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REVIEW

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Research Progress on Traditional Chinese Medicine Targeting and Regulating Mitochondrial Dysfunction to Intervene in Diabetic Nephropathy

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Abstract

Diabetic nephropathy (DN) is the most common cause of adult nephrotic syndrome and of global renal failure. In traditional Chinese medicine (TCM), DN belongs to the category of “renal wasting thirst disorders”. As early as the Han dynasty, historical records documented the efficacy of TCM in reducing albuminuria of DN patients. The chronic hyperglycemia in diabetic patients leads to progressive damage to renal microvessel (especially glomerulus), ultimately disrupting renal structure and function. The changes of mitochondrial morphology and quantification precede the onset of diabetic albuminuria and renal histological changes and development. This study reviews the latest research on TCM targeting and regulating mitochondrial dysfunction to ameliorate DN, with the aim of providing prophylaxis and treatment methods of DN.

1 Introduction

Diabetic nephropathy (DN) is characterized by glomerulosclerosis and fibrosis resulting from the metabolic and hemodynamic changes of diabetes, with clinical manifestations of impaired renal function and increased urinary albumin excretion. DN is the most common cause of adult nephrotic syndrome and of global renal failure. In patients with diabetes mellitus (DM), the lifetime risk of developing renal failure approaches 40% [1]. China currently has the largest DM population globally, among which 32.6% patients concurrently suffer from DN, and notably, the type 2 diabetes (T2D) has emerged as the culprit of chronic kidney disease [2]. Although current guidelines recommend glucose-lowering agents (e.g., sodium-dependent glucose transporters 2 (SGLT2) inhibitors and Glucagon-Like Peptide-1 (GLP-1) receptor agonists), antihypertensives (Angiotensin-Converting Enzyme Inhibitors (ACEIs) and Angiotensin II type 1 receptor blockers (ARBs)) and lipid-lowering agents (statins) to slow DN progression and reduce albuminuria [3], these strategies merely delay rather than halt or reverse disease advancement, highlighting the need for more effective therapies.

In traditional Chinese medicine (TCM), DM is classified as a "wasting thirst disorder" characterized by restlessness, thirst, polyuria, and emaciation, while DN belongs to the category of "renal wasting thirst disorders". Historical records from the Han dynasty document the use of TCM to reduce albuminuria in DN. Modern medicine has validated the efficacy of formulas such as Bawei Dihuang Wan, Guizhi Fuling Wan, Liuwei Dihuang Pills, and Wenpi Tang in treating DN through clinical trials [4]. In addition, based on the development of bioinformatics analysis technology, researchers can screen and predict the active ingredients and therapeutic targets of TCM through network pharmacology and molecular docking technology, combined with wet experiments for verification. The research on TCM has shifted from the clinical efficacy of single empirical formulas to active ingredients and the mechanism of their combination, which not only confirms their efficacy, but also provides deeper insight into the underlying mechanism. For instance, Astragaloside II from Astragali Radix alleviates podocyte injury and mitochondrial dysfunction in DM rats by regulating the nuclear factor erythroid-derived-2-like 2 (Nrf2) and PTEN-induced putative kinase1 (PINK1) pathways [5]. Bavachin from *Psoralea corylifolia* L. seed reduces the production of mitochondrial reactive oxygen species (ROS), increases PGC-1 α and Sirtuin 1 (SIRT1) expressions, and enhances mitochondrial function to improve DN [6].

Given the high mitochondrial content and energy demand in renal tissues, mitochondrial dysfunction-marked by oxidative stress and bioenergetic deficit-plays a central role in DN progression. Therefore, examining mitochondrial pathophysiology in DN and exploring how TCM mitigates renal injury through multi-targeted modulation of mitochondrial function represent promising research directions with significant therapeutic implications.

