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Research Progress on Polysaccharide-Based Drugs in the Treatment of Diabetic Nephropathy

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Abstract : *Diabetic nephropathy (DN) is one of the most common microvascular complications of diabetes mellitus, involving multiple complex pathological processes during its initiation and progression, including glucose metabolism disorders, oxidative stress, inflammation, renal interstitial fibrosis, and gut microbiota dysbiosis. Current clinical treatment options are limited and associated with certain adverse effects. As one of the main active components of traditional Chinese medicine, natural polysaccharides exhibit characteristics such as multi-target action and low toxicity, demonstrating substantial potential in the prevention and treatment of diabetic nephropathy. This article systematically reviews the current research status of polysaccharide-based drugs in DN treatment, exploring their mechanisms of action from the perspectives of improving insulin resistance, inhibiting oxidative stress, alleviating inflammatory responses, combating renal interstitial fibrosis, and regulating intestinal microecology. It summarizes relevant experimental evidence from plant-derived and fungal-derived polysaccharides, and provides insights into quality control, mechanistic research, and clinical application. Studies have demonstrated that polysaccharides exert multi-target synergistic effects by regulating various signaling pathways, including TGF-β1/Smads, PI3K/Akt, NF-κB/NLRP3, cAMP/PKA/CREB, and PI3K/GSK-3β/Nrf2, thereby offering new strategies and directions for the treatment of diabetic nephropathy.*

Keywords: *Polysaccharides; Diabetic nephropathy; Oxidative stress; Inflammatory response; Renal fibrosis; Gut microbiota; Signaling pathways*

1.INTRODUCTION

Diabetic nephropathy represents the most severe microvascular complication in the course of diabetes mellitus and constitutes the primary etiological factor for end-stage renal disease. According to data from the International Diabetes Federation, 30% to 40% or even a higher proportion of diabetic patients worldwide will ultimately develop this condition [1]. Diabetic nephropathy is clinically characterized by persistent proteinuria and progressive decline in glomerular filtration rate, with pathological features typified by glomerular basement membrane thickening, abnormal mesangial matrix proliferation, and renal interstitial fibrosis [2]. Current clinical interventions primarily involve glycemic control, blood pressure management, and the use of renin-angiotensin system inhibitors; however, these approaches can only delay disease progression without fundamentally preventing renal injury. Moreover, these therapeutic agents exhibit varying degrees of adverse effects, and long-term administration may potentially compromise renal function. Natural polysaccharides are macromolecular compounds extracted from plants, fungi, or marine organisms, characterized by structural diversity, rich biological activities, and low toxicity. As active constituents of traditional Chinese medicine, polysaccharides

have demonstrated promising pharmacological effects in anti-tumor, hypoglycemic, immunomodulatory, antioxidant, and antiviral applications [3]. In recent years, extensive basic research has confirmed that polysaccharides achieve renal protection through multiple pathways, including improving insulin resistance, combating oxidative stress and inflammation, inhibiting fibrosis, regulating autophagy processes, and optimizing intestinal microecology. Compared with chemically synthesized drugs, the multi-target action characteristics of polysaccharides align more closely with the complex pathogenesis of diabetic nephropathy, rendering them a focal point in novel drug development. This article reviews recent research progress on polysaccharide-based drugs in the prevention and treatment of diabetic nephropathy, summarizes in vivo experimental evidence from various polysaccharide sources, elaborates on their primary pharmacological mechanisms, and proposes future research directions to address existing challenges.

2. Primary Mechanisms of Polysaccharide Intervention in Diabetic Nephropathy

2.1 Improvement of Insulin Resistance

Insulin resistance is a critical factor in the pathogenesis and progression of diabetic nephropathy, primarily manifested as reduced sensitivity of target tissues to insulin, consequently leading to glucose metabolism disorders. Hyperglycemia can directly damage glomerular endothelial cells, mesangial cells, and renal tubular epithelial cells, initiating a cascade of renal injury. Polysaccharides from traditional Chinese medicine can enhance insulin sensitivity by regulating key signaling pathways involved in glucose metabolism, while simultaneously increasing the number and volume of pancreatic β-cells, ultimately achieving therapeutic goals of improving insulin resistance and reducing blood glucose levels. For instance, yam polysaccharide has been shown to upregulate the expression levels of insulin receptor (InsR), insulin receptor substrate-1 (IRS-1), and phosphatidylinositol 3-kinase (PI3K) in renal tissue, enhancing PI3K signaling pathway efficiency and improving tissue sensitivity to insulin. This optimization of insulin signal transduction results in reduced fasting blood glucose in diabetic model rats, thereby exerting an interventional effect on diabetic nephropathy [1]. In diabetic KKAy mouse models, Ophiopogon japonicus polysaccharide MDG-1 activates the PI3K/protein kinase B signaling pathway, enhancing insulin sensitivity and further reducing blood glucose levels [2]. Additionally, yam polysaccharide inhibits the high glucose-activated aldose reductase/p38 mitogen-activated protein kinase/cAMP response element-binding protein signaling pathway, significantly increasing pancreatic islet volume and number while attenuating pancreatic and renal pathological damage [3]. The PI3K/Akt signaling pathway constitutes the core of insulin signal transduction. Activation of this pathway promotes glucose transporter 4 translocation to the cell membrane, enhancing glucose uptake while inhibiting the expression of key gluconeogenic enzymes. The regulatory effect of polysaccharides on this pathway forms the molecular basis for their insulin-sensitizing properties.

