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REVIEW

Exploring Chinese Herbal Medicines for Acute Kidney Injury: Pharmacological Mechanisms and Clinical Potential

Yuan Zhou[1–4,*], Sijia Li[5,*], Minghai Shao[1–4], Yiling Qian[1–4], Tianying Lan[1–4], Dongsheng Yao[1–4], Tiantian Zhan[1–4], Tingting Li[1], Ziteng Shao[6], Chaoyang Ye[1–4], Shougang Zhuang[7,8]

[1]Department of Nephrology, Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Shanghai, 201203, People's Republic of China; [2]TCM Institute of Kidney Disease, Shanghai University of Traditional Chinese Medicine, Shanghai, 201203, People's Republic of China; [3]Key Laboratory of Liver and Kidney Diseases (Shanghai University of Traditional Chinese Medicine) Ministry of Education, Shanghai, People's Republic of China; [4]Shanghai Key Laboratory of Traditional Chinese Clinical Medicine, Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Shanghai, 201203, People's Republic of China; [5]Department of Rehabilitation, Zhangjiang Community Health Service Center, Shanghai, 201210, People's Republic of China; [6]College of Traditional Chinese Medicine, Hubei University of Chinese Medicine, Wuhan, Hubei, 430065, People's Republic of China; [7]Department of Medicine, Rhode Island Hospital and Alpert Medical School, Brown University, Providence, RI, 02912, USA; [8]Department of Nephrology, Shanghai East Hospital, Tongji University School of Medicine, Shanghai, 200120, People's Republic of China

*These authors contributed equally to this work

Correspondence: Minghai Shao, Department of Nephrology, Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, No. 528 Zhangheng Road, Pudong District, Shanghai, 201203, People's Republic of China, Email meck.wx@163.com; Shougang Zhuang, Department of Medicine, Rhode Island Hospital and Alpert Medical School, Brown University, Providence, RI, 02912, USA, Email szhuang@lifespan.org

Background: Acute kidney injury (AKI) is a serious clinical condition marked by a rapid decline in renal function, leading to high morbidity, mortality, and healthcare burden. Despite advances in supportive care, effective pharmacologic therapies remain lacking, prompting interest in alternative approaches, including Chinese herbal medicines (CHMs).

Purpose: This review summarizes recent experimental and clinical research on CHMs for AKI, highlighting mechanisms of action, translational challenges, and future directions.

Methods: A narrative review was conducted using PubMed, Web of Science, Google Scholar, and ClinicalTrials.gov through May 2025, with search terms including "acute kidney injury", "Chinese herbal medicine", "natural products", and "plant extracts". Both preclinical and clinical studies were included to provide a comprehensive overview.

Results: Various CHMs and traditional formulations have demonstrated renal protective effects in AKI through anti-inflammatory, antioxidant, anti-apoptotic, and mitochondrial-protective mechanisms. Key pathways targeted include NF-κB, Nrf2, PI3K/Akt, MAPK, and apoptotic regulators like Bcl-2/Bax and caspases. Notable agents include berberine, baicalin, puerarin, and multi-herb formulas such as QiShenYiQi and Jianpi Yishen Tang, which offer multi-targeted therapeutic potential.

Conclusion: CHMs present a promising avenue for AKI treatment by modulating multiple cellular pathways implicated in disease progression. While preclinical studies are encouraging, robust clinical trials and standardization of formulations are critical for validating efficacy and ensuring safety. Integrating CHMs into modern nephrology through evidence-based strategies may enhance therapeutic options for AKI and advance the development of novel, nature-derived treatments.

Keywords: acute kidney injury, AKI, Chinese herbal medicine, natural products, phytotherapy, renal protection, inflammation, oxidative stress

Introduction

Acute kidney injury (AKI) is a clinical syndrome characterized by a sudden loss of kidney function, typically indicated by a rapid increase in serum creatinine (SCr) levels or a significant reduction in urine output over hours to days.[1] AKI represents a critical global public health issue due to its high incidence, morbidity, and mortality. It affects up to 7% of general hospital inpatients and as many as 30% of patients in intensive care units (ICUs).[2] A global prospective study has

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reported even higher incidence rates, with 39% in adults and 53% in children.[3] Alarmingly, the in-hospital mortality rate for AKI can range from 30% to 50%, particularly in patients requiring dialysis.[2]

AKI arises from diverse etiologies, most commonly tubulointerstitial diseases such as acute tubular necrosis and acute interstitial nephritis. Major contributing factors include sepsis, renal ischemia-reperfusion injury (IRI), and nephrotoxicity from medications such as antibiotics, contrast agents, and chemotherapeutic drugs like cisplatin.[2,4]

The pathogenesis of AKI is multifactorial, involving a dynamic interplay between injury, repair, and regeneration. Mechanistic pathways include inflammation, apoptosis, oxidative stress, ferroptosis, pyroptosis, mitochondrial dysfunction, and autophagy.[5] In severe cases, pathological processes such as cell cycle arrest, Wnt/p53 signaling disruption, microvascular dysfunction, hypoxia, and epithelial-to-mesenchymal transition can impede renal recovery and promote progression to chronic kidney disease (CKD).[6]

Although advances have been made in biomarker discovery and supportive care, including fluid management, anti-inflammatory therapies, and renal replacement therapy, no pharmacological agents have been approved to specifically target the renal parenchymal injury characteristic of AKI. Promising preclinical interventions, such as stem cell-derived extracellular vesicles, endothelial-targeted nanotherapies, and small molecule inhibitors, have demonstrated protective effects.[7–9] Nevertheless, clinical trials for several candidate therapies, including natriuretic peptides, statins, erythropoietin, N-acetylcysteine, spironolactone, and pentoxifylline, have largely yielded negative or inconclusive outcomes.[10–12] Even novel approaches such as siRNA-based teprasiran and hepatocyte growth factor (HGF) mimetics (ANG-3777), which have shown early-phase potential, face challenges in achieving widespread clinical implementation.[13]

In contrast, Traditional Chinese Medicine (TCM) offers a multi-targeted, holistic therapeutic strategy that may complement current approaches to AKI. TCM formulations and active herbal components have demonstrated efficacy in experimental and some clinical contexts. For example, curcuminoids have shown protective effects against contrast-induced AKI in patients with CKD,[14] Xuebijing injection improved outcomes in sepsis-associated AKI following the Wenchuan earthquake,[15] and Shenfu injection, when combined with hydration, effectively reduced the incidence of AKI in patients with acute coronary syndrome undergoing percutaneous coronary intervention (PCI).[16] Additional clinical and mechanistic studies have supported the role of TCM in both preventing and managing AKI.[17,18]

However, the broader clinical adoption of TCM for AKI treatment remains limited due to challenges such as insufficient high-quality clinical evidence, uncertainty about pharmacological mechanisms, and lack of standardization in herbal preparations.

This review aims to assess whether and how CHMs confer renoprotective effects in AKI through mechanistically diverse pathways. And critically evaluate recent progress in the use of Chinese herbal medicines for the treatment of AKI, emphasizing their pharmacological mechanisms, clinical efficacy, and research gaps, in order to offer new perspectives for integrative nephrology care.

Clinical Studies and TCM Compounds in AKI

Clinical studies have demonstrated that several TCM compounds—particularly injectable formulations—can effectively mitigate AKI caused by various factors such as sepsis, contrast agents, and ischemia-reperfusion injury, especially in critically ill patients in intensive care units. These treatments often exert anti-inflammatory, anti-oxidative, and anti-apoptotic effects, improving renal function and patient prognosis (Table 1).

Shenkang Injection (SKI)

Shenkang Injection (SKI) is a traditional Chinese medicine formulation composed of *Rheum officinale* (rhubarb), *Salvia miltiorrhiza* (danshen), *Carthamus tinctorius* (safflower), and *Astragalus membranaceus*. It is widely used in the management of AKI and CKD. The principal active components include hydroxysafflor yellow A (HSYA), tanshinol, rheum emodin, and astragaloside IV. A meta-analysis of 11 studies involving 416 pairs of patients demonstrated that SKI may significantly reduce SCr, blood urea nitrogen (BUN), cystatin C (CysC), 24-hour urinary protein levels, and APACHE II scores in patients with AKI, while maintaining a favorable safety profile. The incidence of adverse events was comparable to that in the control groups.[19]

Table 1 Clinical Studies and TCM Compounds in AKI

TCM Preparation	Disease	Number of Cases	Outcome	Reference
Shenkang injection (SKI)	(senile multiple organ failure, coronary artery surgery, sepsis, primary nephrotic syndrome, etc.) various AKI	416 pairs	↓SCr, BUN, CysC, 24hUpro ↓APACHE II score	[19]
Xuebijing injection (XBJI)	Meta: Sepsis Patients with AKI	320 pairs	↓Bun, SCr, CysC ↓renal function recovery time (6.12 ± 1.66 days vs 8.66 ± 1.17 days) ↓sequential organ failure score (7.22 ± 0.86 points vs 8.61 ± 0.97 points) ↓ICU time (16.43 ± 2.37 days vs 12.15 ± 2.56 days)	[20]
	Sepsis-AKI patients were injured in an earthquake	55 (27,28)	↓Bun, SCr, IL-6, (P <0.05)	[15]
Danhong injection (DHI)	Con-AKI patients	423 pairs	↓incidence (2.4% vs 5.7%), (P<0.05) ↓Stage I of AKI (P<0.05)	[21]
		40 pairs	↓incidence (5.0% vs 12.5%) SCr level recovery time: 48h vs 72h	[22]
Shenfu injection (SFI)	Con-AKI patients of ACS	74 pairs	↓incidence (2.7% vs 16.2%), (P<0.05); ↓urinary NGAL, 12 h after PCI (P<0.05)	[16]
Chuan Huang Fang (CHF)	AKI (grades 1–2) on CKD (stages 2–4)	9 pairs	↓SCr, Bun, UA, ↓urinary NGAL, IL-18	[23]
Astragalus injection (ASI)	Infants undergoing cardiac surgery with CPB	20 pairs	↓serum TNF-alpha, IL-6 ↓urinary NAG	[24]
Qishen Huoxue Granules (QHG)	Critical AKI patients	52 (25,27)	↓renal function recovery time, ↓mechanical ventilation, vasoactive drugs	[25]
Compound glycyrrhizin	Vancomycin-related AKI in patients undergoing orthopedic / trauma / burn surgery	740 patients	Independent protective factors for AKI	[26]

Note: ↓reduce or inhibit.

