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# Progress on the Mechanism of Action of Cornus Officinalis and Its Active Ingredients in the Treatment of Diabetic Nephropathy

**Wenyu Fan, Lianhua Li***

Heilongjiang Academy of Chinese Medicine Sciences, Harbin 150036, Heilongjiang, China
*Correspondence Author*

**Abstract:** ***Diabetic nephropathy is a chronic kidney disease caused by diabetes mellitus, which is an important cause of end-stage renal failure and even death in diabetic patients. At present, the main treatment of this disease is basic treatment such as regulating blood glucose, controlling blood pressure, lowering blood lipids, and adjusting the lifestyle, and there is a lack of effective means of prevention and treatment. The Chinese medicine Cornus officinalis has been widely used in the treatment of diabetic nephropathy. The mechanisms involved in the treatment of diabetic nephropathy with Cornus officinalis and its active ingredients include relieving renal vasculopathy, improving renal fibrosis, improving renal filtration function, regulating renal glucose and lipid metabolism, and inhibiting inflammatory response. In this paper, we present a brief review on the mechanism of Cornus officinalis and its active ingredients in the treatment of diabetic nephropathy in recent years, with a view to providing new ideas for clinical and experimental research.***

**Keywords:** Diabetic nephropathy, Cornus, Active ingredients, Mechanism of action**.**

## 1. Introduction

Diabetic nephropathy (DN) is a severe microvascular damage. In the early clinical stage, it manifests as mild proteinuria. As the disease progresses, it may gradually deteriorate to end-stage renal disease [1]. However, even with strict regulation of blood glucose, blood pressure, and blood lipid levels as the current standard treatment methods, the disease continues to progress. Once it develops to the stage of renal function decline, it is usually difficult to recover. Cornus officinalis, belonging to the Cornaceae family, has the functions of tonifying the liver and kidneys, astringing, and securing. It is widely used in the clinical treatment of diabetic nephropathy and has exact clinical efficacy. Cornus officinalis is rich in various active ingredients such as iridoids, polysaccharides, tannins, etc., and has good efficacy in preventing and treating many diseases. Pharmacological studies have suggested that the iridoids and polysaccharides in Cornus officinalis can effectively reduce blood glucose and have antioxidant effects [2,3]. Moreover, the iridoids in it can also exert immunosuppressive and anti-inflammatory functions [4,5]. In recent years, the impact of active ingredients in Cornus officinalis on diabetic nephropathy has received increasing attention. This article intends to provide an in-depth review of its mechanisms and offer new insights into the research on Cornus officinalis against diabetic nephropathy.

## 2. The Therapeutic Mechanism of Active Ingredients in Cornus Officinalis on DN

### 2.1 Alleviating Renal Vascular Lesions

The advanced glycosylation end products (AGEs)-receptor of AGEs (RAGE) signaling pathway plays a critical role in the occurrence and progression of renal function impairment in diabetic patients. Long-term clinical studies have observed that the concentration of AGEs in diabetic patients is significantly higher than that in the control group. Meanwhile, inhibiting this signaling pathway and reducing the expression of AGEs in the human body can effectively delay kidney damage in diabetic patients. Vascular endothelial growth factor (VEGF), also known as vascular permeability factor, is a family that mainly includes VEGF-A, VEGF-B, etc. It can promote the formation of new blood vessels, as well as the degeneration of extracellular matrix, migration, and proliferation of vascular endothelial cells. VEGF is involved in the pathogenesis and progression of many angiogenesis-dependent diseases, including diabetic kidney disease. The AGEs-RAGE signaling pathway stimulates the production of VEGF. RAGE is a member of the immunoglobulin superfamily and is a multi-ligand pattern recognition receptor. Related studies have found that this receptor is expressed in various cells in kidney tissues, such as vascular endothelial cells and podocytes [6,7]. The main components of Cornus officinalis include volatile components, glycosides, tannins, etc. Currently, the iridoid glycosides involved in research are one of them. Loganin and morroniside in this category can significantly inhibit the proliferation of renal cortical endothelial cells in DN model rats and protect the integrity of renal vascular endothelium. Studies have found that iridoid glycosides from Cornus officinalis can inhibit the expression of RAGE in human umbilical vein endothelial cells (HUVECs) induced by AGEs. The results indicate that these substances can improve the function of vascular endothelial cells, and the mechanism may be by blocking the RAGE signaling pathway and inhibiting the expression of the NF-κB signaling pathway, thereby delaying the deterioration of renal function in patients with diabetic nephropathy [8]. Guo et al. found that the total iridoid glycosides extracted from Cornus officinalis can down-regulate the levels of various inflammatory cytokines such as IL-6, interleukin-10 (IL-10), tumor necrosis factor-α (TNF-α), and monocyte chemoattractant protein-1 (MCP-1) in rat glomerular mesangial cells, inhibit the recruitment of macrophages and inflammatory status induced by advanced glycosylation end products (AGEs), reduce mesangial injury, and have a good interventional effect on DKD [9]. Huang et al. found that after treatment with Cornus officinalis granules, the 24-hour urine protein, serum creatinine, and urea nitrogen

levels in DKD rats were significantly reduced. The mechanism may be related to the inhibition of the activation of the TGF-β1/Smad signaling pathway in renal tissues, thereby reducing extracellular matrix levels and improving glomerular sclerosis [10].

