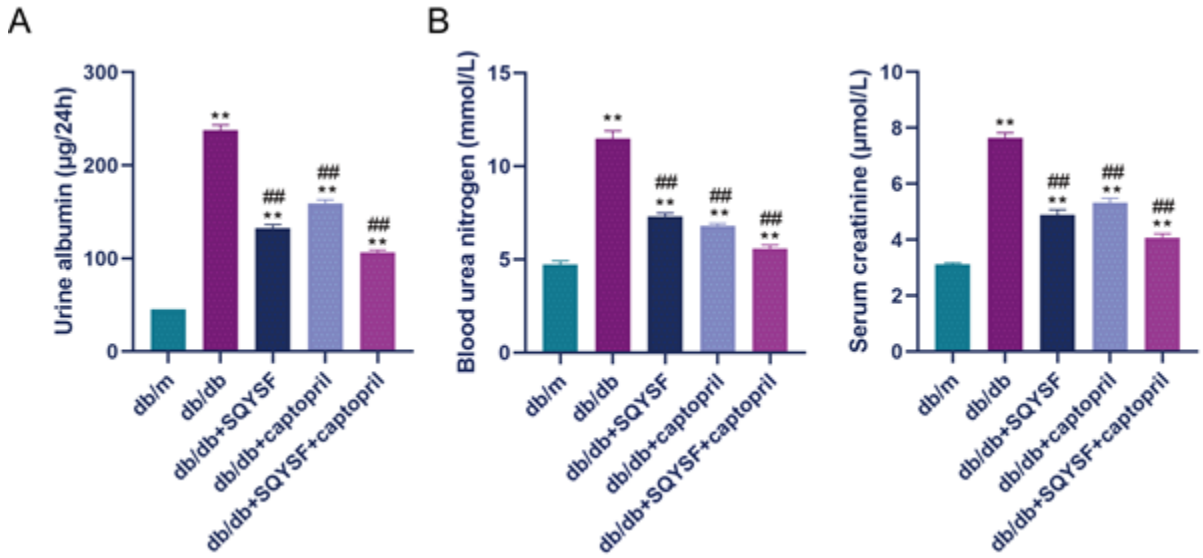

Figure No. 1
SQYSF alleviated proteinuria and renal functional damage of db/db mice. (A) Effective SQYSF administration resulted in a notable reduction in urinary albumin levels in db/db mice. (B) SQYSF treatment led to a decrease in serum creatinine and blood urea nitrogen levels in db/db mice. These findings were presented as the mean ± standard deviation. * indicated statistical significance at $p<0.05$, **indicated statistical significance at $p<0.01$ when compared to db/m group, #indicated statistical significance at $p<0.05$, ##indicated statistical significance at $p<0.01$ when compared to db/db group

SQYSF down-regulated PG, LDL-R, and apoB protein expressions in db/db mice with T2DM

To assess the effects of SQYSF on PG, LDL-R, and apoB, western blotting was employed to detect protein levels. The protein levels of PG, LDL-R, and apoB were notably low in the kidneys of db/m mice. As expected, these levels increased in the kidneys of saline-treated db/db mice. The SQYSF, captopril, and SQYSF + captopril groups produced different degrees of downregulation of PG, LDL-R, and apoB expression. The SQYSF + captopril combination exhibited the most pronounced inhibitory effect (Figure No. 3).

DISCUSSION

DN is a complex condition resulted from multiple factors. Its pathological hallmarks include increased renal perfusion, thickening of the glomerular basement membrane, and accumulation of extracellular matrix in glomerular mesangium (Li *et al*., 2017; Li *et al*., 2018a). Lipid deposition in the kidney can induce and aggravate renal damage, contributing to glomerular sclerosis and renal tubular damage. The underlying mechanisms include: 1) lipoprotein deposition in the glomerular basement membrane directly stimulates basement membrane cell proliferation, leading to an increase in extracellular matrix; 2) lipoprotein deposition in the glomerular mesangium and local oxidative modification, generating a significant amount of ox-LDLs, which can cause proximal tubular detachment and death (Huang *et al*., 2015; Cao *et al*., 2016; Lopes-Virella *et al*., 2016; Zhou *et al*., 2016). These changes trigger an inflammatory response, increase macrophage phagocytosis, and form foam cells, which in turn exacerbate glomerular sclerosis (Zhao *et al*., 2014; Tavridou *et al*., 2015; She *et al*., 2016; Nabi *et al*., 2019). The combination of PG and LDL