Abbreviations: ACS, acute coronary syndrome; AKI, acute kidney injury; BUN, blood urea nitrogen; CKD, chronic kidney disease; Con-AKI, contrast-induced AKI; CPB, cardiopulmonary bypass; CysC, cystatin C; NAG, n-acetyl-d-glucosaminidase; NGAL, neutrophil gelatinase-associated lipocalin; PCI, percutaneous coronary intervention; SCr, serum creatinine; UA, uric acid; 24hUpro, 24-hour urinary protein quantity.

Pharmacological network analyses and animal model studies have further elucidated the mechanisms of SKI, particularly in cisplatin-induced AKI (CIS-AKI). These studies suggest that SKI alleviates kidney injury by modulating inflammatory responses, enhancing antioxidant defenses through the upregulation of superoxide dismutase (SOD) and glutathione (GSH), and reducing malondialdehyde (MDA) levels. Key signaling pathways implicated in its nephroprotective effects include phosphoinositide 3-kinase (PI3K)/AKT, tumor necrosis factor (TNF), mitogen-activated protein kinase (MAPK), and p53, indicating its multifaceted role in regulating inflammation, oxidative stress, and apoptosis.[27]

Xuebijing Injection (XBJI)

Xuebijing injection (XBJI) is derived from the classical TCM formula *Xuefu Zhuyu Decoction*, composed of safflower, Radix Paeoniae Rubra, Rhizoma Ligustici Chuanxiong, Salvia miltiorrhiza, and Angelica sinensis. XBJI has been widely used for the treatment of sepsis-associated AKI (SEP-AKI).

In a retrospective study of 55 patients injured in the Sichuan earthquake, the XBJI group (n=28) showed significantly lower creatine phosphokinase (CPK), BUN, SCr, and IL-6 levels on days 5, 7, and 10 compared to the control group.[15] A meta-analysis involving 640 patients with SEP-AKI further confirmed that XBJI improves renal function, shortens recovery time, reduces ICU stay, and demonstrates superior efficacy compared to conventional Western treatments.[20] Animal studies suggest that XBJI enhances renal perfusion, mitigates cortical microcirculatory disturbances, and

suppresses local inflammation in SEP-AKI rats.[28] It also reduces AKI severity in paraquat poisoning by downregulating pro-inflammatory cytokines interleukin-1b (IL-1β), interleukin-6 (IL-6), and TNF-α, as well as lowering BUN and SCr levels.[29]

Danhong Injection (DHI)

DHI, composed of Salvia miltiorrhiza and safflower, has shown efficacy in the prevention of contrast-induced nephropathy (CIN).

In a large cohort study of 12,867 patients undergoing coronary angiography or enhanced imaging procedures, the incidence of CIN was significantly lower in the DHI group than in the control group (2.4% vs 5.7%).[21] A randomized controlled trial involving 80 patients undergoing PCI revealed that DHI accelerated the normalization of SCr levels post-operation—from 72 hours in the control group to 48 hours in the treatment group—while also reducing the incidence of CIN.[22]

Shenfu Injection (SFI)

Shenfu injection (SFI), composed of red ginseng and aconite, exhibits significant protective effects against both CIN and ischemia-reperfusion injury (IRI)-induced AKI. Its mechanisms include antioxidant, anti-inflammatory, energy metabolism enhancement, and apoptosis inhibition.

A randomized controlled trial involving 148 patients with acute coronary syndrome undergoing PCI found that CIN incidence was significantly lower in the SFI group compared to controls (2 vs 12 cases).[16] Animal studies further demonstrate SFI's protective role in post-cardiopulmonary resuscitation AKI and hemorrhagic shock-induced renal injury by regulating cytokines, enhancing energy metabolism, and reducing urinary neutrophil gelatinase-associated lipocalin (NGAL).[30,31] Additionally, SFI increases SOD activity and decreases MDA levels in IRI-AKI rats, indicating reduced oxidative stress.[32]

Chuan Huang Fang (CHF)

Chuan Huang Fang (CHF) is a compound formula consisting of prepared rhubarb, Rhizoma Ligustici Chuanxiong, Smilacis glabrae, Coptidis rhizome, Codonopsis pilosula, and Cordyceps sinensis, among others. It has shown renal protective effects in patients with CKD complicated by AKI.

A multicenter randomized controlled trial[23] involving 98 patients with CKD stages 2–4 showed that CHF combined with reduced glutathione (RG) led to significantly greater reductions in SCr, BUN, uric acid (UA), urinary NGAL, and IL-18, compared to RG alone. Mechanistically, rhubarb and Rhizoma Ligustici Chuanxiong may suppress the p38 MAPK/p53 pathway, thereby reducing renal tubular apoptosis and fibrosis.[33]

Astragalus Injection (ASI)

Astragalus injection has demonstrated benefits in pediatric patients undergoing cardiopulmonary bypass (CPB). In a clinical study involving 40 infants undergoing cardiac surgery, the ASI group (2 mL/kg dose) showed reduced levels of serum TNF-α, IL-6, and urinary N-acetyl-β-D-glucosaminidase (NAG), indicating lower inflammation and renal tubular damage.[24]

Qishen Huoxue Granules (QHG)

Qishen Huoxue Granules (QHG), composed of *Radix Astragali, Salvia miltiorrhiza, Radix Paeoniae Rubra, Flos Carthami*, and *Radix Angelicae Sinensis*, have shown promising results in critically ill AKI patients.

In a study of 52 ICU patients, those who received QHG in combination with continuous renal replacement therapy (CRRT) experienced significantly faster renal recovery, as well as reduced durations of mechanical ventilation and vasoactive drug use, compared to CRRT alone.[25]

Conclusion

An increasing body of clinical evidence supports the efficacy and safety of TCM formulations in the prevention and treatment of acute kidney injury (AKI). Xuebijing injection (XBJI) has demonstrated effectiveness in the management of SEP-AKI, while DHI and SFI exhibit prophylactic benefits against CIN and IRI-AKI, respectively. CHF and ASI have shown renoprotective effects in patients with CKD and in pediatric populations. Additionally, QHG holds promise for critically ill patients by promoting renal recovery and reducing reliance on supportive interventions. These findings highlight the potential of integrative approaches that combine TCM with conventional therapies to address the complex and multifactorial pathophysiology of AKI. Nonetheless, further large-scale, multicenter randomized controlled trials are essential to standardize treatment protocols, elucidate underlying mechanisms, and establish long-term efficacy and safety profiles.

Experimental Studies of Single Chinese Herbs or Monomers in AKI

A growing body of experimental research has highlighted the potential of TCM interventions in the treatment and prevention of AKI. Among the most extensively studied herbs are *Astragalus, licorice, rhubarb, Rhizoma Coptidis, Salvia miltiorrhiza, Scutellaria baicalensis, and Radix Puerariae*, along with their active extracts or monomeric compounds.

Experimental models commonly employed in this research include SEP-AKI, CIN, IRI-AKI, and cisplatin (CIS)-AKI. The protective effects of these agents are primarily mediated through anti-inflammatory and antioxidant mechanisms, as well as through the regulation of apoptosis, and restoration of mitochondrial structure and function. These findings provide a compelling rationale for further exploration of TCM-derived compounds as potential therapeutic agents in AKI.

Astragalus and Its Components: Astragaloside IV (AS-IV) and Astragalus Polysaccharide (APS)

Astragalus membranaceus, known as *Huangqi* in TCM, has been widely used for over two millennia to alleviate symptoms associated with kidney disorders, particularly edema. Its pharmacologically active constituents include astragaloside IV (AS-IV) and astragalus polysaccharides (APS), which have demonstrated significant renoprotective effects across various AKI models, such as SEP-AKI, CIS-AKI, CIN, IRI-AKI, and crush syndrome (Table 2).

The protective mechanisms of AS-IV and APS involve several aspects: including anti-inflammatory and antioxidant effects; mitochondrial protection and improved energy metabolism; modulation of apoptosis, autophagy, and pyroptosis and Inhibition of endoplasmic reticulum (ER) stress and epithelial-mesenchymal transition (EMT).

In IRI-AKI rat models, AS-IV significantly reduced SCr levels, alleviated renal tubular epithelial injury, upregulated Nrf2 (nuclear factor erythroid 2-related factor 2) and heme oxygenase 1 (HO-1) expression, and enhanced antioxidant enzyme activity—thereby attenuating oxidative stress and apoptosis.[34] Moreover, AS-IV suppressed ferroptosis by increasing GPX4 (glutathione peroxidase 4) and SLC7A11 (a sodium-independent cystine-glutamate antiporter) expression, reducing ROS and Fe^{2+} accumulation, and promoting cell proliferation in hypoxia-reoxygenation injury models.[36] Inflammation was also modulated through downregulation of NLRP2/4 and reduction in serum urea nitrogen and SCr.[35]

APS showed similar protective effects in SEP-AKI mouse models by attenuating renal histopathological damage through the regulation of inflammatory cytokines, apoptosis, ER stress, and EMT.[41]

In SEP-AKI models, AS-IV activated the PI3K/AKT signaling pathway, reduced oxidative stress, preserved mitochondrial function, and downregulated apoptotic proteins such as Bax and cleaved caspase-3.[37,38] It also suppressed cytokine production and inhibited the CCR5 (C-C chemokine receptor 5)/p-ERK (extracellular signal-regulated kinase) pathway, thus enhancing antioxidant defenses during bacterial endotoxinemia[39] Furthermore, AS-IV was found to prevent pyroptosis in lipopolysaccharide (LPS)-stimulated HK-2 cells and septic rats by modulating SIRT1-mediated deacetylation of forkhead box class O 3a (FOXO3a).[40]

In CIS-AKI, AS-IV and APS exhibited renoprotection primarily through the inhibition of inflammation, oxidative stress, and mitochondrial dysfunction.[43–45] The mechanisms included suppression of NLRP3 inflammasome activation, upregulation of Nrf2 (Nuclear factor erythroid 2-related factor 2), inhibition of NF-κB (nuclear factor kappa B) signaling, and protection against mitochondria-mediated apoptosis.[42,43]

Table 2 The Mechanisms of Astragalus Extract AS-IV and APS in Improving AKI

Herbal/Extract	Animal Model	Outcome	Mechanism	Reference
AS-IV	IRI- AKI rat model	↓SCr, prevented AKI from transforming into CKD	↑Nrf2 and HO-1, antioxidant enzyme, SOD,↓apoptosis, MDA	[34]
		↓BUN, SCr and renal pathological damage;	↓NLRP2, NLRP4	[35]
	OGD/R-injured HUVECs	↓Ferroptosis, improved cell proliferation	↓ROS and Fe2+, ↑ GPX4 and SLC7A11	[36]
AS-IV	CLP sepsis mouse model, HK-2 cells treated with LPS	↓renal tubular injury, ↓HK-2 cell viability loss	PI3K/AKT pathway	[37]
	LPS-induced AKI mice	↓kidney tubular injury, improve mitochondrial dysfunction and apoptosis	↓OX; restored cleaved caspase3 pathway	[38]
		↓plasma uric acid, BUN, and urinary albumin	↓Cytokines, CCR5, p-ERK; Anti-OX	[39]
	LPS stimulated HK-2 cells	↓pyroptosis, ↓ IL-18, IL-1β ↓cleaved-caspase-1, GSDMD-N,	↓SIRT1 mediated deacetylation of FOXO3a	[40]
APS	LPS-induced AKI mice	↓BUN, SCr and renal pathological damage	↓inflammation, apoptosis, ERS, and EMT	[41]
APS	CIS-AKI rats	↓renal pathological damage ↓apoptosis	↓oxidative damage, protecting mitochondria	[42]
		↓renal pathological damage	↑autophagy, ↓NLRP3, pro-inflammatory cytokines	[43]
AS-IV	CIS-AKI rats	↓ adrenic acid in serum; ↓ L-histidine and L-methionine in urine	↓inflammatory, OX ↑energy metabolism	[44]
	CIS-AKI mice	Anti-OX, anti-inflamation	↑Nrf2 system, ↓NF-kB activation	[45]
AS-IV	Crush syndrome (CS) rats	↓OX, inflammation, mitochondrial dysfunction	↓shock, metabolic acidosis ↑nitric oxide	[46]

Notes: ↓reduce or inhibit; ↑increase or activate.

