

Research on the Major Active Constituents of Astragalus Membranaceus for the Treatment of Diabetic Kidney Disease

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Abstract. This paper systematically reviews recent domestic and international research on diabetic kidney disease over the past three years. Starting from novel pathogenic mechanisms, This review demonstrates that ferroptosis in renal tubular epithelial cells, long-term low-level inflammation driven by the inflammatory protein complex NOD-like receptor pyrin domain-containing protein 3 (NLRP3), and gut-kidney axis imbalance are three core mechanisms driving diabetic kidney disease progression. Astragalus membranaceus, a traditional Chinese medicine, can specifically regulate renal metabolic disorders, inflammatory responses, and gut microbiota balance, thereby effectively inhibiting renal tissue fibrosis. To slow renal function decline, this paper explains how different active ingredients in Astragalus membranaceus act on ferroptosis, the NLRP3 inflammasome, and the gut-kidney axis, respectively, and summarizes differences in the efficacy of each active ingredient and the synergistic effects of combined use. Finally, the current research limitations are objectively analyzed, and possible future directions for research on mechanisms of action and clinical applications are also pointed out.

Keywords: Astragalus, active ingredient, diabetic kidney disease, ferroptosis, NLRP3 inflammasome

1. Introduction

1.1. Pathogenesis and research progress of diabetic kidney disease

Diabetic kidney disease is a complex complication caused by diabetes. Its pathogenesis extends beyond familiar hemodynamic changes and metabolic disorders. Many interrelated pathways are driving disease progression, such as abnormal metabolic regulation, inflammatory response, oxidative stress, and tissue fibrosis; key molecules such as transforming growth factor β and reactive oxygen species (ROS) cause significant overlap between these pathways; important progress in understanding the mechanism of diabetic kidney disease is that damage does not only occur in the glomeruli, but also in the renal tubules; renal tubular injury also drives disease progression; hyperglycemia, lipid accumulation, hypoxia, and endoplasmic reticulum stress are the main factors that promote renal tubular injury. In recent years, single-cell sequencing and multi-omics techniques have revealed these pathological processes more clearly and helped identify cell-type-specific pathogenic factors. In particular, some studies have integrated transcriptome and proteome analysis

of insulin-resistant kidney cells. As a result, complement component C3, C-X-C motif chemokine ligand 1, and cathepsin S were consistently increased in the glomeruli and renal tubules of diabetic kidney disease biopsy samples. These indicators are also associated with clinical outcomes such as decreased glomerular filtration rate. Multi-omics studies have also identified the AP-1 transcription factor subunit as a key driver of epithelial-mesenchymal transition and fibrosis in proximal renal tubular epithelial cells. At the same time, the electrically neutral sodium bicarbonate cotransporter 1 is a downstream regulator of renal tubular injury. These findings indicate that diabetic kidney disease is a complex pathological process, and advanced molecular analysis methods can identify new therapeutic targets. Conventional treatments have difficulty preventing disease progression effectively.

1.2. Therapeutic advantages of Astragalus active components

The advantages of the active ingredients in *Astragalus membranaceus* in treating diabetic kidney disease are mainly that they can act on multiple targets and pathways simultaneously, unlike conventional drugs that target a single link. Astragaloside IV (AS-IV), Astragalus polysaccharides (APS), and total flavonoids (TFA) act on different but interrelated pathological links. AS-IV can restore the acetylation level of G protein subunit alpha 13 and readjust purine metabolism in specific areas of the kidney. At the same time, astragaloside IV can also upregulate Klotho protein, thereby inhibiting the signal axis of nuclear factor kappa B (NF- κ B) signaling and the NLRP3 inflammasome, and the podocyte injury and pyroptosis are also reduced; astragalus polysaccharides produce more short-chain fatty acids in the intestine by regulating the gut microbiota, and these short-chain fatty acids then activate the G protein-coupled receptors in the kidney, thereby reducing renal interstitial fibrosis; TFA protects the glomerular filtration barrier mainly by maintaining glycocalyx integrity through the VEGF/PI3K/AKT pathway. When multiple components are combined, oxidative stress, inflammation, and fibrosis can be regulated simultaneously; therefore, compared with conventional treatment targeting only one pathway, *Astragalus membranaceus* offers a broader protective range and potentially longer-lasting action.