2 Mitochondrial dysfunction and DN

The kidney participates in glucose homeostasis via renal gluconeogenesis. In T2D patients, the markedly enhanced renal gluconeogenesis results in excessive endogenous glucose output in both postprandial and fasting states and thereby exacerbates hyperglycaemia; moreover, upregulation of SGLT2 promotes excessive glucose reabsorption in the proximal tubule, further aggravating hyperglycaemia [7]. Aerobic glucose oxidation is the principal route for cellular adenosine triphosphate (ATP) production. In healthy renal cells, stable mitochondria generate ATP through the electron-transport chain and oxidative

phosphorylation, providing the energy for reabsorption along the proximal tubule, loop of Henle, distal tubule and collecting duct [8]. The long-term hyperglycemia in diabetic patients continuously damages renal microvessel (especially glomerulus), and thus disrupts renal structure and function. Intriguingly, the changes of mitochondria precede the onset of diabetic albuminuria and renal histological changes and development. Ample evidence indicated that mitochondrial dysfunction is one of the primary pathogenic mechanisms of DN [9-11].

2.1 Mitochondrial oxidative phosphorylation (OXPHOS)

OXPHOS utilizes organic substrates (e.g. glucose, fatty acids) to participate in tricarboxylic acid (TCA) cycle in the mitochondrial matrix. The reduced coenzyme, nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide ($FADH_2$), which are co-produced during catabolism, transfers its electrons via the electron-transport chain (ETC) in the inner mitochondrial membrane (IMM). The released energy promotes the establishment of a proton gradient that drives ATP synthase to synthesize ATP. In the early stage of DM (four weeks), ATP content in proximal-tubule epithelial cells (PTECs) is obviously diminished [12]. Decreased OXPHOS efficiency and ATP production have been identified in advanced DN [13,14]. Aberrant OXPHOS is related to reduced utilization rate of organic substrates, decreased activity of ETC complexes, inability to establish a strong proton gradient and weak driving force for ATP synthesis. Li et al. [15] found that Smad4 deficiency enhances glycolysis and maintains mitochondrial OXPHOS to protect podocytes from high glucose-induced ATP production loss, thus suppressing the development of DN. The decline in mitochondrial ATP synthesis leads to cellular "energy crisis", which compromises functions such as renal tubular reabsorption, and contributes to the development of DN.

2.2 Oxidative stress

Mitochondria are the principal intracellular source of ROS. During aerobic respiration, electron-transport-chain complexes in mitochondria transfer electrons to O_2. A fraction of this O_2 is reduced to superoxide (O_2^-), hydrogen peroxide (H_2O_2), singlet oxygen ($^1O_2$), hydroxyl radicals ($HO\cdot$), hydroperoxyl radicals ($ROO\cdot$), and oxidants such as peroxynitrite ($ONOO^-$). ROS at basal levels plays a critical role in cellular signal transduction [16]. However, persistent hyperglycaemia in DM patients induces mitochondrial swelling and the accumulation of fragmented mitochondria in renal cells, leading to increased ROS production [17]. Excess ROS precipitates oxidative stress, accelerating pathological changes of tissues and cells, including DN progression. In response, the antioxidant defense system is activated to remove excessive ROS. Upon great differences between mitochondrial ROS production and clearance abilities, the levels of antioxidant substances such as superoxide dismutase (SOD) and glutathione (GSH) decline. The inability to effectively clear ROS may disrupt the balance between oxidants and antioxidants, triggering oxidative damage [18]. Accumulated ROS also oxidizes lipids and thus changes their structure, activity and physical properties. When there is abundance of lipoprotein receptors on the surface of glomerular endothelial cells and proximal renal tubules, lipids and lipid peroxides are prone to deposit in the kidneys. Recent research indicated that ectopic lipid deposition and changed lipid composition can induce lipotoxicity-related renal damage. Sphingolipid accumulation and compositional changes within renal cells are of great significance to renal function [19,20]. Nevertheless, mitochondrial oxidative stress can promote sphingosin-1-phosphate (S1P) deposition and lipid droplet formation in the kidneys, and the lipid

peroxidation damages renal tubular cells [21].