Abbreviations: AKI, acute kidney injury; APS, astragalus polysaccharide; AS-IV, astragaloside IV; BUN, blood urea nitrogen; CCR5, C-C motif chemokine receptor 5, CIS-AKI, cisplatin-induced AKI; CKD, chronic kidney disease; CLP, cecum ligation puncture; EMT, epithelial-mesenchymal transition; ERS, endoplasmic reticulum stress; GPX4, glutathione peroxidase 4; GSDMD-N, cleaved gasdermin D; HO-1, heme oxygenase-1; HUVECs, human umbilical vein endothelial cells; IRI, ischemia reperfusion injury; LPS, lipopolysaccharide; MDA, molondialdehyde; NLRP3, NOD-like receptor family; pyrin domain containing 3; Nrf2, nuclear factor-related factor 2; OGD/R, oxygen and glucose deprivation/reperfusion; OX, oxidative stress; p-ERK, phosphorylation-activated extracellular signal-regulated kinase; ROS, reactive oxygen species; SCr, serum creatinine; SIRT1, sirtuin 1; SLC7A11, solvent carrier family 7 member 11; SOD, superoxide dismutase.

Additionally, AS-IV improved survival outcomes in crush syndrome models by exerting both systemic and renal antioxidant effects and enhancing mitochondrial function. Its role as a nitric oxide (NO) donor may contribute to these effects by improving tissue perfusion and reducing inflammation.[46]

In the CIN model, AS-IV reduced oxidative stress and tubular apoptosis, thus preserving renal function.[47]

In conclusion, the experimental evidence strongly supports the renoprotective potential of Astragalus and its active components, particularly AS-IV and APS, in various AKI models. These agents exert multifaceted effects by targeting oxidative stress, inflammation, mitochondrial integrity, and programmed cell death pathways. As such, they represent promising candidates for pharmacological development in the management and prevention of AKI.

Licorice and Its Components: Glycyrrhizin, Glycyrol, Glabridin, Liquiritigenin, Isoliquiritigenin, and Licochalcone A

Licorice (*Gancao* in Chinese) is a classic *Qi*-tonifying herb in Traditional Chinese Medicine, derived from the dried root and rhizome of the *Glycyrrhiza* species (commonly *G. uralensis*). It is traditionally used to harmonize herbal formulas and detoxify various agents. Its major bioactive constituents include glycyrrhizin (glycyrrhizic acid), glycyrol, glabridin, liquiritigenin, isoliquiritigenin, and licochalcone A, among others. These compounds have shown protective efficacy in a variety of AKI models, such as hemorrhagic shock-induced AKI, reperfusion injury IRI-AKI, SEP-AKI, CIS-AKI, LPS-induced AKI (LPS-AKI), CIN, and cadmium chloride-induced AKI (Table 3).

Table 3 The Mechanisms of Licorice and Its Components in Improving AKI

Herbal/Extract	Animal Model	Outcome	Mechanism	Reference
Glabridin	Hemorrhagic shock-AKI rats Hypoxia/reoxygenation-HK-2 cells	↓SCr, BUN, NGAL ↓urinary protein/creatinine ↓kidney tubule injury	↓apoptosis, ↑ mitochondrial morphology, ↑ROS, ATP, PGC-1a, ↑ Nrf2/HO-1 pathway	[48]
Glycyrrhizin	Ischemic AKI in mice	AKI-CKD transition	Anti-HMGB1	[49]
	IRI-induced AKI in mice	↓SCr, BUN, TNF-α, interferon-γ, IL-1β and IL-6	Anti-inflammation, anti-OX, ↓apoptosis, HMGB1	[50,51]
Glycyrol	Folic acid-induced AKI mouse RSL3-induced cell model	↓nephrocyte ferroptosis	↓HO-1-mediated heme degradation	[52]
Liquiritigenin	Folic acid-induced AKI mouse	↓ferroptosis ↑ mitochondrial morphology	↑VKORC1 Anti-OX	[53]
Glycyrrhizin	LPS/D-Gal induced AKI mouse	↓ pyrolysis, kidney damage by regulating the	↓TNF-α/HMGB1 inflammatory signaling pathway	[54]
	Sepsis AKI rat model induced by the cecal ligation and perforation	↓pathological changes, BUN, SCr, ↑ the survival rate	↓NF-κB, anti-inflammation, ↓NO, PGE2, iNOS, COX-2, ↓ apoptosis	[55]
Isoliquiritigenin	LPS-induced AKI mice	↓renal inflammation	↓NF-κB p65	[56]
Licochalcone A	LPS-induced AKI mice	↓renal histopathological changes, BUN, SCr	↓NF-κB anti-inflammation	[57]
Isoliquiritigenin	CIS-AKI model	↓renal injury, anti-renal inflammation	↓Formyl peptide receptors 2 (FPR2) in macrophage	[58]
		↓proximal tubular cell injury	↓apoptosis, Anti-inflammation, anti-OX	[59]
Glycyrrhizin	CIN rats model	↓IL-1α, IL-1β, IL-6 KIM-1, NGAL, IL-18, SCr, BUN, LDH, ↓kidney morphology change	↓HMGB1, anti-OX	[60]
Licorice	Cadmium chloride induced AKI rats	↓SCr, BUN, ↓KIM-1 in renal tissue, ↓vacuolization of tubular epithelial cells and endothelial cells	Anti-OX, ↑SOD, CAT and GSH in renal tissue	[61]
Glycyrrhisoflavone, licochalcone B, isoliquiritigenin	Doxorubicin-induced AKI mouse model	↓SCr, BUN	PAI-1 inhibitors	[62]

Notes: ↓reduce or inhibit; ↑increase or activate.

Abbreviations: AKI, acute kidney injury; ATP, adenosine triphosphate; BUN, blood urea nitrogen; CAT, catalase; CIN, contrast-induced nephropathy; CIS-AKI, cisplatin-induced AKI; CKD, chronic kidney disease; COX-2, cyclooxygenase 2; D-Gal, D-galactose; GSH, glutathione; HO-1, heme oxygenase-1; iNOS, inducible nitric oxide synthase; IRI, ischemia reperfusion injury; KIM-1, Kidney injury molecule 1; LDH, lactate dehydrogenase; LPS, lipopolysaccharide; NGAL, neutrophil gelatinase-associated lipocalin; NO, nitric oxide; PGE2, prostaglandin E2; OX, oxidative stress; p-ERK, phosphorylation-activated extracellular signal-regulated kinase; PAI-1, plasminogen activator inhibitor-1; PGC-1a, peroxisome proliferator-activated receptor-γ coactivator-1α; RSL3, glutathione peroxidase 4 inhibitor; SCr, serum creatinine; SOD, superoxide dismutase;; VKORC1, vitamin K epoxide reductase complex subunit 1.

Glycyrrhizin and Glabridin

Glycyrrhizin and glabridin exerts significant renal protection in hemorrhagic shock-induced AKI (HS-AKI), IRI-AKI, CIN and SEP-AKI by reducing inflammation, oxidative stress, and apoptosis.

In HS-AKI and hypoxia/reoxygenation (H/R)-injured HK-2 cells, glabridin decreased SCr, BUN, NGAL, and proteinuria, while improving mitochondrial morphology and ATP levels.[48] These effects are mediated through activation of the Nrf2/HO-1 pathway and upregulation of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1-α).[48]

In IRI-AKI models, glycyrrhizin reduced renal apoptosis and suppressed High-Mobility Group Box 1 (HMGB1), a key pro-inflammatory mediator, while improving renal function shortly after reperfusion.[50,51] Importantly, although preemptive HMGB1 inhibition did not alter acute injury outcomes, it attenuated the AKI-to-CKD transition, suggesting a longer-term benefit.[49]

Glycyrrhizin also shows efficacy in CIN by attenuating oxidative stress and suppressing HMGB1 activity. In CIN rat models, glycyrrhizin significantly reduced serum levels of SCr, BUN, and LDH (lactate dehydrogenase), as well as

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kidney injury biomarkers such as KIM-1, NGAL, and IL-18. Notably, it also decreased systemic and renal HMGB1 levels, alongside downregulation of pro-inflammatory cytokines (IL-1α, IL-1β, IL-6, TNF-α), highlighting its dual anti-inflammatory and antioxidant roles.[60]

A large-scale clinical study conducted in China involving 740 patients demonstrated that administration of compound glycyrrhizin to patients undergoing orthopedic, trauma, or burn surgery significantly reduced the incidence of vancomycin-associated AKI, suggesting its potential clinical utility as a nephroprotective agent.[26]

Glycyrol and Liquiritigenin

Both glycyrol and liquiritigenin protect against ferroptosis, a regulated cell death mechanism implicated in AKI. In RSL3-induced ferroptosis in vitro, glycyrol showed significant protective effects by inhibiting HO-1-mediated heme degradation.[52] In folic acid-induced AKI, liquiritigenin preserved renal function by reducing iron accumulation, MDA levels, and mitochondrial damage, while increasing glutathione and GPX4 expression. Transcriptomic analyses further implicated Vitamin K epoxide reductase complex subunit 1 (VKORC1) upregulation in its protective mechanism.[53]

Isoliquiritigenin and Licochalcone A

Both compounds are effective in LPS-induced AKI models. Glycyrrhizin, isoliquiritigenin, and licochalcone A reduce renal injury by modulating the NF-κB pathway and decreasing pro-inflammatory mediators such as TNF-α, IL-1β, and IL-6. In LPS/D-Gal-induced AKI, glycyrrhizin inhibited pyroptosis via the TNF-α/HMGB1 pathway.[54] In cecal ligation and perforation (CLP)-induced SEP-AKI, glycyrrhizic acid reduced renal inflammation and apoptosis, while enhancing survival.[55] Licochalcone A protected against LPS-AKI by reducing cytokine expression and blocking NF-κB activation.[57] Isoliquiritigenin similarly blocked NF-κB p65 nuclear translocation, thus suppressing inflammation.[56]

Licorice extract and its bioactive constituents—particularly glycyrrhizin, isoliquiritigenin, and licochalcone B—exhibit significant protective effects against drug- and toxin-induced AKI. These include injuries caused by vancomycin, cisplatin, contrast agents, cadmium chloride, and doxorubicin.