1.3. Innovation and significance of this review

In recent years, understanding of diabetic kidney disease has deepened, and research has gradually shifted from focusing on a single target to a more comprehensive view of multi-component drugs. *Astragalus* and its active ingredients have attracted more attention, on the one hand, because they have been proven effective; on the other hand, because their mechanism of action is more diverse; at present, most of the reviews only list the effects of astragaloside IV, astragalus polysaccharides, and flavonoids, such as inhibiting NLRP3 inflammasome, preventing ferroptosis, and regulating gut microbiota. However, these reviews rarely integrate scattered pathways into a system-level model; this review proposes a different perspective: the therapeutic advantages of *Astragalus membranaceus* mainly come from interconnections among pathways. The anti-inflammatory and antioxidant effects of individual components can be combined to interrupt the vicious cycle between fibrosis and cell death. For example, both astragaloside IV and total flavonoids can affect the transforming growth factor β / small mothers against decapentaplegic (Smad) pathway and nuclear factor erythroid 2-related factor 2 pathway, which indicates that they are more likely to be synergistic rather than simply additive; the reason why this integrated view is important is that it no longer focuses on isolated mechanisms, but provides a theoretical basis for treating *Astragalus* as a multi-target intervention that can change the disease process; this idea may be particularly helpful in solving the

problem that conventional treatment often fails to prevent continued progression of diabetic kidney disease.

2. Novel core pathogenic mechanisms of diabetic kidney disease

2.1. Ferroptosis in renal cells and kidney injury

Ferroptosis is an iron-dependent form of cell death that does not involve apoptosis [1]. It is caused by severe lipid peroxidation. It is now regarded as an important pathogenic mechanism of kidney damage in various disease models. Abnormal ferroptosis occurs in renal tubular epithelial cells. This is closely related to disrupted intracellular redox balance and abnormal iron metabolism. A key driver is dysfunction in the glutathione and glutathione peroxidase 4 (GPX4) system. Glutathione leaks out of the cell through multidrug resistance-associated protein 1, and the cell's ability to resist oxidation worsens. Lipid peroxides accumulate, and impaired glucose metabolism worsens this process. For example, during ischemia-reperfusion injury, cells are first deprived of glucose and then re-exposed to it. As a result, vacuolar-type H⁺-adenosine triphosphatase and mechanistic target of rapamycin (mTOR) signaling pathways are inhibited, and lysosomes release iron. Ferritinophagy also occurs, and excess free iron in cells further promotes a series of reactions in ferroptosis. In addition, recent studies have found that ferroptotic cells do not die passively. They release exosomes that promote fibrosis, thereby promoting disease progression. For example, renal tubular cells undergoing activating transcription factor 3- and nuclear factor erythroid 2-related factor 2 (Nrf2)-mediated ferroptosis secrete exosomes containing microRNA (miR)-1306-5p. These exosomes drive macrophages toward alternative activation, resulting in renal interstitial fibrosis after ischemia-reperfusion injury. In crystal-induced acute kidney injury, the pathogenic effect of ferroptosis is more pronounced. After oxalate treatment, long-chain acyl-CoA synthetase 4 (ACSL4) expression increases, leading to the incorporation of polyunsaturated fatty acids prone to ferroptosis into phospholipids. In contrast, GPX4 expression decreases. As a result, renal tubular cells are particularly prone to ferroptosis. Ferroptosis is not only involved in acute kidney injury but is also considered to promote the development of acute kidney injury to chronic kidney disease. If ferroptosis continues and fibrosis signals appear later, renal function will continue to deteriorate.