2.3 Mitochondrial dynamics

Mitochondria, dynamically changed organelles, maintain their physiological function via stable fusion and division, a process termed mitochondrial dynamics. Mitochondrial dynamics ensures a dynamic equilibrium state of mitochondria morphology, and mitochondrial fusion and division enhance the exchange of substances between mitochondria, the maintenance of mitochondrial DNA (mtDNA), and the clearance of damaged mitochondria [22]. When oxidative stress or energy depletion exceeds the mitochondrion ' s regulatory capacity, mitochondrial dynamics balance is disrupted, impairing the mitochondrial quality-control system and causing the accumulation of dysfunctional mitochondria. In renal cells from diabetic patients, mitochondrial dynamics are shifted toward increased fission and impaired fusion [23-25]. Mitochondrial fission is mainly mediated by dynamin-related protein 1 (Drp1). Members of the dynamin family bind to receptors on the outer mitochondrial membrane (OMM) and assemble into larger oligomers, fragmenting the mitochondrial network into numerous short, isolated organelles [26,27]. Any stimulus that enhances Drp1 translocation to the OMM, boosts Drp1 expression, or modulates Drp1 post-translational modifications contributes to mitochondrial fission [28,29]. Phosphorylation of Drp1 at Ser 600 promotes its recruitment to mitochondria and triggers excessive fission in podocytes [30]. Excessive fission of mitochondria in podocytes is a typical feature of renal injury, and is associated with elevated mitochondrial ROS (mtROS), cell apoptosis, and ultimate proteinuria and glomerular filtration barrier [31,32]. The specific deficiency of Drp1 in podocytes signally reduces albuminuria and mitochondrial fragmentation, and increases mitochondrial adaptability, oxygen consumption, and ATP production, thereby protecting renal function [33].

During mitochondrial fusion, mitofusin 1 (Mfn1) and mitofusin 2 (Mfn2) promote the fusion of the OMM, while OPA1 mitochondrial dynamin like GTPase (OPA1) boosts the fusion of the IMM. The levels of Mfn1 and OPA1 in the kidneys of DN rats are decreased, accompanied by an increase in mitochondrial fragments [34,35]. The degree of mitochondrial fission in DN patients is increased with the decrease of Mfn2 protein level [23]. In Mfn2 KO cells, mitochondrial swelling and fragmentation occur, together with activation of cytochrome C and caspase-3, and enhanced apoptosis [23,36]. Mfn1 knockdown can also promote cell apoptosis [37]. Mfn2 regulates glycolysis by interacting with pyruvate kinase isozyme type M2 (PMK2), one of the rate-limiting enzymes in glycolysis [38].

2.4 Mitophagy

Autophagy is a highly conserved process that degrades and recycles intracellular macromolecules and damaged organelles primarily via the degradation capacity of lysosomes [39,40]. Mitophagy refers to the selective autophagic disposal of dysfunctional mitochondria in cells. In renal diseases, mitophagy is essential for maintaining mitochondrial quality control. In healthy renal mitochondria, PINK1 is transferred across the translocase of the outer membrane (TOM) and translocase of the inner membrane (TIM) complexes into the IMM in a mitochondrial membrane potential (MMP)-dependent manner. PINK1 is cleaved by the IMM protease, presenilin-associated rhomboid-like protein (PARL), generating an N-terminal degradation motif that is subsequently cleared [41,42]. When the MMP is depolarized, PINK1 transfer is blocked and PINK1 accumulates on the damaged OMM. Phosphorylated PINK1 recruits Parkin to the OMM, and translocates ser 65 ubiquitin (PSER65-UB) to the OMM protein, thereby producing more phosphorylated substrates for PINK1 and further