In CIS-AKI, isoliquiritigenin has shown robust renoprotective activity by suppressing macrophage-mediated inflammation via inhibition of formyl peptide receptor 2 (FPR2) signaling.[58] Additionally, isoliquiritigenin mitigates proximal tubular injury by reducing oxidative stress, apoptosis, and inflammation.[59]

Cadmium chloride-induced AKI is another condition where licorice extract offers protection through its antioxidative mechanisms. In vivo studies demonstrated that oral administration of aqueous licorice extract (3 mg/mL/kg/day) for four weeks markedly ameliorated renal damage induced by cadmium chloride (10 mg/kg/day). Improvements included lowered SCr and BUN levels, decreased KIM-1 expression, elevated antioxidant enzyme activities (SOD, CAT, GSH), and histological improvements such as reduced vacuolization in glomerular endothelial and renal tubular epithelial cells.[61]

Additionally, glycyrrhisoflavone, licochalcone B, and isoliquiritigenin, acting as plasminogen activator inhibitor-1 (PAI-1) inhibitors, have been shown to reduce SCr and urea nitrogen levels and alleviate renal inflammation in doxorubicin (DOX)-induced AKI models in mice.[62]

In conclusion, licorice and its diverse bioactive constituents demonstrate multifaceted renoprotective properties across a wide range of AKI models. These effects are largely mediated through anti-inflammatory, antioxidant, anti-ferroptotic, anti-apoptotic, and mitochondrial-protective mechanisms. Among these, glycyrrhizin, isoliquiritigenin, and licochalcone A show particularly broad efficacy and are promising therapeutic candidates for both clinical and experimental management of AKI.

Salvia miltiorrhiza and Its Components: Salvianolic Acid, Tanshinone, Magnesium Lithospermate B

Salvia miltiorrhiza, commonly referred to as "Danshen" in Chinese, is a widely used herbal medicine derived from the dried roots of *Salvia miltiorrhiza* Bunge. Its pharmacologically active compounds include tanshinones (tanshinone I, IIA, and IIB), and hydrophilic constituents such as salvianolic acid A (SAA), salvianolic acid B (SAB), tanshinol, and magnesium lithospermate B (MLB).[63] Among these, sodium tanshinone IIA sulfonate and SAA injections are widely

used in Chinese clinical settings for the management of AKI. Various AKI models, including IRI-AKI, SEP-AKI, LPS-AKI, CIN, CIS-AKI, gentamicin-induced AKI, and folic acid-induced AKI, have shown positive responses to *Salvia miltiorrhiza* and its monomers (Table 4).

IRI-AKI

Studies have shown that salvianolate (SAL), salvianolic acid A (SAA), salvianolic acid B (SAB), and tanshinone IIA significantly reduce serum BUN and SCr levels while ameliorating renal histopathological damage. These effects are achieved through mechanisms such as: Activation of the Keap1-Nrf2-ARE pathway,[66] modulation of the Akt/mTOR/4EBP1 signaling cascade,[67] enhancement of Klotho and vascular endothelial growth factor A (VEGF-A) expression,[68] suppression of pyroptosis through the Nrf2/caspase-1 pathway,[69] anti-inflammatory and antioxidant actions via PI3K/Akt and p38 MAPK signaling.[65,70] Moreover, tanshinone IIA improved renal mitochondrial function and oxidative stress markers through the PI3K/Akt/Bad axis,[64] while MLB attenuated AKI-to-CKD progression by regulating cell cycle arrest via the kruppel-like factor 5 (KLF5)/CDK1/cyclin B1 pathway.[71]

SEP/LPS-AKI

In septic models, SAA and tanshinone IIA significantly reduced BUN, SCr, and histological damage. These compounds exerted anti-inflammatory effects by: inhibiting macrophage infiltration and suppressing cytokine release,[73] modulating the toll-like receptor 4 (TLR4)/ER stress/ROS axis,[74] blocking TLR4 dimerization and its downstream NF-κB/MAPK signaling.[72] SAB, in a crush syndrome model, improved kidney function by reducing mitochondrial damage and restoring endothelial integrity.[75]

CIN

Both tanshinone IIA and SAB provided significant protection in CIN by enhancing Nrf2 activity,[80] activating PI3K/Akt/Nrf2 signaling and inhibiting TLR4/NF-κB/NLRP3 pathways.[81,82]

CIS-AKI

In cisplatin-induced nephrotoxicity, *Salvia miltiorrhiza*, SAC, and MLB (magnesium lithospermate B) significantly reduced renal histological damage and biochemical markers. The protective mechanisms include: modulation of PXR/NF-κB signaling,[77] upregulation of HO-1 and NQO1 via Nrf2 signaling,[76] mitochondrial protection and reduction of oxidative stress and apoptosis by SAC and MLB.[78,79]

Other AKI Models

In gentamicin-induced AKI, SAA improved renal function by inhibiting IL-6, IL-12, and MDA, while enhancing T-SOD and reducing KIM-1, NGAL, and proteinuria.[83] In folic acid-induced AKI, tanshinone IIA provided early and late protection by inhibiting glycogen synthase kinase-3 beta (GSK3β), upregulating proliferating cell nuclear antigen (PCNA),[84] and promoting M2 macrophage polarization, thereby preventing AKI-to-CKD transition.[85,86]

Rhubarb and Its Components: Emodin, Rhein, Chrysophanol

Rhubarb, known as *Dahuang* in traditional Chinese medicine, is a widely used botanical remedy for nephropathy. Its primary active constituents—emodin, rhein, and chrysophanol—exhibit distinct protective effects against various models of AKI. Among them, emodin demonstrates broad-spectrum activity, showing therapeutic and preventive efficacy against LPS/SEP-AKI, IRI-AKI, CIS-AKI, and gentamicin-induced renal injury. In contrast, rhein and chrysophanol display more selective activity, with rhein protecting against LPS/SEP-AKI and chrysophanol being primarily effective in CIS-AKI (Table 5).

LPS/SEP-AKI

Rhein and emodin exert potent anti-inflammatory effects in septic or endotoxin-induced AKI. Rhein ameliorates LPS-AKI by upregulating Klotho expression and downregulating TLR4 and NF-κB signaling in renal macrophages and epithelial cells. Notably, knockdown of Klotho attenuates rhein's protective effects, emphasizing its role as a key

Table 4 The Mechanisms of Salvia Miltiorrhiza and Its Components: Salvianolic Acid, Tanshinone, Magnesium Lithospermate B in Improving AKI

Herbal/Extract	Animal Model	Outcome	Mechanism	Reference
Tan IIA	IRI-AKI in obese rats	Improve renal function ↓cell apoptosis	Anti-inflammatory and anti-ox ↓modulating mitochondrial function through PI3K/Akt/Bad pathway	[64]
	IRI-AKI rats	↓renal injury, inflammation	↓myeloperoxidase (MPO), ↓macrophage migration inhibitory factor (MIF) ↓cleaved caspase-3, p38 MAPK	[65]
Salvianolate	IRI-AKI mice/rats	Improve renal function ↓epithelial tubular injury anti-apoptotic	Anti-inflammatory and anti-ox, ↑Keap1-Nrf2-ARE signaling pathway in renal tubular cells	[66]
SAA		↓renal injury, SCr, BUN, ↓apoptosis, OX, ↓platelet activation, ↓urine KIM-1	↑Akt/mTOR/4EBP1 ↓endothelium damages, ↑peritubular capillary integrity, ↑Klotho, VEGF A, ↓renal hypoxia	[67,68]
SAB		↓OX, inflammation, SCr, BUN, renal injury, ↓pyroptosis	↑PI3K, PI3K/Akt ↓Caspase-1-Mediated Pyroptosis, ↑Nrf2 Pathway	[69,70]
MLB	Unilateral IRI AKI-to-CKD mouse model TGF-β- HK-2 cells	↓AKI-to-CKD progression	↓KLF5/CDK1/Cyclin B1 pathway ↓the G2/M phase cell cycle stalling	[71]
Total tanshinones	LPS-induced AKI mice	↓renal injury, death, anti-inflammation	↓TLR4 dimerization, ↑MyD88-TAK1-NF-κB/MAPK	[72]
Tan IIA	LPS-induced AKI mice and HK-2 cells	↓renal injury, ↓apoptosis of RTEC	↓RIP3/FUNDC1 signal pathway	[73]
SAA	SEP-AKI mice	↓renal injury, SCr, BUN, anti-inflammatory	↓bind to Toll-like receptor 4 (TLR4), ↓ERS, ROS	[74]
SAB	Crush syndrome rat model	↑survival rate, kidney function ↓inflammation	Treating shock and metabolic acidosis, ↓mitochondrial dysfunction and endothelial damage	[75]
Danshen	CIS-AKI	↓SCr, renal pathological injury	↑Nrf2/HO-1 and NQO1 anti-OX, ↑GSH-Px, SOD, MDA	[76,77]
Tan IIA		↑ renal arterial perfusion ↑cell necrosis proliferation ↓ renal inflammation	Regulating nuclear receptors ↑PXR and ↓NF-κB signaling in a PXR-dependent manner	[77]
MLB		↓SCr, and renal pathological damage, improved mitochondrial dynamics	↓MDA SOD ↓Bax/Bcl2, cleaved caspase-3/caspase-3 ↓Drp1 expression.	[78]
SAC		↓renal histological changes, ↓SCr and BUN	Anti-inflammatory and anti-ox	[79]
Tan IIA	CIN rats/mice	↓renal tubular necrosis, apoptosis and anti-OX	↑Nrf2	[80]
SAB		↓SCr, renal tubular injuries, ↓apoptosis	↑PI3K/Akt/Nrf2 pathway, anti-ox	[81]
	CON-AKI HK-2 cell	↑cell viability, ↓ROS, apoptosis	↓TLR4/NF-κB/NLRP3 ↓mitochondrial membrane potential	[82]
SAA	Gentamicin induced AKI rats	↓BUN, SCr, KIM-1, ↓NGAL, urine protein ↓pathological injury	Anti-inflammatory and anti-OX ↓ IL-6 and IL-12, MDA ↑T-SOD	[83]
Tan IIA	Folic acid-induced AKI	↓SCr, BUN, NGAL, ↓renal injury, ECM ↓apoptosis, ↓AKI to CKD transition	↓GSK3β, ↑PCNA, ↓TGFβ1 and MCP-1 anti-inflammation	[84–86]

Notes: ↓reduce or inhibit; ↑increase or activate.