is widely recognized as a major contributor to lipoprotein deposition in the kidneys of individuals with DN (Pan *et al*., 2014; Cikrikcioglu *et al*., 2016; She *et al*., 2016). PG is a macromolecular sugar complex composed of one or more glycosaminoglycan (GAG) chains covalently linked to a core protein. And it is the primary non-collagen component of the basement membrane and extracellular matrix (Gomes *et al*., 2014; Martin *et al*., 2017). The anionic charges in GAG sulfate and uronic acid combine with the positively charged apoB of LDL, resulting in lipoprotein deposition (Sugar *et al*., 2014; Zaferani *et al*., 2014). Factors such as elongated GAG chains, enhanced GAG sulfation, increased density of positively charged ions in LDL, and the presence of molecules such as LPL or apoE can promote this combination. Moreover, lipoprotein modification can alter the GAG affinity of PG by modifying the GAG-binding site. This study confirmed that the expression of PG, apoB, LDL, FBG, and TG is upregulated in db/db mice, accompanied by impaired renal function, consistent with other studies.

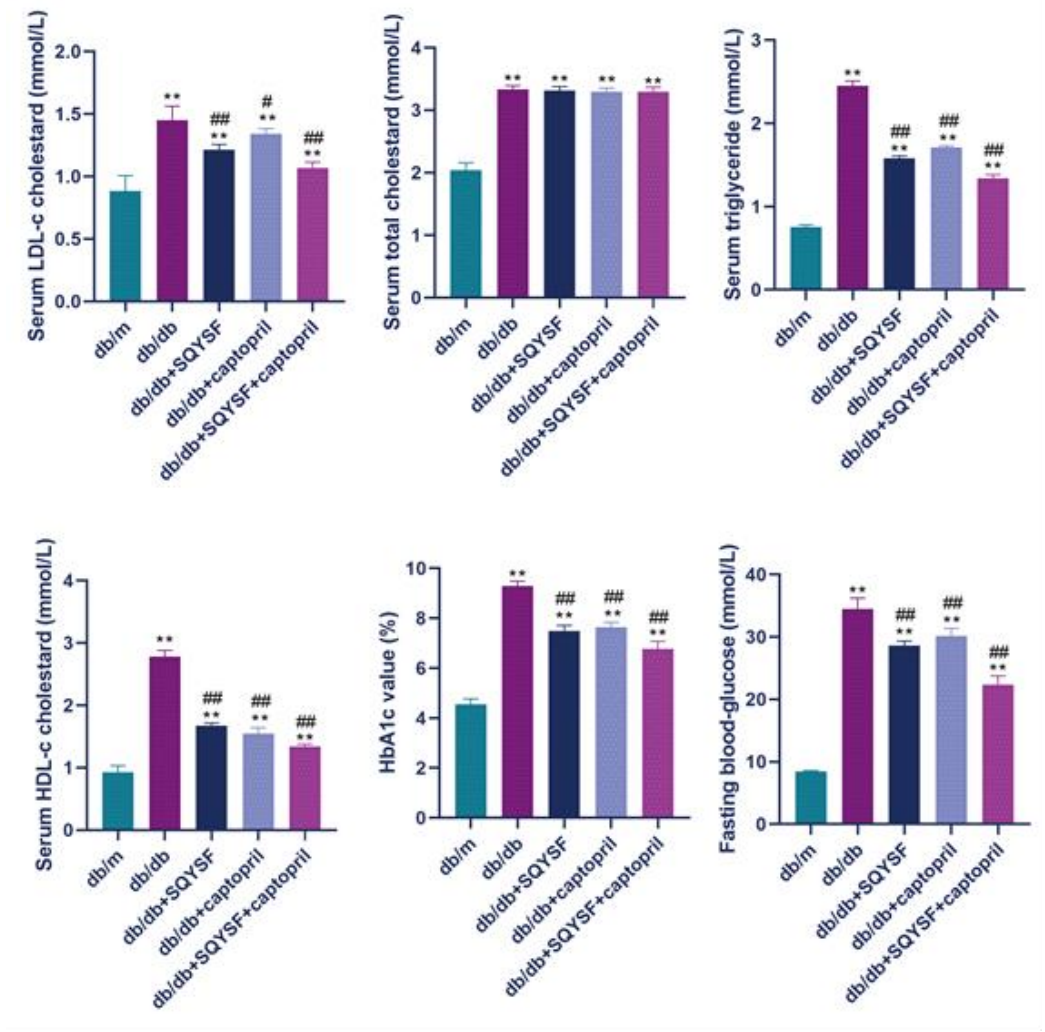

Figure No. 2

SQYSF down-regulated blood lipid and FBG levels. Analysis by automatic analyzer demonstrated that db/db induced marked up-regulation of FBG, HbA1c, TC, TG, LDL-c, and HDL-c protein expression. The elevated levels of FBG, HbA1c, TG, LDL-c, and HDL-c were significantly reduced by SQYSF administration, compared with db/db group. There was no significant difference in TC expression in each group except db/m group. The data were expressed as the mean ± SD. *p<0.05, **p<0.01 compared with db/m group, #p<0.05, ##p<0.01 compared with db/db group