**2.2 Improving Renal Structural Fibrosis**

The pathogenesis of diabetic nephropathy (DN) is very complex. The deposition of a large number of glycosylation end products in the glomerulus is an important pathological basis, and inflammatory factors and tissue fibrosis are also important causes of its onset. Controlling these factors can effectively delay the progression of the disease [11]. Hyperglycemia activates multiple metabolic pathways, such as the polyol pathway, protein kinase C (PKC) pathway, and advanced glycosylation end product (AGE)-related pathways, all of which lead to the accumulation of reactive oxygen species (ROS) [12]. With insufficient intracellular NADPH content, this process can lead to certain inflammatory responses. When reactive oxygen species accumulate in large amounts in the body, structural changes such as fibrosis of the glomerulus and renal tubular interstitium will also occur [13]. The clinical features of diabetic nephropathy (DN) mainly include clinical proteinuria, hypertension, and a gradual decline in renal filtration function. Its pathological changes include: massive deposition of extracellular matrix in the mesangium, thickening of the basement membrane, proliferative changes, renal tubular atrophy, ultimately leading to renal interstitial fibrosis and glomerular sclerosis [14]. In addition, the increased expression of Wnt/β-catenin in DN is a key factor in the occurrence and development of DN fibrosis [15]. Abnormal activation of the Wnt/beta-catenin signaling pathway can induce apoptosis of renal tubular epithelial cells, leading to irreversible damage to renal tissue [16]. Studies have shown that in a rat model of diabetic nephropathy fed with high sugar and high fat, the Wnt/β-catenin signaling pathway was activated, leading to renal functional impairment as detected [17]. The Wnt/β-catenin signaling pathway plays an important regulatory role in the growth, development, and life activities of organisms. Studies have reported that the abnormal activation of the Wnt/β-catenin pathway is closely related to renal fibrosis, which aligns with the "meridian-collateral theory" and "ying-wei theory" in traditional Chinese medicine. This provides a new perspective for studying the mechanisms of microvascular disease and clinical prevention and treatment research [18].

In addition, Chen et al. found that Cornus officinalis granules can inhibit the expression of Wnt4/β-catenin, YKL-40, TGF-β1, and Col-IV in diabetic rat models, thereby alleviating renal fibrosis [19]. During the occurrence and development of diabetic kidney disease, the renal pathological manifestations include the proliferation of glomerular mesangial cells, thickening of the glomerular basement membrane, and deposition of extracellular matrix, which are important links that may ultimately lead to renal tubular interstitial fibrosis (TIF) [20,21]. Meanwhile, TIF is also the inevitable path for DKD and various chronic kidney diseases to progress to end-stage renal disease. Li et al. have demonstrated that in the STZ diabetic rat model, Cornus officinalis can reduce the levels of BMP-7/Smad3/Smad5/Smad7/TGF-β, as well as MCP-1, NF-κb, and phosphorylated Akt in the kidney cells of STZ diabetic rats, reversing DN renal injury and fibrosis. The mechanism by which Cornus officinalis alleviates renal injury and interstitial fibrosis may be related to the inhibition of the BMP-7/Smad3/Smad5/Smad7/TGF-β signaling pathway and the expression of its downstream proteins [22]. Loganin is one of the main characteristic components of Cornus officinalis. Preliminary studies have shown that it reduces blood glucose, serum and renal cortical AGEs, and urea nitrogen levels [23]. In addition, loganin can effectively inhibit the expression of fibronectin (FN) and IL-6 in glomerular mesangial cells stimulated by high glucose, and reduce the expression of MCP-1 and VCAM-1 in human umbilical vein endothelial cells stimulated by AGEs [24,25]. Loganin has significant pharmacological effects in the treatment of kidney diseases, especially in improving renal lesions and fibrosis. Studies have shown that in DN mouse models, mouse glomerular mesangial cells, mouse macrophages, and other in vivo and in vitro experiments, the expression of ED-1 in the renal cortex was significantly reduced in the loganin control group. ED-1 is a macrophage marker, indicating that the infiltration of macrophages in the kidney was reduced, which helps to alleviate renal inflammatory responses and injury. Loganin also inhibits inflammatory responses and immune responses by increasing the expression of the anti-inflammatory factor IL-10. Furthermore, it reduces the expression of the pro-inflammatory factors IL-12 and TNF-α, two important inflammatory mediators, to alleviate inflammatory responses [26]. Xu et al. discovered the significant role of Cornus officinalis iridoid glycosides in the treatment of diabetic nephropathy (DN). Through animal experimental studies, researchers found that this compound not only effectively reduces the level of urinary microalbumin in DN rats and significantly alleviates pathological changes in the kidneys of rats, but also repairs the activity of Na+, K+-ATP enzymes in the kidneys. This discovery indicates that Cornus officinalis iridoid glycosides play a positive role in preventing and treating structural and functional changes in the kidneys caused by DN by inhibiting the polyol bypass pathway [27,28]. An animal experimental study found that in a DN mouse model where male mice were fed a high-fat and high-sugar diet for 2 weeks, under electron microscopy, the Cornus officinalis neosaponin group showed reduced collagen deposition in the renal cortex, fewer fiber-positive stained cells in the renal cortex, lower levels of interstitial fibrosis, and reduced pathological damage compared to the model group. At the same time, Cornus officinalis neosaponin also significantly reduced the expression levels of RAGE protein, COL-IV, and iNOS protein in the renal cortex of model mice [29].

