

Research Progress on the Effect and Mechanism of Astragalus membranaceus in Intervening Podocyte Injury in Diabetic Kidney Disease

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Abstract. Diabetic kidney disease (DKD) is the most common chronic complication of diabetes. Clinically, it features persistent proteinuria and progressive decline in renal function, and it is also the leading cause of end-stage renal disease in patients. Podocytes lie in the outermost layer of the glomerular filtration barrier, and mounting evidence regards podocyte injury as a key event in the early stage of DKD. *Astragalus membranaceus* is a commonly used qi-tonifying Chinese medicinal herb in clinical practice. Its active components, including astragalus polysaccharides, astragaloside IV and flavonoids, act on a wide range of targets. According to available experimental results, *Astragalus membranaceus* protects podocytes by suppressing inflammation, alleviating oxidative stress, and regulating cell apoptosis and autophagy, thereby slowing the progression of renal lesions. This paper reviews recent studies on this topic, aiming to provide references for the prevention and treatment of DKD with traditional Chinese medicine.

Keywords: *Astragalus membranaceus*, diabetic nephropathy, DKD, podocyte injury, mechanism of action

1. Introduction

Among all types of renal damage caused by diabetes, DKD is the dominant form and also one of the most common causes of end-stage renal disease [1]. The term "diabetic nephropathy (DN)" was widely used in the past, but DN focuses on pathological diagnosis and has a narrow scope. DKD covers both clinical manifestations and pathological changes, and has now become the more accepted term in academia. Long-term uncontrolled hyperglycemia damages the kidney through multiple pathways: accumulation of advanced glycation end products in tissues, aggravated oxidative stress, and activated inflammatory pathways are all well-documented mechanisms [2]. These processes interact with each other and eventually damage the glomerular filtration barrier, leading to clinical proteinuria and deterioration of renal function.

2. The role of podocytes in DKD

Podocytes are highly differentiated glomerular epithelial cells, consisting of cell bodies, foot processes and slit diaphragms between adjacent foot processes. This structure enables the glomerulus to perform selective blood filtration. Foot processes attach closely to the outer surface of the basement membrane like fingers. Between adjacent foot processes, proteins such as nephrin, podocin and CD2-associated protein form slit diaphragms, which act as a precise filter that retains large-molecule plasma proteins inside blood vessels. The morphology of foot processes also relies on continuous remodeling of cytoskeletal proteins such as actin; once the cytoskeleton is destabilized, the filtration barrier cannot be maintained. In the course of DKD, podocyte abnormalities occur at a very early stage. Diffuse fusion of foot processes, disorganized cytoskeleton arrangement, rupture of slit diaphragms, and even podocyte detachment from the basement membrane and excretion in urine often take place before clinically detectable proteinuria appears [3]. High glucose environment also drives phenotypic transformation of podocytes via TGF- β /Smad, Wnt/ β -catenin and PI3K/Akt pathways, causing gradual loss of normal podocyte function. Podocyte injury does not stem from a single cause. Under sustained high glucose stimulation, large amounts of reactive oxygen species (ROS) are produced, which first damage mitochondria and then trigger apoptosis. Inflammatory factors such as TNF- α and IL-1 β are continuously released, amplifying inflammatory responses through the NF- κ B pathway. Over-activation of the renin-angiotensin system leads to elevated angiotensin II, which worsens podocyte damage by inducing vasoconstriction, oxidative stress and apoptosis. Impaired autophagy also plays an important role. When autophagy is suppressed, damaged proteins and organelles accumulate inside cells, impairing podocyte survival and function. Unfortunately, podocytes have almost no proliferative capacity. Once injured or shed, they can hardly be replenished, making the damage largely irreversible. As podocyte number decreases, the coverage of podocytes on the basement membrane becomes sparse, leaving denuded areas, which further cause adhesion and segmental sclerosis. The filtration barrier is breached, with sharply increased permeability, and plasma proteins such as albumin leak continuously into the urine, resulting in persistent proteinuria. Importantly, proteinuria itself damages the kidney: it activates inflammatory and fibrotic responses in renal tubular epithelial cells, extending the injury to the tubulointerstitium and forming a "proteinuria-inflammation-fibrosis" cycle, which ultimately accelerates glomerulosclerosis and renal function decline [4]. In summary, podocyte injury is a core link in DKD progression, with early onset, insidious development and severe consequences. For this reason, podocyte protection has become a research hotspot in recent years. Researchers aim to delay podocyte injury by targeting oxidative stress, inflammation and apoptosis pathways, and to maintain the expression of slit diaphragm proteins and stabilize cytoskeletal structure. Traditional Chinese medicine has unique advantages in this field, as it usually acts on multiple targets simultaneously. Existing studies indicate that Chinese medicinal herbs can protect podocytes through anti-oxidative, anti-inflammatory, autophagy-regulating and anti-apoptotic effects [5].

3. Modern pharmacological basis of *Astragalus membranaceus*

Astragalus membranaceus is prepared from the dried root of leguminous plants. It is the most widely used qi-tonifying Chinese medicinal herb, with a medicinal history of over a thousand years. Its main active components fall into three categories: astragalus polysaccharides, astragalosides (represented by astragaloside IV) and flavonoids. These three types of components differ in structure and function, and jointly underpin the pharmacological effects of *Astragalus membranaceus*.

