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Interventional Effects and Molecular Mechanisms of Astragaloside IV in Diabetic Kidney Disease

Jiacheng Wen

Department of Clinical Medicine I, Science and Technology College of Jiangxi University of Traditional Chinese Medicine, Nanchang, China
Jiacheng.Wen0108@outlook.com

Abstract. Diabetic nephropathy is a common microvascular complication of diabetes that is one of the main causes of end-stage renal disease around the world. At present, there are no particular targeted therapeutic drugs that have been used in clinical trials. Astragaloside IV (AS-IV) has good protective effects on the kidneys and is now one of the hot topics in research on DKD pharmacology. AS-IV has several targets in the molecular regulatory network of diabetic kidney disease (DKD), and by activating the SIRT1/PGC1α/Nrf1 and Nrf2-ARE/TFAM pathways, it can reduce renal oxidative stress and mitochondrial damage; by inhibiting the activation of the NLRP3 inflammasome and downregulating IL-6, TNF -α, etc., it can reduce inflammatory infiltration in the kidney; by regulating the TXNIP-NLRP3-GSDMD signaling axis, it can prevent pyroptosis of renal tubules and podocytes; and by targeting the HIF-1α/HMOX1 pathway, it can improve iron accumulation in renal tubular epithelial cells and prevent iron death. Most of the current evidence is obtained from in vitro cell and DKD animal model experiments. There is a lack of extensive data on the human clinical trials of AS-IV monomers, and the exact mechanism of multi-channel cross-regulation has not been fully determined yet. In the future, it is necessary to enhance the development of AS-IV preparations, conduct multi-centre clinical trials, explore more deeply the renal protective molecular network of this drug, and advance the clinical application of traditional Chinese medicine monomers in precision treatment for diabetic nephropathy.

Keywords: Diabetic nephropathy, astragaloside IV, oxidative stress, NLRP3 inflammasome

1. Introduction

The global prevalence of diabetes mellitus has maintained a continuous upward trend in recent decades, evolving into a widespread chronic metabolic disorder that affects all age groups and social populations [1]. Diabetic kidney disease (DKD) is the most important microvascular complication of DM. About 25% - 40% of diabetic patients will progress to DKD. At the same time, DKD is also the first cause of end-stage renal failure worldwide. The core pathological feature of DKD is persistent albuminuria (urinary albumin/creatinine ratio> 30 mg/g), accompanied by glomerular podocyte injury, tubulointerstitial fibrosis and progressive decline of renal function; Hemodynamic disorders,

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oxidative stress, chronic low-grade inflammation, programmed cell death and other multiple mechanisms jointly drive disease progression [2].

Traditional Chinese medicine considers diabetes to be in the category of "diabetes mellitus". Astragalus membranaceus is the basic medicine that doctors have used to treat diabetes mellitus for centuries. Its effect is to tonify Qi and raise Yang, generate fluids, nourish blood, benefit the kidneys, and rectify astringency; thus, it aligns with the main pathology of deficiency of both Qi and Yin, deficiency of kidney Qi, turbidity and blood stasis in people with diabetes mellitus. Astragaloside IV (AS-IV) has the most biological activity. In recent years, pharmacological research has confirmed that it has various effects, such as lowering blood sugar, antioxidant and anti-inflammatory, anti-fibrotic, protecting the kidneys, etc., and can improve DKD kidney injury by regulating multiple signaling pathways [3].

Most of the current reviews only explain the pharmacological effects of AS-IV single pathway separately and do not systematically comb through the integration of the four main injury pathways of oxidative stress, inflammation, pyroptosis and iron death. In short, this paper will organise all the various levels of molecular mechanisms that promote the development of diabetic kidney disease by AS-IV, distinguish among the evidence levels of cellular, animal and clinical studies, and generalize the research bottlenecks that have restricted its clinical application to provide theoretical support for future basic mechanistic research and new drug development. In the following, the molecular pathways of AS-IV protecting the kidney will be analysed in the four dimensions of oxidative stress, inflammatory response, pyroptosis and iron death. Based on the current clinical data of astragalus compounds, the bottlenecks in the conversion of AS-IV monomer will be analyzed, and the future direction of research will be put forward.