2.2 Inhibition of Oxidative Stress

Oxidative stress represents a pivotal pathological mechanism in the initiation and progression of diabetic nephropathy. Under high glucose conditions, mitochondrial electron transport chain function is impaired, leading to excessive generation of reactive oxygen species (ROS). ROS can directly damage intracellular biomacromolecules including lipids, proteins, and nucleic acids, compromising their structure and function, while simultaneously activating apoptosis-related signaling pathways, exerting cytotoxic effects. Concurrently, advanced glycation end products (AGEs) formed under high glucose conditions further promote ROS production, exacerbating oxidative stress injury and initiating multiple inflammatory signaling cascades and fibroblast activation pathways, collectively driving the progression of renal pathology. The organism

possesses a sophisticated endogenous antioxidant defense system, with superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px) serving as core components—critical防线 for scavenging excess ROS and maintaining redox homeostasis. Research indicates that polysaccharides from traditional Chinese medicine can upregulate antioxidant enzyme gene expression, enhance antioxidant enzyme activities, while downregulating oxidative stress-related gene expression, thereby strengthening the body's antioxidant defense capacity and effectively alleviating oxidative stress-induced renal tissue damage, achieving renal protective effects. Dipsacus asper polysaccharide enhances the antioxidant enzyme activities of GSH, SOD, and CAT, reduces malondialdehyde (MDA) levels, and inhibits the expression of oxidative stress-related AGEs and their receptors, thereby preventing or delaying the onset and progression of diabetic nephropathy [4]. Mulberry branch polysaccharide significantly increases the activities of manganese superoxide dismutase (Mn-SOD) and GSH-Px in serum, reduces MDA content, and enhances the activities of mitochondrial respiratory chain complexes I and III in diabetic nephropathy model rats, improving renal antioxidant capacity [5]. Research on Flammulina velutipes residue polysaccharides provides direct antioxidant evidence. A research team from Shandong Agricultural University extracted three residual polysaccharides from Flammulina velutipes mushroom residue, all of which significantly enhanced renal SOD, CAT, and GSH-Px activities in diabetic mice. The enzyme-extracted residual polysaccharide at 800 mg/kg demonstrated the most pronounced effect, increasing SOD activity by 178.68% and GSH-Px activity by 202.14%, while reducing the lipid peroxidation product MDA by 49.39% [6]. Cyclocarya paliurus polysaccharides [7], seaweed polysaccharides [8], and okra polysaccharides [9] have also been confirmed to significantly elevate antioxidant enzyme activities and reduce renal ROS levels, exerting protective effects in diabetic nephropathy rats. Nuclear factor erythroid 2-related factor 2 (Nrf2) plays a central role in regulating antioxidant enzyme expression as a key transcription factor. Research by Mei et al. on Phellodendron amurense polysaccharide revealed that this polysaccharide activates the PI3K/GSK-3β/Nrf2 signaling pathway, significantly upregulating the expression levels of antioxidant enzymes HO-1 and NQO1, thereby mitigating oxidative stress-induced renal damage in diabetic nephropathy [39].

2.3 Alleviation of Inflammatory Responses

Inflammatory responses constitute a core factor driving the initiation and progression of diabetic nephropathy [10]. During the pathological process of diabetic nephropathy, aberrant activation of transcription factors and kinases induces substantial synthesis of pro-inflammatory cytokines, chemokines, and adhesion molecules, subsequently promoting leukocyte infiltration into renal tissue and triggering local inflammation. Inflammation and renal injury form a vicious cycle: inflammation exacerbates renal tissue damage, while renal injury further activates inflammatory pathways, accelerating disease progression. Polysaccharides from traditional Chinese medicine can effectively alleviate renal inflammatory pathological damage by downregulating the expression levels of pro-inflammatory cytokines, chemokines, adhesion molecules, and inflammation-related proteins in the kidney, while inhibiting inflammation-associated signaling pathways. Ganoderma lucidum polysaccharide inhibits the nuclear factor-κB/NOD-like receptor family pyrin domain-containing 3 (NF-κB/NLRP3) signaling pathway, downregulating the protein expression levels of NLRP3 inflammasome and NF-κB in renal tissue. This significantly reduces the expression of interleukin-1β (IL-1β), interleukin-6 (IL-6), interleukin-18 (IL-18), and tumor necrosis factor-α (TNF-α) in diabetic nephropathy mice, ameliorating mild tubulointerstitial inflammation, attenuating inflammatory responses, and improving renal function [11]. Mulberry leaf polysaccharide similarly alleviates glomerular and tubular pathological damage by reducing

serum levels of TNF-α and C-reactive protein (CRP) in diabetic rats, thereby protecting renal function [12]. Angelica sinensis polysaccharide inhibits the TLR4/NF-κB signaling pathway, reducing the mRNA and protein expression of Toll-like receptor 4, myeloid differentiation factor 88, and NF-κB. This consequently decreases the activities of TNF-α, IL-1, and monocyte chemoattractant protein-1 in renal tissue of streptozotocin-induced diabetic nephropathy rats, alleviating renal inflammatory responses and delaying disease progression [13].

2.4 Anti-Renal Fibrosis

Renal fibrosis represents the common pathological pathway in the progression of diabetic nephropathy to end-stage renal disease, characterized by excessive extracellular matrix (ECM) deposition, basement membrane thickening, glomerulosclerosis, and interstitial fibrosis [14]. Transforming growth factor-β1 (TGF-β1) is recognized as the core driver of fibrosis [15]. Upon receptor binding, TGF-β1 activates downstream phosphorylation of Smad2 and Smad3; the resulting complex translocates to the nucleus, initiating transcription of fibrosis-related genes, promoting excessive ECM deposition while inhibiting matrix-degrading enzyme activity. Smad7, as a negative regulator of this pathway, feedback-inhibits TGF-β1 signal transduction.