Abbreviations: AKI, acute kidney injury; ATP, adenosine triphosphate; BUN, blood urea nitrogen; CDK1, Cyclin dependent kinases 1; CIN, contrast-induced nephropathy; CIS-AKI, cisplatin-induced AKI; Con-AKI, contrast-induced AKI; CKD, chronic kidney disease; ECM, extracellular matrix; GSK3β, glycogen synthase kinase 3β; KIM-1, Kidney injury molecule 1; KLF5, Krüppel-like factor 5; LDH, lactate dehydrogenase; LPS, lipopolysaccharide; MCP-1, monocyte chemoattractant protein-1; MDA, molondialdehyde; MLB, Magnesium lithospermate B, Nrf2, nuclear factor-related factor 2; OX, oxidative stress; PCNA, proliferating cell nuclear antigen; PXR, pregnane X receptor; RTEC, renal tubular epithelial cell; SAA/B/C, Salvianolic acid A/B/C; SCr, serum creatinine; SEP, sepsis; SOD, superoxide dismutase; Tan IIA, Tanshinone IIA; TGFβ1, Transforming growth factor β1.

Table 5 The Mechanisms of Rhubarb and Its Components: Emodin, Rhein, Chrysophanol in Improving AKI

Herbal/Extract	Animal Model	Outcome	Mechanism	Reference
Rhein	LPS/sepsis-induced AKI rats	↓BUN, SCr, TNF-α, IL-1β anti-inflammation,	↑Klotho, ↓TLR4, NF-κB	[87,88]
Emodin	LPS-NRK-52E cells	↓inflammation, TNF-α, IL-1 β, IL-6	↓TLR2 / NF-κB	[89]
	LPS-RAW264.7 macrophages to M1 polarization model	Inhibits M1 macrophage activation	EGFR/MAPK pathway	[90]
	H/R-induced human renal tubular cells	↓apoptosis	↑oxidative stress, MAPK, ↑ Bax/Bcl-2 ratio	[91]
	H/R induced human renal tubular epithelial cells	↓mitochondria-mediated apoptosis, ↓mitochondrial ROS, ↑ adenosine triphosphate	↓phosphorylation of DRP1 at Ser616, ↓mitochondrial fission, restore mitochondrial dynamic balance	[92]
	IRI-AKI mouse	↓renal insufficiency	↓CAMKII/DRP1-mediated mitochondrial fission	[92]
Emodin	IRI-AKI rats Vancomycin-induced HK-2 cells	Improved renal function and renal tubular injury ↓apoptosis	↓p53 ↓cleaved-caspase-3 and pro-caspase-9, ↑Bcl-2, ↓HIF-1α,↑VEGF	[93]
	Gentamicin sulfate induced AKI rats	↓renal pathological injury, total urine protein, BUN, SCr, ↓D-lactic acid, bacterial endotoxin	↓intestinal escherichia coli, enterococcus, ↑ lactic acid bacteria, bifidobacteria	[94]
	DOX-induced AKI mouse	↓SCr, BUN	↓sphingosine kinase 1	[62]
Emodin	CIS-induced NRK-52E cells	↓cell damage, apoptosis	Modulating AMPK/mTOR, ↑ autophagy	[95]
Chrysophanol	CIS-AKI mouse	Improved the kidney function and morphology	Anti-ox, ↓apoptosis ↓IKKβ/IκBα/p65/- NF-κB to anti-inflammation	[96]
Chrysophanol	Hypoxia/reoxygenation-induced renal cell injury	↓apoptosis ↓ERS, ferroptosis	↓cleaved Caspase-3, p-JNK, Bax, ↑ Bcl-2; ↓CHOP, p-IRE1α	[97]
Rhubarb extract	AKI rabbits induced by CPR after cardiac arrest	↓BUN, SCr	↓ NGAL, IL-18 in kidney	[98]

Notes: ↓reduce or inhibit; ↑increase or activate.
Abbreviations: AKI, acute kidney injury; AMPK, Adenosine 5'-monophosphate (AMP)-activated protein kinase; BUN, blood urea nitrogen; CAMKII, calcium/calmodulin-dependent protein kinase II, CHOP, C/EBP-homologous protein; CIS, cisplatin; CPR, cardiopulmonary resuscitation; DOX, doxorubicin; DRP1, dynamin-related protein 1, EGFR, epidermal growth factor receptor; ERS, endoplasmic reticulum stress; H/R, hypoxia/reoxygenation; IκBα, nuclear factor κB inhibitor protein α, IKKβ, inhibitor of kappa B kinase; IRI, ischemia reperfusion injury; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinases; NGAL, neutrophil gelatinase associated lipocalin; OX, oxidative stress; p-IRE1, phospho-inositol-requiring enzyme 1; p-JNK, phospho-c-Jun N-terminal kinase; SCr, serum creatinine; TLR, toll like receptors.

mediator.[87] Rhein also significantly reduces BUN, SCr, TNF-α, and IL-1β in septic models.[88] Emodin, meanwhile, inhibits TLR2-mediated NF-κB signaling, thereby reducing inflammation in LPS-treated renal tubular epithelial cells.[89]

IRI-AKI

In ischemia-reperfusion injury, emodin protects renal function by inhibiting mitochondrial fission and apoptosis. It downregulates pro-apoptotic markers such as p53 and cleaved caspase-3 while upregulating Bcl-2.[93] Emodin also suppresses calcium-calmodulin-dependent protein kinase II (CAMKII)/dynamin-related protein 1(DRP1)-mediated mitochondrial fission, helping restore mitochondrial homeostasis and reduce oxidative stress.[92] It improves ATP production, limits ROS overproduction, and inhibits mitochondrial apoptosis in H/R-injured HK-2 cells. Additionally, emodin regulates MAPK activation and the Bax/Bcl-2 balance to prevent cell death.[91] Rhubarb extract has similarly demonstrated protective effects post-cardiac arrest by lowering BUN, SCr, NGAL, and IL-18 levels in rabbits.[98] Furthermore, chrysophanol reduces apoptosis, ERS and ferroptosis induced by hypoxia/reoxygenation in renal cells. The mechanism is related to the downregulation of cleaved Caspase-3, p-JNK, Bax, CHOP, p-IRE1α and the upregulation of Bcl-2.[97]

CIS-AKI and DOX-AKI

In cisplatin-induced AKI, chrysophanol improves renal function by reducing oxidative stress, inflammation, and apoptosis via the IKKβ/IκBα/NF-κB pathway.[96] Emodin, on the other hand, activates AMP-activated protein kinase (AMPK)/mTOR (mammalian target of rapamycin) -mediated autophagy to protect against cisplatin-induced cell damage.[95] Furthermore, emodin alleviates doxorubicin-induced AKI by inhibiting sphingosine kinase 1, thereby reducing renal injury.[62]

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Gentamicin-Induced AKI

Emodin has shown efficacy in mitigating gentamicin-induced nephrotoxicity by reducing total urinary protein, BUN, SCr, D-lactic acid, and bacterial endotoxin levels. Its mechanism involves modulation of gut microbiota, notably increasing beneficial bacteria (Lactobacillus, Bifidobacterium) while reducing pathogenic strains (Escherichia coli, Enterococcus).[94] It also inhibits M1 macrophage polarization via the epidermal growth factor Receptor (EGFR)/MAPK pathway, helping maintain immune homeostasis and support renal tissue repair.[90]

Rhizoma Coptidis and Its Component: Berberine

Rhizoma Coptidis (*Huanglian*), a traditional Chinese herb, and its primary active compound berberine, are known for their broad pharmacological activities—including anti-inflammatory, antioxidant, antimicrobial, antihypertensive, and metabolic-regulating effects. Notably, Rhizoma Coptidis and berberine have shown renoprotective effects in various types of AKI, such as SEP-AKI, IRI-AKI, CIN) and drug/toxin-induced AKI (eg, cisplatin, gentamicin, doxorubicin, diclofenac, lead, folic acid, and aristolochic acid) (Table 6).

Table 6 The Mechanisms of Rhizoma Coptidis and Its Components Berberine in Improving AKI

Herbal/Extract	Animal Model	Outcome	Mechanism	Reference
Berberine	CIN rats	↓apoptosis and ferroptosis	↑Akt/Foxo3a/Nrf2 signal	[99]
		↓BUN, SCr, KIM-1, DAMPs, HMGB1, HSP70, MCP-1, TNF-α, IL-6, IL-1β	↑mitophagy ↓mitochondrial damage ↓NLRP3 inflammasome	[100]
	CIN rats model and ioversol-treated HK-2 cells	↑autophagy, ↓apoptosis	↓ HDAC4 and FoxO3a	[101]
Berberine	Sepsis-induced AKI	Regulation of metabolism, anti-ox	↑PPARα, ↓NOS2 ↑Nrf2, HO-1	[102]
	CLP-induced sepsis AKI in aged rats	Preserving mitochondrial integrity	↓TLR4/NF-κB and NLRP3 inflammasome, anti-OX	[103]
	Sepsis-induced inner medullary collecting duct3 cells	Anti-inflammation	↓NF-κB	[104]
RCE	SEP-AKI rats	↓BUN, SCr, histological injury ↓ROS	↑Nrf2, HO-1, PPARα ↓nitric oxide synthase 2 (NOS2)	[102]
Berberine	IRI AKI rats	Regulation of intestinal microbiota ↓intestinal inflammation	Sirt1-NF-κB-TLR4 anti-inflammation	[105]
		Improve renal function, ↓apoptosis, anti-inflammation, anti-OX; rearranged intercellular ion concentration	↓Bax, ↑Bcl-2, regulating caspase-mitochondria-dependent pathway; ↑Na(+)/K(+)-ATPase and Ca(2+-) ATPase levels	[106–108]
	H/R-induced renal tubular epithelial cells	↓apoptosis, mitochondrial oxidative stress	↓SPHK1, p38 MAPK, Sirt1/p53, ↑hif-1α in the PI3K/Akt	[109–111]
Berberine	CIS-induced AKI mice	↑ autophagy, Anti-OX, Anti-nflammation, ↓apoptosis	↑Klotho,↓MDA, ↑SOD, ↓HMGB1, RAGE, ↑Bcl-2, ↓Bax	[112]
		↑mitophagy in renal tubular epithelial cells	↑LC3 II/LC3 I, PINK1, Parkin, ↓p62	[113]
		↓ox, inflammation, apoptosis, autophagy	↑Nrf2/HO-1, ↓JNK/p38MAPKs/PARP/Beclin-1	[114,115]
		↓renal pathological injury	↓methylation of N6-methyladenosine	[116]
Berberine and RCE	CIS-AKI rats	↓renal function damage, ↓renal histological damage	↑antioxidant enzyme ↓MDA, ↓TLR4	[117]
Berberine	Aristolochic acid (AA) induced AKI zebrafish and mice	↓ acute nephrotoxicity, ↓ activation of the immune system and tumorigenesis-related pathways	Supramolecular self-assembly formed by berberine and AA (A-B)	[118]

(*Continued*)

Table 6 (Continued).