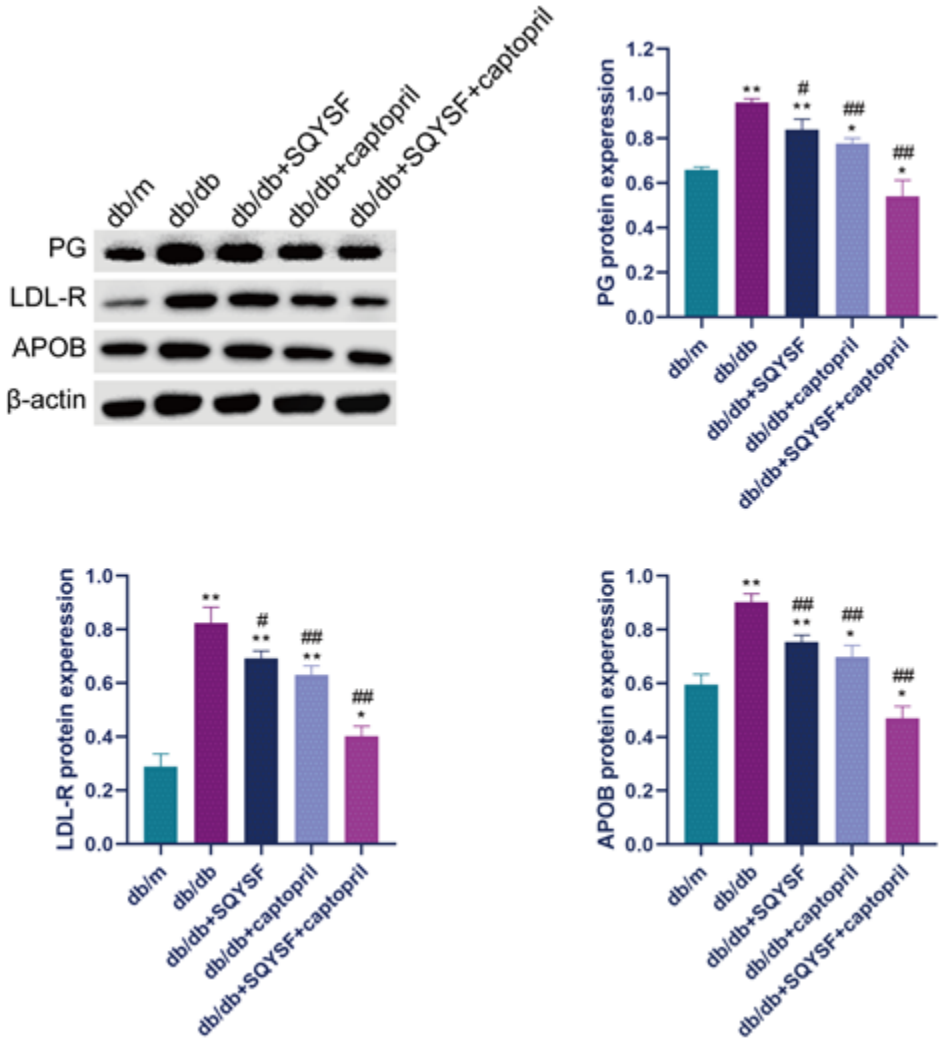

Figure No. 3

SQYSF down-regulated PG, LDL-R, and apoB protein expression. Our results from the Western blot analysis revealed decreased protein levels of PG, LDL-R, and apoB in control group. However, in db/db groups, a marked increase in the expression of these proteins was observed. In both SQYSF and SQYFS + captopril groups, there was a significant down-regulation of protein expression. Our data was presented as the mean ± standard deviation. *p<0.05, **p<0.01 when compared to the db/m group, #p<0.05, ##p<0.01 when compared to db/db group

The accumulation of GAG chains in the intercellular stroma pathologically disrupts the exchange of substances and information between local cells and the entire regulatory system. This disruption eventually affects normal cellular metabolism and function (Zhang *et al*., 2014; Xu *et al*., 2015). This study demonstrated that the protein levels of PG, LDL-R, and apoB were significantly elevated in the kidneys of db/db mice compared to db/m mice. SQYSF treatment significantly downregulated the expression of these proteins, with the most pronounced inhibitory effect observed in the SQYSF + captopril combination group. SQYSF is a herbal formula composed of seven botanical components, each with distinct actions based on TCM principles. Red ginseng and astragalus root, the

monarch (principle) herbs, synergistically tonify the spleen and kidney (Zhang *et al*., 2019; Zhang *et al*., 2024). Epimedii and raw rhubarb, the minister (adjuvant) herbs, warm Yang and tonify the kidney (epimedii) and dispels turbidity and removes blood stasis to promote coronary circulation (raw rhubarb) (Yap *et al*., 2007; Li *et al*., 2024). *Ligusticum wallichii*, rehmannia