Multiple studies have confirmed the regulatory effects of polysaccharides on this pathway. Li Chengde et al. investigated the effects of Astragalus polysaccharide on the renal TGF-β1/Smads signaling pathway in diabetic rats. Following 8 weeks of Astragalus polysaccharide intervention, model rats exhibited significantly reduced urinary kidney injury molecule-1 and osteopontin levels, downregulated expression of renal TGF-β1, p-Smad2, and p-Smad3, while upregulated expression of Smad7 and matrix metalloproteinases MMP-2 and MMP-9 was observed. These findings confirmed that Astragalus polysaccharide attenuates renal fibrosis by inhibiting TGF-β1/Smads pathway activity [16]. Another study corroborated the renal protective effect of Astragalus polysaccharide in diabetic rats, with mechanisms related to inhibition of the TGF-β/Smad signaling pathway [17]. Ginseng polysaccharide has been demonstrated to inhibit TGF-β1 and Smad2/3 phosphorylation, attenuating glomerular mesangial matrix expansion and collagen deposition. Liu Yuzhu's master's research systematically evaluated the protective effects of ginseng polysaccharide against diabetic nephropathy in db/db mice. Results showed that ginseng polysaccharide significantly reduced urinary urea nitrogen, urinary creatinine, and urinary protein levels in model animals, ameliorated dyslipidemia, and decreased serum inflammatory factor levels. Renal histopathological examination revealed that ginseng polysaccharide effectively alleviated pathological changes including glomerular enlargement, basement membrane thickening, and foot process fusion, while reducing abnormal ECM accumulation and excessive collagen fiber proliferation. Mechanistic studies confirmed that ginseng polysaccharide significantly downregulated renal tissue expression of TGF-β1, p-Smad2/Smad2, and p-Smad3/Smad3 proteins, suggesting that its anti-fibrotic effects are associated with inhibition of the TGF-β1/Smad2/3 signaling pathway [18]. Huang Qian et al. provided novel insights into the molecular mechanisms underlying ginseng polysaccharide anti-fibrotic effects from a distinct perspective. Their research confirmed that ginseng polysaccharide inhibits activation of the cAMP/PKA/CREB signaling pathway, thereby reducing the expression of renal tubular epithelial cell phenotypic transformation markers, including α-smooth muscle actin (α-SMA), as well as ECM-associated proteins laminin (LN) and fibronectin (FN), effectively delaying the pathological progression of renal fibrosis [19]. Polygonatum sibiricum polysaccharide exhibits analogous mechanisms. Fu Tingting et al. investigated the renal protective effects of Polygonatum polysaccharide in diabetic nephropathy rat models, finding that it reduced kidney index, creatinine, and urea nitrogen levels while attenuating renal injury [20]. Mei Xiyu et al. evaluated the

ameliorative effects of Polygonatum polysaccharide on diabetic nephropathy in db/db mouse models over 16 weeks of continuous administration. Results demonstrated that Polygonatum polysaccharide significantly improved renal function and attenuated renal pathological damage in model mice. Masson staining revealed reduced collagen deposition in renal tissue following Polygonatum polysaccharide treatment, while immunoblotting confirmed downregulated TGF-β expression, upregulated Smad7, and inhibited Smad2 phosphorylation. This study confirmed that Polygonatum polysaccharide achieves anti-fibrotic effects through targeted inhibition of the TGF-β/Smad2 signaling pathway [31]. Research by Mei et al. on Phellodendron amurense polysaccharide provided additional evidence for anti-fibrotic mechanisms from an alternative perspective, demonstrating that Phellodendron polysaccharide regulates the TGF-β/Smad signaling pathway to inhibit epithelial-mesenchymal transition in renal tubular epithelial cells, reducing abnormal deposition of α-SMA and ECM-associated proteins, thereby alleviating the extent of renal interstitial fibrosis [39].

2.5 Regulation of Gut Microbiota

The "gut-kidney axis," representing the interaction between intestinal microbiota and renal function, has emerged as a research focus in recent years [21]. Significant differences exist in gut microbiota species composition and bacterial abundance between healthy individuals and patients with diabetes or diabetic nephropathy [22], and distinct gut microbiota profiles are observed in diabetic nephropathy mice with varying degrees of renal damage [23]. Research has revealed that excessive acetate production resulting from gut microbiota dysbiosis may contribute to early diabetic nephropathy renal injury through overactivation of the renin-angiotensin system [24], and can also mediate cholesterol homeostasis disruption via G protein-coupled receptor 43 activation, subsequently leading to tubulointerstitial damage in diabetic nephropathy [25]. Polysaccharides from traditional Chinese medicine can increase the relative abundance of beneficial bacterial populations while reducing that of harmful bacteria, enhancing intestinal microbial diversity and richness, optimizing community structure, and thereby reversing gut microbiota dysbiosis. Concurrently, they improve intestinal barrier function and alleviate intestinal inflammation, indirectly modulating intestinal microecology through multiple pathways to ameliorate diabetic nephropathy-associated renal injury [26]. FENG et al. employed Bupleurum chinense polysaccharide and Bupleurum smithii polysaccharide to intervene in diabetic nephropathy mice. Results demonstrated that both types of Bupleurum polysaccharides effectively corrected gut microbiota dysbiosis in model mice, restoring microbial community structure toward levels comparable to the normal control group [25]. Alpha diversity analysis revealed significantly increased Shannon, Ace, and Chao1 indices, indicating markedly enhanced microbial species richness and diversity. Beta diversity analysis demonstrated reorganization of intestinal microbial community structure. Furthermore, Bupleurum polysaccharides increased ileal villus length, elevated colonic protein expression levels, attenuated abnormal colonic villus lobulation and goblet cell hyperplasia, improved intestinal barrier function, and reduced colonic inflammatory responses. Through regulation of gut microbiota, repair of intestinal barrier function, and inhibition of intestinal inflammation, these polysaccharides collectively delayed diabetic nephropathy progression. Research on Cordyceps cicadae polysaccharide intervention in diabetic nephropathy rats similarly confirmed its regulatory effects on gut microbiota. YANG et al. employed 16S rRNA high-throughput sequencing technology to examine gut microbiota in diabetic nephropathy rats following Cordyceps cicadae polysaccharide intervention. Through operational taxonomic unit analysis and alpha diversity evaluation, they found significantly enhanced intestinal microbial species richness and diversity. Beta diversity analysis revealed markedly increased relative