**2.3 Improve Renal Filtration Function**

Renal podocytes are the largest cells in the glomerulus, consisting of a cell body, primary processes, and foot processes, and are attached to the outer side of the basement membrane. This structure is involved in the formation of the renal blood filtration barrier [30]. During the progression of DN, hyperperfusion and hyperfiltration of the glomerulus can lead to podocyte injury. Podocyte injury can also be caused by other mechanisms, such as immune complex-mediated injury and abnormal glomerular cell function. Desmin protein can

serve as a marker protein reflecting the degree of podocyte injury [31]. In an in vitro experiment, compared with the model group, the expression levels of RAGE and Desmin proteins in each loganin dose group were significantly downregulated, the apoptosis rate of podocytes induced by AGEs was significantly reduced, and the AGEs-induced renal podocyte injury was alleviated compared with the model group [32]. In addition, morroniside can promote the expression of LC3-II, inhibit the expression of p62 and NOX4, and reduce the ratio of apoptosis-related proteins Bax and Bax/Bcl-2. The experimental results suggest that morroniside has a protective effect on podocyte apoptosis. Inhibiting the overexpression of NOX4 induced by H2O2 and restoring blocked autophagic flux may be effective ways to prevent podocyte apoptosis [33]. Loganin, an iridoid glycoside component of Cornus officinalis, can protect renal function from damage, prevent extracellular matrix proliferation and glycogen deposition, and reduce podocyte loss detected by histological and immunohistochemical assays by inhibiting the AGEs/RAGE signaling pathway, thereby inhibiting podocyte apoptosis [34].

**2.4 Regulate Renal Glycolipid Metabolism**

Studies have shown that a long-term hyperglycemic environment increases the demand for insulin, keeping pancreatic beta cells in a continuously activated state, which exacerbates hyperglycemia. In turn, the toxicity of high glucose further impairs the function of pancreatic beta cells, leading to further increases in blood glucose levels. This phenomenon can be referred to as glucose toxicity [35]. At the same time, adipokines and ectopic lipid accumulation in the kidneys stimulate insulin resistance and oxidative stress in podocytes in response to the pressure of renal hyperfiltration. Changes in fatty acid and cholesterol metabolism are considered key pathways leading to renal lipid accumulation, inflammation, oxidative stress, and fibrosis, causing severe damage to renal function [36]. Studies have shown that Cornus officinalis can effectively improve insulin resistance, reduce blood glucose levels, and alleviate symptoms of diabetic nephropathy. Its active ingredients have a reliable therapeutic effect on diabetes [37,38]. Lv et al. [39] found that morroniside can significantly reduce blood glucose levels in STZ-induced DN mice, effectively improve insulin resistance, alleviate symptoms of diabetic nephropathy, significantly reduce urinary protein, and improve glomerular filtration function. Additionally, it can inhibit the proliferation and degeneration of endothelial cells, mesangial cells, and podocytes. The study suggests that its mechanism may be related to reducing AGEs levels in serum and kidneys, and downregulating the expression of renal cortical RAGE mRNA and protein. In addition, Cornus officinalis can increase the body's sensitivity to insulin, and its active ingredients may interact with PIK3R1 (phosphatidylinositol-3-kinase regulatory subunit 1), reducing endoplasmic reticulum stress and insulin resistance [40]. An in vitro study by Gao et al. [41] suggested that in a mouse renal tubular epithelial cell (mRTEC) model stimulated by sodium palmitate (PA) or high glucose (HG), the Cornus officinalis extract morroniside helps reduce cholesterol accumulation in mouse renal tubular epithelial cells, alleviating renal lipotoxicity damage in diabetic nephropathy (DKD). Experiments showed that morroniside may promote cholesterol efflux in mRTECs through the peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC-1α)/liver X receptor (LXR) pathway to regulate lipid metabolism in the kidneys. Jiang et al. [42] showed that in an STZ-induced DN rat model, loganin effectively reduced 24-hour urinary albumin and the expression levels of connective tissue growth factor (CTGF) in the proximal renal tubules of DN rats. Histological results suggested that pathological changes such as glomerular basement membrane thickening were also improved. In vitro experiments showed that loganin reduced the expression of CTGF in a high glucose (HG)-stimulated human renal proximal tubular epithelial cell (HK-2) model, and its mechanism may involve downregulating the extracellular signal-regulated kinase (ERK) signaling pathway. Jing et al. [43] observed that in normal mice, the terpene components of Cornus officinalis did not have a significant effect on blood glucose levels; however, these components showed a significant ability to lower blood glucose in diabetic animal models, including ALX-induced diabetic mice and STZ-induced diabetic rats.