2.2. NLRP3 inflammasome-mediated chronic inflammation

The role of the NLRP3 inflammasome in kidney disease has received increasing attention. It has become a core link between chronic inflammation and fibrosis. Many different pathogenic factors cause tissue damage through it [2]. In the kidney microenvironment, resident cells or infiltrating immune cells can easily activate NLRP3. Once abnormally activated, it releases interleukin-1 β and interleukin-18 and also causes pyroptosis, promoting glomerular damage, renal tubulointerstitial inflammation, and fibrosis. A key upstream driver is the P2X7 purinoceptor. In chronic kidney disease, renal tubules release adenosine triphosphate (ATP) extracellularly, which activates the P2X7 receptor on macrophages around the renal tubules. As a result, the NLRP3 inflammasome is continuously activated, forming a positive feedback loop. In addition, P2X7 receptor activation allows calcium ions to flow into cells, depolarizing mitochondria. This process produces mitochondrial ROS. Mitochondrial ROS are critical for secreting monocyte-derived hematopoietic factor 1, which in turn promotes leukocyte infiltration and worsens oxidative damage to renal tubules. In addition, a protein called transient receptor potential cation channel 6 also aggravates the inflammatory response. Transient receptor potential cation channel 6 (TRPC6) promotes renal

fibrosis through the signaling pathway of ROS, thioredoxin-interacting protein, and NLRP3. In the animal model of unilateral ureteral obstruction, inhibiting TRPC6 significantly reduces fibrosis markers and NLRP3-mediated pyroptosis. However, the body also has an antagonistic mechanism: mitophagy mediated by HIF-1 α and BNIP3 clears damaged mitochondria and reduces ROS, thereby inhibiting NLRP3 inflammasome activation. If there is a problem with mitophagy, NLRP3 will remain activated and chronic inflammation will continue, so that the development of acute kidney injury to chronic kidney disease will be accelerated; these results suggest that there is a balance between the pro-inflammatory pathway and the protective pathway, so finding ways to restore mitochondrial quality control may be more conducive to preventing the progression of chronic kidney disease than broad-spectrum anti-inflammatory approaches.

2.3. Gut-kidney axis in diabetic kidney disease

The gut-kidney axis is an important communication channel between the intestine and the kidney. Gut microbiota dysbiosis promotes diabetic kidney disease progression through this axis [3]. In patients with diabetic kidney disease, gut microbiota imbalance is mainly characterized by a decrease in bacteria that produce short-chain fatty acids, such as Ruminococcaceae and Lachnospiraceae, while harmful bacteria such as Proteobacteria increase; bacterial composition shifts, and metabolites become unbalanced. Beneficial short-chain fatty acids are decreasing, while uremic toxins such as trimethylamine N-oxide and p-cresyl sulfate accumulate in the body. As a consequence, the intestinal barrier is disrupted, and tight junction proteins zonula occludens-1 and occludin between intestinal cells are reduced, so lipopolysaccharide is more likely to pass through the intestine into systemic circulation. After lipopolysaccharide enters the blood, it activates the nuclear factor kappa B (NF- κ B) signaling pathway, phosphorylates the NF- κ B p65 subunit, and promotes the assembly of the NLRP3 inflammasome, which in turn produces inflammatory factors such as interleukin-1 β , tumor necrosis factor α , and interleukin-6, causing kidney inflammation. Recent Mendelian randomization analyses have provided genetic evidence for a causal link between the gut and the kidney, thereby avoiding confounding factors that interfere with results in traditional observational studies; however, the composition of each person's gut microbiota varies greatly, which is still a major problem when applying the research results to clinical practice, because it is difficult to predict how a given patient will respond to treatment. These studies suggest that regulating gut microbiota composition may interrupt the inflammatory response at the source, rather than waiting until the kidney is damaged.