root, and vinegar-processed carapax trionycis combined with red ginseng, prevent overheating and balance Yin and Yang, acting as assistant (auxiliary) and guide (conductor) herbs. SQYSF reinforcing Qi and discharging turbidity, tonifying Qi in the kidney, activating blood circulation, and clearing dampness-heat syndrome caused by irregular fluid distribution.

In the present study, SQYSF significantly alleviated proteinuria and improved renal function. Compared to db/m mice, db/db mice displayed higher FBG, HbA1c, TC, TG, LDL-c, and HDL-c protein expression levels. These elevated protein levels were significantly decreased by SQYSF treatment, except for TC. PG is a crucial component of the extracellular matrix, and its interaction with lipoproteins through electrostatic forces is associated with lipid deposition. Here, abnormal levels of PG, LDL-R, and apoB protein expression in db/db mice at week 12, which were significantly restored by SQYSF treatment. Captopril partially inhibited the expression of PG, LDL-R, and apoB proteins in db/db mice, possibly due to the relatively low dose of captopril used. SQYSF significantly enhanced this inhibitory effect, suggesting that PG may be a channel for DN treatment using SQYSF. Further research is required to elucidate the precise mechanisms by which SQYSF modulates lipoprotein deposition in DN.

CONCLUSION

Our research indicates that PG could serve as a potential treatment for DN via SQYSF. Additionally, our findings revealed that SQYSF lowered lipid accumulation by suppressing PG expression.

Statement of Ethics

This study protocol was reviewed and approved by the Ethics Committee of Chongqing Hospital of Traditional Chinese Medicine, approval number [2020-DWSY-SL].

