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REVIEW

# Anthraquinones from *Rheum officinale* Ameliorate Renal Fibrosis in Acute Kidney Injury and Chronic Kidney Disease

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**Abstract:** Renal diseases including acute kidney injury (AKI) and chronic kidney disease (CKD) has become a significant public health concern due to its high morbidity and mortality. *Rheum officinale* Baill (Polygonaceae) exhibits diuretic, renoprotective, lipid-lowering, anti-inflammatory, and antifibrotic properties. Accumulating evidence has highlighted the anthraquinones in *R. officinale* as key components contributing to its renoprotective effects. The available information on *R. officinale* was searched by several electronic database such as PubMed, Web of Science, Springer, ScienceDirect, etc. This review summarizes the anthraquinones and their renoprotective effects in *R. officinale*, evaluating its clinical potential for managing renal disease including AKI and CKD. Studies demonstrate that *R. officinale* contains bioactive components such as anthraquinones, stilbenes, phenylbutazones, and tannins. This review discusses the renoprotective effects of *R. officinale*, including improvements in renal function, reduction of podocyte damage, and inhibition of renal fibrosis. These effects are mediated through the regulation of pro-inflammatory (IκB/NF-κB and Keap1/Nrf2), pro-fibrotic (TGF-β1/Smad and Wnt/β-catenin), AMP-activated protein kinase and phosphoinositide 3-kinase signaling pathways in AKI and CKD. Additional mechanisms include modulation of anti-ageing Klotho expression, autophagy, and apoptosis. These findings expand the understanding of the therapeutic effects on AKI and CKD of *R. officinale* and provide valuable information on its clinical application in traditional Chinese medicine. This review presents a concept-driven therapeutic strategy for renal disease management.
**Keywords:** acute kidney injury, chronic kidney disease, *Rheum officinale*, anthraquinones, oxidative stress and inflammation, TGF-β/Smad

## Introduction

Acute kidney injury (AKI) and chronic kidney disease (CKD) are important clinical problems and global health burdens with rising prevalence.[1,2] Substantial studies have demonstrated that increasing incidence of AKI and kidney injury required dialysis and kidney transplantation worldwide.[3,4] This increase has coincided with increasing incidence of end-stage renal disease (ESRD), which has exceeded that expected based upon morbidity and mortality of CKD.[5,6] AKI is a clinical symptom of sudden loss of excretory kidney function that leads to long-term kidney damage.[7,8] AKI is characterized by a rapid decline in renal function, leading to the accumulation of uremic toxins, such as creatinine and urea, and a reduction in urine output.[9] AKI can be caused by various initial injuries, including ischemia-reperfusion injury (IRI), cardiovascular surgery, radiographic contrast agents, and sepsis.[10–12] CKD has become an increasingly significant public health problem due to its high morbidity and mortality, with a prevalence of 8–16% worldwide and more than 850 million people.[13–15] Considerable evidence suggests that AKI is closely associated with the progression of CKD and, eventually, ESRD.[16–19] Many patients who survive an episode of AKI subsequently develop CKD, which can

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progress to ESRD.[20–23] The number of patients requiring dialysis therapy and kidney transplantation continues to increase worldwide owing to the lack of effective treatments for CKD.[24] Furthermore, no curative treatments for AKI and CKD have been established.[25,26]

In clinical practice, traditional Chinese medicine (TCM) has long been used as an important therapy for the prevention and treatment of renal disease.[27–31] TCM demonstrates unique advantages due to its multi-component, multi-pathway, and multi-target characteristics.[32,33] *Rheum officinale* Baill. (Polygonaceae), known for its heat-clearing, purging, blood-cooling, detoxifying, and hemostatic properties, is a widely used herb for the treatment of renal disease in Asia, offering a range of pharmacological effects that may delay disease progression.[34–37] *R. officinale* contains various compounds, including anthraquinones, anthracenes, tannins, and stilbenes. Anthraquinones, such as rhein, emodin, chrysophanol, physcion, and aloe-emodin, are among the most important active components of *R. officinale* and play a critical role in improving renal function.[38–41] A growing body of research has highlighted the bioactive compounds of *R. officinale* in mitigating renal fibrosis by inhibiting the Wnt/β-catenin, inhibitor of kappa B (IκB)/nuclear factor kappa B (NF-κB), and Wnt/β-catenin signaling pathways, as well as by enhancing the kelch-like ECH-associated protein 1 (Keap1)/nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway.[42,43] This review aims to summarize the therapeutic effects of the anthraquinones from *R. officinale* for AKI and CKD, and to further elucidate their underlying molecular mechanisms, including antioxidative, anti-inflammatory, anti-fibrotic, and anti-apoptotic effects.

## Renoprotective Components in *R. officinale*

*R. officinale*, a group of plants belonging to the genus *Rheum* L. in the family Polygonaceae, is one of the oldest and best-known Chinese herbal medicines, with a long history of medicinal use in China and other Asian countries, dating back to the "Shen Nong Ben Cao Jing".[44] To date, many compounds have been identified from *R. officinale*[45,46] (Figure 1, Tables 1 and 2), which can be mainly classified into seven categories: anthraquinones, anthracenes, stilbenes, tannins, phenylbutanoids, chromones, and other components such as organic acids and volatile constituents[47,48] (Figure 1, Tables 1 and 2). The main anthraquinone components of *R. officinale* and their wide range of pharmacological activities are described as follows.

### Anthraquinones

Anthraquinones are the main components of *R. officinale*, comprising 1.5–4.0% of its total content.[49] Anthraquinones, including rhein, emodin, chrysophanol, physcion, and aloe-emodin, are the primary characteristic and pharmacodynamic components of *R. officinale*.[50] The anthraquinones in medicinal plants of the genus *Rheum* are mainly emodin-type anthraquinones, with hydroxyl groups distributed on the benzene ring on both sides. Over 30 free and combined anthraquinones have been isolated and identified from *R. officinale*. Free anthraquinones include rhein, emodin, chrysophanol, physcion, aloe-emodin, isoemodin, chrysaron, isoemodin, and urachic acid D[46] (Figure 1, Tables 1 and 2).

#### Rhein

Rhein (1,8-dihydroxy-3-carboxylic anthraquinone), an anthraquinone monomer, exhibits a wide range of pharmacological activities, including anti-inflammatory,[51] antioxidant,[52] antitumor,[53] antifibrotic,[54] lipid-regulating,[55] glucose-lowering,[56] antiviral, and antibacterial effects.[57] Previous studies have demonstrated that rhein protects against renal fibrosis in diabetic kidney disease (DKD). Its beneficial effects on DKD are mediated through the amelioration of transforming growth factor beta 1 (TGF-β1) levels, oxidative stress reduction, and renal fibrosis attenuation.[58]

#### Emodin

Emodin (1,3,8-trihydroxy-6-methylanthraquinone), a key monomer derived from *R. officinale*, exhibits a broad spectrum of pharmacological effects, including antitumor,[43,44] antimicrobial,[45] antioxidant,[46] anti-inflammatory[47] and antifibrotic[48,49] activities. Additionally, emodin has been shown to reduce hypertension, lower blood lipid levels, enhance microcirculation, and protect against liver and kidney injury. As a validated renoprotective agent in DKD rat models, emodin was found to reduce proteinuria and alleviate renal fibrosis, functioning as a natural regulator without influencing blood glucose levels.[59] Furthermore, emodin attenuates renal IRI through its anti-inflammatory effects in rats and mice, which are critical for mitigating AKI.

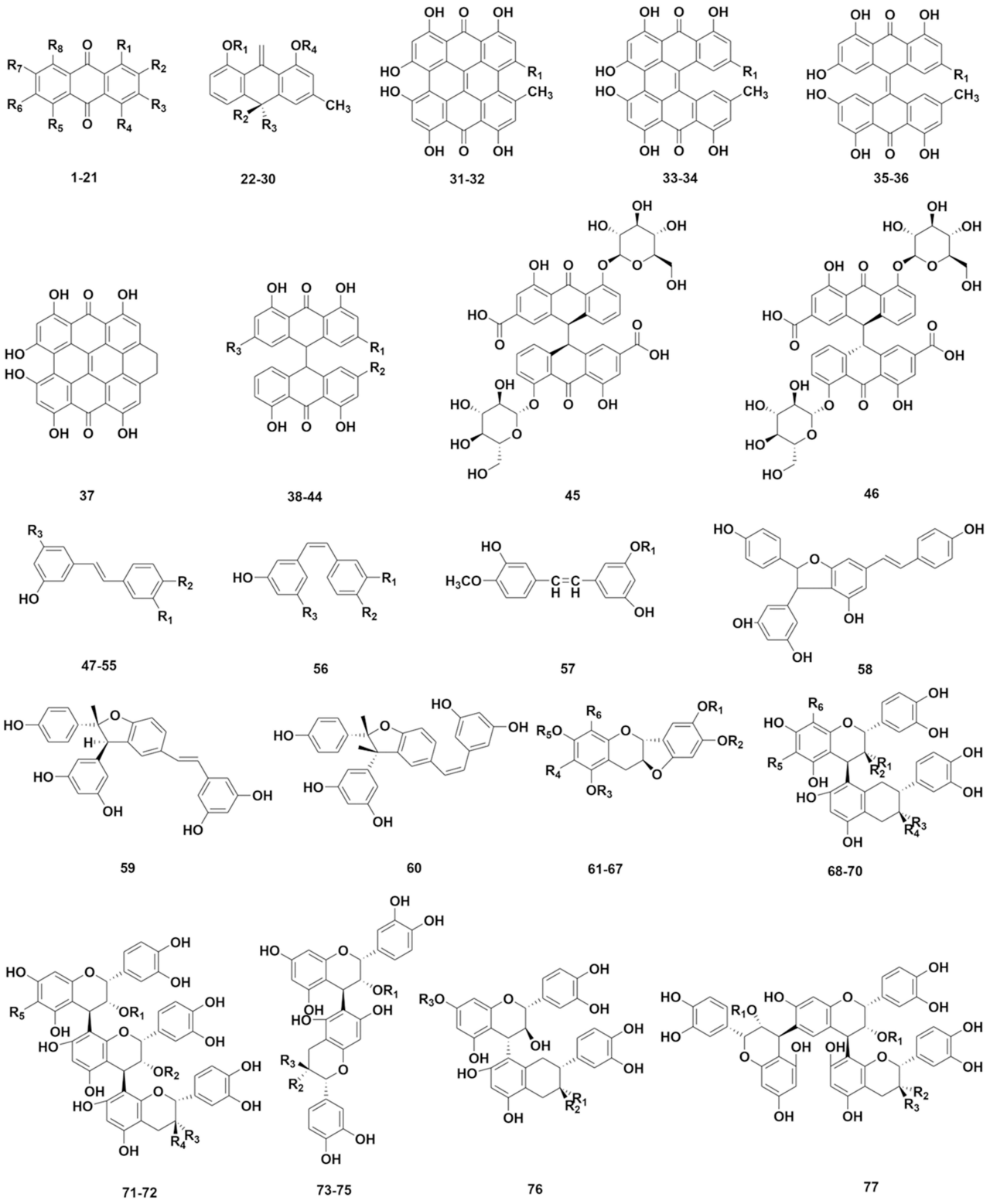


**Figure 1** The structures of chemical components of *R. officinale*. Compounds 1–21 indicate anthraquinones, Compounds 22–46 indicate anthranones, Compounds 47–60 indicate stilbenoid, and Compounds 61–77 indicate tannin in *R. officinale*.


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**Table 1** Chemical Structures of Anthraquinones (1–21) and Anthranones (22–46) in *R. officinale*

| No. | Compound | Substituent |
|---|---|---|
| 1 | Rhein | $R_1$=$R_8$=OH, $R_3$=COOH, $R_2$=$R_4$=$R_5$=$R_6$=$R_7$=H |
| 2 | Emodin | $R_1$=$R_3$=$R_8$=OH, $R_6$=$CH_3$, $R_2$=$R_4$=$R_5$=$R_7$=H |
| 3 | Chrysophanol | $R_1$=$R_8$=OH, $R_3$=$CH_3$, $R_2$=$R_4$=$R_5$=$R_6$=$R_7$=H |
| 4 | Physcion | $R_1$=$R_8$=OH, $R_6$=$CH_3$, $R_3$=$OCH_3$, $R_2$=$R_4$=$R_5$=$R_7$=H |
| 5 | Aloe-emodin | $R_1$=$R_8$=OH, $R_3$=$CH_2OH$, $R_2$=$R_4$=$R_5$=$R_6$=$R_7$=H |
| 6 | Citreorosein | $R_1$=$R_3$=$R_8$=OH, $R_6$=$CH_2OH$, $R_2$=$R_4$=$R_5$=$R_7$=H |
| 7 | Emodin 1-O-β-D-glucopyranoside | $R_1$=O-Glc, $R_3$=$R_8$=OH, $R_6$=$CH_3$, $R_2$=$R_4$=$R_5$=$R_7$=H |
| 8 | Emodin 8-O-β-D-glucopyranoside | $R_1$=$R_3$=OH, $R_6$=$CH_3$, $R_8$=O-Glc, $R_2$=$R_4$=$R_5$=$R_7$=H |
| 9 | Aloe-emodin 1-O-β-D-glucopyranoside | $R_1$=O-Glc, $R_3$=$CH_2OH$, $R_8$=OH, $R_2$=$R_4$=$R_5$=$R_6$=$R_7$=H |
| 10 | Aloe-emodin 8-O-β-D-glucopyranoside | $R_1$=OH, $R_3$=$CH_2OH$, $R_8$=O-Glc, $R_2$=$R_4$=$R_5$=$R_6$=$R_7$=H |
| 11 | Chrysophanol 1-O-β-D-glucopyranoside | $R_1$=O-Glc, $R_3$=$CH_3$, $R_8$=OH, $R_2$=$R_4$=$R_5$=$R_6$=$R_7$=H |
| 12 | Chrysophanol 8-O-β-D-glucopyranoside | $R_1$=$R_8$=OH, $R_3$=$CH_3$, $R_2$=$R_4$=$R_5$=$R_6$=$R_7$=H |
| 13 | Physcion 8-O-β-D-glucopyranoside | $R_1$=OH, $R_3$=$OCH_3$, $R_6$=$CH_3$, $R_8$=O-Glc, $R_2$=$R_4$=$R_5$=$R_7$=H |
| 14 | Rhein 1-O-β-D-glucopyranoside | $R_8$=OH $R_3$=COOH $R_1$=O-Glc $R_2$=$R_4$=$R_5$=$R_6$=$R_7$=H |
| 15 | Rhein 8-O-β-D-glucopyranoside | $R_1$=OH, $R_3$=COOH, $R_8$=O-Glc, $R_2$=$R_4$=$R_5$=$R_6$=$R_7$=H |
| 16 | Emodin 6-O-β-D-glucopyranoside | $R_1$=$R_8$=OH, $R_3$=$CH_3$, $R_6$=O-Glc, $R_2$=$R_4$=$R_5$=$R_6$=$R_7$=H |
| 17 | Chrysaron | $R_4$ =$R_6$=OH, $R_7$=$OCH_3$, $R_1$=$R_2$=$R_4$=$R_5$=$R_8$=H |
| 18 | Laccaic acid D | $R_1$=$CH_3$, $R_2$=COOH, $R_5$=$R_8$=H, $R_3$=$R_4$=$R_6$=$R_7$=OH |
| 19 | 6-Methyl-rhein | $R_1$=$R_8$=OH$R_3$=COOH $R_6$=$CH_3$ $R_2$=$R_4$=$R_5$= $R_7$=H |
| 20 | 6-Methyl-aloe-emodin | $R_1$=$R_8$=OH, $R_3$=$CH_2OH$, $R_6$=$CH_3$, $R_2$=$R_4$=$R_5$= $R_7$=H |
| 21 | Chrysophanol-8-Me ether | $R_1$=OH, $R_3$=$R_8$=$CH_3$, $R_2$=$R_4$=$R_5$=$R_6$=$R_7$=H |
| 22 | 10-hydroxycascaroside C | $R_1$=$R_2$=Glc, $R_3$=OH, $R_4$=H |
| 23 | 10-hydroxycascaroside D | $R_2$=OH, $R_4$=H, $R_1$=$R_3$=Glc |
| 24 | 10R-chrysaloin 1-O-β-D-glucopyranoside | $R_1$=$R_2$=H, $R_3$=$R_4$=Glc |
| 25 | Cascaroside C | $R_1$=$R_2$=Glc, $R_3$=$R_4$=H |
| 26 | Cascaroside D | $R_1$=$R_3$=Glc, $R_2$=$R_4$=H |
| 27 | Rheinoside A | $R_1$=$R_2$=Glc, $R_3$=OH, $R_4$=H |
| 28 | Rheinoside B | $R_1$=$R_3$=Glc, $R_2$=OH, $R_4$=H |
| 29 | Rheinoside C | $R_1$=$R_2$=Glc, $R_3$=$R_4$=H |
| 30 | Rheinoside D | $R_1$=$R_3$=Glc, $R_2$=$R_4$=H |
| 31 | Hypericin | $R_1$=$CH_3$ |
| 32 | Protohypericin | $R_1$=$CH_2OH$ |
| 33 | Pseudohypericin | $R_1$=$CH_3$ |
| 34 | Protopseudohypericin | $R_1$=$CH_2OH$ |
| 35 | Hypericode hydrodianthrone | $R_1$=$CH_3$ |
| 36 | Pseudohypericodehydrodianthrone | $R_1$=$CH_2OH$ |
| 37 | Cyclopseudohypericin | |
| 38 | Palmidin A | $R_1$=$CH_3$, $R_2$=$CH_2OH$, $R_3$=OH |
| 39 | Palmidin B | $R_1$=$CH_3$, $R_2$=$CH_2OH$, $R_3$=H |
| 40 | Palmidin C | $R_1$=$CH_3$, $R_2$=$CH_3$, $R_3$=OH |
| 41 | Rendin A | $R_1$=$CH_3$, $R_2$=COOH, $R_3$=OH |
| 42 | Rendin B | $R_1$=$CH_3$, $R_2$=COOH, $R_3$=H |
| 43 | Rendin C | $R_1$=$CH_3$, $R_2$=COOH, $R_3$=$OCH_3$ |
| 44 | Sennidin C | $R_1$=COOH, $R_2$=$CH_2OH$, $R_3$=H |
| 45 | Sennoside A | |
| 46 | Sennoside B | |