Herbal/Extract	Animal Model	Outcome	Mechanism	Reference
Berberine	Gentamicin/ diclofenac/lead/ doxorubicin -induced AKI animal models	↓acute nephrotoxicity	Anti-OX, anti-nflammation, ↓apoptosis, ↓mitochondrial dysfunction	[119–123]
	Doxorubicin-induced AKI rats	↓BUN, SCr, KIM-1, renal injury	Anti-OX, anti-inflammation	[121]
	Folic acid-induced AKI	↑pyroptosis in renal tubular epithelial cells	↓METTL3, regulates the ASC/caspase-1/ Gasdermin D axis	[124]

Notes: ↓reduce or inhibit; ↑increase or activate.

Abbreviations: AA, Aristolochic acid; AKI, acute kidney injury; AKT, protein kinase B; ASC, apoptosis - associated speck - like protein containing a CARD; BUN, blood urea nitrogen; CIN, contrast-induced nephropathy; CIS, cisplatin; CLP, cecal ligation and puncture; CIS, cisplatin; DAMPs, damage-associated molecular patterns; Foxo3a, fork head box O3; H/R, hypoxia/reoxygenation; HDAC4, histone deacetylase 4; HMGB1, high mobility group box 1; HO-1, heme oxygenase 1; HSP70, heatshockprotein70; IRI, ischemia reperfusion injury; JNK, c-Jun N-terminal kinase; KIM-1, Kidney injury molecule 1; LC3, microtubule-associated protein 1 light chain 3; MAPK, mitogen-activated protein kinases; MCP-1, monocyte chemoattractant protein-1; MDA, malondialdehyde; METTL3, methyltransferase 3; NLRP3, NOD-like receptor thermal protein domain associated protein 3; NOS2, nitric oxide synthase 2; Nrf2, nuclear factor-related factor 2; OX, oxidative stress; PARP, poly ADP-ribose polymerase; PINK1, PTEN induced kinase 1; PPARα, perixisome proliferator-activated receptor alpha; RCE, rhizoma coptidis extracts; SCr, serum creatinine; SEP, sepsis; Sirt1, silent information regulator 1; SOD, super oxide dismutase; SPHK1, sphingosine kinase 1; TLR, toll like receptors.

SEP-AKI

Rhizoma Coptidis extracts and their primary active component, berberine, exhibit significant renoprotective effects in SEP-AKI, largely attributed to their anti-inflammatory, antioxidant, and mitochondrial-protective activities. In animal models of SEP-AKI, Rhizoma Coptidis extract administration improved renal function and histopathological outcomes, accompanied by a notable reduction in ROS production. Mechanistically, these extracts promote the nuclear translocation of Nrf2, upregulate HO-1protein expression, increase PPARα mRNA levels, and suppress nitric oxide synthase 2 (NOS2) activity, collectively contributing to oxidative stress mitigation.[102] In vitro, berberine suppressed NF-κB signaling to reduce lipopolysaccharide (LPS)-induced inflammatory responses in mouse inner medullary collecting duct 3 (mIMCD3) cells.[104] Furthermore, in aged rat models of SEP-AKI, berberine preserved mitochondrial structural integrity and attenuated inflammation by inhibiting both TLR4/NF-κB signaling and NLRP3 inflammasome activation, highlighting its potential utility in age-related renal vulnerability during septic states.[103]

IRI-AKI

Berberine demonstrates substantial renoprotective efficacy in IRI-AKI, primarily through its anti-apoptotic, anti-inflammatory, and organelle-protective mechanisms. In IRI-AKI rat models, berberine administration significantly improved renal function and tubular morphology, mediated by the suppression of both ER and mitochondrial oxidative stress in hypoxia/reoxygenation (H/R)-injured renal tubular epithelial cells. Mechanistically, berberine regulates multiple apoptotic and stress-related pathways. It modulates intestinal microbiota composition and reduces systemic and intestinal inflammation,[105] while inhibiting pro-apoptotic Bax expression and upregulating anti-apoptotic Bcl-2.[106] It also influences the caspase-dependent mitochondrial apoptosis pathway[107] and improves renal cellular homeostasis by enhancing Na^+/K^+-ATPase and Ca^{2+}-ATPase activities.[108] Additional mechanistic studies indicate that berberine suppresses sphingosine kinase 1 (SPHK1) expression, inhibits p38 MAPK activation, and alleviates mitochondrial stress.[109] Furthermore, berberine activates the Sirt1/p53 signaling axis,[110] promotes HIF-1α expression via the PI3K/Akt pathway,[111] and reduces ER and mitochondrial stress-induced cellular injury.[125] Collectively, these findings support the potential of berberine as a multifaceted therapeutic agent in the management of IRI-AKI.

CIS-AKI

Berberine has demonstrated substantial efficacy in alleviating CIS-AKI through the modulation of multiple pathophysiological pathways. Its protective mechanisms involve attenuation of oxidative stress, inflammation, apoptosis, and autophagy. Specifically, berberine regulates Klotho expression and the AMPK/mTOR/ULK1/Beclin-1 signaling axis, promoting protective autophagy while simultaneously reducing oxidative and inflammatory damage.[112] Both berberine alone and in combination with Rhizoma coptidis hydroalcohol extract have been shown to improve renal function and

histopathological features in CIS-AKI rat models, evidenced by enhanced antioxidant enzyme activities, decreased MDA levels, and suppressed TLR4 gene expression.[117]

The renoprotective effects of berberine are further mediated through activation of the Nrf2/HO-1 antioxidant signaling pathway and inhibition of JNK, p38 MAPKs, PARP, and Beclin-1 expression, thereby dampening oxidative and autophagy-related injury in renal tissues.[114,115] Berberine also exerts mitochondria-targeted protection by modulating mitophagy through the PINK1/Parkin signaling pathway in renal tubular epithelial cells.[113] In addition, it has been reported to reduce N6-methyladenosine (m^6A) RNA methylation on specific target genes, contributing to transcriptomic regulation during CIS-AKI.[116] These multi-level mechanisms highlight berberine's therapeutic potential as a pleiotropic modulator of kidney injury in the context of cisplatin nephrotoxicity.

CIN

Berberine exhibits notable renoprotective effects in CIN primarily through the inhibition of apoptosis, suppression of ferroptosis, and promotion of autophagy. Mechanistically, berberine activates the Akt/Foxo3a/Nrf2 signaling pathway, which contributes to cellular antioxidative defense and anti-apoptotic responses.[99] Furthermore, berberine modulates histone deacetylase 4 (HDAC4) and FoxO3a, thereby enhancing autophagic activity and attenuating apoptosis in both in vitro and in vivo CIN models.[101] Additionally, berberine protects against CIN by inhibiting NLRP3 inflammasome activation, a key driver of sterile renal inflammation, and by regulating mitophagy, which helps maintain mitochondrial homeostasis and limits damage from reactive oxygen species.[100] These combined mechanisms underscore berberine's multifaceted ability to mitigate renal injury following contrast agent exposure, positioning it as a promising candidate for CIN prevention and therapy.

Drug- and Toxin-Induced AKI

Berberine has demonstrated substantial efficacy in mitigating drug- and poison-induced AKI, primarily through its antioxidant, anti-inflammatory, anti-apoptotic, and mitochondrial-protective properties. In animal models of AKI induced by agents such as gentamicin, diclofenac, lead, and doxorubicin, berberine significantly attenuated renal damage by reducing oxidative stress, suppressing pro-inflammatory cytokine production, preventing apoptotic signaling, and preserving mitochondrial function.[119–123]

A novel mechanism was identified in studies involving zebrafish and mice, where berberine self-assembled with aristolochic acid (AA) into linear heterogeneous supramolecular structures (A–B complexes). This supramolecular assembly markedly decreased AA toxicity, virtually abolishing AA-induced AKI, likely by mitigating gut microbiota dysbiosis and suppressing immune pathways associated with carcinogenesis.[118]

Moreover, in folic acid-induced AKI (FA-AKI), berberine has been shown to exert a renoprotective effect by inhibiting METTL3 expression, a key regulator of RNA methylation. This downregulation modulates the ASC/caspase-1/Gasdermin D axis, thereby inducing controlled pyroptosis in renal tubular epithelial cells and alleviating renal injury.[124] These findings further support berberine's multifaceted potential in preventing or ameliorating nephrotoxicity induced by a range of pharmacological and environmental agents.

Radix Puerariae and Its Component: Pueraria

Puerarin, a natural isoflavone glycoside extracted from *Radix puerariae* (commonly known as "Gegen"), has demonstrated substantial renoprotective effects in LPS-AKI or IRI-AKI, and other nephrotoxicant-induced AKI models, including those caused by cisplatin, methotrexate (MTX), carbon tetrachloride, lead, and cadmium (Table 7).