Conflict of interest statement

The authors have no conflicts of interest to declare.

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REFERENCES

Bilian Z, Jingjing H, Shijia Y. 2024. Treatment of diabetic nephropathy based on the theory of “Interconnection of Phlegm and Stasis”. **Clin J Tradit Chin Med** 36: 19 - 22. **https://doi.org/10.16448/j.cjtcm.2024.0105**

Cao A, Wang L, Chen X, Guo H, Chu S, Zhang X, Peng W. 2016. Ursodeoxycholic acid ameliorated diabetic nephropathy by attenuating hyperglycemia-mediated oxidative stress. **Biol Pharm Bull** 39: 1300 - 1308. **https://doi.org/10.1248/bpb.b16-00094**

Chen X, Han Y, Gao P, Yang M, Xiao L, Xiong X, Zhao H, Tang C, Chen G, Zhu X, Yuan S, Liu F, Dong LQ, Liu F, Kanwar YS, Sun L. 2019. Disulfide-bond A oxidoreductase-like protein protects against ectopic fat deposition and lipid-related kidney damage in diabetic nephropathy. **Kidney Int** 95: 880 - 895. **https://doi.org/10.1016/j.kint.2018.10.038**

Cheng HT, Xu X, Lim PS, Hung KY. 2020. Worldwide epidemiology of diabetes-related end-stage renal disease, 2000-2015. **Diabetes Care** 44: 89 - 97. **https://doi.org/10.2337/dc20-1913**

Cikrikcioglu MA, Erturk Z, Kilic E, Celik K, Ekinci I, Yasin Cetin AI, Ozkan T, Cetin G, Dae SA, Kazancioglu R, Erkoc R. 2016. Endocan and albuminuria in type 2 diabetes mellitus. **Ren Fail** 38: 1647 - 1653. **https://doi.org/10.1080/0886022x.2016.1229966**

Gomes CL, Leão CL, Venturotti C, Barreira AL, Guimarães G, Fonseca RJ, Fortunato RS, Mourão PA, Delgado AG, Takiya CM, Leite M. 2014. The protective role of fucosylated chondroitin sulfate, a distinct glycosaminoglycan, in a murine model of streptozotocin-induced diabetic nephropathy. **Plos One** 9: e106929. **https://doi.org/10.1371/journal.pone.0106929**

Guimarães JPT, Queiroz LAD, Menikdiwela KR, Pereira N, Ramalho T, Jancar S, Moustaid-Moussa N, Martins JO. 2023. The role of captopril in leukotriene deficient type 1 diabetic mice. **Sci Rep** 13: 22105. **https://doi.org/10.1038/s41598-023-49449-8**

Guoying L, Wanli J, Qingwei L. 2024. On application of metabonomies in TCM syndrome differentiation from Qi, blood and body fluid. **Liaoning J Tradit Chin Med** 51: 217 - 220. **https://doi.org/10.13192/j.issn.1000-1719.2024.06.056**

Hu SJ, Shu B, Jin H, Li XF, Mao JR, Ren KJ, Gao L, Yang L, Wu YW, Wang YJ. 2018. Therapeutic role of tangshenkang granule (糖肾康颗粒) in rat model with diabetic nephropathy. **Chin J Integr Med** 24: 600 - 605. **https://doi.org/10.1007/s11655-016-2607-x**

Huang Z, Nooeaid P, Kohl B, Roether JA, Schubert DW, Meier C, Boccaccini AR, Godkin O, Ertel W, Arens S, Schulze-Tanzil G. 2015. Chondrogenesis of human bone marrow mesenchymal stromal cells in highly porous alginate-foams supplemented with chondroitin sulfate. **Mater Sci Eng C Mater Biol Appl** 50: 160 - 172. **https://doi.org/10.1016/j.msec.2015.01.082**