3. Astragalus active components and novel mechanisms of diabetic kidney disease

3.1. Inhibition of renal cell ferroptosis by Astragalus active components

Astragalus membranaceus and its active ingredients have shown marked anti-ferroptotic effects in various kidney injury models. Astragaloside IV can protect podocytes in lupus nephritis. It activates the phosphatidylinositol 3-kinase/protein kinase B/nuclear factor erythroid 2-related factor 2 pathway, allows Nrf2 to enter the nucleus, and upregulates antioxidant enzymes such as GPX4 and solute carrier family 7 member 11 (SLC7A11), thereby reducing lipid peroxidation and iron accumulation. The drug pair of *Astragalus membranaceus* and *Ligustrum lucidum* can reduce ischemia-reperfusion injury [4]. Studies have shown that GPX4 is upregulated, mitochondrial cristae structure is restored, and malondialdehyde (MDA) and tissue iron levels decrease. Transcriptome sequencing and molecular docking also support these results; in addition, astragaloside IV can

regulate prolyl hydroxylase domain-containing protein 2 (PHD2)/hypoxia-inducible factor 1 alpha (HIF-1 α), inhibit podocyte ferroptosis, and improve diabetic kidney disease. These interventions suggest that precise regulation of phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/Nrf2, PHD2/HIF-1 α , and GPX4 may be more targeted than broad-spectrum antioxidant therapy alone; however, this diversity also poses a problem. When different active ingredients are combined, can ferroptosis be inhibited more effectively through interactions between pathways?

3.2. Targeting NLRP3 inflammasome by Astragalus active components

Astragalus membranaceus and its active ingredients can protect the kidney by regulating the NLRP3 inflammasome across various kidney injury models. AS-IV, one of the most studied active saponins, ameliorates diabetic kidney disease by inhibiting cluster of differentiation 36 (CD36)-mediated lipid accumulation and subsequent NLRP3 inflammasome activation in renal tubular epithelial cells, thereby reducing IL-1 β secretion and interstitial inflammation. In cisplatin-induced acute kidney injury, AS-IV can inhibit lysine acetyltransferase 5 (KAT5)-mediated NLRP3 acetylation, thereby downregulating the cleavage of caspase-1 and gasdermin D (GSDMD) and reducing pyroptosis; another active saponin astragaloside I protects podocytes by inhibiting the NLRP3/caspase-1/GSDMD pyroptosis pathway, which is manifested by decreased serum IL-1 β and interleukin-18 levels and restored nephrin expression [5]; in addition, calycosin is a major isoflavone in *Astragalus*, which regulates the activation of NLRP3 inflammasome through the advanced glycation end products / receptor for advanced glycation end products / NF- κ B axis and provides multi-target protection against kidney disease; these different mechanisms of action suggest that although AS-IV has been able to inhibit NLRP3 activation, its upstream pathways differ, some involving CD36 and ROS, some involving KAT5 acetylation, and some involving NF- κ B signaling, so different active ingredients may be more suitable for different pathological conditions, rather than being replaced at will.

3.3. Regulation of gut microbiota by Astragalus

The therapeutic effect of *Radix Astragali* seu *Hedysari* on diabetic kidney disease: *Radix Astragali* seu *Hedysari* extract exerts therapeutic effects on diabetic kidney disease by significantly reducing hyperglycemia and improving renal function, as shown by decreased serum creatinine and blood urea nitrogen levels. Metagenomic sequencing showed that this extract could reverse flora imbalance, inhibit the harmful *Aerococcus urinaeequi*, and increase the beneficial *Thomasciavelia cocleata*. Metabolomics analysis further linked these bacterial changes to the reprogramming of host metabolic pathways, especially glycerophospholipid metabolism and bile acid synthesis [6]. Notably, AS-IV has low oral bioavailability but strong physiological activity, which seems somewhat contradictory [6]. Studies suggest this may relate to its interaction with the gut microbiota; this evidence suggests that *Astragalus* components may exert systemic effects through a 'drug-bacteria-host' dynamic relationship via the intestinal ecosystem.