abundance of probiotic bacteria, decreased relative abundance of harmful bacteria, and substantially reduced lipopolysaccharide-producing bacterial content in model rat intestines, thereby exerting interventional effects on diabetic nephropathy and ameliorating renal injury [26]. Mei et al.'s research on Phellodendron amurense polysaccharide provided new evidence for this mechanism, demonstrating that Phellodendron polysaccharide modulates gut microbiota structure by increasing the relative abundance of probiotic bacteria such as Lactobacillus, reducing inflammation-associated opportunistic pathogens, decreasing intestinal permeability, and limiting endotoxin entry into the bloodstream, thereby inhibiting renal inflammatory responses and protecting renal function [39]. Studies have confirmed that yam polysaccharide and mulberry branch polysaccharide similarly regulate gut microbiota structure, increasing the relative abundance of beneficial bacteria while reducing harmful bacterial proportions, enhancing microbial species richness and diversity, consequently improving renal function and delaying diabetic nephropathy progression [27,28].

3. Experimental Research Evidence from Different Polysaccharide Sources

3.1 Plant-Derived Polysaccharides

3.1.1 Astragalus Polysaccharide

Astragalus polysaccharide is an active constituent of the traditional Qi-tonifying herbal medicine Astragalus membranaceus and represents one of the most extensively studied polysaccharides. Early research demonstrated its protective effects against polyuria in the early stages of diabetic rats. Kang Bai et al. established diabetic rat models using streptozotocin and found that Astragalus polysaccharide significantly ameliorated ultrastructural damage in renal distal convoluted tubules and collecting duct principal cells, while increasing 24-hour urine volume. The mechanism may involve downregulation of renal medullary aquaporin-2 mRNA expression by Astragalus polysaccharide [29]. Subsequent research further confirmed that Astragalus polysaccharide reduces AQP-2 content in renal tissue of diabetic rats and improves water-salt metabolism balance [30], suggesting its potential utility in ameliorating early renal tubular dysfunction in diabetic nephropathy. Regarding anti-fibrotic effects, Li Chengde et al. further investigated the influence of Astragalus polysaccharide on the renal TGF-β1/Smads signaling pathway in diabetic rats, confirming that Astragalus polysaccharide attenuates renal fibrosis through inhibition of TGF-β1/Smads pathway activity [16]. MENG et al.'s research also corroborated that Astragalus polysaccharide regulates the TGF-β/Smad signaling pathway to protect renal function in diabetic rats [17].

3.1.2 Ginseng Polysaccharide

Ginseng polysaccharide, an active component isolated from Panax ginseng roots, possesses multiple pharmacological effects including immunomodulation and antioxidant activity. Liu Yuzhu comprehensively investigated the preventive and therapeutic effects of ginseng polysaccharide against diabetic nephropathy in db/db mice [18]. Results indicated that ginseng polysaccharide significantly reduced urinary urea nitrogen, urinary creatinine, and urinary albumin levels in model mice, ameliorated dyslipidemia, and decreased serum inflammatory factor levels. Renal histopathological examination revealed that ginseng polysaccharide alleviated glomerular enlargement, basement membrane thickening, and podocyte foot process fusion, while inhibiting renal interstitial collagen deposition and collagen synthesis. Experimental studies confirmed that ginseng polysaccharide significantly downregulated renal tissue expression of TGF-β1, p-Smad2/Smad2, and p-Smad3/Smad3 proteins, suggesting that its anti-fibrotic efficacy is associated with inhibition of the TGF-β1/Smad2/3 signaling pathway. Huang Qian et al. elucidated the molecular mechanisms underlying ginseng polysaccharide anti-fibrotic effects from an

alternative perspective [19]. Using streptozotocin-induced diabetic nephropathy mouse models, they found that ginseng polysaccharide significantly reduced fasting blood glucose, 24-hour urinary microalbumin, serum creatinine, and blood urea nitrogen levels in model mice. Masson staining demonstrated that ginseng polysaccharide substantially reduced renal interstitial collagen deposition. Further mechanistic investigation revealed that ginseng polysaccharide inhibits activation of the cAMP/PKA/CREB signaling pathway, thereby reducing expression of the renal tubular epithelial cell phenotypic transformation protein α-SMA and ECM-associated proteins LN and FN, consequently delaying renal fibrosis progression.