Khramova A, Boi R, Fridén V, Granqvist AB, Nilsson U, Tenstad O, Oveland E, Haraldsson B, Ebefors K, Nyström J. 2021. Proteoglycans contribute to the functional integrity of the glomerular endothelial cell surface layer and are regulated in diabetic kidney disease. **Sci Rep** 11: 8487. **https://doi.org/10.1038/s41598-021-87753-3**

Li Z, Zhang W. 2017. Protective effect of berberine on renal fibrosis caused by diabetic nephropathy. **Mol Med Rep** 16: 1055 - 1062. **https://doi.org/10.3892/mmr.2017.6707**

Li J, Li N, Yan S, Liu M, Sun B, Lu Y, Shao Y. 2018a. Ursolic acid alleviates inflammation and against diabetes-induced nephropathy through TLR4-mediated inflammatory pathway. **Mol Med Rep** 18: 4675 - 4681. **https://doi.org/10.3892/mmr.2018.9429**

Li Z, Hong Z, Peng Z, Zhao Y, Shao R. 2018b. Acetylshikonin from Zicao ameliorates renal dysfunction and fibrosis in diabetic mice by inhibiting TGF-β1/Smad pathway. **Hum Cell** 31: 199 - 209. **https://doi.org/10.1007/s13577-017-0192-8**

Li JN, Wang MY, Tan YR, Wang LL. 2024. Multidirectional intervention of Chinese Herbal Medicine in the prevention and treatment of atherosclerosis: From endothelial protection to immunomodulation. **Am J Chin Med** 52: 925 - 947. **https://doi.org/10.1142/S0192415X24500381**

Lopes-Virella MF, Hunt KJ, Baker NL, Virella G. 2016. High levels of AGE-LDL, and of IgG antibodies reacting with MDA-lysine epitopes expressed by oxLDL and MDA-LDL in circulating immune complexes predict macroalbuminuria in patients with type 2 diabetes. **J Diabetes Compl** 30: 693 - 699. **https://doi.org/10.1016/j.jdiacomp.2016.01.012**

Martin L, Gombert A, Chen J, Liebens J, Verleger J, Kalder J, Marx G, Jacobs M, Thiemermann C, Schuerholz T. 2017. The β-d-endoglucuronidase heparanase is a danger molecule that drives systemic inflammation and correlates with clinical course after open and endovascular thoracoabdominal aortic aneurysm repair: Lessons learnt from mice and men. **Front Immunol** 8: 681. **https://doi.org/10.3389/fimmu.2017.00681**

Nabi R, Alvi SS, Saeed M, Ahmad S, Khan MS. 2019. Glycation and HMG-CoA reductase inhibitors: Implication in diabetes and associated complications. **Curr Diabetes Rev** 15: 213 - 223. **https://doi.org/10.2174/1573399814666180924113442**

Nahon JE, Hoekstra M, Van Eck M. 2018. Total body proteoglycan 4 (Prg4) deficiency increases atherosclerosis susceptibility in apolipoprotein E knockout and low-density lipoprotein receptor knockout mice. **Atherosclerosis** 278: 315 - 316. **https://doi.org/10.1016/j.atherosclerosis.2018.06.883**

Pan D, Zhang D, Wu J, Chen C, Xu Z, Yang H, Zhou P. 2014. A novel proteoglycan from *Ganoderma lucidum* fruiting bodies protects kidney function and ameliorates diabetic nephropathy via its antioxidant activity in C57BL/6 db/db mice. **Food Chem Toxicol** 63: 111 - 118. **https://doi.org/10.1016/j.fct.2013.10.046**

She ZG, Chang Y, Pang HB, Han W, Chen HZ, Smith JW, Stallcup WB. 2016. NG2 proteoglycan ablation reduces foam cell formation and atherogenesis via decreased low-density lipoprotein retention by synthetic smooth muscle cells. **Arterioscler Thromb Vasc Biol** 36: 49 - 59. **https://doi.org/10.1161/atvbaha.115.306074**

Sugar T, Wassenhove-McCarthy DJ, Esko JD, van Kuppevelt TH, Holzman L, McCarthy KJ. 2014. Podocyte-

specific deletion of NDST1, a key enzyme in the sulfation of heparan sulfate glycosaminoglycans, leads to abnormalities in podocyte organization *in vivo*. **Kidney Int** 85: 307 - 318. **https://doi.org/10.1038/ki.2013.281**