3.4. Antioxidant, anti-fibrotic, and anti-apoptotic effects of Astragalus

The classical renoprotective effect of *Astragalus membranaceus* is mainly achieved through three interrelated aspects: antioxidation, anti-fibrosis, and apoptosis regulation. The Nrf2/heme oxygenase-1 (HO-1) pathway mainly mediates antioxidant capacity. Active ingredients such as calycosin can upregulate antioxidant enzymes and reduce oxidative stress; in terms of controlling fibrosis, astragaloside inhibits renal fibrosis by regulating the transforming growth factor beta 1 /

Smad2 / 3 pathway, reducing extracellular matrix deposition and epithelial-mesenchymal transition; in terms of regulating apoptosis, Astragalus and its active ingredients protect podocytes by restoring mitochondrial function and regulating endoplasmic reticulum stress; these pathways do not work alone but form a cooperative network, in which oxidative stress triggers inflammatory signals and apoptosis cascades, and ultimately promotes fibrosis; a meta-analysis of 23 animal studies provided preclinical evidence that AS-IV can significantly reduce serum creatinine and proteinuria through these combined effects; the multi-target characteristics of these effects indicate that the active ingredients of Astragalus membranaceus may provide more extensive cytoprotection than a single drug, but which component dominates these effects in vivo requires further study.

4. Pharmacological differences and synergistic effects of Astragalus active components

4.1. Astragaloside: renoprotection, ferroptosis inhibition, and anti-fibrosis

AS-IV, the principal bioactive saponin derived from Astragalus membranaceus, has emerged as a key renoprotective agent by coordinating inhibition of ferroptosis and fibrosis. In high-glucose-treated podocytes, nephrin, phosphorylated glycogen synthase kinase 3 beta (p-GSK3 β), Nrf2, and GPX4 were reduced. After AS-IV treatment, these markers were restored, lipid peroxidation and iron overload were alleviated, and glutathione levels recovered; this inhibition of ferroptosis involves not only one link but also multiple signaling pathways. One of them is the GSK3 β / Nrf2 / GPX4 axis, the PHD2 / HIF-1 α axis that degrades HIF-1 α [7], and the activation of the Nrf2 / HO-1 pathway. In unilateral ureteral obstruction (UUO) rats, AS-IV significantly reduced blood urea nitrogen (BUN) and fibrosis markers alpha-smooth muscle actin, fibronectin, and collagen type I alpha 1 chain, and restored the expression of GPX4, HO-1, and cystine/glutamate antiporter by regulating the cyclic adenosine monophosphate/protein kinase A pathway. These multi-pathway effects suggest that AS-IV can disrupt the pathogenic link between ferroptosis-induced cell death and fibrotic matrix deposition. This effect is often difficult to replicate with single-target drugs.

4.2. Astragalus polysaccharides: immune regulation, gut microbiota, and anti-inflammation

APS functions as a multifunctional bioactive macromolecule that integrates immune modulation, gut microbiota regulation, and anti-inflammatory action. As a non-starch polysaccharide, APS cannot be fully digested in the upper gastrointestinal tract and thus reaches the colon to serve as a prebiotic substrate. In this process, APS can selectively promote the growth of bacteria that produce short-chain fatty acids and increase acetic acid, propionic acid, and butyric acid levels in feces. These short-chain fatty acids then activate the G protein-coupled receptors GPR41 and GPR43 in the kidney, reducing renal tubular interstitial damage and fibrosis; mechanistically, APS inhibits renal inflammation through the Toll-like receptor 4 (TLR4)/nuclear factor- κ B (NF- κ B) pathway. In streptozotocin-induced diabetic kidney disease/CKD rats, APS treatment reduces serum interleukin-1 β , interleukin-6, and monocyte chemoattractant protein-1 levels in a dose-dependent manner and downregulates TLR4 and NF- κ B p65 expression in renal tissue [8]. This anti-inflammatory effect has also been confirmed in high-glucose-stimulated podocytes. APS-containing serum can inhibit high glucose-induced inflammatory responses and cell proliferation [8]; in addition, APS can also promote autophagy through the Gm41268 / prolactin receptor (PRLR) pathway, reduce the levels of sequestosome 1 and phosphorylated mechanistic target of rapamycin, and increase the ratio of microtubule-associated protein 1A/1B-light chain 3 (LC3)-II / LC3-I, thereby reducing renal fibrosis in a diabetic mouse model. APS's immunomodulatory ability also includes regulating macrophage