promoting Parkin activation [43]. In the early stage of DM, mitophagy of PINK1/Parkin pathway is activated to remove dysfunctional mitochondria in the kidneys; however, as DN progresses, the accumulation of damaged mitochondria and apoptosis are promoted [42]. Under high-glucose conditions, the Pink1/Parkin pathway is suppressed in renal tubular cells, leading to mitophagy deficiency. This deficiency is related to excessive production of mtROS and abnormal mitochondrial dynamics, collectively resulting in mitochondrial dysfunction, accumulation of mitochondrial fragments, and ultimate renal cell apoptosis. Treatment with MitoQ, a mitochondrial targeted antioxidant, facilitates PINK transcription in the nucleus and restores mitophagy, thereby maintaining mitochondrial quality control and mitigating tubular injury and cell apoptosis [44]. In addition, mitophagy improves loss of apoptosis in podocytes [45], glomerulosclerosis, and proteinuria by attenuating the activation of the mammalian target of rapamycin (mTOR) signaling pathway, hence slowing the progression of DN [46].

2.5 Mitochondrial biogenesis

Mitochondrial biogenesis involves the synthesis of IMM, OMM and mitochondrial encoded proteins, the introduction of nuclear encoded mitochondrial proteins, and mtDNA replication. Mitochondrial biogenesis is jointly regulated by mtDNA and nuclear genes (nDNA), with the participation of multiple transcription factors [47]. Peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC-1 α) is the main regulatory factor of mitochondrial biogenesis [48]. Activated PGC-1 α translocates into the nucleus and activates nuclear respiratory factors 1 and 2 (Nrf1 and Nfr2), followed by transcription and encoding of respiratory chain components and mitochondrial transcription factor A (TFAM), thus promoting the generation of new mitochondria [49]. Mitochondrial biogenesis generates new mitochondria and coordinates mitochondrial homeostasis with mitophagy to remove damaged mitochondria. A study has found that promoting PGC-1α expression in pancreatic β cells can repress glucose stimulated insulin secretion [50], while another study revealed that PGC-1α deficiency in β cells leads to reduced insulin secretion [51], implying that PGC-1α has a dual role in DM. Besides, PGC-1α regulators have potential therapeutic value in DN. Overexpression of PGC-1α may exert a protective effect on renal tubular cells to delay DN progression, while overexpression of PGC-1α in podocytes causes collapsing glomerulopathy [52]. A previous study found that the expression of SIRT1 in the glomeruli of DN patients is decreased, and the specific deletion of SIRT1 in podocytes accelerates disease progression. Promoting SIRT1 expression in podocytes can potentiate the activation of PGC-1α, which reverses the high glucose-induced mitochondrial damage of podocytes [53]. In addition, PGC-1α overexpression can prevent mitochondrial dysfunction, ROS accumulation and cell death in human proximal renal tubular cells cultured in a diabetic environment [54]. In mesangial cells, activating the AMP-activated protein kinase (AMPK)-PGC-1α pathway can alleviate the lipid toxicity of the cells [55].

3 TCM targeting and regulating mitochondrial dysfunction to intervene in DN

Grounded in well-established TCM theory, TCM has been clinically used to relieve DN-related clinical progression and ameliorate renal damage. The existing clinical research proved TCM compound formulas (e.g. Tangshen Formula [56], Liuwei Dihuang Pills [57], and Zicuiyin Decoction [58]) and TCM monomers (e.g. silymarin [59] and Astragaloside [60]) can reduce albuminuria and abnormal oxidative stress levels in patients with DN. Moreover, the ability of TCM to regulate mitochondrial dynamics and thus improve mitochondrial dysfunction has been widely

recognized. Therefore, investigating the potential of TCM to target and regulate mitochondrial dysfunction is of great significance for DN treatment.

3.1 TCM compound formulas

Numerous TCM compound formulas have demonstrated therapeutic potential for DN by targeting mitochondrial dysfunction. Their mechanisms involve modulating key pathways related to mitochondrial biogenesis, dynamics, mitophagy, and oxidative stress, as summarized in Table 1.

Table 1 Mechanism of TCM compound formulas for treating DN.