3.1.3 Polygonatum Polysaccharide

Polygonatum, a medicinal and edible traditional Chinese herb, has garnered increasing attention for its polysaccharide constituents in recent years. Fu Tingting et al. investigated the effects of Polygonatum polysaccharide on the kidneys of diabetic nephropathy rats, demonstrating that it effectively reduces kidney index, creatinine, and urea nitrogen levels while attenuating renal damage [20]. Mei Xiyu et al. examined the ameliorative effects of Polygonatum polysaccharide on diabetic nephropathy in db/db mouse models over 16 weeks of continuous administration. Results revealed that Polygonatum polysaccharide significantly alleviated renal injury while benefiting lipid metabolism balance and restoring oxidative stress indicators [31]. Masson staining showed reduced renal collagen deposition following Polygonatum polysaccharide treatment, while immunoblotting confirmed downregulated TGF-β expression, upregulated Smad7, and inhibited Smad2 phosphorylation. This study confirmed that Polygonatum polysaccharide exerts anti-fibrotic effects through inhibition of TGF-β/Smad2 pathway activity, regulation of dyslipidemia, and attenuation of oxidative stress injury.

3.1.4 Yam Polysaccharide

Yam polysaccharide exhibits multi-target characteristics in diabetic nephropathy prevention and treatment. Yang Hongli et al. discovered that yam polysaccharide elevates expression levels of InsR, IRS-1, and PI3K in renal tissue, enhancing PI3K signaling pathway transduction and improving tissue insulin sensitivity. This optimization of insulin signal transmission subsequently reduces fasting blood glucose in diabetic model rats, exerting interventional effects on diabetic nephropathy [1]. Gao Zihan et al. further confirmed that yam polysaccharide inhibits the high glucose-activated AR/p38MAPK/CREB signaling pathway, significantly increasing pancreatic islet volume and number while effectively attenuating pancreatic and renal pathological damage, thereby protecting renal function in diabetic nephropathy mice [3]. Additionally, yam polysaccharide improves renal function through gut microbiota regulation. Zhang Wenjie et al. demonstrated that yam polysaccharide increases relative abundance of beneficial bacteria, reduces harmful bacterial proportions, enhances microbial species richness and diversity, and optimizes intestinal microbial community structure, consequently delaying diabetic nephropathy progression [27].

3.1.5 Mulberry Leaf Polysaccharide and Mulberry Branch Polysaccharide

Mulberry leaf polysaccharide, derived from Morus alba, has garnered increasing attention for its potential in diabetic nephropathy prevention and treatment. A systematic review and meta-analysis encompassing 8 studies with 270 experimental animals demonstrated that mulberry leaf polysaccharide significantly reduces serum creatinine, blood urea nitrogen, 24-hour urinary protein, and urinary microalbumin levels, while decreasing fasting blood glucose, total cholesterol, TGF-β1 protein expression, and CTGF mRNA expression, thereby slowing glomerular pathological changes [40]. Mulberry leaf polysaccharide achieves renal protection through multiple mechanisms including blockade of the growth hormone-insulin-like growth factor axis,

intervention in insulin receptor pathways, delay of renal fibrosis, and inhibition of inflammatory mediator release.Mulberry branch polysaccharide exhibits prominent antioxidant and anti-inflammatory properties. Guo Futuan et al. found that mulberry branch polysaccharide significantly increases serum activities of Mn-SOD and GSH-Px, reduces MDA content, and enhances activities of mitochondrial respiratory chain complexes I and III in diabetic nephropathy model rats, thereby strengthening renal tissue antioxidant capacity, attenuating oxidative stress-induced renal damage, and consequently alleviating diabetic nephropathy pathological progression [5]. GUO et al.'s research also confirmed the protective effects of mulberry branch polysaccharide against renal injury in STZ-induced diabetic mice [32]. Pan Yong et al. further discovered that mulberry branch polysaccharide exerts hypoglycemic and renal protective effects through gut microbiota regulation, increasing beneficial bacterial abundance while reducing harmful bacterial populations and optimizing intestinal microbial community structure [28].

3.1.6 Other Plant Polysaccharides

Beyond the aforementioned polysaccharides, numerous plant-derived polysaccharides demonstrate efficacy against diabetic nephropathy. Cyclocarya paliurus polysaccharide regulates SOD, CAT, GSH, and MDA levels while reducing TGF-β1 expression, thereby alleviating oxidative stress injury [7]. Seaweed polysaccharide downregulates inflammatory factors including IL-6, IL-1β, and TNF-α, while inhibiting expression of TGF-β1, Col-I, and α-SMA, exerting anti-fibrotic effects [8]. Okra polysaccharide improves oxidative stress status and protects renal function through modulation of the AMPK/Sirt1/PGC-1α signaling pathway [9]. Dipsacus asper polysaccharide reduces expression of Col-IV, FN, and α-SMA, delays renal sclerosis, and modifies microecological composition while repairing intestinal mucosa through gut microbiota regulation [4]. Lycium barbarum polysaccharide has been demonstrated to exert anti-diabetic nephropathy effects through modulation of NF-κB expression levels [33,34].

Mei et al.'s recent research systematically elucidated the multiple mechanisms underlying Phellodendron amurense polysaccharide efficacy against diabetic nephropathy [39]. This study confirmed that Phellodendron polysaccharide enhances renal antioxidant capacity through activation of the PI3K/GSK-3β/Nrf2 signaling pathway, while simultaneously regulating the TGF-β/Smad signaling pathway to inhibit renal fibrosis progression. Furthermore, Phellodendron polysaccharide improves gut microbiota structure by increasing probiotic abundance and reducing pathogenic bacterial colonization, exerting synergistic protective effects through the "gut-kidney axis."