2. Molecular regulatory mechanisms of AS-IV in diabetic kidney disease

2.1. Alleviation of renal oxidative stress and restoration of mitochondrial function

Oxidative stress (OS) is a disease state where there is an imbalance in the body's oxidative and antioxidant systems; too many reactive oxygen species (ROS) accumulate and cause permanent damage to cells [4]. The first pathological changes at the beginning of diabetic kidney disease (DKD) in a high-glucose microenvironment are an increase in ROS and damage to the structure and function of mitochondria in renal podocytes and renal tubular epithelial cells. Inhibit the oxidation of free radicals in DKD.

2.1.1. The SIRT1/PGC1α/Nrf1 signalling pathway

Liu and others have carried out in vitro and in vivo experiments to find that AS-IV can activate the SIRT1/PGC1α/Nrf1 signaling pathway, reduce reactive oxygen species (ROS) in podocytes under high-glucose conditions, repair damage to mitochondrial morphology, restore mitochondrial respiratory function, and the inhibitors of this pathway can eliminate the antioxidant protection effect of AS-IV ($P < 0.01$) [5].

2.1.2. The Nrf2-ARE/TFAM mitochondrial protective signaling pathway

AS-IV can increase the expression of TFAM in the mitochondria and promote further down the Nrf2-ARE pathway; it will boost mitochondrial biogenesis, reduce harmful reactive oxygen species (ROS) generated by high glucose, and protect renal cells from damage caused by mitochondrial

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injury [6]. Qian and others. It has also been found that AS-IV can increase the expression of key proteins in mitochondrial synthesis, such as Nrf1, PGC-1α and TFAM, improve the function of mitochondria, and reduce oxidative damage [6].

In short, AS-IV can reduce oxidative stress in DKD kidneys by virtue of the combined effect of the two pathways; that is to say, it activates the SIRT1/PGC1α/Nrf1 pathway to eliminate free radicals first. The second is to activate the Nrf2-ARE/TFAM pathway to repair mitochondria and reduce the production of reactive oxygen species by the source.

2.2. Inhibition of NLRP3 inflammasome activation and mitigation of renal inflammatory lesions

An excessive activation of the nucleotide oligomerisation domain-like receptor 3 (NLRP3) inflammasome is the main reason for chronic inflammation in DKD. Activation of Caspase-1 and other pro-inflammatory factors will lead to the release of IL-1β and IL-18, thus damaging the glomeruli and tubules.

Feng and others have found in the db/db diabetic mouse model that AS-IV can reduce the protein expression of NLRP3, pro-caspase-1 and activated caspase-1 in damaged podocytes due to high glucose to some extent to alleviate podocyte injury in a dose-dependent manner; however, the overexpression of NLRP3 can eliminate this renoprotective effect of AS-IV [7]. At the same time, AS-IV reduced the amount of pro-inflammatory factors in the blood, such as IL-6, MCP-1, TNF-α, and also inhibited local inflammation in the kidney.

Another study has found that AS-IV can reduce the expression of scavenger receptor CD36 in the renal tissue of HK-2 and DKD rats, decrease lipid accumulation and ROS production, inhibit NLRP3 inflammasome activation, reduce pyroptosis effector GSDMD cleavage, and therefore reduce tubulointerstitial injury [8].

2.3. Modulation of the TXNIP-NLRP3-GSDMD cascade to inhibit renal cell pyroptosis

TXNIP-NLRP3-GSDMD axis is a typical signal transduction pathway that leads to pyroptosis, which is a type of controlled cell death different from apoptosis. Pyroptosis is accompanied by the release of a large amount of pro-inflammatory mediators from the extracellular space, and it has the dual effects of causing cell death and aggravating local inflammation; thus, it is one of the reasons for podocyte loss in the development of diabetic kidney disease (DKD). Hu and others have shown in their experiments that AS-IV treatment can reduce blood urea nitrogen, urinary albumin-to-creatinine ratio, serum creatinine and fasting blood glucose in DKD model rats, and alleviate renal pathological changes. At the same time, AS-IV can reduce the expression of TXNIP, NLRP3, activated caspase-1, cleaved GSDMD, IL-1β and IL-18, and increase podocyte-specific marker proteins podocin and NPHS1 to maintain the structural integrity of glomerular slit diaphragms [9].