TCM compound formulas	Experiment model	Effect	References
Tangshenning compound formula	KK-Ay mice	Improved renal function, Alleviated tubular injury; Restored mitochondrial function	[61]
Huangqi Danshen Decoction	db/db mice	Reduced blood glucose; Improved renal function; Alleviated renal injury; Reduced mitochondrial fission; Inhibited excessive mitophagy	[62]
Jinchan YiShen TongLuo Formula	STZ-induced DN in SD rats	Reduced proteinuria and improved renal function; Reduced apoptosis; Improved mitochondrial dysfunction	[63]
Yishen capsule (patent medicine)	STZ-induced DN in SD rats	Reduced proteinuria; Ameliorated renal pathological damage	[64]
San-Huang-Yi-Shen capsule (patent medicine)	STZ-induced DN in SD rats	Reduced blood glucose; Reduced proteinuria; Improved renal function; Reduced inflammation and oxidative stress; Increased mitophagy levels; Reduced mitochondrial damage	[65]
Danzhi Jiangtang capsule (patent medicine)	STZ-induced DN in SD rats	Improved renal function; Increased antioxidant capacity; Reduced inflammatory response	[66]
Jinlida granules	db/db mice	Restored renal function; Improved glomerular morphology; Attenuated podocyte damage; Inhibited mitochondrial fission; Alleviated mitochondrial dysfunction	[67]
Danggui Buxue Decoction	STZ-induced DN in SD rats	Improved kidney function; Alleviated mitochondrial dysfunction; Inhibited inflammation and oxidative stress; Inhibited podocyte apoptosis	[68]

Note: STZ, streptozotocin.

Tangshenning compound formula, with the principle of tonifying kidneys and promoting circulation, can restore mitochondrial dysfunction and alleviate renal tubular injury in DN mice through activating Sestrin2/AMPK/PGC-1α axis [61]. Huangqi Danshen Decoction is composed of Astragali Radix and Salviae Miltiorrhizae Radix. Astragali Radix has sweet flavor and slightly warm nature, impacting the lung, spleen, liver and kidney meridians, and according to modern medicine, it can bidirectionally modulate blood glucose and combat free-radical damage. Salviae Miltiorrhizae Radix has a bitter taste and mild warm nature, and is commonly used to treat renal injury. In T2D-induced renal damage, Huangqi Danshen Decoction has been reported to ameliorate DN by suppressing PINK1/Parkin-mediated mitophagy and mitochondrial fission [62]. Jinchan YiShen TongLuo Formula has the function of “tonifying kidneys and clearing collaterals”, and drug-containing serum increases MMP, alleviates the activities of respiratory-chain complexes I, III and IV, and ameliorates mitochondrial dysfunction and cell apoptosis in DN through the hypoxia-inducible

factor-1alpha (HIF-1α)-PINK1-Parkin pathway [63].

The Chinese patent medicine, Yishen capsule, ameliorates pathological changes in rats, reduces urine protein, and promotes podocyte autophagy through SIRT1/nuclear factor kappaB (NF- κ B) signaling pathway to improve DN [64]. San-Huang-Yi-Shen capsule can enhance the activities of superoxide dismutase (SOD) and glutathione peroxidase in renal tissues and downregulate malondialdehyde (MDA) level to ameliorate renal mitochondrial cristae and mitochondrial membrane damage in DN model rats. Also, the capsule activates PINK1/Parkin-mediated mitophagy and increases the co-localization levels of Parkin and mitochondrial membrane protein voltage dependent anion channel 1 (VDAC1) [65]. Danzhi Jiangtang capsule exerts anti-oxidative effects via inhibition of the JAK2-STAT1/STAT3 cascade reaction to improve DN [66]. Jinlida granules are an innovative TCM formula developed under the guidance of the " collateral disease" theory. The granules can activate AMPK to upregulate PGC-1 α , inhibit Drp1-mediated mitochondrial fission, ameliorate mitochondrial dysfunction, and attenuate podocyte damage, thereby improving the kidney function of db/db mice [67]. Danggui BuXue Decoction can increase the expression levels of PGC-1α and MnSOD in the podocytes of DN rats, reduce the expression levels of NLRP3 and IL-1β, mitigate the mitochondrial dysfunction of podocytes, oxidative stress and inflammatory responses, and ultimately hinder the progression of DN [68].