Modern research shows that *Astragalus membranaceus* has a broad spectrum of effects: it regulates inflammation, reduces oxidative damage, inhibits apoptosis, and improves immune function [6]. For inflammation, it reduces the levels of TNF- α , IL-6 and other factors, inhibits over-activation of NF- κ B and related pathways, and thus alleviates chronic low-grade inflammation. For oxidative stress, it scavenges excess ROS while increasing the activity of antioxidant enzymes such as SOD, restoring cellular redox homeostasis. For apoptosis, it adjusts the ratio of Bcl-2 to Bax and modulates caspase signaling, reducing the incidence of cell death. In the context of DKD, *Astragalus membranaceus* clearly acts on multiple targets. Astragalus polysaccharides correct metabolic disorders under high glucose conditions and enhance cellular resistance to injury. Astragalosides mainly protect glomeruli and podocytes, and attenuate fibrosis via TGF- β /Smad, PI3K/Akt and other pathways. Flavonoids relieve chronic renal tissue damage through antioxidant and anti-inflammatory effects. Some studies also note that *Astragalus membranaceus* regulates autophagy and mitochondrial function to maintain cellular homeostasis. This "multi-component, multi-target, multi-pathway" mode of action fits well with the complex nature of DKD. As metabolism, inflammation, oxidation and fibrosis are intertwined, single-target drugs often fail to address all pathological processes. In contrast, *Astragalus membranaceus* acts on multiple links simultaneously to slow down the overall disease progression [7]. For this reason, the value of *Astragalus membranaceus* and its active components in DKD prevention and treatment has drawn increasing attention, and related mechanistic studies also provide evidence for the modernization of traditional Chinese medicine and new drug development [8, 9].

4. Mechanisms underlying the podocyte-protective effect of *Astragalus membranaceus*

4.1. Anti-inflammatory effect

Inflammation is a key driver of glomerular injury in DKD. Long-term high glucose induces chronic low-grade inflammation in renal tissue, with sustained release of various inflammatory factors that directly affect podocytes. Studies show that active components of *Astragalus membranaceus* inhibit the abnormal activation of the classic TLR4/NF- κ B inflammatory pathway, and reduce the production and secretion of TNF- α , IL-1 β , IL-6 and other mediators, which cuts off the inflammatory cascade at the source [10]. It also regulates related transcription factors and reduces repeated stimulation of podocytes by the inflammatory microenvironment, thereby improving the local inflammatory state of glomeruli [11].

4.2. Anti-oxidative stress

High glucose markedly increases intracellular ROS. Excessive ROS cause lipid peroxidation, protein denaturation and DNA damage, which directly destroy podocyte structure. Persistent oxidative stress also continuously drives DKD progression. *Astragalus membranaceus* exerts favorable antioxidant effects. Its components activate the Nrf2/HO-1 pathway, increase the activity of endogenous antioxidant enzymes such as SOD and GSH-Px, and enhance ROS scavenging capacity [12, 13]. It also inhibits lipid peroxidation and reduces secondary cellular damage caused by oxidation products. With reduced oxidative stress, the cytoskeleton and slit diaphragms of podocytes are more likely to remain intact [14].

4.3. Inhibition of cell apoptosis

Increased podocyte apoptosis is a hallmark change in early DKD, and it is closely associated with the destruction of the filtration barrier. *Astragalus membranaceus* inhibits apoptosis through multiple pathways. The direct pathway is regulation of the mitochondrial pathway: it up-regulates the anti-apoptotic protein Bcl-2, down-regulates pro-apoptotic Bax and caspase family proteins, restores the Bcl-2/Bax ratio, and thus suppresses apoptosis [15]. The indirect pathway is reducing upstream apoptotic triggers through antioxidant and anti-inflammatory effects [16]. The combined action of these two pathways reduces podocyte programmed death, maintains podocyte number, and slows the progression of glomerular injury.

4.4. Regulation of autophagy

Autophagy is a cellular self-cleansing mechanism that degrades and recycles damaged organelles and misfolded proteins to maintain intracellular homeostasis. In DKD, however, autophagy is often suppressed, leading to accumulation of metabolic wastes and worsening podocyte injury. *Astragalus membranaceus* activates AMPK/SIRT1 and mTOR pathways to restore autophagic activity, enabling the degradation and reuse of damaged intracellular substances [17]. Moderately enhanced autophagy improves podocyte tolerance to adverse environments, and reduces apoptosis and inflammation, resulting in synergistic protective effects [18].

4.5. Maintenance of filtration barrier integrity

Podocytes are the main structural component of the filtration barrier, and their integrity directly determines the onset and severity of proteinuria. *Astragalus membranaceus* up-regulates the expression of slit diaphragm proteins such as nephrin and podocin, stabilizes the connections between foot processes, and preserves the selective permeability of the filtration barrier [19]. It also stabilizes cytoskeletal proteins, reduces foot process fusion and podocyte detachment, and lowers the risk of basement membrane denudation. Combined with the aforementioned antioxidant and anti-inflammatory effects, it protects the overall barrier structure from multiple aspects. Through such multi-level regulation, proteinuria is reduced and DKD progression is delayed [18, 19].

5. Summary and prospect

Overall, *Astragalus membranaceus* protects podocytes through multiple mechanisms. However, current evidence is mostly derived from basic experiments, and high-quality clinical data remain insufficient. Future studies should carry out more randomized controlled trials and apply multi-omics approaches to further elucidate the mechanisms of action, so as to truly promote the clinical application of *Astragalus membranaceus*.

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