**Abbreviations**: Glc, glucose; O-glc, O-glucose.

**Table 2** Chemical Structures of Stilbenoids (47–60) and Tannins (61–77) in *R. officinale*

| No. | Compound | Substituent |
|---|---|---|
| 47 | Rhapontigenin | $R_1$=$R_3$=OH, $R_2$=$OCH_3$ |
| 48 | Rhapontigenin 3′-O-β-D-glucopyranoside | $R_1$=O-Glc, $R_2$=$OCH_3$, $R_3$=OH |
| 49 | Isohapontigenin | $R_1$=$OCH_3$, $R_2$=$R_3$=OH |
| 50 | Rhaponticin | $R_1$=OH, $R_2$=$OCH_3$, $R_3$=O-Glc |
| 51 | Isorhapontin | $R_1$=$OCH_3$, $R_2$=OH, $R_3$=O-Glc |
| 52 | Deoxyrhapontigenin | $R_1$=OH, $R_2$=$OCH_3$, $R_3$=OH |
| 53 | Piceatannol 3-O-β-D-glucopyranoside | $R_1$=$R_2$=OH, $R_3$=O-Glc |
| 54 | Piceatannol 3′-O-β-D-glucopyranoside | $R_1$=O-Glc, $R_2$=$R_3$=OH |
| 55 | Piceatannol 4′-O-β-D-glucopyranoside | $R_1$=$R_3$=OH, $R_2$=O-Glc |
| 56 | Cis-3,5,3′-Trihydroxyl-4′-methoxystibene | $R_1$=$R_3$=OH, $R_2$=$OCH_3$ |
| 57 | 3,3′,5′-Trihydroxy-4-methoxystibene-3′-β-D-glucopyranoside | $R_1$=Glc |
| 58 | Gnetin C | |
| 59 | Maximol A | |
| 60 | Maximol B | |
| 61 | (+)-Catechin | $R_1$=$R_2$=$R_3$=$R_4$=$R_5$=$R_6$=H |
| 62 | (+)-Catechin5-O-β-D-glucopyranoside | $R_1$=$R_2$=$R_4$=$R_5$=$R_6$=H, $R_3$=Glc |
| 63 | (+)-Catechin 7-O-β-D-glucopyranoside | $R_1$=$R_2$=$R_3$=$R_4$=$R_6$=H, $R_5$=Glc |
| 64 | (+)-Catechin 3′-O-β-D-glucopyranoside | $R_2$=$R_3$=$R_4$=$R_5$=$R_6$=H, $R_1$=Glc |
| 65 | (+)-Catechin 4′-O-β-D-glucopyranoside | $R_1$=$R_3$=$R_4$=$R_5$=$R_6$=H, $R_2$=Glc |
| 66 | (+)-catechin8-C-β-D-glucopyranoside | $R_1$=$R_2$=$R_3$=$R_4$=$R_5$=H, $R_6$=Glc |
| 67 | (+)-Catechin 6-C-β-D-glucopyranoside | $R_1$=$R_2$=$R_3$=$R_5$=$R_6$=H, $R_4$=Glc |
| 68 | Procyanidin B-1 | $R_1$=$R_4$=OH, $R_2$=$R_3$=$R_5$=$R_6$=H |
| 69 | Procyanidin B-1 8-C-β-D-glucopyranoside | $R_1$=$R_4$=OH, $R_2$=$R_3$=$R_5$=H, $R_6$= Glc |
| 70 | Procyanidin B-1 6-C-β-D-glucopyranoside | $R_1$=$R_4$=OH, $R_2$=$R_3$=$R_6$=H, $R_5$=Glc |
| 71 | Procyanidin C-1 3,3”-di-O-gallate | $R_1$=$R_4$=H, $R_2$=G, $R_3$=OG |
| 72 | Procyanidin C-1 3,3,3”-tri-O-gallate | $R_1$=$R_2$=G, $R_3$=OG, $R_4$=H |
| 73 | Procyanidin B-7 | $R_1$=$R_2$=H |
| 74 | Procyanidin B-5 | |
| 75 | Epicatechin-(4β-6)-epicatechin-(4β-8)-epi-catechin | $R_1$=$R_3$=H, $R_2$=OH |
| 76 | Procyanidin B-3 | $R_1$=$R_3$=H, $R_2$=OH |
| 77 | Procyanidin B-3 7-O-β-D-glucopyranoside | $R_1$=H, $R_2$=OH, $R_3$=Glc |

**Abbreviations**: G, gallate; Glc, glucose; O-gallate, OG, O-glc, O-glucose.

## Chrysophanol

Chrysophanol (1,8-dihydroxy-3-methyl-anthraquinone), the most abundant free anthraquinone compound in *R. officinale*,[60] exhibits a wide array of pharmacological effects, including anticancer, antiviral, antidiabetic, anti-inflammatory, antibacterial, hypolipidemic, hepatoprotective, neuroprotective, anti-ulcer, and anti-obesity activities.[61,62] Additionally, chrysophanol has been shown to protect against nervous system disorders by enhancing the activity of antioxidant enzymes and mitigating cellular damage caused by oxygen-free radicals.[63]

## Physcion

Physcion (1,8-dihydroxy-3-methoxy-6-methyl-anthraquinone), also known as parietin, is an anthraquinone derivative isolated and characterized from terrestrial and marine sources. As a primary active component of *R. officinale*, physcion has attracted significant attention for its remarkable pharmacological activities.[64] Notably, physcion exhibits neuroprotective effects by suppressing inflammatory responses following cerebral ischemia and mitigating nerve damage caused by reperfusion.[65] Furthermore, physcion demonstrates antitumor activity against various cancer cell types by inhibiting cell proliferation, inducing apoptosis, and arresting the cell cycle.[58]

### Aloe-Emodin

Aloe-emodin (1,8-dihydroxy-3-[hydroxymethyl]-anthraquinone), an active compound in *R. officinale*, has been widely utilized in TCM for the treatment of various diseases.[59–61] Aloe-emodin has extensive renoprotective effects. In addition, it has received significant attention for its cardiovascular protective, hepatoprotective, antitumor, antibacterial, antifungal, antiviral, anti-inflammatory, immune-regulatory, and laxative properties.[66–68]

## Stilbene

Stilbene is a compound characterized by two benzene rings connected by a vinyl group. Stilbenes are key components of *R. officinale* and exhibit various pharmacological activities, including anticancer, antibacterial, antioxidative, anti-inflammatory, antidiabetic, anti-ageing, neuroprotective, and hepatoprotective effects.[69] Resveratrol (3,5,4-trihydroxystilbene), a naturally occurring polyphenolic phytoprotectant found in many plants and products, is also present in *R. officinale*. Resveratrol has demonstrated numerous beneficial properties, including anticancer,[66] antioxidative,[67] anti-inflammatory[68,69] and neuroprotective[70,71] activities. The stilbenes in *R. officinale* act as effective antioxidants, primarily through the action of resveratrol, which scavenges oxygen radicals.[70] Additionally, resveratrol has been reported to protect against AKI and CKD.[71,72]

## Anthrones and Dianthrones

Anthracenes and dianthrones are characteristic constituents of *R. officinale* and are primarily responsible for its diarrhea-inducing effects.[47] Numerous anthracene derivatives have been isolated from *R. officinale*.[73] Among these, sennosides can be metabolized in vivo into anthraquinones, which exhibit potent laxative properties.

# Molecular Mechanism of Renoprotective Effects of Anthraquinones from *R. officinale* in AKI

AKI can result from various pathogenic factors, including renal hypoperfusion, urethral obstruction, rapidly progressive glomerular disease, acute vasculitis, and acute interstitial nephritis.[7,8,74,75] Based on etiology, AKI can be classified into drug-induced AKI, septic AKI, and IRI-induced AKI.[9,10,76]

Renal IRI, commonly occurring after renal transplantation and surgery, is a leading cause of AKI.[77] Due to the kidney's unique physiological structure and its central role in drug excretion, drug-induced AKI is particularly common, with acute tubular or tubulointerstitial injury being the most frequent cause.[78,79] Septic AKI, associated with infection, represents a syndrome of acute functional impairment and organ damage and is the most prevalent form of AKI among intensive care unit patients.[80] IRI-induced AKI arises from ischemia and hypoxia caused by blood supply interruption, followed by reperfusion, leading to further organ dysfunction.[77]

In recent years, the emergence of coronavirus disease 2019 (COVID-19) has shown AKI as a frequent complication of severe infection associated with high mortality rates.[81,82] Alarmingly, only 30% of AKI patients regain full renal function after discharge.[83] Given the complexity of AKI pathogenesis, multi-component extracts and isolated compounds derived from natural products present a promising alternative therapeutic strategy due to their multi-target mechanisms and established biosafety profiles.[84–86] Modern medical studies have demonstrated that anthraquinones such as emodin and chrysophanol can alleviate kidney injury associated with AKI. This review focuses on the renoprotective effects of anthraquinones derived from *R. officinale* in treating AKI.

## Emodin in Improving AKI

Mitochondria play a key role in various pathophysiological processes by regulating calcium homeostasis, cell signaling pathways, transcriptional regulation, and apoptosis.[87–89] Increasing evidence indicates that mitochondria are central to the progression of AKI, which is pathologically characterized by sublethal and lethal damage to renal tubules, often leading to tubular cell death through regulatory necrosis or apoptosis.[84,85,90] Studies have shown that stimulated mitochondrial biogenesis can reduce necrosis and improve renal function in AKI models.[86,91] Mechanistically, apoptotic cell death in AKI involves both intrinsic and extrinsic pathways, with mitochondria serving as the central hub. During cellular stress, mitochondria become fragmented and exhibit increased membrane permeability, releasing cell-death-inducing factors.[92]

Previous studies have demonstrated that emodin alleviates IRI in the heart, brain, and small intestine of rats and mice through its anti-inflammatory effects.[93] Emodin, a key active compound in *R. officinale*, exhibits antibacterial, anti-inflammatory, antioxidative, immunosuppressive, and antifibrotic properties.[94–96] It has been shown to reduce mitochondria-mediated apoptosis, inhibit excessive production of mitochondrial reactive oxygen species (ROS), and accelerate the recovery of adenosine triphosphate (ATP) both in vivo and in vitro (Table 3). Emodin also prevents mitochondrial fission and restores the balance of mitochondrial dynamics.[97] Specifically, emodin improves and prevents IRI-induced renal injury by regulating mitochondrial homeostasis in renal tubular epithelial cells, restoring the dynamic equilibrium of mitochondrial fusion and fission, and protecting these cells from IRI-induced apoptosis.[98]

A randomized clinical trial revealed that emodin reduces glucose regeneration in renal tubular cells and ATP levels in epithelial mitochondria.[99] Additionally, emodin restores the dynamic balance of mitochondrial fusion and fission by inhibiting calcium/calmodulin-dependent protein kinase II activity and downregulating the phosphorylation of dynamin-associated protein 1 at Ser616, a key regulator of mitochondrial fission. This regulation maintains mitochondrial homeostasis and reduces renal tubular cell death.

Toll-like receptors (TLRs) also significantly recognize exogenous pathogens associated with septic AKI and are involved in numerous cellular processes activated during AKI.[103,104] Experimental findings indicate that emodin inhibits the expression of inflammatory cytokines and TLR2 in lipopolysaccharide (LPS)-stimulated cells. By suppressing the TLR2-mediated NF-κB signaling pathway, emodin reduces the inflammatory response and protects against LPS-induced AKI.[100] Furthermore, emodin inhibits the expression of TLR2 and NF-κB in normal rat kidney epithelial cells exposed to LPS.

## Chrysophanol in Improving AKI

AKI is a major cause of renal IRI or hypoxia-reperfusion (H/R), as demonstrated in both cellular and mouse models.[105,106] Evidence suggests that HK-2 cells are susceptible to renal IRI and are widely used as a cellular model for H/R injury to simulate acute renal IRI.[107] Chrysophanol is effective in treating AKI.

Ferroptosis, an iron- and ROS-dependent lipid peroxidation process, is a distinct form of programmed cell death that differs from apoptosis and necrosis at both morphological and biochemical levels.[108,109] It has received significant attention in AKI and CKD.[110,111] Morphologically, ferroptosis is characterized by mitochondrial contraction, rupture of the mitochondrial membrane, increased membrane density, and reduction or disappearance of mitochondrial cristae.[112,113] Biochemically, ferroptosis is associated with glutathione depletion and reduced glutathione peroxidase 4 (GPX4) activity. GPX4 is a critical enzyme that mitigates lipoxygenase activity and oxidative damage to phospholipids and cardiolipin.[114] Iron imbalance, amino acid dysregulation, and excessive ROS production are closely linked to ferroptosis.[115]

Chrysophanol has been shown to inhibit H/R-induced apoptosis by downregulating the expression of cleaved phosphorylated c-Jun N-terminal kinase, caspase-3, and B-cell lymphoma-2-associated X (Bax) while upregulating

**Table 3** Molecular Mechanism of Renoprotective Effects of Anthraquinones in the Treatment of AKI

| Compounds | Cell/Animal Models | Dosage | Targets | Ref |
|---|---|---|---|---|
| Emodin | IRI-induced mice | 1, 3 and 10 mg/kg/day | Downregulated protein expressions of Bax and cytochrome C | [98] |
| Emodin | H/R-induced HK-2 cells | 3 μM | Downregulated protein expressions of p-CAMKII | [98] |
| Emodin | LPS-induced NRK-52E cells | 20 and 40 μM | Downregulated mRNA and protein expressions of TLR2, NF-ƙB, TNF-α and IL-1β | [100] |
| Chrysophanol | H/R-induced HK-2 cells | 30 μM | Downregulated protein expressions of cleaved caspase-3, Bax, CHOP and p-IRE1α | [101] |
| Chrysophanol | Cisplatin-induced AKI mice | 20 and 40 mg/kg/day | Downregulated mRNA expressions of TNF-α, IL-1β, IL-6, caspase-3 and Bax as well as downregulated protein expression of p-p53, p-NF-κB p65, p-IKKβ, Bax, NOX2 and NOX4 | [102] |

**Abbreviations**: AKI, acute kidney injury; Bax, Bcl-2-associated X protein; CHOP, CCAAT-enhancer-binding protein homologous protein; H/R, hypoxia-reperfusion; IL-1β, interleukin-1β; IL-6, interleukin-6; IRI, ischemia-reperfusion injury; LPS, lipopolysaccharide; NOX2, nicotinamide adenine dinucleotide phosphate oxidase 2; NOX4, nicotinamide adenine dinucleotide phosphate oxidase 4; NF-κB, nuclear factor kappa B; p-CAMKII, phosphorylated calcium/calmodulin-dependent protein kinase II; p-IKKβ, phosphorylated inhibitor of nuclear factor kappa-B kinase subunit beta; p-IRE1α, phosphorylated inositol-requiring enzyme 1α; p-p53, phosphorylated p53; p-NF-κB p65, phosphorylated NF-κB p65; TLR2, Toll-like receptor 2; TNF-α, tumor necrosis factor alpha.