3.2 TCM monomers

Numerous TCM monomers have documented therapeutic potential for DN, potentially through modulating mitochondria (Table 2).

Table 2 Mechanism of TCM monomers for treating DN.

TCM monomer	Botanical source	Experiment model	Effect	References
Ginsenoside Rb1	*Panax notoginseng*	STZ-induced DN in FVB mice	Inhibited podocyte apoptosis; Alleviated mitochondrial damage and oxidative stress; Mitigated glomerular injury	[69]
Orientin	Fenugreek	High glucose-induced MPC-5 cells	Restored Autophagy; Inhibited podocyte apoptosis and mitochondrial damage	[70]
Poricoic acid A	*Poria cocos*	High glucose-induced MPC-5 cells	Induced mitophagy; Attenuated podocyte injury and inflammation	[71]
Andrographolide	*Andrographis paniculata*	High glucose-induced HK-2 cells; diabetic mice with high-fat diet	Inhibited renal tubular cell apoptosis, tubulointerstitial fibrosis, mitochondrial dysfunction and NLRP3 inflammasome activation	[72]
Diosgenin	wild yam (*Dioscorea villosa*), fenugreek	STZ-induced DN in SD rat	Attenuated mitochondrial dysfunction; Inhibited ROS production and cell apoptosis	[73]
Astragaloside IV		High glucose induced-podocyte	Attenuated kidney injury and podocyte apoptosis; Improved mitochondrial function	[74]
Bavachin	*Psoralea corylifolia* L.			[6]
Astragaloside II	Astragali Radix	STZ-induced DN in SD rats	Restored mitochondrial morphological changes and autophagy; Attenuated podocyte apoptosis; Ameliorated mitochondrial dysfunction	[5]
Berberine		C57BLKS/J db/db mice	Inhibited oxidative stress; Enhanced mitochondrial function	[75]
Kaempferol	*Kaempferia* L. and vegetables	STZ-induced DN in SD rats	Promoted mitochondrial fusion and mitophagy; Restored mitophagy; Ameliorated mitochondrial dysfunction	[35]

In streptozotocin-induced DN in mice, treatment with ginsenoside Rb1 from *Panax notoginseng* significantly alleviates glomerular hypertrophy and mesangial matrix expansion, as well as high glucose-induced podocyte apoptosis and mitochondrial damage, effectively mitigating DN progression [69]. Orientin, a bioactive constituent of Fenugreek, has antihyperglycemic properties, which can attenuate high glucose-induced podocyte apoptosis and mitochondrial damage, thereby blocking the progression of DN [70]. Poricoic acid A, isolated from the TCM Poria cocos, can reduce blood glucose and suppress fibrosis, while downregulating FUN14 domain containing 1 (FUNDC1) to induce mitophagy and thus ameliorates high glucose-induced podocyte injury [71]. Andrographolide, a diterpenoid lactone isolated from the traditional Chinese herb *Andrographis paniculata*, constitutes the principal pharmacophore of the plant. In high glucose-induced HK-2 human renal proximal tubular cells and DN mice, andrographolide decreases mtROS, ameliorates mitochondrial dysfunction and prevents tubular injury of DM mice [72]. Diosgenin, a steroidal sapogenin primarily derived from wild yam (*Dioscorea villosa*), fenugreek, *Smilax bockii* Warb., and *Dioscorea nipponoc*a Makino., suppresses NADPH oxidase 4 (NOX4) expression and the mitochondrial respiratory-chain complexes in DN mice to block ROS generation, thereby repressing mitochondria- and ER stress-mediated cell death [73]. Astragaloside IV competitively binds to specific amino-acid residues in Kelch-like ECH-associated protein 1 (Keap1), then enhances the Keap1-Nrf2 interaction, increases ATP synthesis and mtDNA content, reduces ROS levels and improves mitochondrial function, ultimately protecting against oxidative stress-induced diabetic renal injury and podocyte apoptosis [74]. *Psoralea corylifolia* L. seed is a traditional medicine that is effective for various diseases. Its main active ingredient Bavachin can upregulate the protein expressions of antioxidant enzymes (superoxide dismutase 2 (SOD2), catalase and heme oxygenase-1 (HO-1)) and mitochondrial function-related factors (SIRT1, PGC1 α , Nrf1 and mitochondrial transcription factor A (mtTFA)) in db/db mouse kidney tissue, thereby inhibiting oxidative stress and enhancing mitochondrial function to improve DN [6]. Astragaloside II is a novel saponin purified from Astragali Radix, which can increase PINK1 and Parkin expressions in DM rats, regulate mitophagy, Mfn2 expression, fission, and mitochondrial 1 (Fis1) expression to restore mitochondrial dynamics, thereby improving podocyte damage and mitochondrial dysfunction [5]. Berberine is a plant alkaloid that prevents DN by restoring PGC-1 α activity and mitochondrial energy homeostasis [75]. Kaempferol, a key bioactive compound abundant in the rhizomes of *Kaempferia* L. and vegetables, possesses potent antioxidant properties. It restores mitochondrial dynamics by upregulated fusion proteins (Mfn1 and OPA1) and downregulated fission proteins (Drp1 and Fis1), enhances mitochondrial biogenesis through PGC-1α and TFAM upregulation, modulates the PINK1/Parkin pathway to promote mitophagy, increases SOD activity and decreases MDA level to suppress oxidative stress. These combined effects restore MMP and structural integrity, reduce ROS generation and boost ATP production, ultimately decelerating the progression of DN [35].