Complementation experiments have shown that siRNAs targeting TXNIP can reduce the activation of GSDMD; overexpressing TXNIP promotes pyroptosis; AS-IV can reduce this damage; CY-09, a specific inhibitor of NLRP3, has been found to work in synergy with AS-IV, and it has been determined that the main pathway of AS-IV in inhibiting pyroptosis is via TXNIP-NLRP3-GSDMD.

AS-IV activates the Nrf2-ARE/TFAM pathway to enhance the function of mitochondria, decrease the production of ROS, lower the expression level of the upstream TXNIP protein, and thus

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indirectly inhibit the activation of the pyroptosis pathway; therefore, a chain of protective factors that are antioxidant, anti-inflammatory and suppress pyroptosis has been formed.

2.4. The purpose of the HIF-1α/HMOX1 pathway is to limit iron death in the renal tubular epithelium

Iron death is involved in the occurrence and development of diabetic nephropathy. Most scholars agree that there is iron deposition in the renal tubular epithelial cells of DKD patients. The level of transferrin and iron in renal tubular epithelial cells of DKD patients is higher than that in healthy people [10]. Rosiglitazone is a blocker of ACSL4, which is an indicator of iron death; thus, based on research, blocking iron death in renal tubular cells has attenuated diabetic nephropathy. The experiment showed that iron death is a cause of diabetic nephropathy [11]. Liu and others have found that iron death and hypoxia-inducible factor-1 (HIF)-δ signaling pathways are enriched in the treatment of diabetic nephropathy with AS-IV. According to the results of validation, AS-IV can inhibit the activity of the HIF-1α/differential protein heme oxygenase (HMOX)1 pathway in renal tubular epithelial cells of diabetic nephropathy to reduce iron death, increase the expression of glutathione peroxidase 4 and ferritin heavy chain 1, and decrease the expression of acyl CoA synthetase long chain family member 4 and transferrin receptor 1. Based on the above results, it was found that AS-IV can inhibit iron death in renal tubular epithelial cells by reducing the HIF-1α/HMOX1 signaling pathway and mitigating the pathological process of diabetic nephropathy [12].

2.5. Anti-fibrotic effect of AS-IV on renal interstitial fibrosis

Tubulointerstitial fibrosis is the main pathological change in the progression of DKD to end-stage renal disease, and TGF-β/Smad is the core pathway of fibrosis. Research has shown that AS-IV can lower the phosphorylation level of TGF-β1/Smad2/3 in kidney tissue, increase the inhibitory protein Smad7, reduce the deposition of type I and type III collagen, and curb the growth of fibroblasts and accumulation of the extracellular matrix; at the same time, it can reduce oxidative stress and control chronic inflammation indirectly to interfere with the process of fibrosis and provide another pathway for the main pathological mechanism of DKD mentioned above.

AS-IV has a large number of targets and is a cascade regulator of the renal protective effect. High glucose promotes the generation of reactive oxygen species (ROS) and oxidative stress; thus, it can increase the expression of TXNIP and activate the NLRP3 inflammasome to induce GSDMD-mediated pyroptosis. At the same time, metabolic disorders of ROS are also related to changes in the iron homeostasis of kidney tubular cells and promote ferroptosis. All of the above pathways are working together to advance the development of irreversible renal fibrosis. AS-IV can break all links in the pathological chain of DKD lesions by decreasing antioxidant function at the beginning, controlling inflammation in the middle stage, suppressing pyroptosis and ferroptosis further down the line, and thus reducing long-term fibrotic remodelling.

3. Clinical therapeutic observations of astragalus-derived preparations

Astragalus Granule is a form of Chinese medicinal granules. Traditional Chinese medicine believes that Astragalus has the function of Invigorating Qi and Yang, promoting water and swelling, strengthening the surface and stopping sweating, generating fluids and nourishing blood. Clinical trials have shown that astragalus granules can enhance the immune function of the body and protect the kidneys. Cao divided the patients into two groups: the control group and the observation group.