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B-cell lymphoma 2 (Bcl-2) expression. Furthermore, chrysophanol reduces H/R-induced endoplasmic reticulum (ER) stress by downregulating CCAAT-enhancer-binding protein homologous protein (CHOP) and phosphorylated inositol-requiring enzyme 1α.[101] It also alleviates H/R-induced lipid ROS accumulation and ferroptosis, thereby mitigating renal cell damage by inhibiting ferroptosis. Chrysophanol may represent a novel therapeutic option for improving H/R-induced renal tubular cell injury by targeting ferroptosis (Table 3). As an antioxidant, chrysophanol enhances cellular antioxidant capacity by increasing the expression of GPX4 and solute carrier family 7 member 11 (SLC7A11).

Cisplatin, a widely used chemotherapy drug, is effective against solid tumors, such as ovarian, head, neck, and testicular germ cell cancers.[116,117] However, its clinical application is limited by severe renal toxicity, which often leads to AKI.[118] Clinically, AKI occurs in approximately one-third of patients receiving cisplatin chemotherapy. Cisplatin-induced AKI is associated with disruptions in various signal transduction pathways, leading to renal tubular injury, tubulointerstitial inflammation, and vascular damage.[119,120] The underlying mechanisms involve DNA damage, apoptosis (both intrinsic and extrinsic), inflammation, and oxidative stress, with cell death and inflammatory pathology being the primary drivers of organ dysfunction.

Studies have shown that chrysophanol intervention significantly reduces serum creatinine and urea levels in cisplatin-induced AKI mouse models.[102] Experimental findings confirm that chrysophanol alleviates renal function decline and pathological damage in cisplatin-induced AKI by inhibiting ROS production in damaged renal tubular epithelial cells. Chrysophanol emerges as a promising candidate for protecting renal tubular cells from cytotoxic damage and demonstrates significant therapeutic potential for cisplatin-induced AKI (Table 3).

## Renoprotective Mechanism of Anthraquinones in CKD

CKD is one of the major causes of mortality worldwide due to renal failure.[14] Current treatments, such as dialysis and kidney transplantation, are costly and not curative.[121–123] Therefore, the treatment and management of renal diseases present a leading global challenge and necessitating innovative therapeutic strategies.[124–126] Extensive studies have demonstrated that various naturally derived compounds can attenuate CKD through diverse molecular mechanisms.[127–132] An increasing number of publications have highlighted that several anthraquinones ameliorate DKD, immunoglobulin A nephropathy (IgAN), and chronic glomerulonephritis by modulating key signaling pathways, including TGF-β1/small mothers against decapentaplegic (Smad), IκB/NF-κB, Keap1/Nrf2, Wnt/β-catenin, TLR4, AMP-activated protein kinase (AMPK), mammalian target of rapamycin (mTOR), phosphoinositide 3-kinase (PI3K), protein kinase B (Akt), and glycogen synthase kinase-3 beta (GSK-3β) (Table 4, Figures 2 and 3).

**Table 4** Molecular Mechanism of Renoprotective Effects of Anthraquinones in the Treatment of CKD

| Compounds | Cell/Animal Models | Dosage | Targets | Ref |
|---|---|---|---|---|
| Rhein | *db/db* mice | 150 mg/kg/day | Downregulated protein expressions of TGF-β1 and fibronectin | [133] |
| Rhein | STZ-induced DKD mice | 150 mg/kg/day | Downregulated protein expressions of Rac1 and NOX1 | [43] |
| Rhein | IgAN rats | 100 mg/kg/day | Downregulated mRNA and protein expressions of TLR4 and TGF-β1 | [134] |
| Rhein | IgAN rats | 100 mg/kg/day | Upregulated protein expression of zonula occluden-1 and occludin | [135] |
| Rhein | UUO mice | 150 mg/kg/day | Downregulated protein expression of α-SMA, fibronectin and TGF-β1 | [136] |
| Rhein | NX rats | 25 and 50 μg/mL | Downregulated protein expression of NF-κB p65, NF-κB p50 and p-IκBα | [137] |
| Rhein | UUO mice | 120 mg/kg | Upregulated protein expression of Klotho | [54] |
| Rhein | NX rats | 50, 100 and 150 mg/kg | Upregulated protein expression of SIRT3 and FOXO3a | [138] |
| Rhein-8-O-Glc | HG-induced mesangial cells | 20 and 80 μM | Regulated lincRNA ANRIL/let-7a/TGF-β1/Smad pathway | [139] |
| Rhein | HG-induced human podocytes | 25 μg/mL | Downregulated protein expressions of p-GSK-3β and β-catenin while upregulated protein expressions of PPARγ | [140] |
| Rhein | TGF-β1-induced NRK-49F cells | 0.01, 0.1 and 1.0 ng/mL | Downregulated protein expression of *α-SMA*, fibronectin and TGF-β1 | [136] |
| Rhein | LPS-induced HK-2 cells | 25 or 50 μg/mL | Downregulated protein expressions of NF-κB p65, NF-κB p50 and p-IκBα | [137] |
| Rhein | HG-induced RMC cells | 10–40 μM | Upregulated mRNA and protein expressions of PPARγ while downregulated GSK-3β protein expression | [141] |

(*Continued*)

**Table 4** (Continued).

| Compounds | Cell/Animal Models | Dosage | Targets | Ref |
|---|---|---|---|---|
| Emodin | KK-Ay mice | 40 and 80 mg/kg/day | Upregulated nephrin protein expression while downregulated protein expressions of p-PERK, p-eIF2α, ATF4 and CHOP | [142] |
| Emodin | STZ-induced rats | 40 mg/kg/day | Downregulated protein expression of fibronectin, p-p38MAPK and p-CREB | [143] |
| Emodin | Unilateral nephrectomy combined with STZ rats | 20 and 40 mg/kg/day | Downregulated protein expression of p62 and p-mTOR while upregulated protein expressions of LC3-II/LC3-I, Beclin-1 and p-AMPK | [144] |
| Emodin | STZ-induced diabetic rats | 100 mg/kg/3day | Downregulated protein expression of intercellular adhesion molecule 1 and Bax while upregulated protein expression of p-Akt and p-GSK-3β | [59] |
| Emodin | NX rats | 0.3 or 1 mg/kg/day | Downregulated protein expressions of TGF-β1 and Smurf 2 while upregulated protein expressions of Smad7 | [145] |
| Emodin | HG-induced rat mesangial cells | 30 and 60 μM | Downregulated protein expression of fibronectin, p-p38MAPK and p-CREB while upregulated protein expressions of PPARγ | [146] |
| Emodin | HG-induced-mouse podocytes | 20 and 40 μM | Upregulated nephrin protein expression while downregulated protein expressions of p-PERK, p-eIF2α, ATF4 and CHOP | [142] |
| Emodin | HG-induced rat mesangial cells | 20–40 μM | Inhibiting NF-ƙB pathway and downregulated protein expressions of TGF-β1 and fibronectin | [147] |
| Emodin | HG-induced HK-2 cells | 40μm | Upregulated mRNA and protein expressions of Nrf2 | [148] |
| Chrysophanol | STZ-induced diabetic mice | 50 and 100 mg/kg | Downregulated protein expressions of α-SMA, fibronectin, p-Smad2 and p-Smad3 | [149] |
| Chrysophanol | HG and fat diet and injecting STZ mice | 2.5, 5 and 10 mg/kg/day | Downregulated protein expression of Keap1 while upregulated protein expression of Nrf2 | [42] |
| Chrysophanol | UUO mice | 10–40 mg/kg | Downregulated protein expression of TGF-β1 and p-Smad3 while upregulated protein expression of Smad7 | [150] |
| Chrysophanol | UUO mice | 20 and 40 mg/kg | Downregulated protein expressions of TLR4, MyD88 and NF-ƙB | [151] |
| Chrysophanol | HG-induced AB8/13 cells | 40 μM | Inhibiting TGF-β1/Smad pathway | [149] |
| Chrysophanol | TGF-β1-induced HK-2 cells | 0–100 μM | Downregulated protein expression of p-Smad3 | [150] |
| Aloe-emodin | STZ-induced diabetic rats | 20 mg/kg/day | Downregulated protein expressions of collagen I, Notch 1 and p-Akt | [152] |
| Aloe-emodin | UUO mice | 20 mg/kg | Inhibited mRNA and protein expressions of PI3K, p-Akt and mTOR | [153] |
| Aloe-emodin | TGF-β1-induced HK-2 cells | 20–100 μM | Inhibited the expression of TGF-β1, collagen I, collagen IV and fibronectin | [153] |

**Abbreviations**: ATF4, activating transcription factor 4; DKD, diabetic kidney disease; FOXO3a, forkhead box O3a; HG, High glucose; IgAN, immunoglobulin A nephropathy; Keap1, kelch-like ECH-associated protein 1; LPS, lipopolysaccharide; MYD88, myeloid differentiation primary response 88; NF-κB p50, nuclear factor kappa B p50; NF-κB p65, nuclear factor kappa B p65; NOX1, nicotinamide adenine dinucleotide phosphate oxidase 1; Nrf2, nuclear factor erythroid 2-related factor 2; NX, 5/6 nephrectomized; p-Akt, phosphorylated protein kinase B; p-AMPK, phosphorylated AMP-activated protein kinase; p-CREB, phosphorylated CREB; p-eIF2α, phosphorylated eukaryotic initiation factor-2α; p-GSK-3β, phosphorylated glycogen synthase kinase 3 beta; PI3K, phosphoinositide 3-kinases; p-IƙBα, phosphorylated IƙB alpha; p-mTOR, phosphorylated mammalian target of rapamycin; p-p38MAPK, phosphorylated p38 mitogen-activated protein kinases; PPARγ, peroxisome proliferator-activated receptor gamma; p-PERK, phosphorylated protein kinase-like endoplasmic reticulum kinase; Rac1, Rac family small GTPase 1; RMC, rat kidney mesangial cells; SIRT3, Sirtuin 3; Smad, suppressor of mothers against decapentaplegic; STZ, streptozotocin; TGF-β1, transforming growth factor beta 1; TLR4, Toll-like receptor 4; UUO, unilateral ureteral obstruction; α-SMA, alpha-smooth muscle actin.

## Inhibition of DKD by Anthraquinones

Diabetes mellitus is the leading cause of ESRD worldwide.[154] Poor glycemic control significantly contributes to the development and progression of complications in patients with diabetes mellitus.[155] DKD, a common microvascular complication of diabetes, is primarily characterized by the proliferation of glomerular mesangial cells and the accumulation of extracellular matrix (ECM).[124,156] However, the underlying pathogenesis of DKD remains incompletely understood. Several pathways have been implicated in the disease's progression, including the hemodynamic pathway (involving the renin-angiotensin-aldosterone system and the urotensin system), pro-fibrotic and inflammatory cytokines such as TGF-β1 and tumor necrosis factor alpha (TNF-α), and kinases, such as protein kinase C (PKC) and Janus kinase pathway. Additionally, oxidative stress mediators play a critical role, particularly nicotinamide adenine dinucleotide phosphate oxidase (NOX).

Emerging research has revealed that several anthraquinones can attenuate DKD by targeting multiple signaling pathways. These include TGF-β1, NF-κB, and Ras-related C3 Botulinum toxin substrate 1 (Rac1); oxidative stress mediators such as NOX1; and regulatory pathways such as Keap1/Nrf2, interferon regulatory factor 4 (IRF4), glycogen synthase kinase-3 beta (GSK-3β), AMP-activated protein kinase (AMPK), phosphoinositide 3-kinase (PI3K), protein kinase B (Akt), and mammalian target of rapamycin (mTOR) (Table 4, and Figures 2 and 3).

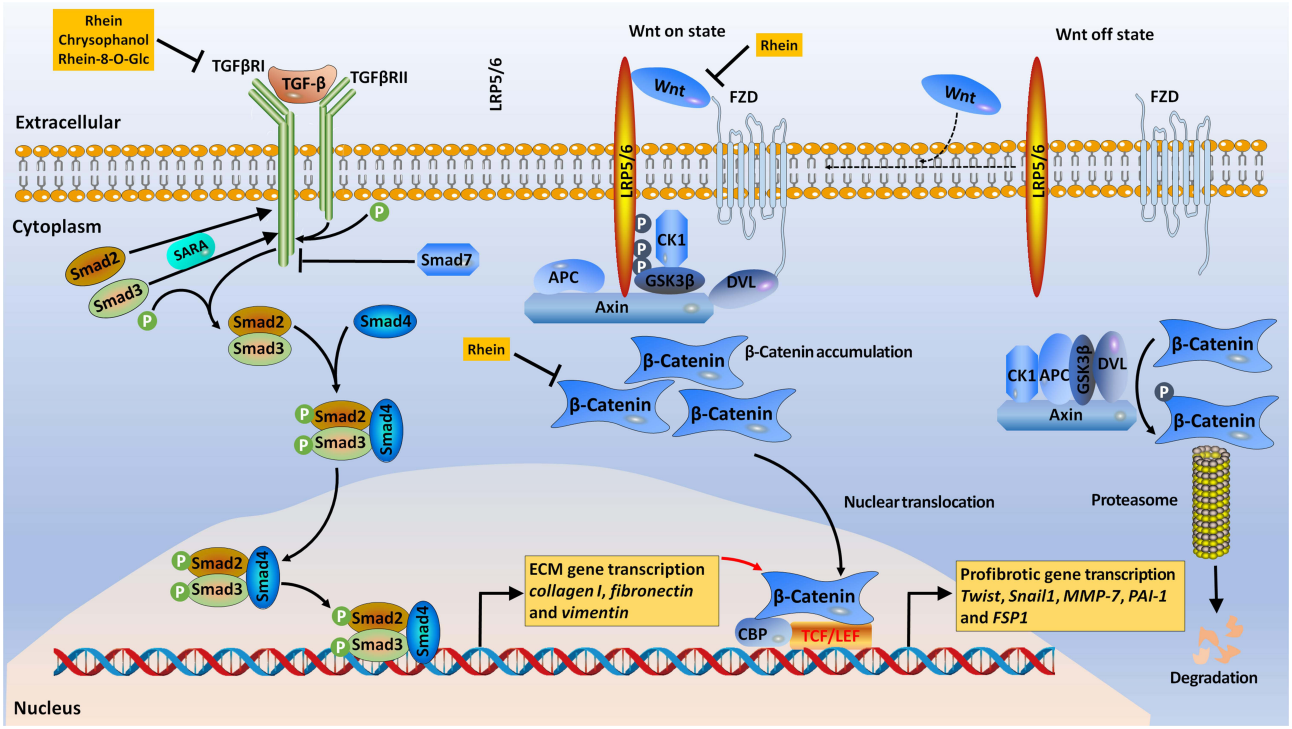


**Figure 2** The underlying renoprotective mechanisms of anthraquinones by inhibiting TGF-β1/Smad and Wnt1/β-catenin signaling pathways. AKI and CKD lead to the activations of profibrotic TGF-β1/Smad and Wnt/β-catenin signaling pathways. Treatment with anthraquinones such as rhein, chrysophanol, and rhein-8-O-glc could improve renal function and inhibit renal fibrosis by inhibiting the TGF-β1/Smad signaling pathway. Rhein could improve renal function and inhibit renal fibrosis by inhibiting the Wnt1/β-catenin signaling pathway.