3.2 Fungal-Derived Polysaccharides

3.2.1 Flammulina velutipes Residue Polysaccharides

Mushroom cultivation generates spent mushroom substrate rich in polysaccharide content; recycling and reutilizing this waste aligns with green development principles while generating economic value. Lin from Shandong Agricultural University pioneered the extraction of residual polysaccharides from Flammulina velutipes mushroom residue and investigated their antioxidant and renal protective effects in diabetic mice [6]. Three residual polysaccharides were extracted using enzymatic, acid, and alkaline methods respectively, and administered at low, medium, and high doses for 15 days to streptozotocin-induced diabetic mouse models. Results demonstrated that all three residual polysaccharides dose-dependently enhanced renal tissue antioxidant enzyme activities while reducing MDA levels. The enzyme-extracted residual polysaccharide at 800 mg/kg exhibited the most pronounced effects, increasing SOD activity by 178.68%, GSH-Px activity by 202.14%, and achieving 49.39% MDA inhibition. Blood biochemical parameter measurement indicated that enzyme-extracted residual polysaccharide effectively improved serum creatinine,

blood urea nitrogen, and albumin levels in diabetic mice. Renal pathological examination revealed that residual polysaccharide treatment significantly attenuated pathological changes including glomerular injury, renal tubular epithelial cell degeneration, and inflammatory cell infiltration. This research pioneered high-value utilization of edible mushroom waste while providing novel experimental evidence for fungal polysaccharide therapy in diabetic nephropathy.

3.2.2 Other Fungal Polysaccharides

Ganoderma lucidum polysaccharide inhibits the NF-κB/NLRP3 signaling pathway, downregulating renal tissue expression of NLRP3 inflammasome and NF-κB proteins, significantly reducing IL-1β, IL-6, IL-18, and TNF-α expression in diabetic nephropathy mice, ameliorating mild tubulointerstitial inflammation, attenuating inflammatory responses, and improving renal function [11]. Cordyceps cicadae polysaccharide reduces inflammatory indicators including IL-1β, IL-6, and TNF-α, inhibits the TLR4/NF-κB signaling pathway, while modulating gut microbiota by increasing probiotic relative abundance and enhancing species richness and diversity, thereby improving renal interstitial fibrosis in diabetic nephropathy rats [26]. Grifola frondosa polysaccharide reduces inflammatory indicators IL-6, IL-1β, and TNF-α while decreasing TGF-β1 expression levels, exerting renal protective effects [35].

3.3 Comparative Analysis of Polysaccharide Sources and Action Characteristics

In summary, polysaccharides from different sources exhibit distinct characteristics in diabetic nephropathy treatment. Plant-derived polysaccharides represent the most extensively studied category, with Astragalus polysaccharide possessing the most abundant research evidence, enabling comprehensive intervention from early tubular protection to late-stage anti-fibrosis. Both ginseng and Polygonatum polysaccharides demonstrate favorable lipid-regulating and anti-inflammatory effects, with Polygonatum polysaccharide exhibiting higher safety as a medicinal and edible substance. Yam polysaccharide shows pronounced efficacy in improving insulin resistance, while mulberry leaf and mulberry branch polysaccharides possess robust antioxidant capacity. Among fungal-derived polysaccharides, Flammulina velutipes residue polysaccharide warrants particular attention for its prominent antioxidant activity and waste recycling value. Table 1 systematically summarizes the sources, research models, and primary mechanisms of action for various polysaccharides.

Table 1: *Comparison of Mechanisms of Action of Different Polysaccharides in Preventing and Treating Diabetic*

Polysaccharide Type	Source	Research Model	Primary Mechanisms of Action	References
Astragalus polysaccharide	Astragalus root	STZ-induced rats	Downregulates AQP-2 to improve early polyuria; inhibits TGF-β1/Smads pathway for anti-fibrosis; anti-inflammatory and antioxidant effects |	[16,17,29,30]
Ginseng polysaccharide	Ginseng root and rhizome	db/db mice; STZ-induced mice	Inhibits TGF-β1/Smad2/3 pathway; inhibits cAMP/PKA/CREB pathway; regulates lipid metabolism; anti-	[18,19]

Polysaccharide Type	Source	Research Model	Primary Mechanisms of Action	References
			inflammatory and antioxidant effects	
Polygonatum polysaccharide	Polygonatum root and rhizome	db/db mice; STZ-induced rats	Inhibits TGF-β/Smad2 pathway; upregulates Smad7; improves lipid metabolism disorders; anti-oxidative stress	[20,31]
Yam polysaccharide	Yam tuber	STZ-induced rats	Enhances PI3K signaling pathway; inhibits AR/p38MAPK/CREB pathway; regulates gut microbiota	[1,3,27]
Mulberry leaf/mulberry branch polysaccharide	Mulberry leaf/mulberry branch	STZ-induced mice/rats	Enhances antioxidant enzyme activities; inhibits inflammation; regulates gut microbiota; reduces TGF-β1 expression	[5,28,32,40]
Flammulina velutipes residue polysaccharide	Flammulina velutipes residue	STZ-induced mice	Enhances SOD, CAT, GSH-Px activities; reduces MDA content; attenuates histopathological damage	[6]
Ganoderma lucidum polysaccharide	Ganoderma lucidum fruiting body	STZ-induced mice	Inhibits NF-κB/NLRP3 signaling pathway; reduces IL-1β, IL-6, IL-18, TNF-α expression	[11]
Cordyceps cicadae polysaccharide	Cordyceps cicadae	STZ-induced rats	Inhibits TLR4/NF-κB pathway; regulates gut microbiota; improves renal interstitial fibrosis	[26]
Phellodendron polysaccharide	Phellodendron amurense	STZ-induced rats; HK-2 cells	Activates PI3K/GSK-3β/Nrf2 pathway to enhance antioxidant capacity; regulates TGF-β/Smad pathway to inhibit fibrosis; modulates gut microbiota to improve "gut-kidney axis" function	[39]

4.