LPS-AKI

Puerarin has demonstrated significant renoprotective effects in LPS-AKI models. Its treatment ameliorated histopathological damage, including renal interstitial edema and tubular epithelial cell detachment, lowered the renal tubular injury score and reduced apoptosis of renal cells, decreased serum levels of BUN, SCr, kidney injury molecule-1 (KIM-1), TNF-α, and IL-1β, inhibited NF-κB p65 expression in renal tissues and upregulated SIRT1, a key regulator of oxidative stress and inflammation.[127]

Table 7 The Mechanisms of Rhizoma Coptidis and Its Components Puerarin in Improving AKI

Herbal/Extract	Animal Model	Outcome	Mechanism	Reference
Puerarin	LPS-induced AKI mice UUO-induced mouse LPS-treated macrophages (Raw264.7)	↓macrophage M1 polarization ↓renal inflammatory damage	↓TLR4/MyD88 pathway ↓ NF-κB p65 and JNK/FoxO1	[126]
	LPS-induced AKI mice	↓BUN, SCr, KIM, TNF-α, IL-1β, ↓ renal tubular injury, ↓ apoptosis	↑SIRT1/↓NF-κB pathway	[127]
Puerarin	IRI-AKI rats	Anti-OX, anti-inflammation ↓pyroptosis	NLRP3/Caspase-1/GSDMD pathway	[128]
Puerarin	CIS-induced AKI rats	↓renal pathological injury, ↓BUN, SCr, anti-OX, anti-inflammation, ↓apoptosis,	↑miR-31, ↓Numb/Notch1, ↓TLR4/NF-kappaB	[129,130]
Puerarin	Lead induced rat proximal tubule cells cytotoxicity	↓ apoptosis, ↑autophagy anti-OX	↑PI3K/Akt/eNOS, ↓mitochondrial permeability transition pores opening regulating AMPK-mTOR	[131–133]
	Cadmium-induced AKI	↓ apoptosis, ↓lysosomal dysfunction, ↑ autophagy ↓proximal tubule cells damage	Restoring mitochondrial function, ↓inhibiting Nrf2 pathway, ↓ERS	[134–136]
	MTX-AKI	Promotion of renal excretion of toxins	↑renal Oat1/3 via BCL6	[137]
	CCl4-AKI	↓ox, inflammation	Regulating ERK/Nrf2/ARE	[138]

Notes: ↓reduce or inhibit; ↑increase or activate.

Abbreviations: AKI, acute kidney injury; AKT, protein kinase B; AMPK, Adenosine 5'-monophosphate (AMP)-activated protein kinase; ARE, antioxidant response element; BCL6, B-cell lymphoma 6; BUN, blood urea nitrogen; CIS, cisplatin; IRI, ischemia reperfusion injury; CCl4, Carbon tetrachloride; eNOS, endothelial nitric oxide synthase; ERK, extracellular regulated protein kinases; ERS, endoplasmic reticulum stress; FoxO1, fork head box O1; GSDMD, gasdermin D; JNK, c-Jun N-terminal kinase; KIM, Kidney injury molecule; LPS, lipopolysaccharide; mTOR, mammalian target of rapamycin; MTX, methotrexate; MyD88, myeloid differentiation primary response 88; NLRP3, NOD-like receptor thermal protein domain associated protein 3; Nrf2, nuclear factor-erythroid 2 related factor 2; Oat, ornithine acetyltransferase; OX, oxidative stress; PI3K, phosphatidyqinositol-3 kinase; SCr, serum creatinine; Sirt1, silent information regulator 1; TLR, toll like receptors; UUO, unilateral ureteral obstruction.

Mechanistically, puerarin suppresses activation of the TLR4/MyD88 signaling cascade, leading to reduced activity of downstream inflammatory mediators NF-κB p65 and JNK/FoxO1. This modulation impairs macrophage polarization toward the pro-inflammatory M1 phenotype, thereby attenuating renal inflammation and injury.[126]

IRI-AKI

Puerarin can inhibit the activation of NLRP3/Caspase-1/GSDMD pathway, inhibit inflammatory response and pyroptosis, and enhance the antioxidant capacity of kidney, thereby protecting renal.[128]

CIS-AKI

Puerarin alleviated renal injury by reducing levels of BUN, SCr, and malondialdehyde, while improving renal histopathology. These protective effects were mediated by upregulation of miR-31 and inhibition of both the Numb/Notch1 and TLR4/NF-κB signaling pathways.[129,130]

Toxicant-Induced AKI

In MTX- and carbon tetrachloride-induced AKI, puerarin improved renal function through upregulation of organic anion transporters OAT1 and OAT3 via BCL6, thereby facilitating toxin clearance.[137] Additionally, it activated the ERK/Nrf2/ARE pathway, resulting in decreased oxidative DNA damage and inflammation.[138] In lead-induced AKI model, puerarin exerted anti-apoptotic and antioxidative effects by modulating the PI3K/Akt/eNOS pathway,[131,139] inhibiting mitochondrial permeability transition pore opening,[132] and restoring autophagic balance via the AMPK-mTOR signaling axis.[133] Against cadmium-induced nephrotoxicity, puerarin attenuated apoptosis and restored mitochondrial function in renal tubular cells.[134] It also alleviated lysosomal dysfunction through inhibition of Nrf2 signaling[135] and improved autophagic flux, which in turn reduced endoplasmic reticulum stress in NRK52E cells.[136]

Scutellaria Baicalensis and Its Components: Baicalin, Baicalein, Wogonin, Oroxylin A, Skullcapflavones

Scutellaria baicalensis, commonly known as "Huangqin" in traditional Chinese medicine, contains several bioactive flavonoids, including baicalin, baicalein, wogonin, oroxylin A, skullcapflavone I and II, and wogonoside, among others. These constituents have demonstrated diverse renoprotective effects in various animal models of AKI (Table 8).

Virus-Induced AKI

Wogonin significantly inhibited the replication of nephropathogenic infectious bronchitis virus (NIBV), leading to a reduction in mitochondrial membrane potential and abnormal opening of the mitochondrial permeability transition pore (mPTP). Furthermore, it markedly alleviated NIBV-induced apoptosis and necrosis in chicken renal tubular epithelial cells.[140] Baicalin, an activator of CPT1A, enhances cellular energy production by promoting fatty acid oxidation and improving mitochondrial function. Additionally, it reduces the activation of pro-inflammatory bone marrow-derived macrophages (BMDMs), which are key targets in COVID-19. This action helps mitigate the kidney-related inflammatory state associated with COVID-19, thereby reducing kidney injury.[141]

IRI-AKI

Baicalin and baicalein, two major flavonoids derived from *Scutellaria baicalensis*, have demonstrated significant renoprotective effects in animal models of IRI-AKI.

Baicalin has been shown to reduce oxidative stress and inflammatory responses in cardiac surgery-associated AKI models when administered enterally.[142] Its protective effects are largely attributed to the inhibition of inflammation and mitochondria-mediated apoptosis, primarily through modulation of the TLR2/4 signaling pathway and attenuation of mitochondrial stress.[143] In vitro, baicalin also ameliorated H_2O_2-induced cytotoxicity in HK-2 cells by suppressing endoplasmic reticulum (ER) stress and activating the Nrf2 signaling pathway, which enhances the cellular antioxidant defense system.[164]

Baicalein, on the other hand, has demonstrated efficacy in mitigating renal injury following myocardial ischemia/reperfusion.[146] The underlying mechanisms include: (1) inhibition of apoptosis via downregulation of tumor necrosis factor-α (TNF-α), (2) regulation of Bcl-2 and Bax protein expression, (3) activation of Akt and ERK1/2 signaling pathways.[144] Furthermore, baicalein effectively reduces renal tubular epithelial cell apoptosis in hypoxia/reoxygenation injury models by suppressing the expression of inflammatory cytokines and mitigating oxidative stress.[145]

SEP/LPS-AKI

Baicalin has shown significant protective effects against sepsis-induced AKI, particularly in cecal ligation and puncture (CLP)-induced murine models. Its administration improves survival and preserves renal function, as evidenced by significant reductions in SCr, BUN, as well as plasma NGAL and KIM-1 levels. Histopathological examination reveals that baicalin mitigates renal tubular degeneration, necrosis, luminal dilatation, and interstitial inflammatory cell infiltration.[147] The renoprotective mechanisms are associated with upregulation of cellular FLICE-inhibitory protein (c-FLIP), which plays a role in inhibiting apoptosis.

Clinical data also support baicalin's efficacy; in pediatric patients with sepsis, baicalin administration has been shown to reduce renal cell apoptosis and improve AKI outcomes, paralleling findings from the CLP-AKI mouse model.[148] Furthermore, in vitro studies indicate that baicalin alleviates LPS-induced injury in renal tubular epithelial cells by suppressing the TXNIP/NLRP3 inflammasome pathway, mediated via the upregulation of microRNA-223-3p.[149] These findings collectively highlight baicalin's multifaceted anti-inflammatory and anti-apoptotic roles in SEP-AKI.

CIS-AKI

Scutellaria baicalensis and its active flavonoid constituents—baicalein and wogonin—have demonstrated promising renoprotective effects against CIS-AKI. Scutellaria baicalensis not only attenuates cisplatin-induced nephrotoxicity but also enhances the therapeutic efficacy of cisplatin and alleviates chemotherapy-associated cachexia.[150] Baicalein offers protection against CIS-AKI by enhancing antioxidant defense mechanisms and simultaneously suppressing the activation of mitogen-activated protein kinases (MAPKs) and the NF-κB signaling pathway.[151] Baicalein reduced the expression of

Table 8 The Mechanisms of Scutellaria Baicalensis and Its Components: Baicalin, Baicalein, Wogonin, Oroxylin A, Skullcapflavones in Improving AKI