## Amelioration of Podocyte Injury by the Components of Anthraquinones

Proteinuria is a significant clinical feature of DKD and is often associated with podocyte injury.[157,158] Previous studies have suggested that a broad spectrum of compounds derived from TCM can reduce proteinuria levels and improve DKD outcomes.[159–161] Controlled clinical studies have demonstrated that rhein is critical in inhibiting proteinuria and slowing the progression of DKD.[162] The renoprotective effects of rhein in DKD are closely related to its regulation of nephrin gene expression, which is essential for maintaining podocyte integrity through nephrin protein. Experimental evidence suggests that rhein improves metabolic disorders and reduces fat mass by modulating the peroxisome proliferator-activated receptor gamma (PPARγ) signaling pathway, a key insulin sensitizer in treating type II diabetes.[163] High glucose (HG) conditions notably decrease PPARγ expression at both mRNA and protein levels in podocytes, reducing podocin and nephrin expression and consequent podocyte injury.[164] Thus, rhein exhibits significant therapeutic potential in DKD by preserving podocyte function.

Early evidence also demonstrates that emodin exerts renoprotective effects by inhibiting mesangial cell proliferation and epithelial–mesenchymal transition (EMT).[146] Animal studies have shown that emodin reduces serum creatinine and urea levels and urinary albumin levels in DKD mice while improving pathological kidney injury. Additionally, emodin enhances renin activity and decreases markers of podocyte apoptosis and ER stress, such as glucose-regulated protein 78 (GRP78). Recent studies indicate that emodin reduces podocyte apoptosis in DKD by inhibiting the protein kinase R-like ER kinase-eukaryotic initiation factor 2 alpha (PERK-eIF2α) signaling pathway.[142] Experimental results further demonstrate that emodin reduces proteinuria and alleviates renal fibrosis without affecting blood glucose levels in DKD rats.

## Inhibition of Mesangial Cell Injury by the Components of *R. officinale*

Mesangial cells are crucial for maintaining renal filtration. Protecting these cells in patients with DKD can improve filtration, reduce proteinuria, and mitigate renal injury.[165] Rhein has been shown to inhibit the proliferation of mesangial cells and the expression of ECM components induced by HG conditions. This effect is mediated by upregulating pro-

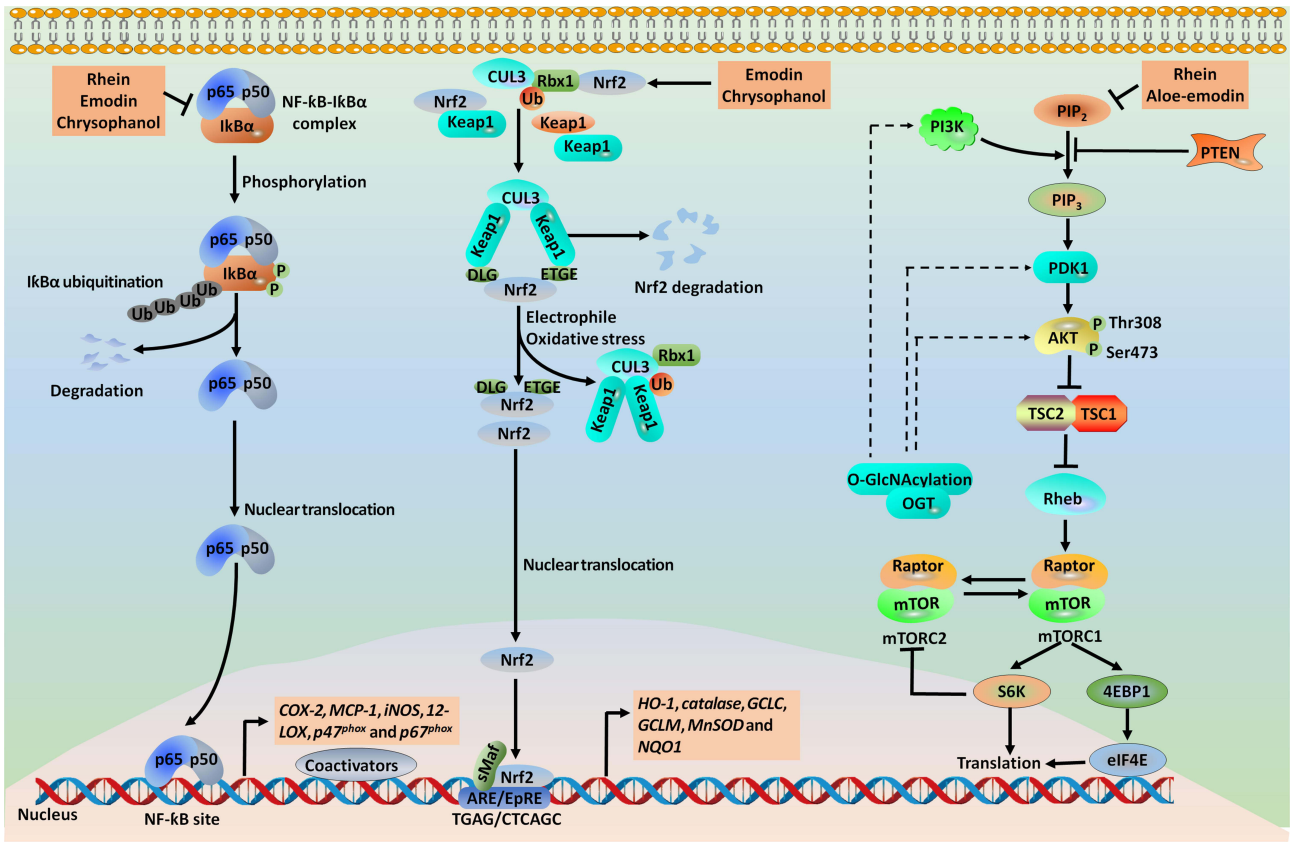


**Figure 3** The underlying renoprotective mechanisms of anthraquinones by regulating IκB/NF-κB, Keap1/Nrf2 and PI3K/Akt/mTOR signaling pathways. AKI and CKD lead to the activations of proinflammatory IκB/NF-κB and impaired Keap1/Nrf2 signaling pathways as well as PI3K/Akt/mTOR signaling pathways. Treatment with anthraquinones such as rhein, emodin, and chrysophanol could improve renal function and inhibit renal fibrosis by inhibiting oxidative stress and inflammation. Treatment with anthraquinones such as emodin and aloe-emodin could improve renal function, reduce podocyte damage, and inhibit renal fibrosis by regulating the PI3K/Akt/mTOR signaling pathway.

apoptotic proteins Bax and caspase-3, leading to cell cycle arrest at the G1 phase and promoting apoptosis.[166] Similarly, emodin inhibits HG-induced mesangial cell proliferation by inducing cell cycle arrest at the G1 phase through the upregulation of Bax and activation of caspases.[167]

## Inhibition of TGF-β1/Smad Signalling Pathway by Anthraquinones

Extensive studies have identified TGF-β1 signaling as a central pathway in the progression of various renal diseases.[168,169] Numerous publications have demonstrated the beneficial effects of rhein and related anthraquinones in mitigating DKD by inhibiting TGF-β1 signaling (Figure 2). For example, Guo et al reported that chrysophanol improved DKD by suppressing HG-induced growth and migration of human podocytes (AB8/13 cells) by inactivating the TGF-β1 signaling pathway.[149] Similarly, Wang et al showed that emodin alleviated DKD in streptozotocin (STZ)-induced diabetic rats by reducing intrarenal expression of phosphorylated p38 MAPK and fibronectin.[143] Furthermore, Zhang et al demonstrated that rhein-8-O-β-D-glucopyranoside (Rhein-8-O-Glc), a derivative of rhein, inhibited HG-induced apoptosis in human mesangial cells by regulating the lincRNA ANRIL/let-7a/TGF-β1/Smad signaling pathway.[139] Jia et al found that rhein reduced plasma glucose, creatinine, cholesterol, triglyceride, and low-density lipoprotein levels while also downregulating protein expressions of TGF-β1 and fibronectin in db/db mice.[133] These findings suggest that anthraquinones inhibit DKD progression by suppressing the TGF-β1/Smad signaling pathway, offering a promising therapeutic target for DKD treatment (Figure 2).


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### Regulation of Iκb/NF-Κb and Keap1/Nrf2 Signalling Pathway by Anthraquinones

Inflammation plays a key role in the development of DKD. NF-κB regulates the expression of numerous genes involved in the inflammatory response, contributing significantly to experimental and clinical renal injury.[170] Yang et al demonstrated that emodin downregulates fibronectin protein expression by inhibiting the NF-κB signaling pathway in DKD rats[147] (Figure 3). Similarly, Xiong et al showed that rhein mitigates DKD by inhibiting ferroptosis and EMT by regulating the Rac1/NOX1/β-catenin signaling axis[28] (Table 4).

Resveratrol has been shown to exert antioxidant effects by directly scavenging ROS or by enhancing the levels and activity of superoxide dismutase 2 in mitochondria. It also inhibits nicotinamide adenine dinucleotide phosphate oxidase activity, thereby reducing ROS production in DKD and protecting cells from oxygen-low-density lipoprotein-induced damage.[171]

Extensive studies have highlighted the importance of the Keap1/Nrf2 signaling pathway as a critical anti-inflammatory mechanism[172] (Figure 3). Nrf2 regulates basal activity and the coordinated induction of genes encoding antioxidant and Phase 2 detoxifying enzymes and proteins. Yuan et al recently reported that chrysophanol downregulates Keap1 protein expression while preserving Nrf2 protein expression in DKD mice fed a high-sugar and high-fat diet and treated with streptozotocin. This effect was achieved by activating the Keap1/Nrf2 signaling pathway.[42] Similarly, Ji et al found that emodin alleviates DKD by inhibiting ferroptosis through upregulation of Nrf2 expression in STZ-induced diabetic rats.[148]

Collectively, these findings suggest that anthraquinones can attenuate DKD by mitigating oxidative stress and inflammation (Figure 3).

### Inhibition of Wnt/β-Catenin Signalling Pathway by Anthraquinones

The Wnt/β-catenin signaling pathway is an evolutionarily conserved cascade critical in regulating tissue development and maintaining homeostasis[173,174] (Figure 2). Numerous studies have reported that Wnt/β-catenin signaling is activated in various CKDs, including DKD, adriamycin nephropathy, polycystic kidney disease, obstructive nephropathy, and chronic allograft nephropathy.[175–178] Several TCMs have been shown to improve CKD by inhibiting the Wnt/β-catenin signaling pathway.[179,180]

Duan et al demonstrated that rhein downregulates the protein expression of GSK-3β and β-catenin, improving podocyte structure and function. This suggests that rhein ameliorates HG-induced podocyte injury through the Wnt1/β-catenin signaling pathway[141] (Figure 2). In a subsequent study, the same research group showed that rhein preserves nephrin protein expression by inhibiting the expression of Wnt1, phosphorylated GSK-3β (p-GSK-3β), and phosphorylated β-catenin (p-β-catenin) in DKD mice.[140] Additionally, Xiong et al reported that rhein mitigates DKD by inhibiting EMT by suppressing β-catenin signaling.[43] These findings suggest that anthraquinones can attenuate DKD by inhibiting the Wnt/β-catenin signaling pathway (Figure 2).

### Regulation of AMPK and PI3K/Akt/mTOR Signalling Pathways by Anthraquinones

Several anthraquinones have been shown to attenuate DKD by regulating key signaling pathways, including GSK-3β, AMPK, PI3K, Akt, and mTOR (Figure 3). Liu et al demonstrated that emodin alleviates renal injury and podocyte damage in DKD rats by modulating the AMPK/mTOR-mediated autophagy signaling pathway.[144] Similarly, Jing et al reported that emodin protects against DKD in rats via the PI3K/Akt/GSK-3β and Bax/caspase-3 signaling pathways.[59] These findings suggest that anthraquinones attenuate DKD through mechanisms involving AMPK and PI3K/Akt/mTOR signaling pathways (Figure 3).

### Regulation of ER Stress and IRF4 Signalling by Anthraquinones

Several studies have demonstrated that the beneficial effects of anthraquinones are closely associated with ER stress and interferon regulatory factor 4 (IRF4) signaling. Tian et al reported that emodin mitigates podocyte apoptosis induced by ER stress by inhibiting the protein kinase RNA-like ER kinase (PERK) signaling pathway in DKD.[142] Similarly, Yuan et al found that aloe-emodin ameliorates DKD by targeting IRF4 signaling.[152]

## Rhein Blunted IgAN by Inhibiting TLR4 Signaling and Improved the Intestinal Barrier

An earlier study demonstrated that rhein protects against IgAN by inhibiting fibronectin expression in rats.[181] TLR4, an intrinsic immune receptor, plays a significant role in the onset of various diseases. Chen et al showed that both rhein-preventive and rhein-therapeutic interventions alleviated glomerular pathological changes and tubulointerstitial fibrosis

(TIF) in IgAN rats by inhibiting the expression of TLR4 and TGF-β1.[134] Additionally, extensive studies have highlighted gut microbiota dysbiosis in patients with CKD.[182–187] Peng et al reported that rhein preserves the protein expression of Zonula occludens-1 and occludin, repairs damaged tight junctions, and protects the intestinal barrier.[135] These findings suggest that rhein ameliorates IgAN by inhibiting TLR4 signaling and protecting the intestinal barrier.

## Rhein Abolished Chronic Glomerulonephritis by Improving Disorders of Endogenous Metabolites

Substantial studies have demonstrated that metabolomics has been extensively applied in CKD research to identify altered metabolic profiles and endogenous metabolites.[188–190] Extensive studies have demonstrated that natural products ameliorated CKD by improving metabolic disorders.[191–193] Chronic glomerulonephritis, a major cause of renal failure, significantly increases mortality in critically ill patients. Functional metabolomics analysis revealed that rhein modulated 16 biomarkers toward normal levels, involving six metabolic pathways: phenylalanine, tyrosine, and tryptophan biosynthesis; phenylalanine metabolism; arachidonic acid metabolism; the tricarboxylic acid (TCA) cycle; alanine, aspartate, and glutamate metabolism; and arginine and proline metabolism. The therapeutic effects of Rhein may be mediated by regulating amino acid metabolism, arachidonic acid metabolism, and the TCA cycle, contributing to anti-inflammatory, antioxidant, and immune-regulatory activities in chronic glomerulonephritis.[194] Additionally, metabolomic analysis identified fatty acid oxidation disorders in unilateral ureteral obstruction (UUO) rats.[195] These findings suggest that rhein ameliorates chronic glomerulonephritis by modulating amino acid and arachidonic acid metabolism.

## Inhibition of Renal Fibrosis by Anthraquinones

Extensive studies have demonstrated that renal fibrosis is associated with various signaling pathways, including TGF-β1/Smad, IκB/NF-κB, Keap1/Nrf2, AMPK, and PI3K/Akt/mTOR (Table 4, Figures 2 and 3). Additionally, several other pathways, such as signal transducer and activator of transcription 3 (STAT3), high mobility group AT-hook 2 (HMGA2), Forkhead box O (FOXO), and Sonic hedgehog-glioma-associated oncogene 1 (Shh-GLI1), have also been implicated in the progression of renal fibrosis.

### Inhibition of TGF-β1/Smad Signalling Pathway by Anthraquinones

Based on the UUO model, numerous studies have demonstrated that several anthraquinones can attenuate TIF by targeting the TGF-β1/Smad signaling pathway (Figure 2). For example, He et al reported that rhein inhibits the protein expression of TGF-β1, its type I receptor, alpha-smooth muscle actin (α-SMA), and fibronectin in the obstructed kidneys of UUO mice. In vitro experiments further confirmed that rhein reduces the expression of α-SMA and fibronectin in TGF-β1-induced NRK-49F cells.[136] Dou et al showed that chrysophanol downregulates the protein expression of TGF-β1 and phosphorylated Smad3 while upregulating Smad7 in obstructed kidneys of UUO mice. However, the protein expression of Smad2, Smad4, and TGF-β1 receptors was not affected[150] (Figure 2).