Action Characteristics of Polysaccharide Intervention in Diabetic Nephropathy

4.1 Multi-Pathway, Multi-Target Synergistic Effects

The regulatory effects of individual polysaccharides from traditional Chinese medicine on diabetic nephropathy are not mediated through单一 pathways but rather through multi-target synergistic actions. For example, the hypoglycemic mechanism of yam polysaccharide operates through three aspects: first, enhancing PI3K signal transduction pathway to improve insulin sensitivity; second, inhibiting the high glucose-activated AR/p38MAPK/CREB signaling pathway to increase insulin synthesis and secretion; and third, modulating intestinal microbial community structure to indirectly improve glucose metabolism through the gut-kidney axis [1,3,27]. Mulberry branch polysaccharide exerts multi-pathway renal protection by regulating oxidative stress levels to enhance antioxidant capacity and attenuate oxidative stress-induced renal tissue damage, simultaneously inhibiting inflammatory responses to alleviate renal inflammatory pathological injury, and reducing harmful bacteria while increasing beneficial bacteria to modulate gut microbiota structure [5,28,32]. Mulberry leaf polysaccharide activates the IR signaling pathway, increasing hepatic IRS-1 expression levels to improve insulin resistance, while reducing inflammation-related indicators to attenuate renal inflammatory pathological damage. Additionally, it inhibits activation of the NF-κB/TGF-β1 signaling pathway, reducing expression levels of NF-κB and TGF-β1, thereby suppressing renal fibrosis progression and reducing renal injury-related indicators to achieve renal protection [12]. Mei et al.'s research on Phellodendron amurense polysaccharide systematically revealed its multi-mechanistic anti-diabetic nephropathy effects through gut microbiota regulation, activation of the PI3K/GSK-3β/Nrf2 antioxidant pathway, and inhibition of the TGF-β/Smad pro-fibrotic pathway, providing new experimental evidence for the multi-target therapeutic characteristics of polysaccharides [39]. Cordyceps cicadae polysaccharide, Astragalus polysaccharide, and numerous other traditional Chinese medicine polysaccharides have similarly been confirmed through relevant research to exert interventional effects on diabetic nephropathy through multi-pathway, multi-target regulatory mechanisms[11,16,26]. By virtue of their multi-pathway, multi-target regulatory characteristics, polysaccharides from traditional Chinese medicine demonstrate substantial application potential in diabetic nephropathy prevention and treatment.

4.2 Dose-Dependency and Temporal Efficacy

Comprehensive analysis of relevant literature reveals that high-dose groups of traditional Chinese medicine polysaccharides exhibit more pronounced interventional effects on diabetic nephropathy, with superior regulatory effects on various parameters and certain dose-dependent relationships observed among different dose groups. For instance, the high-dose yam polysaccharide group demonstrated significant effects in elevating InsR, IRS-1, and PI3K expression levels in renal tissue, and showed markedly superior effects in elevating insulin levels and reducing glucagon levels compared to low-dose and medium-dose groups [1]. The 200 mg/kg ginseng polysaccharide dose group exhibited superior effects in reducing urinary protein, regulating lipids, and inhibiting inflammatory factors compared to the 100 mg/kg dose group [18]. The high-dose mulberry branch polysaccharide group showed more pronounced effects in regulating gut microbiota species diversity [28]. Mei et al. also observed clear dose-dependent effects in their research on Phellodendron amurense polysaccharide, with the 800 mg/kg high-dose group demonstrating significantly superior effects in improving renal function indicators and inhibiting renal fibrosis compared to the 200 mg/kg and 400 mg/kg dose groups, providing reference data for clinical dose selection of Phellodendron polysaccharide [39]. Furthermore, longer treatment courses generally yield superior effects. Continuous administration of Lycium barbarum polysaccharide for 12

weeks produced significantly better effects in reducing blood glucose and protecting renal function compared to the 4-week administration group [34]. Mulberry branch polysaccharide showed sustained declining trends in blood glucose during the 30-60 day post-administration period [5]. Meta-analysis of mulberry leaf polysaccharide also suggested that intervention duration significantly affects the improvement of urinary microalbumin [40].

5. Summary and Prospects

5.1 Summary of Current Research Status

In summary, natural polysaccharides possess multi-target, multi-pathway network regulatory characteristics, demonstrating unique advantages in diabetic nephropathy treatment. Plant-derived and fungal-derived polysaccharides can regulate multiple signaling pathways including TGF-β1/Smads, cAMP/PKA/CREB, PI3K/Akt, NF-κB/NLRP3, TLR4/NF-κB, and PI3K/GSK-3β/Nrf2, achieving various functions such as improving insulin resistance, anti-oxidative stress, anti-inflammation, anti-fibrosis, and gut microbiota regulation [38]. These effects are interconnected and mutually influential, constituting the molecular basis for polysaccharide regulation of diabetic nephropathy pathogenesis. In recent years, with deepening research by Mei et al. on Phellodendron amurense polysaccharide and others, the mechanisms by which polysaccharides regulate diabetic nephropathy through the "gut-kidney axis" have been progressively elucidated, bringing new perspectives to this field [39]. Concurrently, systematic evaluations of mulberry leaf polysaccharide and related research provide higher-level evidence supporting clinical application of polysaccharides [40].