Tavridou A, Georgoulidou A, Roumeliotis A, Roumeliotis S, Giannakopoulou E, Papanas N, Passadakis P, Manolopoulos VG, Vargemezis V. 2015. Association of plasma adiponectin and oxidized low-density lipoprotein with carotid intima-media thickness in diabetic nephropathy. **J Diabetes Res** 2015: 507265. **https://doi.org/10.1155/2015/507265**

Teijeiro A, Garrido A, Ferre A, Perna C, Djouder N. 2021. Inhibition of the IL-17A axis in adipocytes suppresses diet-induced obesity and metabolic disorders in mice. **Nature Metab** 3: 496 - 512. **https://doi.org/10.1038/s42255-021-00371-1**

Xu K, Pan X, Sun Y, Xu W, Njunge L, Yang L. 2015. Psoralen activates cartilaginous cellular functions of rat chondrocytes *in vitro*. **Pharm Biol** 53: 1010 - 1015. **https://doi.org/10.3109/13880209.2014.952835**

Yap SP, Shen P, Li J, Lee LS, Yong EL. 2007. Molecular and pharmacodynamic properties of estrogenic extracts from the traditional Chinese medicinal herb, Epimedium. **J Ethnopharmacol** 113: 218 - 224. **https://doi.org/10.1016/j.jep.2007.05.029**

Ying L, Tai-Jun Z, Hong L, Wei-Jian X, Lei L, Jin Z, Xiao-Qin O, Ling Z. 2019. Clinical observation on patients with chronic kindey disease stage 3-5 treated by the Chinese herbs formula of shenqiyanshenfang. **Guide China Med** 17: 1 - 2.

Zaferani A, Talsma DT, Yazdani S, Celie JW, Aikio M, Heljasvaara R, Navis GJ, Pihlajaniemi T, van den Born J. 2014. Basement membrane zone collagens XV and XVIII/proteoglycans mediate leukocyte influx in renal ischemia/reperfusion. **Plos One** 9: e106732. **https://doi.org/10.1371/journal.pone.0106732**

Zhang LG, Ouyang XW, Wu TT, Ni LJ, Shi WZ. 2014. Quantitative evaluation of *in vitro* effects and interactions of active fractions in a Chinese medicinal formula (Yaotongning Capsule) on rat chondrocytes. **J Ethnopharmacol** 155: 1424 - 1432. **https://doi.org/10.1016/j.jep.2014.07.011**

Zhang L, Shergis JL, Yang L, Zhang AL, Guo X, Zhang L, Zhou S, Zeng L, Mao W, Xue CC. 2019. *Astragalus membranaceus* (Huang Qi) as adjunctive therapy for diabetic kidney disease: An updated systematic review and meta-analysis. **J Ethnopharmacol** 239: 111921. **https://doi.org/10.1016/j.jep.2019.111921**

Zhang YL, Chen SM, Song YJ, Islam MA, Rao PL, Zhu MJ, Gu WY, Xu Y, Xu HX. 2024. Red ginseng ameliorates lipotoxicity-induced renal fibrosis in hyperuricemia mice. **J Ethnopharmacol** 327: 118014. **https://doi.org/https://doi.org/10.1016/j.jep.2024.118014**

Zhao L, Wu F, Jin L, Lu T, Yang L, Pan X, Shao C, Li X, Lin Z. 2014. Serum CXCL16 as a novel marker of renal injury in type 2 diabetes mellitus. **Plos One** 9: e87786. **https://doi.org/10.1371/journal.pone.0087786**

Zhou X, Liu R, Duan S, Huang G, Ye Y, Kong Y. 2016. High glucose enhances oxLDL-induced apoptosis in human renal proximal tubular epithelial cells largely via inducing lectin-like ox-LDL receptor-1. **Pharmacology** 98: 20 - 28. **https://doi.org/10.1159/000444934**