Xu et al revealed that emodin suppresses collagen deposition and reduces the protein expression of Smad3 and connective tissue growth factor in obstructed kidneys and NRK-49F cells. These effects were associated with the downregulation of the zeste homolog 2 (EZH2) enhancer and decreased trimethylation of histone H3 on lysine 27. Inhibition of EZH2 using 3-DZNeP partially attenuated the antifibrotic effects of emodin in both obstructed kidneys and NRK-49F cells.[196] Additionally, Yang et al demonstrated that emodin alleviates renal fibrosis by modulating HGF and the TGF-β1/Smad signaling pathway.[197] Ma et al reported that emodin mitigates renal fibrosis in rats by targeting the TGF-β1/Smad signaling pathway and suppressing Smad-specific E3 ubiquitin protein ligase 2 expression.[145] Guan et al showed that a combination of rhein and *Danshensu* attenuates renal damage by inhibiting the TGF-β1/Smad3 pathway in 5/6 nephrectomized (NX) rats.[198] These findings suggest that anthraquinones attenuate renal fibrosis by modulating the TGF-β1/Smad signaling pathway (Figure 2).

### Regulation of Iκb/NF-Κb Signalling Pathway by Anthraquinones

Using the 5/6 nephrectomized rat model, several studies have demonstrated that anthraquinones can inhibit renal fibrosis by targeting the IκB/NF-κB signaling pathway (Figure 3). For example, Liu et al reported that rhein protects against renal

injury by reducing the expression of TNF-α, interleukin-6 (IL-6), and monocyte chemoattractant protein-1 (MCP-1) via the NF-κB signaling pathway in 5/6 nephrectomized rats.[137] Similarly, in vitro experiments revealed that rhein suppresses LPS-mediated NF-κB activation by inhibiting the phosphorylation of IκBα, blocking its nuclear translocation.[137]

In addition, Gu et al found that chrysophanol protects against TIF by suppressing the Naked cuticle 2/NF-κB pathway.[199] Lu et al demonstrated that treatment with nanoparticle-mediated delivery of emodin via colonic irrigation reduces serum levels of IL-1β, IL-6, and LPS, improves intestinal barrier function, and downregulates the protein expression of TLR4, myeloid differentiation primary response protein 88 (MyD88), and NF-κB.[151] Furthermore, 16S rDNA analysis indicated that nanoparticle-mediated emodin delivery effectively regulates microbiota disturbances in CKD.[151] These findings suggest that anthraquinones mitigate renal fibrosis by reducing oxidative stress and inflammation by regulating the IκB/NF-κB signaling pathway (Figure 3).

### Rhein Blunted CKD and Renal Fibrosis by Improving Klotho Expression

Klotho, a crucial anti-ageing protein, is highly expressed in the main tubular segments of healthy adult kidneys.[200] However, Klotho expression is significantly reduced in ageing animals and humans. Zhang et al identified rhein as a potent Klotho upregulator, significantly preserving Klotho protein expression in UUO-induced TIF in mice.[54] Further investigation revealed that Klotho loss in TIF is associated with promoter hypermethylation caused by aberrant expression of DNA methyltransferases (DNMT) 1 and 3a. Notably, the anti-TIF effects of rhein were abolished mainly in shRNA-Klotho-transfected cells, demonstrating the dependence of these effects on Klotho.[54]

The same research group further demonstrated that rhein significantly reverses renal Klotho deficiency in adenine-induced CKD in mice.[201] Mechanistic studies revealed that rhein inhibits the induction of DNMT1 and DNMT3a, reducing Klotho promoter hypermethylation. However, Klotho knockdown partially abrogated the renoprotective effects of rhein.[201] Additionally, Bi et al reported that Klotho preservation by rhein promotes TLR4 proteolysis and mitigates LPS-mediated AKI.[202] These findings suggest that regulating Klotho expression by rhein contributes to its renoprotective effects, offering new insights into Klotho-targeted therapies for kidney disease.

### Activation of SIRT/FOXO Signalling Pathway by Anthraquinones

Among the four FOXO transcription factors, FOXO1, FOXO3α, FOXO4, and FOXO6, FOXO3α plays a key role in regulating oxidative stress.[203] Wu et al demonstrated that rhein inhibits TGF-β1-induced EMT and oxidative stress by activating the Sirtuin 3 (SIRT3)/forkhead box O3a (FOXO3α) signaling pathway, providing renoprotective effects in 5/6 nephrectomized-induced CKD.[138] The antioxidant and antifibrotic functions of rhein are closely associated with increased FOXO3α nuclear translocation mediated by SIRT3 activation, highlighting the critical role of the SIRT3/FOXO3α signaling pathway in the renal protection conferred by rhein.[138]

As a SIRT1 agonist, resveratrol protects against oxidative stress by activating the SIRT1 signaling pathway, inhibiting ROS production,[204] preventing NF-κB activation, and stimulating AMPK.[205] Resveratrol treatment enhances SIRT1 deacetylase activity, reduces acetylated FOXO3α expression, and mitigates hyperglycemia-induced oxidative stress in vivo and in vitro.[206] These findings suggest anthraquinones may attenuate renal fibrosis by modulating the SIRT/FOXO signaling pathway.

### Regulation of AMPK and PI3K/Akt/mTOR Signalling Pathways by Anthraquinones

Excessive exogenous adenine induces metabolic abnormalities that mimic chronic renal insufficiency in humans. Tu et al reported that rhubarb inhibits autophagic activation and renal fibrosis in rats with adenine-induced renal tubular injury.[207] Further studies revealed that rhein suppresses autophagy by regulating AMPK-dependent mTOR, extracellular signal-regulated kinase (ERK), and p38 MAPK signaling pathways[207] (Figure 3). Similarly, Dou et al demonstrated that aloe-emodin attenuates TIF by inhibiting the PI3K/Akt/mTOR signaling pathway in the obstructed kidneys of UUO mice and TGF-β1-induced HK-2 cells[153] (Figure 3).

### Regulation of STAT3, Shh-GLI1 and HMGA2 Signalling Pathways by Anthraquinones

Several studies have shown that the beneficial effects of anthraquinones are associated with the STAT3, Sonic hedgehog-Glioma-associated oncogene 1 (Shh-GLI1), and high mobility group AT-hook 2 (HMGA2) signaling pathways. Recent

evidence suggests that STAT3 is a critical pathway in the progression of CKD.[208] Chen et al reported that rhein suppresses TIF by regulating the expression of phosphorylated STAT3, Bax, and Bcl-2.[209]

The Shh signaling pathway regulates renal development, patterning, and proliferation. GLI1-expressing cells are a primary source of activated fibroblasts in multiple organs. Luo et al demonstrated that rhein alleviates TIF by modulating the Shh-GLI1 signaling pathway.[210] HMGA2 is implicated in TGF-β1-mediated EMT through various mechanisms. Wang et al showed that emodin mitigates renal injury and TIF by regulating the miR-490-3p/HMGA2 signaling pathway.[211] These findings suggest that anthraquinones can attenuate renal fibrosis by targeting the STAT3, Shh-GLI1, and HMGA2 signaling pathways.

## Conclusions

This review highlights the anthraquinones in *R. officinale* on treating AKI and CKD, emphasizing their underlying molecular mechanisms. Anthraquinones exert their effects by modulating key signaling pathways, including TGF-β1/Smad, IκB/NF-κB, Keap1/Nrf2, and Wnt/β-catenin, as well as through the regulation of apoptosis and autophagy. These mechanisms highlight the critical role of anthraquinones in providing anti-inflammatory, antioxidative, and anti-fibrotic effects. These pharmacological data provide evidence for treatment of AKI and CKD of *R. officinale* and present a concept-driven therapeutic strategy for renal disease management. However, most current studies are based on animal models or cell experiments, with limited clinical trials or real-world applications. Despite evidence of the broad renoprotective effects of *R. officinale*, certain limitations persist. These include poor solubility, low bioavailability, suboptimal intestinal absorption, long-term dose dependence for specific targets, and potential hepatotoxicity or nephrotoxicity. Thus, although *R. officinale* has significant promise, challenges remain in advancing its clinical applications, presenting opportunities and obstacles for future research and development.

## Abbreviations

AKI, Acute kidney injury; ATP, adenosine triphosphate; α-SMA, alpha smooth muscle actin; AMPK, AMP-activated protein kinase; Bcl-2, B-cell lymphoma 2; Bax, B-cell lymphoma 2 associated X; CKD, chronic kidney disease; DKD, diabetic kidney disease; ER, endoplasmic reticulum; ESRD, end-stage renal disease; EMT, epithelial–mesenchymal transition; EMC, extracellular matrix; FOXO, Forkhead box O; GSK-3β, glycogen synthase kinase-3 beta; HG, high glucose; HMGA2, high mobility group AT-hook 2; H/R, hypoxia-reoxygenation; IgAN, immunoglobulin A nephropathy; IκB, inhibitor of kappa B; IRF4, interferon regulatory factor 4; IRI, ischemia-reperfusion injury; Keap1, kelch-like ECH-associated protein 1; LPS, lipopolysaccharide; mTOR, mammalian target of rapamycin; NOX1, nicotinamide adenine dinucleotide phosphate oxidase 1; Nrf2, nuclear factor erythroid 2-related factor 2; NF-κB, nuclear factor kappa B; PPARγ, peroxisome proliferator-activated receptor gamma; PI3K, phosphoinositide 3-kinases; Akt, protein kinase B; PKC, protein kinase C; Rac1, Ras-related C3 Botulinum toxin substrate 1; ROS, reactive oxygen species; Rhein-8-O-Glc, rhein-8-O-β-D-glucopyranoside; STAT3, signal transducer and activator of transcription 3; SIRT1, Sirtuin 1; Smad, small mothers against decapentaplegic; Shh-GLI1, sonic hedgehog-glioma-associated oncogene 1; STZ, streptozotocin; TLR, toll-like receptors; TCM, traditional Chinese medicine; TGF-β1, transforming growth factor beta1; TIF, tubulointerstitial fibrosis; TNF-α, tumor necrosis factor alpha; UUO, unilateral ureteral obstruction.

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## Disclosure

Hao-Yu Feng and Yi-Qi Wang are co-first authors for this study. The authors declare that they have no conflicts of interest in this work.

## References


1. Sanz AB, Sanchez-Niño MD, Ramos AM, Ortiz A. Regulated cell death pathways in kidney disease. *Nat Rev Nephrol*. 2023;19(5):281–299. doi:10.1038/s41581-023-00694-0
2. Song Z, Gong X. Research progress on the potential mechanisms of acute kidney injury and chronic kidney disease induced by proton pump inhibitors. *Integr Med Nephrol Androl*. 2023;10:e00027.
3. Brogan M, Ross MJ. COVID-19 and kidney disease. *Annu Rev Med*. 2023;74(1):1–13. doi:10.1146/annurev-med-042420-104753
4. Pérez-Aizpurua X, Cabello Benavente R, Bueno Serrano G, et al. Obstructive uropathy: overview of the pathogenesis, etiology and management of a prevalent cause of acute kidney injury. *World J Nephrol*. 2024;13(2):93322. doi:10.5527/wjn.v13.i2.93322
5. Gao L, Zhong X, Jin J, Li J, Meng XM. Potential targeted therapy and diagnosis based on novel insight into growth factors, receptors, and downstream effectors in acute kidney injury and acute kidney injury-chronic kidney disease progression. *Signal Transduct Target Ther*. 2020;5(1):9. doi:10.1038/s41392-020-0106-1
6. Mimura I, Chen Z, Natarajan R. Epigenetic alterations and memory: key players in the development/progression of chronic kidney disease promoted by acute kidney injury and diabetes. *Kidney Int*. 2025;107(3):434–456. doi:10.1016/j.kint.2024.10.031
7. Ostermann M, Lumlertgul N, Jeong R, et al. Acute kidney injury. *Lancet*. 2025;405(10474):241–256. doi:10.1016/S0140-6736(24)02385-7
8. Zarbock A, Forni LG, Ostermann M, et al. Designing acute kidney injury clinical trials. *Nat Rev Nephrol*. 2024;20(2):137–146. doi:10.1038/s41581-023-00758-1
9. Tang C, Livingston MJ, Safirstein R, Dong Z. Cisplatin nephrotoxicity: new insights and therapeutic implications. *Nat Rev Nephrol*. 2023;19:53–72. doi:10.1038/s41581-022-00631-7
10. Zhang M, Liu Q, Meng H, et al. Ischemia-reperfusion injury: molecular mechanisms and therapeutic targets. *Signal Transduct Target Ther*. 2024;9(1):12. doi:10.1038/s41392-023-01688-x
11. Lumpuy-Castillo J, Amador-Martínez I, Díaz-Rojas M, et al. Role of mitochondria in reno-cardiac diseases: a study of bioenergetics, biogenesis, and GSH signaling in disease transition. *Redox Biol*. 2024;76:103340. doi:10.1016/j.redox.2024.103340
12. Zhao BR, Hu XR, Wang WD, Zhou Y. Cardiorenal syndrome: clinical diagnosis, molecular mechanisms and therapeutic strategies. *Acta Pharmacol Sin*. 2025;46(6):1539–1555. doi:10.1038/s41401-025-01476-z
13. Kalantar-Zadeh K, Jafar TH, Nitsch D, Neuen BL, Perkovic V. Chronic kidney disease. *Lancet*. 2021;398(10302):786–802. doi:10.1016/S0140-6736(21)00519-5
14. Khandpur S, Mishra P, Mishra S, Tiwari S. Challenges in predictive modelling of chronic kidney disease: a narrative review. *World J Nephrol*. 2024;13(3):97214. doi:10.5527/wjn.v13.i3.97214
15. Zhang Z, Zhao Z, Qi C, et al. Butyrolactone I blocks the transition of acute kidney injury to chronic kidney disease in mice by targeting JAK1. *MedComm*. 2025;6(2):e70064. doi:10.1002/mco2.70064
16. Geetha D, Kronbichler A, Rutter M, et al. Impact of the COVID-19 pandemic on the kidney community: lessons learned and future directions. *Nat Rev Nephrol*. 2022;18(11):724–737. doi:10.1038/s41581-022-00618-4
17. Allinson CS, Pollock CA, Chen X. Mesenchymal stem cells in the treatment of acute kidney injury (AKI), chronic kidney disease (CKD) and the AKI-to-CKD transition. *Integr Med Nephrol Androl*. 2023;10:e00014.
18. Grange C, Bussolati B. Extracellular vesicles in kidney disease. *Nat Rev Nephrol*. 2022;18(8):499–513. doi:10.1038/s41581-022-00586-9
19. Chesnaye NC, Carrero JJ, Hecking M, Jager KJ. Differences in the epidemiology, management and outcomes of kidney disease in men and women. *Nat Rev Nephrol*. 2024;20(1):7–20. doi:10.1038/s41581-023-00784-z
20. Mahalingasivam V, Su G, Iwagami M, et al. COVID-19 and kidney disease: insights from epidemiology to inform clinical practice. *Nat Rev Nephrol*. 2022;18(8):485–498. doi:10.1038/s41581-022-00570-3
21. Lee K, Jang HR, Rabb H. Lymphocytes and innate immune cells in acute kidney injury and repair. *Nat Rev Nephrol*. 2024;20(12):789–805. doi:10.1038/s41581-024-00875-5
22. Du Y, Li J, Ye M, et al. Hyperuricemia-induced acute kidney injury in the context of chronic kidney disease: a case report. *Integr Med Nephrol Androl*. 2023;10:e00008.
23. Hinze C, Lovric S, Halloran PF, Barasch J, Schmidt-Ott KM. Epithelial cell states associated with kidney and allograft injury. *Nat Rev Nephrol*. 2024;20(7):447–459. doi:10.1038/s41581-024-00834-0
24. O'Hara DV, Lam CSP, McMurray JJV, et al. Applications of SGLT2 inhibitors beyond glycaemic control. *Nat Rev Nephrol*. 2024;20(8):513–529. doi:10.1038/s41581-024-00836-y
25. Vanholder R, Annemans L, Braks M, et al. Inequities in kidney health and kidney care. *Nat Rev Nephrol*. 2023;19(11):694–708. doi:10.1038/s41581-023-00745-6
26. Perreault S, Boivin Proulx LA, Lenglet A, Massy ZA, Dorais M. Effectiveness and safety of apixaban and rivaroxaban vs warfarin in patients with atrial fibrillation and chronic kidney disease. *World J Nephrol*. 2023;12(5):132–146. doi:10.5527/wjn.v12.i5.132
27. Chen H, Cheng Q. Therapeutic effects of Jin Shui Bao capsules on kidney diseases. *Integr Med Nephrol Androl*. 2023;10:e00025.
28. Chu A, Wei W, Liu N, et al. Therapeutic effects of Kangxian Yanshen formula on patients with chronic kidney disease stages 3-4: a retrospective cohort study. *Front Med Lausanne*. 2024;11:1450561. doi:10.3389/fmed.2024.1450561
29. Guo ZY, Wu X, Zhang SJ, et al. *Poria cocos*: traditional uses, triterpenoid components and their renoprotective pharmacology. *Acta Pharmacol Sin*. 2024;46(4):836–851. doi:10.1038/s41401-024-01404-7
30. Vagopoulou A, Theofilis P, Karasavvidou D, et al. Pilot study on the effect of flavonoids on arterial stiffness and oxidative stress in chronic kidney disease. *World J Nephrol*. 2024;13(3):95262. doi:10.5527/wjn.v13.i3.95262
31. Geng Y, Dong Z, Wang Y, et al. Efficacy of huangkui capsules in the treatment of diabetic kidney disease: a systematic review and using network pharmacology. *Integr Med Nephrol Androl*. 2023;10:e00020.
32. Zhong Y, Wen W, Luo Z, Cheng N. A multi-component, multi-target, and multi-pathway prediction method for Chinese medicine based on the combination of mass spectrometry analysis and network analysis: an example using Weifuchun. *J Chromatogr A*. 2024;1731:465164. doi:10.1016/j.chroma.2024.465164
33. Dong YP, Chen SZ, He HS, et al. Skullcapflavone II, a novel NQO1 inhibitor, alleviates aristolochic acid I-induced liver and kidney injury in mice. *Acta Pharmacol Sin*. 2023;44(7):1429–1441. doi:10.1038/s41401-023-01052-3