**2.5 Inhibition of Inflammatory Response**

Inflammatory response plays a critical role in various stages of DN progression. This response involves numerous regulatory molecules and signaling pathways, including the NF-κB pathway and several mechanisms involving nuclear transcription factor E2-related factor 2. NLRs are a class of protein receptors containing nucleotide-binding domains (NBD) and leucine-rich repeats (LRR), which are closely related to immune and inflammatory responses. Their signals can stimulate the formation of inflammatory factors such as interleukin (IL)-1 and IL-18 [44]. Inflammatory factors such as tumor necrosis factor-α (TNF-α) and IL-6 can activate the NF-κB pathway, and activated NF-κB can in turn induce the production of pro-inflammatory cytokines [45]. Recent studies have shown that Nrf2 can effectively inhibit inflammatory responses, and when the Nrf2 gene is inhibited in experimental groups, macrophage-mediated inflammatory responses are significantly exacerbated [46]. In an in vitro cell model where advanced glycation end products (AGEs) induce endoplasmic reticulum stress in glomerular mesangial cells (GMCs), researchers found that experimental results suggested that loganin at various doses significantly reduced the protein expression of RAGE, had a significant inhibitory effect on cell proliferation caused by AGEs, inhibited inflammatory responses, improved subcellular organelle damage caused by AGEs, and alleviated endoplasmic reticulum pathology. These effects were closely related to the downregulation of RAGE protein expression and the inhibition of the IRE1 signaling pathway [47]. In addition, the study also observed that loganin could enhance the antioxidant capacity of leukocytes in diabetic rats, reduce the production of ROS, optimize the antioxidant level of leukocytes, and increase the enzymatic activities of GR, GPx, and CAT, thereby increasing the concentration of GSH in leukocytes. These findings suggest the potential of Cornus officinalis in combating DN may be related to its ability to improve oxidative stress responses [48]. Meanwhile, in a macrophage model stimulated by lipopolysaccharide (LPS), loganin significantly reduced the phagocytic activity and release of nitric oxide (NO) and prostaglandin E2, eliminated the generation of reactive oxygen species (ROS), and

inhibited the production of pro-inflammatory cytokines. The upregulation of the Nrf2/HO-1 signaling pathway involved was closely related to loganin, suggesting that loganin may be a potential functional agent for preventing inflammation and oxidative damage [49].

## 3. Summary

The mechanisms of Cornus officinalis (dogwood fruit) in preventing and treating diabetic nephropathy (DN) have been explored by many researchers, but current basic research remains relatively limited. The pathogenesis of DN is highly complex and also involves genetic factors, cellular autophagy, etc., necessitating deeper exploration of its potential mechanisms of action. To comprehensively understand its therapeutic mechanisms and optimize its clinical applications, future research needs to strengthen the study of the synergistic effects of different signaling pathways and delve into the regulatory roles among these pathways. Cornus officinalis contains diverse effective components, with current research mainly focusing on loganin, morroniside, and polysaccharides. Further research is still needed to provide more evidence for new candidate drugs in clinical DN treatment. Therefore, systematic research on the effective components of Cornus officinalis and their mechanisms of action provides important scientific foundations for both theoretical development and clinical treatment of diabetic nephropathy.

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