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The control group received only the standard treatment for DKD and did not have a personalised hypoglycaemic plan. For the three months of treatment, Valsartan capsules were given to the treatment group and Astragalus granules were administered to the control group. Based on the evaluation of quantitative indicators such as treatment effect, blood glucose index, renal function index and inflammatory factor level, it was found that the observation group showed improvement in all these indicators compared with the control group, and the difference was statistically significant ($P < 0.05$). It has been shown that Astragalus granule is beneficial in the treatment of diabetic nephropathy. Traditional Chinese medicine believes that diabetes is a type of "diabetes". Patients with these diseases often have syndromes such as Qi and Yin deficiency, deficiency of body fluids, deficiency of kidney Qi, spleen dysfunction, etc. The therapeutic effect of Astragalus Granule for DKD is closely related to the ability of Astragalus to nourish qi and strengthen the kidneys; it can promote the clearing of heat and dampness, regulate water metabolism and reduce edema, strengthen the skin's surface and stop sweating. In short, Astragalus granule has good therapeutic effects for DKD, can lower blood sugar levels, improve indicators of kidney function, and reduce the amount of inflammatory factors [13].

4. Comprehensive analysis of the mechanism of AS-IV multi-target renal protection

The four main injury routes and their anti-fibrotic mechanisms will be introduced in this paper. It can be seen that AS-IV is different from Western medicine's single-target inhibitors and has the synergistic advantage of multiple pathways in the natural active ingredients of traditional Chinese medicine. AS-IV can reduce ROS and mitochondrial damage in the initial stage, inhibit the NLRP3 inflammatory pathway, and also suppress pyroptosis and iron death, which are both kinds of programmed cell death. Long-term treatment can delay the onset of kidney fibrosis and control all stages of DKD. There are upstream and downstream connections in many pathways. Oxidative stress is the beginning of all damage pathways. Inflammation, iron death and pyroptosis are in a cycle. AS-IV is part of all links in the injury cascade network.

4.1. Current academic disputes in the field

A low level of HIF-1α can reduce damage to the kidney under hypoxia, but if HIF-1α/HMOX1 is over-activated for an extended period, it will lead to iron death. The dose of AS-IV to inhibit HIF-1α is in a dose-dependent manner, and the optimal dose has not been determined yet. AS-IV is a weak antioxidant, and this is its main function. Whether there is cytotoxicity at high concentrations is not consistent with the different dose ranges of various model organisms. It is unknown whether pyroptosis of podocytes or iron death of renal tubules is the main reason for the development of DKD, as shown by different research models.

4.2. General limitations of the present study

Most of the basic research models are high-glucose cell and db/db mouse models; they do not have a compound DKD model of type 2 diabetes mellitus combined with hyperlipidemia and hypertension, and there is a gap in the pathological characteristics of real clinical patients. Research on the mechanism is scattered, and although some single-path verification has been achieved in the current studies, there has been no systematic investigation of multi-channel cross-interaction or the whole upstream and downstream regulatory network. The research foundation of combined traditional Chinese and Western medicine is weak. Few studies have identified the molecular targets of AS-IV

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and the mechanism by which it can tonify Qi and nourish the kidneys in Traditional Chinese Medicine. The extent of the combination of traditional Chinese and Western medicine theory is too small.

5. Conclusion

The cause of DKD is not simple. Oxidative stress, chronic inflammation, pyroptosis, iron death and renal fibrosis are all related to the loss of kidney function over time. There are no specific drugs to inhibit the progression of the disease that have been found yet. AS-IV is an active monomer of Astragalus membranaceus that can regulate all kinds of injury signals in different areas to protect the kidneys from damage caused by high blood sugar. It is a natural kidney-protective active ingredient that has good development potential. At this time, only the research results from in vitro cell experiments and animal models have been obtained. Only a small number of clinical observation data have been obtained for Astragalus compounds. Many studies have yet to be conducted on the actual effect of AS-IV monomer, long-term drug safety, optimisation of the preparation process and so on. Further research can be carried out in the three directions above. First, an animal model with all sorts of pathological features of DKD was built to study the interactive regulatory network of AS-IV in different pathways. Develop Kidney-Targeted, High-Bioavailability AS-IV New Drugs. Thirdly, a suitable dose for the general public that is safe and will check for any long-term side effects of the drug will be conducted at many centers in a large-scale randomised controlled trial. Based on the research idea of integrated traditional Chinese and Western medicine, the molecular biological connotation corresponding to the effect of AS-IV tonifying qi and kidney can be continuously excavated; thus, it may promote the research and development process of traditional Chinese medicine monomers and provide new candidate drugs for the precise treatment of diabetic nephropathy.

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