34. Yu L, Zhao Y, Zhao Y. Advances in the pharmacological effects and molecular mechanisms of emodin in the treatment of metabolic diseases. *Front Pharmacol*. 2023;14:1240820. doi:10.3389/fphar.2023.1240820
35. Xia C, Su J, Liu C, et al. Human microbiomes in cancer development and therapy. *MedComm*. 2023;4:e221.
36. Dai L, Cao X, Miao X, et al. The chemical composition, protective effect of *Rheum officinale* leaf juice and its mechanism against dextran sulfate sodium-induced ulcerative colitis. *Phytomedicine*. 2024;129:155653. doi:10.1016/j.phymed.2024.155653
37. Mao M, Cao X, Liang Y, et al. Neuroprotection of rhubarb extract against cerebral ischaemia-reperfusion injury via the gut-brain axis pathway. *Phytomedicine*. 2024;126:155254. doi:10.1016/j.phymed.2023.155254
38. Huang W, Rao Y, Li L, Li C, An Y. Clinical effect of rhubarb on the treatment of chronic renal failure: a meta-analysis. *Front Pharmacol*. 2023;14:1108861. doi:10.3389/fphar.2023.1108861
39. Xun T, Wang X, Zhao J, et al. Advanced oxidation protein products regulate the pharmacokinetics of aloe-emodin, emodin, rhein, and chrysophanol in chronic kidney disease rats. *Clin Complement Med Pharmacol*. 2023;3(3):100087. doi:10.1016/j.ccmp.2023.100087
40. Wang YN, Zhang ZH, Liu HJ, et al. Integrative phosphatidylcholine metabolism through phospholipase $A_2$ in rats with chronic kidney disease. *Acta Pharmacol Sin*. 2023;44(2):393–405. doi:10.1038/s41401-022-00947-x
41. Lu L, Shuang R, Cao F, et al. Emodin inhibits AIM2 inflammasome activation via modulating K27-linked polyubiquitination to attenuate renal fibrosis. *Phytother Res*. 2024;2024:1.
42. Yuan X, Tang W, Lin C, He H, Li L. Chrysophanol ameliorates oxidative stress and pyroptosis in mice with diabetic nephropathy through the Kelch-like ECH-associated protein 1/nuclear factor erythroid 2-related factor 2 signaling pathway. *Acta Biochim Pol*. 2023;70(4):891–897. doi:10.18388/abp.2020_6778
43. Xiong D, Hu W, Han X, Cai Y. Rhein inhibited ferroptosis and emt to attenuate diabetic nephropathy by regulating the Rac1/NOX1/β-Catenin axis. *Front Biosci*. 2023;28(5):100. doi:10.31083/j.fbl2805100
44. Xiang H, Zuo J, Guo F, Dong D. What we already know about rhubarb: a comprehensive review. *Chin Med*. 2020;15(1):88. doi:10.1186/s13020-020-00370-6
45. Yao M, Li J, He M, et al. Investigation and identification of the multiple components of *Rheum officinale* Baill. using ultra-high-performance liquid chromatography coupled with quadrupole-time-of-flight tandem mass spectrometry and data mining strategy. *J Sep Sci*. 2021;44(3):681–690. doi:10.1002/jssc.202000735
46. Wang Y, Yu F, Li A, et al. The progress and prospect of natural components in rhubarb (*Rheum ribes* L.) in the treatment of renal fibrosis. *Front Pharmacol*. 2022;13:919967. doi:10.3389/fphar.2022.919967
47. Cao YJ, Pu ZJ, Tang YP, et al. Advances in bio-active constituents, pharmacology and clinical applications of rhubarb. *Chin Med*. 2017;12(1):36. doi:10.1186/s13020-017-0158-5
48. Wen Y, Yan PJ, Fan PX, et al. The application of rhubarb concoctions in traditional Chinese medicine and its compounds, processing methods, pharmacology, toxicology and clinical research. *Front Pharmacol*. 2024;15:1442297. doi:10.3389/fphar.2024.1442297
49. Tan P, Zhang L, Zhao YL, et al. A practical method for the simultaneous quantitative determination of twelve anthraquinone derivatives in rhubarb by a single-marker based on ultra-performance liquid chromatography and chemometric analysis. *Anal Methods*. 2016;8(19):3927–3934. doi:10.1039/C5AY03299G
50. Wang J, Zhao Y, Xiao X, et al. Assessment of the renal protection and hepatotoxicity of rhubarb extract in rats. *J Ethnopharmacol*. 2009;124(1):18–25. doi:10.1016/j.jep.2009.04.018
51. Gao Y, Chen X, Fang L, et al. Rhein exerts pro- and anti-inflammatory actions by targeting IKKβ inhibition in LPS-activated macrophages. *Free Radic Biol Med*. 2014;72:104–112. doi:10.1016/j.freeradbiomed.2014.04.001
52. Zhong XF, Huang GD, Luo T, Deng ZY, Hu JN. Protective effect of rhein against oxidative stress-related endothelial cell injury. *Mol Med Rep*. 2012;5:1261–1266. doi:10.3892/mmr.2012.793
53. Xu S, Zheng S, Ma N, et al. Rhein potentiates doxorubicin in treating triple negative breast cancer by inhibiting cancer-associated fibroblasts. *Biochem Pharmacol*. 2024;223:116139. doi:10.1016/j.bcp.2024.116139
54. Zhang Q, Yin S, Liu L, Liu Z, Cao W. Rhein reversal of DNA hypermethylation-associated Klotho suppression ameliorates renal fibrosis in mice. *Sci Rep*. 2016;6(1):34597. doi:10.1038/srep34597
55. Ji L, Gu H. The anti-obesity effects of rhein on improving insulin resistance (IR) and blood lipid levels are involved in endoplasmic reticulum stress (ERs), inflammation, and oxidative stress in vivo and vitro. *Bioengineered*. 2021;12(1):5797–5813. doi:10.1080/21655979.2021.1969196
56. Deng T, Du J, Yin Y, et al. Rhein for treating diabetes mellitus: a pharmacological and mechanistic overview. *Front Pharmacol*. 2022;13:1106260. doi:10.3389/fphar.2022.1106260
57. Yin C, Han X, Lu Q, et al. Rhein incorporated silk fibroin hydrogels with antibacterial and anti-inflammatory efficacy to promote healing of bacteria-infected burn wounds. *Int J Biol Macromol*. 2022;201:14–19. doi:10.1016/j.ijbiomac.2021.12.156
58. Hu HC, Zheng LT, Yin HY, et al. A significant association between rhein and diabetic nephropathy in animals: a systematic review and meta-analysis. *Front Pharmacol*. 2019;10:1473. doi:10.3389/fphar.2019.01473
59. Jing D, Bai H, Yin S. Renoprotective effects of emodin against diabetic nephropathy in rat models are mediated via PI3K/Akt/GSK-3 β and Bax/caspase-3 signaling pathways. *Exp Ther Med*. 2017;14:5163–5169. doi:10.3892/etm.2017.5131
60. PrateekshaYusuf MA, Singh BN, Singh BN, et al. Chrysophanol: a natural anthraquinone with multifaceted biotherapeutic potential. *Biomolecules*. 2019;9(2):68. doi:10.3390/biom9020068
61. Lu J, Miao Z, Jiang Y, et al. Chrysophanol prevents IL-1β-Induced inflammation and ECM degradation in osteoarthritis via the Sirt6/NF-κB and Nrf2/NF-κB axis. *Biochem Pharmacol*. 2023;208:115402. doi:10.1016/j.bcp.2022.115402
62. Jiang F, Jiang J, He W, et al. Chrysophanol alleviates acute lung injury caused by *Klebsiella pneumoniae* infection by inhibiting pro-inflammatory cytokine production. *Phytother Res*. 2023;37:2965–2978. doi:10.1002/ptr.7792
63. Zhao Y, Fang Y, Li J, et al. Neuroprotective effects of chrysophanol against inflammation in middle cerebral artery occlusion mice. *Neurosci Lett*. 2016;630:16–22. doi:10.1016/j.neulet.2016.07.036
64. Liu D, Mao X, Zhang G, et al. Antifungal activity and mechanism of physcion against *Sclerotium rolfsii*, the causal agent of peanut southern blight. *J Agric Food Chem*. 2024;72(28):15601–15612. doi:10.1021/acs.jafc.4c02519
65. Dong X, Wang L, Song G, et al. Physcion protects rats against cerebral ischemia-reperfusion injury via inhibition of TLR4/NF-κB signaling pathway. *Drug Des Devel Ther*. 2021;15:277–287. doi:10.2147/DDDT.S267856

66. He Y, Xi J, Fang J, Zhang B, Cai W. Aloe-emodin alleviates doxorubicin-induced cardiotoxicity via inhibition of ferroptosis. *Free Radic Biol Med*. 2023;206:13–21. doi:10.1016/j.freeradbiomed.2023.06.025
67. Li X, Yao M, Li L, et al. Aloe-emodin alleviates cerebral ischemia-reperfusion injury by regulating microglial polarization and pyroptosis through inhibition of NLRP3 inflammasome activation. *Phytomedicine*. 2024;129:155578. doi:10.1016/j.phymed.2024.155578
68. Yu J, Zhao X, Yan X, et al. Aloe-emodin ameliorated MI-induced cardiac remodeling in mice via inhibiting TGF-β/SMAD signaling via up-regulating SMAD7. *Phytomedicine*. 2023;114:154793. doi:10.1016/j.phymed.2023.154793
69. Teka T, Zhang L, Ge X, et al. Stilbenes: source plants, chemistry, biosynthesis, pharmacology, application and problems related to their clinical application-a comprehensive review. *Phytochemistry*. 2022;197:113128. doi:10.1016/j.phytochem.2022.113128
70. Li L, Wei T, Liu S, et al. Complement C5 activation promotes type 2 diabetic kidney disease via activating STAT3 pathway and disrupting the gut-kidney axis. *J Cell Mol Med*. 2021;25(2):960–974. doi:10.1111/jcmm.16157
71. Chen S, Li B, Chen L, Jiang H. Uncovering the mechanism of resveratrol in the treatment of diabetic kidney disease based on network pharmacology, molecular docking, and experimental validation. *J Transl Med*. 2023;21(1):380. doi:10.1186/s12967-023-04233-0
72. Wang Y, Wang B, Qi X, Zhang X, Ren K. Resveratrol protects against post-contrast acute kidney injury in rabbits with diabetic nephropathy. *Front Pharmacol*. 2019;10:833. doi:10.3389/fphar.2019.00833
73. Agarwal SK, Singh SS, Lakshmi V, Verma S, Kumar S. Chemistry and pharmacology of rhubarb (Rheum species) - A review. *J Sci Ind Res*. 2001;60:1–9.
74. Meng XM, Wang L, Nikolic-Paterson DJ, Lan HY. Innate immune cells in acute and chronic kidney disease. *Nat Rev Nephrol*. 2025. doi:10.1038/s41581-025-00958-x
75. Lathiya MK, Errabelli P, Roy S, Mareedu N. Severe acute kidney injury due to oxalate crystal induced severe interstitial nephritis: a case report. *World J Nephrol*. 2024;13(2):93976. doi:10.5527/wjn.v13.i2.93976
76. Peng X, Li H, Zhang W, Zhang D. Discovery and verification of mmu_Circ_26986/hsa_Circ_0072463 as a potential biomarker and intervention target for sepsis-associated acute kidney injury. *Cell Mol Life Sci*. 2024;81(1):154. doi:10.1007/s00018-023-05079-x
77. Ibanez B, Heusch G, Ovize M, Van de Werf F. Evolving therapies for myocardial ischemia/reperfusion injury. *J Am Coll Cardiol*. 2015;65:1455–1471. doi:10.1016/j.jacc.2015.02.032
78. Garcia G, Pacchini VR, Zamoner W, Balbi AL, Ponce D. Drug-induced acute kidney injury: a cohort study on incidence, identification of pathophysiological mechanisms, and prognostic factors. *Front Med*. 2024;11:1459170. doi:10.3389/fmed.2024.1459170
79. Wang Y, Kuang Z, Xing X, et al. Proximal tubular FHL2, a novel downstream target of hypoxia inducible factor 1, is a protector against ischemic acute kidney injury. *Cell Mol Life Sci*. 2024;81(1):244. doi:10.1007/s00018-024-05289-x
80. Bellomo R, Kellum JA, Ronco C, et al. Acute kidney injury in sepsis. *Intensive Care Med*. 2017;43(6):816–828. doi:10.1007/s00134-017-4755-7
81. Hsiao CY, Pan HC, Wu VC, et al. Acute kidney injury in patients with COVID-19 compared to those with influenza: a systematic review and meta-analysis. *Front Med*. 2023;10:1252990. doi:10.3389/fmed.2023.1252990
82. Fu Y, Dong Z. Immune response in COVID-19-associated acute kidney injury and maladaptive kidney repair. *Integr Med Nephrol Androl*. 2023;10:e00022.
83. Fisher M, Neugarten J, Bellin E, et al. AKI in hospitalized patients with and without COVID-19: a comparison study. *J Am Soc Nephrol*. 2020;31:2145–2157. doi:10.1681/ASN.2020040509
84. Li JY, Sun XA, Wang X, et al. PGAM5 exacerbates acute renal injury by initiating mitochondria-dependent apoptosis by facilitating mitochondrial cytochrome c release. *Acta Pharmacol Sin*. 2024;45:125–136. doi:10.1038/s41401-023-01151-1
85. Deng F, Zhang H, Zhou W, et al. TRPA1 promotes cisplatin-induced acute kidney injury via regulating the endoplasmic reticulum stress-mitochondrial damage. *J Transl Med*. 2023;21:695. doi:10.1186/s12967-023-04351-9
86. Jesinkey SR, Funk JA, Stallons LJ, et al. Formoterol restores mitochondrial and renal function after ischemia-reperfusion injury. *J Am Soc Nephrol*. 2014;25(6):1157–1162. doi:10.1681/ASN.2013090952
87. Li XL, Liu XW, Liu WL, et al. Inhibition of TMEM16A improves cisplatin-induced acute kidney injury via preventing DRP1-mediated mitochondrial fission. *Acta Pharmacol Sin*. 2023;44:2230–2242. doi:10.1038/s41401-023-01122-6
88. Oh H, You JS, Bae H, Park GB, Chung YE. Delivery of recombinant sestrin2 ameliorates oxidative stress, mitochondrial damage and renal dysfunction in contrast-induced acute kidney injury. *Biochem Pharmacol*. 2023;215:115761. doi:10.1016/j.bcp.2023.115761
89. Xiong YB, Huang WY, Ling X, et al. Mitochondrial calcium uniporter promotes kidney aging in mice through inducing mitochondrial calcium-mediated renal tubular cell senescence. *Acta Pharmacol Sin*. 2024;45:2149–2162. doi:10.1038/s41401-024-01298-5
90. Cai F, Li D, Xie Y, et al. Sulfide: quinone oxidoreductase alleviates ferroptosis in acute kidney injury via ameliorating mitochondrial dysfunction of renal tubular epithelial cells. *Redox Biol*. 2024;69:102973. doi:10.1016/j.redox.2023.102973
91. Pei S, Zheng L, Tian Z, et al. High concentration hydrogen attenuates sepsis-induced acute kidney injury by promoting mitochondrial biogenesis and fusion. *Int Immunopharmacol*. 2024;143:113410. doi:10.1016/j.intimp.2024.113410
92. Linkermann A, Chen GC, Dong GE, et al. Regulated cell death in AKI. *J Am Soc Nephrol*. 2014;25(12):2689–2701. doi:10.1681/ASN.2014030262
93. Lutz J, Thurmel K, Heemann U. Anti-inflammatory treatment strategies for ischemia/reperfusion injury in transplantation. *J Inflamm*. 2010;7(1):27. doi:10.1186/1476-9255-7-27
94. Liu S, Luo XH, Liu YF, Zouboulis CC, Shi G. Emodin exhibits anti-acne potential by inhibiting cell growth, lipogenesis, and inflammation in human SZ95 sebocytes. *Sci Rep*. 2023;13(1):21576. doi:10.1038/s41598-023-48709-x
95. Gao J, Li Y, Chen J, et al. Emodin ameliorates acute radiation proctitis in mice by regulating AKT/MAPK/NF-κB/VEGF pathways. *Int Immunopharmacol*. 2024;132:111945. doi:10.1016/j.intimp.2024.111945
96. Wang L, Wang X, Li G, et al. Emodin ameliorates renal injury and fibrosis via regulating the miR-490-3p/HMGA2 axis. *Front Pharmacol*. 2023;14:1042093. doi:10.3389/fphar.2023.1042093
97. Lin SY, Lai WW, Ho CC, et al. Emodin induces apoptosis of human tongue squamous cancer SCC-4 cells through reactive oxygen species and mitochondria-dependent pathways. *Anticancer Res*. 2009;29(1):327–335.
98. Wang Y, Liu Q, Cai J, et al. Emodin prevents renal ischemia-reperfusion injury via suppression of CAMKII/DRP1-mediated mitochondrial fission. *Eur J Pharmacol*. 2022;916:174603. doi:10.1016/j.ejphar.2021.174603