5.2 Existing Problems and Challenges

Despite significant progress in research on polysaccharides for diabetic nephropathy prevention and treatment, this field still faces numerous challenges:

5.2.1 Depth of Mechanistic Research

Regarding the mechanisms of action of traditional Chinese medicine polysaccharides in diabetic nephropathy intervention, the mechanisms related to improving insulin resistance, attenuating oxidative stress, inhibiting inflammatory responses, and renal protection have been relatively well-established. However, research on gut microbiota regulation remains insufficiently, with certain aspects of the mechanisms yet to be clarified. Although disordered gut microbiota in diabetic nephropathy model animals can be reversed and normalized following polysaccharide intervention, most studies have not examined gut microbiota metabolites affecting renal function injury in diabetic nephropathy, nor have they systematically analyzed the abundance and proliferative capacity of bacterial strains producing relevant metabolites. The specific mechanisms by which polysaccharides from traditional Chinese medicine intervene in diabetic nephropathy through gut microbiota improvement require further investigation.

5.2.2 Network Regulation of Signaling Pathways

Polysaccharides from traditional Chinese medicine primarily exert effective interventional effects on diabetic nephropathy through activation or inhibition of multiple signaling pathways. However, the in vivo signaling pathway network is complex with numerous pathway types, and the functions of regulatory molecules within each pathway vary. Current understanding of how polysaccharides simultaneously regulate multiple signaling pathways, as well as the interrelationships and mutual influences among various pathways and regulatory molecules, remains to be further elucidated. Future research could integrate polysaccharide intervention studies in diabetic nephropathy with modern research methods such as data mining and network pharmacology to screen for signaling pathways with strong relevance to polysaccharide effects, deeply investigate the regulatory patterns of polysaccharides on different signaling pathways, and explore the interactions and

mutual influences among regulatory molecules across different signaling pathways. This would provide new insights and support for clarifying the core mechanisms of polysaccharide intervention in diabetic nephropathy.

5.2.3 Quality Control and Structural Elucidation Issues

The extraction processes and structural characteristics of polysaccharides directly influence their biological activities. Current research exhibits varying depth in chemical characterization of polysaccharides, with some studies merely describing extraction methods without systematic structural analysis. Although multiple polysaccharides with interventional effects on diabetic nephropathy have been identified, relevant longitudinal studies remain relatively scarce. Considerable gaps exist in research areas including optimization of polysaccharide extraction processes and structural elucidation, determination of optimal doses and treatment courses for diabetic nephropathy intervention, screening of core signaling pathways, and analysis of gut microbiota metabolites. Future efforts should establish quality control standards for polysaccharides, clarify the structural characteristics of active components, and lay foundations for pharmacodynamic mechanism research and subsequent development.

5.2.4 Clinical Translation Research Issues

Current research on polysaccharide intervention in diabetic nephropathy predominantly remains at the cellular and animal model levels, focusing on exploration of basic mechanisms. High-quality clinical studies in humans are relatively scarce, lacking large-sample, long-term follow-up clinical data support to adequately validate their efficacy and safety in clinical applications. Human effective doses, safety profiles, and pharmacokinetic characteristics of polysaccharides urgently require clarification. Given that polysaccharides are typically mixtures, determining their pharmacodynamic material basis and establishing quality control indicators correlated with clinical efficacy are critical for promoting their clinical translation. Systematic reviews and meta-analyses reveal issues including substantial heterogeneity and variable methodological quality among existing studies, necessitating more rigorously designed preclinical and clinical studies to validate the efficacy and safety of polysaccharides [38,40].

5.3 Future Research Directions

5.3.1 In-Depth Mechanistic Studies

Integrate techniques including data mining, network pharmacology, and molecular docking to screen key targets and signaling pathways involved in polysaccharide effects, elucidate the intrinsic relationships and temporal sequence changes among polysaccharide multi-target effects. Conduct in-depth research on direct binding evidence between polysaccharides and cell membrane receptors or action targets, revealing the molecular mechanisms by which polysaccharides, as macromolecular compounds, enter cells or interact with membrane receptors, thereby providing more direct experimental evidence for polysaccharide mechanisms of action.

5.3.2 Gut Microbiota Mechanism Research

Strengthen research on polysaccharide regulation of diabetic nephropathy through the "gut-kidney axis," systematically analyze the effects of polysaccharides on gut microbiota metabolites, identify key bacterial populations and metabolites influencing diabetic nephropathy renal injury, and elucidate the specific mechanisms by which polysaccharides regulate gut microbiota to intervene in diabetic nephropathy. Recent research on Phellodendron amurense polysaccharide and others has provided important directions in this regard [39]. Future studies could further explore the specificity of interactions between polysaccharides and gut microbiota, clarifying target differences among various polysaccharides in regulating gut microbiota.

5.3.3 Structure-Activity Relationship Research

Conduct in-depth chemical property analysis and structural elucidation of polysaccharides, establishing relationship models between polysaccharide structure and biological function. Based on these findings, pursue structural modification and activity optimization research on polysaccharides through chemical modification and molecular approaches to enhance the biological activity and stability of polysaccharides, providing theoretical foundations for developing efficient, low-toxicity polysaccharide-based drugs.

5.3.4 Clinical Translation Research

Conduct rigorously designed clinical studies employing randomized, controlled, double-blind trial designs to evaluate the efficacy, safety, and pharmacokinetic characteristics of polysaccharide-based drugs in diabetic nephropathy patients. Explore synergistic effects of polysaccharides combined with first-line clinical drugs, as well as their potential to reduce adverse reactions associated with chemical medications. Develop novel drug delivery systems to improve the water solubility, stability, and bioavailability of polysaccharides, promoting clinical translation and application of polysaccharide-based drugs. It is anticipated that with continued deepening of research on polysaccharides from traditional Chinese medicine, their mechanisms of action will be further elucidated, thereby expanding the promising prospects of polysaccharides in both basic research and clinical applications. This will provide new strategies and methods for diabetic nephropathy treatment, offering novel therapeutic options for patients.

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