Collectively, TCM has great potential in treating DN, and targeting mitochondrial function represents a valuable research direction. TCM alleviates renal podocyte injury and renal tissue damage possibly through restoring mitochondrial energy, inhibiting mtROS generation and oxidative stress, attenuating excessive mitochondrial fission, improving impaired mitochondrial fusion, and mediating dysregulated mitophagy and mitochondrial biogenesis, mirroring its significant role in the treatment of DN.

4 Conclusion

TCM has great advantages in targeting mitochondrial dysfunction to treat DN. Ample research has confirmed that TCM can control disease progression by regulating mitochondrial function. Moreover, TCM underscores disease prophylaxis, early intervention, the elimination of pathogenic factors, the cultivation of healthy and regular lifestyle habits, and the enhancement of the body ' s immunity, which are closely associated with the crucial management strategy of curbing the progression of DM and DN. Therefore, targeting mitochondrial function represents an important and promising therapeutic approach of TCM for DN.

5 Limitations and prospects

Despite the evident therapeutic promise of TCM, there are limitations of current research on TCM targeting mitochondria for DN. Firstly, TCM compound formulas exhibit a high degree of heterogeneity. Their multi-component and multi-target nature complicates the interpretation of mechanism and standardization, which affects the clarity and reproducibility of research results. Secondly, most current evidence is derived from preclinical studies. In the future, rigorous, appropriately sized randomized controlled clinical trials are required to further validate the clinical efficacy and safety of these preclinical findings.

Currently, most research focuses on exploring isolated mechanisms. Future research should extend directions to illuminating the connections between mitochondrial function and other cellular processes such as ferroptosis and pyroptosis, which will yield deeper insights into DN pathogenesis and TCM's therapeutic effects. Additionally, investigating integrative treatment strategies that combine the strengths of TCM and Western medicine holds promise for achieving superior therapeutic outcomes in DN patients.

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Conflicts of Interest

The author declares no conflicts of interest.

Author Contributions

J.X. made substantial intellectual contributions to all aspects of this work, including conceptualization, methodology, investigation, formal analysis, data curation, visualization, writing-original draft preparation, writing-review and editing, supervision, and project administration. J.X. has read and approved the final manuscript, and accepts full responsibility for the integrity and accuracy of all content.

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The data presented in this study are available on request from the corresponding author.

Supplementary

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