99. Mei JX, Yang LL, Wang DQ, Wang HX. Efficacy and safety of Shenkang injection in the treatment of chronic renal failure a protocol of a randomized controlled trial. *Medicine*. 2021;100:e27748.
100. Li Y, Xiong WJ, Yang J, et al. Attenuation of inflammation by emodin in lipopolysaccharide-induced acute kidney injury via inhibition of Toll-like receptor 2 signal pathway. *Iran J Kidney Dis*. 2015;9(3):202–208.
101. Lin CH, Tseng HF, Hsieh PC, et al. Nephroprotective role of chrysophanol in hypoxia/reoxygenation-induced renal cell damage via apoptosis, ER stress, and ferroptosis. *Biomedicines*. 2021;9(9):1283. doi:10.3390/biomedicines9091283
102. Ma S, Xu H, Huang W, et al. Chrysophanol relieves cisplatin-induced nephrotoxicity via concomitant inhibition of oxidative stress, apoptosis, and inflammation. *Front Physiol*. 2021;12:706359. doi:10.3389/fphys.2021.706359
103. Vazquez-Carballo C, Guerrero-Hue M, Garcia-Caballero C, et al. Toll-like receptors in acute kidney injury. *Int J Mol Sci*. 2021;22(2):816. doi:10.3390/ijms22020816
104. Li H, Ren Q, Hu Y, et al. SKLB023 protects against inflammation and apoptosis in sepsis-associated acute kidney injury via the inhibition of toll-like receptor 4 signaling. *Int Immunopharmacol*. 2024;139:112668. doi:10.1016/j.intimp.2024.112668
105. Song N, Xu Y, Paust HJ, et al. IKK1 aggravates ischemia-reperfusion kidney injury by promoting the differentiation of effector T cells. *Cell Mol Life Sci*. 2023;80(5):125. doi:10.1007/s00018-023-04763-2
106. Wang J, Wang J, Lu C, et al. ISL1-overexpressing BMSCs attenuate renal ischemia-reperfusion injury by suppressing apoptosis and oxidative stress through the paracrine action. *Cell Mol Life Sci*. 2024;81(1):312. doi:10.1007/s00018-024-05354-5
107. Xie J, Guo Q. Apoptosis antagonizing transcription factor protects renal tubule cells against oxidative damage and apoptosis induced by ischemia-reperfusion. *J Am Soc Nephrol*. 2006;17(12):3336–3346. doi:10.1681/ASN.2006040311
108. Chen Y, Wu MF, Xie MM, et al. Cpd-A1 alleviates acute kidney injury by inhibiting ferroptosis. *Acta Pharmacol Sin*. 2024;45(8):1673–1685. doi:10.1038/s41401-024-01277-w
109. Du X, Ma X, Tan Y, et al. B cell-derived anti-beta 2 glycoprotein I antibody mediates hyperhomocysteinemia-aggravated hypertensive glomerular lesions by triggering ferroptosis. *Signal Transduct Target Ther*. 2023;8(1):103. doi:10.1038/s41392-023-01313-x
110. Ni L, Yuan C, Wu X. Targeting ferroptosis in acute kidney injury. *Cell Death Dis*. 2022;13(2):182. doi:10.1038/s41419-022-04628-9
111. Qiao YY, Ji JL, Hou WL, et al. tRF3-IleAAT reduced extracellular matrix synthesis in diabetic kidney disease mice by targeting ZNF281 and inhibiting ferroptosis. *Acta Pharmacol Sin*. 2024;45(5):1032–1043. doi:10.1038/s41401-024-01228-5
112. Otasevic V, Vucetic M, Grigorov I, Martinovic V, Stancic A. Ferroptosis in different pathological contexts seen through the eyes of mitochondria. *Oxid Med Cell Longev*. 2021;2021(1):5537330. doi:10.1155/2021/5537330
113. Lai W, Huang R, Wang B, et al. Novel aspect of neprilysin in kidney fibrosis via ACSL4-mediated ferroptosis of tubular epithelial cells. *MedComm*. 2023;4(4):e330. doi:10.1002/mco2.330
114. Liang H, Yoo S-E, Na R, et al. Short form glutathione peroxidase 4 is the essential isoform required for survival and somatic mitochondrial functions. *J Biol Chem*. 2009;284(45):30836–30844. doi:10.1074/jbc.M109.032839
115. Zheng J, Conrad M. The metabolic underpinnings of ferroptosis. *Cell Metab*. 2020;32(6):920–937. doi:10.1016/j.cmet.2020.10.011
116. Zhao X, Wu X, Wang H, Lai S, Wang J. Targeted therapy for cisplatin-resistant lung cancer via aptamer-guided nano-zinc carriers containing USP14 siRNA. *MedComm*. 2023;4:e237.
117. Torso NG, Quintanilha JCF, Cursino MA, et al. miR-6805-5p as a biomarker of cisplatin-induced nephrotoxicity in patients with head and neck cancer. *Front Pharmacol*. 2023;14:1275238. doi:10.3389/fphar.2023.1275238
118. Chen HC, Hou HY, Sung JM, Shieh CC. Deletion of NADPH oxidase 2 attenuates cisplatin-induced acute kidney injury through reducing ROS-induced proximal tubular cell injury and inflammation. *Front Med*. 2023;10:1097671. doi:10.3389/fmed.2023.1097671
119. Moreno-Gordaliza E, González-Nicolás M, Lázaro A, et al. Untargeted metabolomics analysis of serum and urine unveils the protective effect of cilastatin on altered metabolic pathways during cisplatin-induced acute kidney injury. *Biochem Pharmacol*. 2024;227:116435. doi:10.1016/j.bcp.2024.116435
120. Qian Y, Zhao N, Wang M, Zou Z, Xie K. P2X7 receptor deficiency attenuates cisplatin-induced kidney injury via inhibiting NLRP3 inflammasome activation. *Biochem Pharmacol*. 2024;226:116369. doi:10.1016/j.bcp.2024.116369
121. Chesnaye NC, Ortiz A, Zoccali C, Stel VS, Jager KJ. The impact of population ageing on the burden of chronic kidney disease. *Nat Rev Nephrol*. 2024;20(9):569–585. doi:10.1038/s41581-024-00863-9
122. Ndongo M, Nehemie LM, Coundoul B, Diouara AAM, Seck SM. Prevalence and outcomes of polycystic kidney disease in African populations: a systematic review. *World J Nephrol*. 2024;13(1):90402. doi:10.5527/wjn.v13.i1.90402
123. Araji G, Keesari PR, Chowdhry V, et al. Vitamin B12 deficiency in dialysis patients: risk factors, diagnosis, complications, and treatment: a comprehensive review. *World J Nephrol*. 2024;13(4):100268. doi:10.5527/wjn.v13.i4.100268
124. Glastras SJ, Pollock CA. Targeted identification of risk and treatment of diabetic kidney disease. *Nat Rev Nephrol*. 2024;20(2):75–76. doi:10.1038/s41581-023-00796-9
125. Meliambro K, He JC, Campbell KN. Podocyte-targeted therapies - progress and future directions. *Nat Rev Nephrol*. 2024;20(10):643–658. doi:10.1038/s41581-024-00843-z
126. Chinnadurai R, Wu HHL, Abuomar J, et al. Antihypertensive prescribing patterns in non-dialysis dependent chronic kidney disease: findings from the Salford kidney study. *World J Nephrol*. 2023;12(5):168–181. doi:10.5527/wjn.v12.i5.168
127. Yin J, Chen H, Zhu B. The safety and efficacy of using uremic clearance granules for treating stages 3 to 5 of chronic kidney disease: a meta-analysis. *Integr Med Nephrol Androl*. 2023;10:e00013.
128. Wang B, Yang LN, Yang LT, et al. Fisetin ameliorates fibrotic kidney disease in mice via inhibiting ACSL4-mediated tubular ferroptosis. *Acta Pharmacol Sin*. 2024;45(1):150–165. doi:10.1038/s41401-023-01156-w
129. Zhong X, Jia J, Tan R, Wang L. Hederagenin improves Adriamycin-induced nephropathy by inhibiting the JAK/STAT signaling pathway. *Integr Med Nephrol Androl*. 2024;11(2):e22–00016. doi:10.1097/IMNA-D-22-00016
130. Sun MY, Ye HJ, Zheng C, et al. Astragalin ameliorates renal injury in diabetic mice by modulating mitochondrial quality control via AMPK-dependent PGC1α pathway. *Acta Pharmacol Sin*. 2023;44(8):1676–1686. doi:10.1038/s41401-023-01064-z
131. Wang YN, Li XJ, Wang WF, et al. Geniposidic acid attenuates chronic tubulointerstitial nephropathy through regulation of the NF - ƙB /Nrf2 pathway via aryl hydrocarbon receptor signaling. *Phytother Res*. 2024;38(11):5441–5457. doi:10.1002/ptr.8324

132. Li XJ, Wang YN, Wang WF, et al. Barleriside A, an aryl hydrocarbon receptor antagonist, ameliorates podocyte injury through inhibiting oxidative stress and inflammation. *Front Pharmacol*. 2024;15:1386604. doi:10.3389/fphar.2024.1386604
133. Jia ZH, Liu ZH, Zheng JM, Zeng CH, Li LS. Combined therapy of rhein and benazepril on the treatment of diabetic nephropathy in db/db mice. *Exp Clin Endocrinol Diabetes*. 2007;115(09):571–576. doi:10.1055/s-2007-981469
134. Chen X, Peng S, Zeng H, Fu A, Zhu Q. Toll-like receptor 4 is involved in a protective effect of rhein on immunoglobulin A nephropathy. *Indian J Pharmacol*. 2015;47(1):27–33. doi:10.4103/0253-7613.150319
135. Peng SN, Zeng HH, Fu AX, Chen XW, Zhu QX. Effects of rhein on intestinal epithelial tight junction in IgA nephropathy. *World J Gastroenterol*. 2013;19(26):4137–4145. doi:10.3748/wjg.v19.i26.4137
136. He D, Lee L, Yang J, Wang X. Preventive effects and mechanisms of rhein on renal interstitial fibrosis in obstructive nephropathy. *Biol Pharm Bull*. 2011;34(8):1219–1226. doi:10.1248/bpb.34.1219
137. Liu M, Wang L, Wu X, et al. Rhein protects 5/6 nephrectomized rat against renal injury by reducing inflammation via NF-κB signaling. *Int Urol Nephrol*. 2021;53(7):1473–1482. doi:10.1007/s11255-020-02739-w
138. Wu X, Liu M, Wei G, et al. Renal protection of rhein against 5/6 nephrectomied-induced chronic kidney disease: role of SIRT3-FOXO3α signalling pathway. *J Pharm Pharmacol*. 2020;72(5):699–708. doi:10.1111/jphp.13234
139. Zhang LS, Li J, Jia-Ping L. Rhein-8-O-β-D-glucopyranoside inhibited high glucose-induced apoptosis of human mesangial cells by regulating the lincRNA ANRIL/let-7a/TGF-β1/Smad signaling pathway. *Exp Ther Med*. 2020;19(4):2871–2878. doi:10.3892/etm.2020.8544
140. Duan S, Wu Y, Zhao C, et al. The Wnt/β-catenin signaling pathway participates in rhein ameliorating kidney injury in DN mice. *Mol Cell Biochem*. 2016;411(1–2):73–82. doi:10.1007/s11010-015-2569-x
141. Duan SY, Zhang SH, Zhang CN, et al. Therapeutic effect of rhein on high glucose-induced podocyte injury via GSK3β-wnt/β-catenin-PPARγ signaling pathway. *Int J Clin Exp Pathol*. 2017;10:6279–6289.
142. Tian N, Gao Y, Wang X, et al. Emodin mitigates podocytes apoptosis induced by endoplasmic reticulum stress through the inhibition of the PERK pathway in diabetic nephropathy. *Drug Des Devel Ther*. 2018;12:2195–2211. doi:10.2147/DDDT.S167405
143. Wang J, Huang H, Liu P, et al. Inhibition of phosphorylation of P38 MAPK involved in the protection of nephropathy by emodin in diabetic rats. *Eur J Pharmacol*. 2006;553(1–3):297–303. doi:10.1016/j.ejphar.2006.08.087
144. Liu H, Wang Q, Shi G, et al. Emodin ameliorates renal damage and podocyte injury in a rat model of diabetic nephropathy via regulating AMPK/mTOR-mediated autophagy signaling pathway. *Diabetes Metab Syndr Obes*. 2021;14:1253–1266. doi:10.2147/DMSO.S299375
145. Ma L, Li H, Zhang S, et al. Emodin ameliorates renal fibrosis in rats via TGF-β1/Smad signaling pathway and function study of Smurf 2. *Int Urol Nephrol*. 2018;50(2):373–382. doi:10.1007/s11255-017-1757-x
146. Li X, Liu W, Wang Q, et al. Emodin suppresses cell proliferation and fibronectin expression via p38MAPK pathway in rat mesangial cells cultured under high glucose. *Mol Cell Endocrinol*. 2009;307(1–2):157–162. doi:10.1016/j.mce.2009.03.006
147. Yang J, Zeng Z, Wu T, et al. Emodin attenuates high glucose-induced TGF-β 1 and fibronectin expression in mesangial cells through inhibition of NF-κB pathway. *Exp Cell Res*. 2013;319(20):3182–3189. doi:10.1016/j.yexcr.2013.10.006
148. Ji J, Tao P, Wang Q, et al. Emodin attenuates diabetic kidney disease by inhibiting ferroptosis via upregulating Nrf2 expression. *Aging*. 2023;15(15):7673–7688. doi:10.18632/aging.204933
149. Guo C, Wang Y, Piao Y, Rao X, Yin D. Chrysophanol inhibits the progression of diabetic nephropathy via inactivation of TGF-β pathway. *Drug Des Devel Ther*. 2020;14:4951–4962. doi:10.2147/DDDT.S274191
150. Dou F, Ding Y, Wang C, et al. Chrysophanol ameliorates renal interstitial fibrosis by inhibiting the TGF-β/Smad signaling pathway. *Biochem Pharmacol*. 2020;180:114079. doi:10.1016/j.bcp.2020.114079
151. Lu Z, Ji C, Luo X, et al. Nanoparticle-mediated delivery of emodin via colonic irrigation attenuates renal injury in 5/6 nephrectomized rats. *Front Pharmacol*. 2020;11:606227. doi:10.3389/fphar.2020.606227
152. Lu L, Li Y. Aloe-emodin ameliorates diabetic nephropathy by targeting interferon regulatory factor 4. *Evid Based Complement Alternat Med*. 2022;2022:2421624. doi:10.1155/2022/2421624
153. Dou F, Liu Y, Liu L, et al. Aloe-emodin ameliorates renal fibrosis via inhibiting PI3K/Akt/mTOR signaling pathway in vivo and in vitro. *Rejuvenation Res*. 2019;22(3):218–229. doi:10.1089/rej.2018.2104
154. Lu X, Xie Q, Pan X, et al. Type 2 diabetes mellitus in adults: pathogenesis, prevention and therapy. *Signal Transduct Target Ther*. 2024;9(1):262. doi:10.1038/s41392-024-01951-9
155. Cao R, Tian H, Zhang Y, et al. Signaling pathways and intervention for therapy of type 2 diabetes mellitus. *MedComm*. 2023;4:e283.
156. Correa-Rotter R, Maple-Brown LJ, Sahay R, Tuttle KR, Ulasi II. New and emerging therapies for diabetic kidney disease. *Nat Rev Nephrol*. 2024;20(3):156–160. doi:10.1038/s41581-023-00782-1
157. Zhou Y, Hou S, Huang XY, et al. Association of podocyte ultrastructural changes with proteinuria and pathological classification in type 2 diabetic nephropathy. *Diabetes Metab*. 2024;50(4):101547. doi:10.1016/j.diabet.2024.101547
158. Zhang R, Wang Q, Li Y, et al. A new perspective on proteinuria and drug therapy for diabetic kidney disease. *Front Pharmacol*. 2024;15:1349022. doi:10.3389/fphar.2024.1349022
159. Ruan Z, Liu J, Liu W, Huang W. Qufeng tongluo decoction may alleviate podocyte injury induced by high glucose and hydrogen peroxide by regulating autophagy. *Integr Med Nephrol Androl*. 2024;11(4):e24–00023. doi:10.1097/IMNA-D-24-00023
160. Zou TF, Liu ZG, Cao PC, et al. Fisetin treatment alleviates kidney injury in mice with diabetes-exacerbated atherosclerosis through inhibiting CD36/fibrosis pathway. *Acta Pharmacol Sin*. 2023;44(10):2065–2074. doi:10.1038/s41401-023-01106-6
161. Zhu X, Deng Z, Cao Y, et al. Resveratrol prevents Drp1-mediated mitochondrial fission in the diabetic kidney through the PDE4D / PKA pathway. *Phytother Res*. 2023;37(12):5916–5931. doi:10.1002/ptr.8004
162. Wolf G, Chen SD, Ziyadeh FN. From the periphery of the glomerular capillary wall toward the center of disease - Podocyte injury comes of age in diabetic nephropathy. *Diabetes*. 2005;54(6):1626–1634. doi:10.2337/diabetes.54.6.1626
163. Zhang Y, Fan S, Hu N, et al. Rhein reduces fat weight in db/db mouse and prevents diet-induced obesity in C57B1/6 mouse through the inhibition of PPARγ signaling. *PPAR Res*. 2012;2012:9. doi:10.1155/2012/374936
164. Zhang Y, Li X, Ruan J, et al. Oleanane type saponins from the stems of *Astragalus membranaceus* (Fisch.) Bge var mongholicus (Bge) Hsiao. *Fitoterapia*. 2016;109:99–105. doi:10.1016/j.fitote.2015.12.006