polarization through TLR4/NF- κ B/signal transducer and activator of transcription 3 signaling, which may also explain its kidney-protective effects. These multi-target effects suggest that APS improves renal injury not by a single mechanism, but by coordinating multiple aspects that affect microbial-derived metabolites, inflammatory signals, and cell homeostasis.

4.3. Astragalus flavonoids: antioxidant, anti-inflammatory, and podocyte protection

The flavonoids in *Astragalus membranaceus* protect the kidney not through a single pathway but through a cooperative network affecting oxidative stress, inflammatory pathways, and podocyte integrity; in diabetic kidney disease mice, after TFA treatment, 24-hour urinary albumin excretion and serum creatinine were significantly reduced, and the decrease of superoxide dismutase (SOD) caused by diabetes was also effectively reversed. The level of MDA in glomerular endothelial cells also decreased [9]; the antioxidant effect directly suppresses inflammatory signals, because TFA treatment inhibits serum interleukin-1 β and tumor necrosis factor α levels in vivo, and similar effects are observed in endothelial cells stimulated by high glucose in vitro [9]; the protective effect of TFA also extended to the glomerular filtration barrier: the tissue structure of the nephron was maintained, glomerular sclerosis was inhibited, and the reduction of key glycocalyx components syndecan-1 and glypican-1 was also reversed. Among the flavonoid components, calycosin regulates mitochondrial permeability transition, and formononetin supports the anti-inflammatory response by regulating the NF- κ B pathway.

4.4. Multi-component synergy

The therapeutic effect of *Astragalus membranaceus* in kidney disease cannot be attributed to a single component; it derives more from synergy among multiple active ingredients. This multi-component feature is manifested in the mutual coordination of drug absorption and effect in the body, which a single component cannot achieve; a study on the drug metabolism of the Huangqi-Shanzhuyu drug pair showed that the absorption of flavonoids and saponins in the whole body increased significantly after the use of iridoid glycosides, which indicated that some components could improve the absorption and utilization of other components by the body. Continuous metabolic processes also support this compatibility. Saponins play a role first; their metabolites affect flavonoids, and flavonoids finally affect iridoid glycosides; in renal fibrosis, the combination of astragalus polysaccharides and other active ingredients can allow them to reach different parts along the digestive tract at different times so that each component can be more suitable for the site of action; this integration method has greatly alleviated kidney tissue damage in animal models, reduced collagen deposition, and restored gut microbiota balance. These synergistic mechanisms indicate that the therapeutic advantage of *Astragalus* lies in the overall and multi-target effects, rather than a single component acting alone; it is worth noting that most of the synergistic results come from traditional Chinese medicine compounds, and few experiments use purified single components to combine directly, so further verification is needed.

5. Current research limitations

Despite growing mechanistic insights, ferroptosis and gut-kidney axis research remain predominantly confined to preclinical stages, with robust clinical evidence notably lacking. A comprehensive review highlighted that the interplay between ferroptosis and innate immunity in diabetic kidney disease "remains largely speculative and requires further exploration through well-designed fundamental research". This gap is evident in clinical translation: while ferroptosis