165. Thomas HY, Ford Versypt AN. Pathophysiology of mesangial expansion in diabetic nephropathy: mesangial structure, glomerular biomechanics, and biochemical signaling and regulation. *J Biol Eng*. 2022;16(1):19. doi:10.1186/s13036-022-00299-4
166. Xu S, Lv Y, Zhao J, et al. The inhibitory effect of rhein on proliferation of high glucose-induced mesangial cell through cell cycle regulation and induction of cell apoptosis. *Pharmacogn Mag*. 2016;12:S257–S63.
167. Wang L, Hu C, Liu S, et al. Plasma lipidomics investigation of hemodialysis effects by using liquid chromatography-mass spectrometry. *J Proteome Res*. 2016;15(6):1986–1994. doi:10.1021/acs.jproteome.6b00170
168. Meng XM, Nikolic-Paterson DJ, Lan HY. TGF-β: the master regulator of fibrosis. *Nat Rev Nephrol*. 2016;12(6):325–338. doi:10.1038/nrneph.2016.48
169. Ren LL, Miao H, Wang YN, et al. TGF-β as a master regulator of aging-associated tissue fibrosis. *Aging and Disease*. 2023;10:5.
170. Ren N, Wang WF, Zou L, et al. The nuclear factor kappa B signaling pathway is a master regulator of renal fibrosis. *Front Pharmacol*. 2023;14:1335094. doi:10.3389/fphar.2023.1335094
171. Sharma S, Anjaneyulu M, Kulkarni SK, Chopra K. Resveratrol, a polyphenolic phytoalexin, attenuates diabetic nephropathy in rats. *Pharmacology*. 2006;76(2):69–75. doi:10.1159/000089720
172. Wang YN, Miao H, Yu XY, et al. Oxidative stress and inflammation are mediated via aryl hydrocarbon receptor signalling in idiopathic membranous nephropathy. *Free Radic Biol Med*. 2023;207:89–106. doi:10.1016/j.freeradbiomed.2023.07.014
173. Xue W, Yang L, Chen C, et al. Wnt/β-catenin-driven EMT regulation in human cancers. *Cell Mol Life Sci*. 2024;81(1):79. doi:10.1007/s00018-023-05099-7
174. Liu HY, Sun XJ, Xiu SY, et al. Frizzled receptors (FZDs) in Wnt signaling: potential therapeutic targets for human cancers. *Acta Pharmacol Sin*. 2024;45(8):1556–1570. doi:10.1038/s41401-024-01270-3
175. Cohen C, Mhaidly R, Croizer H, et al. WNT-dependent interaction between inflammatory fibroblasts and FOLR2+ macrophages promotes fibrosis in chronic kidney disease. *Nat Commun*. 2024;15(1):743. doi:10.1038/s41467-024-44886-z
176. Miao H, Wang YN, Su W, et al. Sirtuin 6 protects against podocyte injury by blocking the renin-angiotensin system by inhibiting the Wnt1/β-catenin pathway. *Acta Pharmacol Sin*. 2023;45(1):137–149. doi:10.1038/s41401-023-01148-w
177. Gu M, Jiang H, Tan M, et al. Palmitoyltransferase DHHC9 and acyl protein thioesterase APT1 modulate renal fibrosis through regulating β-catenin palmitoylation. *Nat Commun*. 2023;14(1):6682. doi:10.1038/s41467-023-42476-z
178. Ming WH, Luan ZL, Yao Y, et al. Pregnane X receptor activation alleviates renal fibrosis in mice via interacting with p53 and inhibiting the Wnt7a/β-catenin signaling. *Acta Pharmacol Sin*. 2023;44(10):2075–2090. doi:10.1038/s41401-023-01113-7
179. Jin B, Liu J, Zhu Y, et al. Kunxian capsule alleviates podocyte injury and proteinuria by inactivating β-catenin in db/db mice. *Front Med*. 2023;10:1213191. doi:10.3389/fmed.2023.1213191
180. Wang M, Chen DQ, Chen L, et al. Novel inhibitors of the cellular renin-angiotensin system components, poricoic acids, target Smad3 phosphorylation and Wnt/β-catenin pathway against renal fibrosis. *Br J Pharmacol*. 2018;175(13):2689–2708. doi:10.1111/bph.14333
181. Peng SN, Zeng HH, Fu AX, Chen XW, Zhu QX. Protection of rhein on IgA nephropathy mediated by inhibition of fibronectin expression in rats. *Indian J Pharmacol*. 2013;45(2):174–179. doi:10.4103/0253-7613.108309
182. Tao P, Huo J, Chen L. Bibliometric analysis of the relationship between gut microbiota and chronic kidney disease from 2001–2022. *Integr Med Nephrol Androl*. 2024;11:e00017.
183. Miao H, Liu F, Wang YN, et al. Targeting *Lactobacillus johnsonii* to reverse chronic kidney disease. *Signal Transduct Target Ther*. 2024;9(1):195. doi:10.1038/s41392-024-01913-1
184. Shi X, Li Z, Lin W, et al. Altered intestinal microbial flora and metabolism in patients with idiopathic membranous nephropathy. *Am J Nephrol*. 2023;54(11–12):451–470. doi:10.1159/000533537
185. Ren Y, Chen L, Guo R, et al. Altered gut mycobiome in patients with end-stage renal disease and its correlations with serum and fecal metabolomes. *J Transl Med*. 2024;22(1):202. doi:10.1186/s12967-024-05004-1
186. Miao H, Wang YN, Yu XY, et al. *Lactobacillus* species ameliorate membranous nephropathy through inhibiting the aryl hydrocarbon receptor pathway via tryptophan-produced indole metabolites. *Br J Pharmacol*. 2024;181(1):162–179. doi:10.1111/bph.16219
187. Li XJ, Shan QY, Wu X, Miao H, Zhao YY. Gut microbiota regulates oxidative stress and inflammation: a double-edged sword in renal fibrosis. *Cell Mol Life Sci*. 2024;81(1):480. doi:10.1007/s00018-024-05532-5
188. Miao H, Wu XQ, Wang YN, et al. 1-Hydroxypyrene mediates renal fibrosis through aryl hydrocarbon receptor signalling pathway. *Br J Pharmacol*. 2022;179(1):103–124. doi:10.1111/bph.15705
189. Cao G, Miao H, Wang YN, et al. Intrarenal 1-methoxypyrene, an aryl hydrocarbon receptor agonist, mediates progressive tubulointerstitial fibrosis in mice. *Acta Pharmacol Sin*. 2022;43:2929–2945. doi:10.1038/s41401-022-00914-6
190. Chen D, Guo Y, Li P. New insights into a novel metabolic biomarker and therapeutic target for chronic kidney disease. *Integr Med Nephrol Androl*. 2024;11(3):e24–00019. doi:10.1097/IMNA-D-24-00019
191. Miao H, Zhang YM, Yu XY, Zou L, Zhao YY. Membranous nephropathy: systems biology-based novel mechanism and traditional Chinese medicine therapy. *Front Pharmacol*. 2022;13:969930. doi:10.3389/fphar.2022.969930
192. Zhao H, Zhao T, Li P. Gut microbiota-derived metabolites: a new perspective of traditional Chinese medicine against diabetic kidney disease. *Integr Med Nephrol Androl*. 2024;11(2):e23–00024. doi:10.1097/IMNA-D-23-00024
193. Miao H, Cao G, Wu XQ, et al. Identification of endogenous 1-aminopyrene as a novel mediator of progressive chronic kidney disease via aryl hydrocarbon receptor activation. *Br J Pharmacol*. 2020;177(15):3415–3435. doi:10.1111/bph.15062
194. Yu W, Yang W, Zhao MY, Meng XL. Functional metabolomics analysis elucidating the metabolic biomarker and key pathway change associated with the chronic glomerulonephritis and revealing action mechanism of rhein. *Front Pharmacol*. 2020;11:554783. doi:10.3389/fphar.2020.554783
195. Song X, Du Z, Yao Z, Tang X, Zhang M. rhein improves renal fibrosis by restoring Cpt1a-mediated fatty acid oxidation through SirT1/STAT3/Twist1 pathway. *Molecules*. 2022;27(7):2344. doi:10.3390/molecules27072344
196. Xu L, Gao J, Huang D, et al. Emodin ameliorates tubulointerstitial fibrosis in obstructed kidneys by inhibiting EZH2. *Biochem Biophys Res Commun*. 2021;534:279–285. doi:10.1016/j.bbrc.2020.11.094

197. Ren L, Guo HN, Yang J, et al. Dissecting efficacy and metabolic characteristic mechanism of taxifolin on renal fibrosis by multivariate approach and ultra-performance liquid chromatography coupled with mass spectrometry-based metabolomics strategy. *Front Pharmacol*. 2020;11:608511. doi:10.3389/fphar.2020.608511
198. Guan Y, Wu XX, Duan JL, et al. effects and mechanism of combination of rhein and danshensu in the treatment of chronic kidney disease. *Am J Chin Med*. 2015;43(07):1381–1400. doi:10.1142/S0192415X15500780
199. Gu M, Zhou Y, Liao N, et al. Chrysophanol, a main anthraquinone from *Rheum palmatum* L. (rhubarb), protects against renal fibrosis by suppressing NKD2/NF-κB pathway. *Phytomedicine*. 2022;105:154381. doi:10.1016/j.phymed.2022.154381
200. Zhu X, Lin Q, Yang Y, et al. αKlotho modulates BNIP3-mediated mitophagy by regulating FoxO3 to decrease mitochondrial ROS and apoptosis in contrast-induced acute kidney injury. *Cell Mol Life Sci*. 2024;81(1):454. doi:10.1007/s00018-024-05473-z
201. Zhang Q, Liu L, Lin W, et al. Rhein reverses Klotho repression via promoter demethylation and protects against kidney and bone injuries in mice with chronic kidney disease. *Kidney Int*. 2017;91(1):144–156. doi:10.1016/j.kint.2016.07.040
202. Bi F, Chen F, Li Y, Wei A, Cao W. Klotho preservation by Rhein promotes toll-like receptor 4 proteolysis and attenuates lipopolysaccharide-induced acute kidney injury. *J Mol Med*. 2018;96(9):915–927. doi:10.1007/s00109-018-1644-7
203. Santos BF, Grenho I, Martel PJ, Ferreira BI, Link W. FOXO family isoforms. *Cell Death Dis*. 2023;14(10):702. doi:10.1038/s41419-023-06177-1
204. Xu Y, Nie L, Yin YG, et al. Resveratrol protects against hyperglycemia-induced oxidative damage to mitochondria by activating SIRT1 in rat mesangial cells. *Toxicol Appl Pharmacol*. 2012;259(3):395–401. doi:10.1016/j.taap.2011.09.028
205. Kim MY, Lim JH, Youn HH, et al. Resveratrol prevents renal lipotoxicity and inhibits mesangial cell glucotoxicity in a manner dependent on the AMPK-SIRT1-PGC1 α axis in db/db mice. *Diabetologia*. 2013;56(1):204–217. doi:10.1007/s00125-012-2747-2
206. Wang XL, Meng LH, Zhao L, et al. Resveratrol ameliorates hyperglycemia-induced renal tubular oxidative stress damage via modulating the SIRT1/FOXO3a pathway. *Diabet Res Clin Pract*. 2017;126:172–181. doi:10.1016/j.diabres.2016.12.005
207. Tu Y, Gu L, Chen D, et al. Rhein inhibits autophagy in rat renal tubular cells by regulation of AMPK/mTOR signaling. *Sci Rep*. 2017;7(1):43790. doi:10.1038/srep43790
208. Pace J, Paladugu P, Das B, He JC, Mallipattu SK. Targeting STAT3 signaling in kidney disease. *Am J Physiol Renal Physiol*. 2019;316:F1151–F61.
209. Chen Y, Mu L, Xing L, Li S, Fu S. Rhein alleviates renal interstitial fibrosis by inhibiting tubular cell apoptosis in rats. *Biol Res*. 2019;52(1):50. doi:10.1186/s40659-019-0257-0
210. Luo Y, Jiang J, Cheng J, et al. inhibitory effects of rhein on renal interstitial fibrosis via the SHH-Gli1 signal pathway. *Evid Based Complement Alternat Med*. 2022;2022:4398265. doi:10.1155/2022/4398265
211. Liang L, Wang W, Chen J, et al. SARS-CoV-2 N protein induces acute kidney injury in diabetic mice via the Smad3-Ripk3/MLKL necroptosis pathway. *Signal Transduct Target Ther*. 2023;8(1):147. doi:10.1038/s41392-023-01410-x



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