inhibitors have been proposed for applications including kidney transplantation, cardiac surgery, and prevention of acute kidney injury (AKI)-to-CKD progression, a recent review confirmed that no ferroptosis-modulating therapy is currently used routinely for kidney disease. The gut-kidney axis also faces similar limitations. Although Mendelian randomization provides genetic causal evidence for the association between gut microbiota and diabetic kidney disease, these results come from summary data from genome-wide association studies (GWAS), not human intervention trials [10]. Encouragingly, some early clinical work is emerging, such as the Phase I-II IRON-I.C. trial, which evaluates the role of the iron chelator MEX-CD1 in sepsis-associated AKI, and traditional Chinese medicine preparations such as Qingshen Granules, which also show preliminary effects in patients with CKD and can regulate ferroptosis-related proteins such as GPX4, ferroptosis suppressor protein 1 (FSP1) and ACSL4; these findings indicate that basic research has laid a solid foundation, but there is still an urgent need to translate these findings into verified clinical applications.

6. Future perspectives

Emerging evidence shows that *Astragalus membranaceus* and its active ingredients can more precisely regulate ferroptosis and the NLRP3 inflammasome through clearer molecular pathways; AS-IV can regulate the Kelch-like ECH-associated protein 1 (Keap1)/Nrf2/HO-1 pathway, making it easier for Nrf2 to enter the nucleus and increasing HO-1 expression. In this way, AS-IV inhibits lipid peroxidation- and ferroptosis-induced cell death. Transcriptome analysis further confirmed that AS-IV reduces renal fibrosis by blocking the NOD-like receptor (NLR) signaling cascade; in addition, the tumor protein p53 (p53)/SLC7A11/GPX4 axis is also an important regulatory point. AS-IV downregulates p53 expression and upregulates SLC7A11 and GPX4, restoring glutathione levels and limiting lipid peroxidation. For APS, mechanistic studies show that the Nrf2/Keap1 signaling pathway is activated, ferroptosis is inhibited, and the production of inflammatory factors such as interleukin-6, IL-1 β , and tumor necrosis factor alpha is reduced. Transcriptome analysis of APS-treated cells showed enrichment of the ferroptosis pathway and increased expression of key antioxidant genes, heme oxygenase 1 (HMOX1) and NAD(P)H quinone dehydrogenase 1. These findings suggest that *Astragalus* components converge on the regulatory points of Nrf2 and GPX4 to coordinate ferroptosis and inflammasome inhibition, but how specific molecules act and how the pathways interact require further study.

7. Conclusion

This review systematically illustrates that the effect of *Astragalus membranaceus* on diabetic kidney disease is not based on a single component, but on the three main active components of AS-IV, APS, and TFA, which act on ferroptosis, NLRP3 inflammasome activation, and gut-kidney axis disorders. In the acute kidney injury model, AS-IV inhibited podocyte ferroptosis by regulating the PHD2/HIF-1 α axis and reduced pyroptosis by inhibiting KAT5-mediated NLRP3 acetylation. At the same time, APS can be used as a prebiotic substrate to selectively promote the growth of short-chain fatty acid-producing bacteria, thereby activating renal G-protein-coupled receptors and reducing interstitial fibrosis. After the TLR4 / NF- κ B pathway is inhibited, renal inflammation is also alleviated; comprehensive evidence also shows that TFA maintains the integrity of the glomerular filtration barrier through the vascular endothelial growth factor / PI3K / AKT pathway and glycocalyx protection, and calycosin and formononetin provide additional anti-inflammatory effects by regulating NF- κ B; these findings together verify a hypothesis that the multi-component synergy of *Astragalus membranaceus* can make the pathways interact with each other, especially on the

regulatory points of Nrf2 and GPX4, thus interrupting the pathogenic coupling between ferroptotic cell death, the inflammatory cascade and fibrotic matrix deposition. This review's main contribution is to propose a holistic model explaining why interventions that target multiple pathways simultaneously may be more effective than single-drug approaches. It also highlights key gaps from research to application. For example, in kidney disease, reliable clinical evidence for regulating ferroptosis, a form of cell death, remains limited; in addition, the dose-response relationship of individual active ingredients is not well understood, so future research should prioritize these issues.

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