Herbal/Extract	Animal Model	Outcome	Mechanism	Reference
Wogonin	NIBV induced chicken RTEC	↓apoptosis, ↓necroptosis	↓the copy number of NIBV, ↓mitochondrial membrane potential and the aberrant opening of mPTP	[140]
Baicalin	UUO folic acid-induced AKI TGF-β induce RTEC	↓covid-19 induced AKI ↑cellular energy production, improves mitochondrial function	↑enhancing fatty acid oxidation, ↓proinflammatory bone marrow-derived macrophages (BMDMs)	[141]
Baicalin	Cardiac surgery-AKI rats	↓SCr, NGAL, Kim1, IL-18, iNOS ↓MDA, MPO, ↑SOD	↓oxidative stress, inflammation ↑Nrf2/HO-1	[142]
	IRI-AKI in rats	↓inflammation, mitochondria-mediated apoptosis	↓TLR2/4, ↓mitochondrial stress	[143]
Baicalein	Myocardial I/R-AKI	↓renal injury ↓apoptosis i	↓TNF-α, ↑Bcl-2, ↓ Bax ↑Akt, ↑ERK1/2	[144]
	H/R-HK-2	↓apoptosis ↓ROS, IL-1β	↓inflammatory cytokine, anti-ox	[145]
	IRI-AKI in rats	Improved renal function	↓AOPP, MDA, inflammatory factors	[146]
Baicalin	Cecal ligation and puncture (CLP) induced-AKI mice	↓SCr, BUN, pNGAL and pKIM-1, ↓pathological damage	↑c-FLIP ↓apoptosis	[147]
	SEP-AKI pediatric patients CLP-AKI mice	↓SCr, BUN ↓kidney injury	↓apoptosis ↓BAX, ↑BCL2	[148]
	LPS-induced RTEC	↓tubular epithelial cells injury	↑ microRNA-223-3p, ↓TXNIP/NLRP3 inflammasome pathway	[149]
Scutellaria baicalensis	CIS-AKI mice	Improved renal function, ↓tumor growth, ↑body weight	↓apoptosis of renal tubular cells	[150]
Baicalein	CIS-AKI		Anti-ox, ↓MAPKs and NF-κB	[151]
	CIS/Folic acid-induced AKI cisplatin-induced HK2 cell	↓phospholipid peroxidation ↓ferroptosis, ↓pathological damage	↓12-lipoxygenase (ALOX12)	[152]
Wogonin	CIS-AKI	↓ BUN, SCr, IL-1β, TNF-α, NF-kB, caspase-3,↑GSH, catalase	↓oxidative stress, inflammation, ↓PPAR-γ, ↓apoptosis, Wnt/β-catenin	[153]
	CIS-AKI	↓necroptosis	RIPK1	[154]
Oroxylin A	CIS-AKI IRI-AKI mice HR induced HK-2 cells	↓tubular damage, ↓BUN, SCr, Kim-1, NGAL ↓AKI-to-CKD transition	↑PPARα-BNIP3 signaling pathway maintaining mitochondrial homeostasis	[155]
Skullcapflavone II	AA-AKI mouse	↓renal injury and dysfunction	↓NQO1, ↓DNA damage, apoptosis	[156]
Baicalin	AA-AKI mice	↓BUN, SCr, renal injury	↑CYP1A by the aromatic hydrocarbon receptor	[157]
	CON-induced HK-2 cells	↓pyroptosis, IL-18, IL-1β, LDH, SOD, MDA, ROS	↓ROS/NLRP3/Caspase-1/GSDMD	[158]
	Lead-induced AKI	↓ weight loss, ↓kidney coefficient, ↑ renal function and structure	↓apoptosis, Bcl-2/Bax ratio ↑SOD, GSH-Px, ↓MDA	[159]
Baicalein	Polymyxin B-AKI	↓BUN, SCr, ferroptosis, iron levels, lipid peroxidation	↓MDA, HO-1, PTGS2,4HNE ↑SCL7A11, GPX4, GSH ↓p53 acetylation levels by ↑ SIRT1	[160]
	C57BL/6 mice (X-ray, 15 Gy)	↓kidney inflammatory ↑catalase and SOD	↑MAPKs, Akt,↓NF-κB ↑FOXO	[161]
Baicalin-2-ethoxyethyl ester	Gentamicin-induced AKI	↓BUN, SCr, renal injury anti-inflammatory, anti-OX	↓NF-κB signaling pathway	[162]
Baicalein	Myoglobin-induced HK-2 cell	↓ferroptosis	↓ERS	[163]

Notes: ↓reduce or inhibit; ↑increase or activate.

Abbreviations: AA, Aristolochic acid; AKT, protein kinase B; AOPP, advanced oxidative protein product; BAX, BCL2 associated X protein; BCL2, B-cell lymphoma-2; BNIP3, BCL2 interacting protein 3; BUN, blood urea nitrogen; c-FLIP, FADD-like intedeukin-1-β converting enzyme inhibitory protein; CIS, cisplatin; CON, contrast; CLP, cecal ligation and puncture; ERK, extracellular regulated protein kinases; ERS, endoplasmic reticulum stress; FOXO, fork head box O; GSH, glutathione; GSDMD, gasdermin D; H/R, Hypoxia reoxygenation; FOXO, fork head box O; HO-1, heme oxygenase 1; iNOS, inducible nitric oxide synthase; IRI, ischemia reperfusion injury; KIM-1, Kidney injury molecule 1; LDH, lactate dehydrogenase; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinases; MDA, malondialdehyde; MPO, myeloperoxidase; mPTP, mitochondrial permeability transition pore; NGAL, neutrophil gelatinase associated lipocalin; NIBV, nephropathogenic infectious bronchitis virus; NLRP3, NOD-like receptor thermal protein domain associated protein 3; NQO1, NAD (P)H quinone oxidoreductase 1; Nrf2, nuclear factor-related factor 2; OX, oxidative stress; PPAR-γ, peroxisome proliferator activated receptor gamma; RIPK1, receptor-interacting protein kinase 1; ROS, reactive oxygen species; RTEC, renal tubular epithelial cells; SCr, serum creatinine; SIRT1, silent information regulator 1; SOD, super oxide dismutase; TLR, toll like receptors; TXNIP, thioredoxin interacting protein; UUO, unilateral ureteral obstruction.

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12-lipoxygenase (ALOX12), inhibited phospholipid peroxidation and ferroptosis, and alleviated cisplatin-and folate-induced renal dysfunction and pathological damage, as well as cisplatin-induced HK2 cell injury.[152]

Wogonin contributes to renal protection through multiple mechanisms: it inhibits peroxisome proliferator-activated receptor gamma (PPAR-γ) activity, suppresses inflammation and apoptosis, and blocks the Wnt/β-catenin signaling pathway.[153] Moreover, wogonin also targets receptor-interacting protein kinase 1 (RIPK1)-mediated necroptosis, a programmed form of necrosis involved in cisplatin-induced renal damage.[154]

Collectively, these findings highlight the therapeutic potential of Scutellaria baicalensis and its components in mitigating cisplatin nephrotoxicity through antioxidant, anti-inflammatory, and anti-necroptotic pathways.

Drug or Poison-Induced AKI

The bioactive compounds baicalin, baicalein, and skullcapflavone II, derived from *Scutellaria baicalensis*, demonstrate notable efficacy in preventing AKI induced by various pharmaceuticals, environmental toxins, and physicochemical insults, including contrast media, aristolochic acid (AA), polymyxin B, gentamicin, lead exposure, and ionizing radiation.

Baicalin significantly mitigates CON-AKI by attenuating pyroptosis via modulation of the ROS/NLRP3/Caspase-1/GSDMD signaling pathway.[158] It also protects against AA-induced AKI in mice by upregulating cytochrome P450 1A (CYP1A) through activation of the aromatic hydrocarbon receptor.[157] In a murine model of lead-induced nephrotoxicity, baicalin alleviated renal dysfunction by enhancing superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) activities, reducing MDA levels, and modulating apoptotic balance through an increased Bcl-2/Bax ratio, in a dose-dependent manner.[159] Baicalin-2-ethoxyethyl ester, a derivative of baicalin, demonstrates anti-inflammatory and anti-oxidative properties by modulating the NF-κB signaling pathway. It effectively reduces serum creatinine and urea nitrogen levels, ameliorates renal pathological changes, and provides therapeutic benefits in cases of gentamicin-induced AKI.[162]

Baicalein shows significant protective effects against polymyxin B-induced AKI by reducing p53 acetylation through upregulation of SIRT1, thereby inhibiting ferroptosis.[160] Additionally, baicalein offers radioprotection in the kidneys of C57BL/6 mice exposed to 15 Gy X-ray irradiation by suppressing NF-κB-mediated inflammation via the activation of MAPK, Akt, and FOXO signaling, enhancing the expression of downstream antioxidant enzymes including catalase and SOD.[161]

Skullcapflavone II also exhibits a dose-dependent protective effect against AA-induced AKI, potentially through inhibition of NAD(P)H quinone dehydrogenase 1 (NQO1), which contributes to decreased DNA damage and apoptosis in renal tubular epithelial cells.[156]

Prevent the Transformation of AKI Into CKD

Moreover, Oroxylin A, another active component of *Scutellaria baicalensis*, contributes to preventing the transition from AKI to CKD. This is achieved through the maintenance of mitochondrial homeostasis via the activation of the PPARα-BNIP3 signaling pathway, as shown in ischemia-reperfusion injury (IRI)-AKI and cisplatin-induced AKI models, as well as in hypoxia/reoxygenation (HR)-treated HK-2 cells.[155]

In addition to these effects, baicalin provides renal protection in a rat model of preeclampsia-induced AKI, primarily through its anti-apoptotic activity.[165] Baicalein reduces myoglobin-induced ferroptosis in HK-2 cells by inhibiting ER stress and may treat AKI in patients with hypermyoglobin due to rhabdomyolysis after exertional heatstroke.[163] Collectively, these findings underscore the broad therapeutic potential of *Scutellaria baicalensis* and its constituents in diverse models of nephrotoxicity and AKI.

Experimental Studies on TCM Compounds in the Prevention and Treatment of AKI

Recent studies have demonstrated that several TCM compound formulations exert significant protective effects against AKI, particularly CIS-AKI, IRI-AKI, LPS-AKI. These protective effects are largely attributed to their anti-inflammatory, antioxidant, and anti-apoptotic properties (Table 9).

Table 9 Experimental Study on the Intervention of Traditional Chinese Medicine Compound on AKI

Model	TCM Compound	Outcome	Mechanism	Reference
CIS-AKI	A&P	Protected kidney, anti-inflammation ↓IL-1β, IL-6, TNFα and MCP-1 in kidney and serum	↓Mincle(Macrophage-inducible C-type lectin) and iNOS in macrophage, ↓Syk and NF-κB	[166]
		↓ ferroptosis, ↓ renal fibrosis	↓ LncRNA A33	[167]
	JPYS	↓apoptosis and anti-inflammation, ↓TNF-α, IL-1β, and IL-6	↓NF-κB, ↓TUNEL-positive cell counts, ↓Bax, Bad and caspase 3,↑Bcl-2,	[168]
		↓SCr, renal pathological injury	Regulating renal metabolic disorders	[169]
	QiShenYiQi Pills (QSYQ)	↓SCr, BUN, and histological damage, such as tubular necrosis, protein cast, and desquamation of epithelial cells ↓mitochondrial dysfunction ↓apoptosis,	Anti-ox, improved the renal microcirculation ↓mitochondrial complex activity, NDUFA10, ATP5D, and Sirt3 ↓renal thiobarbituric acid-reactive substances, caspase9, cleaved-caspase9, and cleaved-caspase3	[170]
	San-Huang decoction (SHD)	↓glomerular and tubule damage anti-inflammation, ↓apoptosis	↓NF-κB signaling pathway ↑ PI3K/AKT anti-apoptotic pathway	[171]
	Zhibai Dihaung Granule (ZDG)	↓renal pathological injury	↓apoptosis and anti-inflammation	[172]
	Qiong-Yu-Gao (QYG)	↓uremic toxins, ↓ fibrosis, inflammation, and apoptosis in renal tissue	↓gut dysbiosis, altered the levels of bacterial metabolites, ↑short-chain fatty acids (SCFAs)	[173]
	Zhen-Wu-Tang (ZWT)	Anti-fibrotic and anti-apoptotic ↓SCr, renal pathological injury	↓TGF-β, Wnt, ↑Nrf2, PI3K/Akt, caspase-3, Bax, α-SMA	[174]
IRI-AKI H/R cells	Wuling San (WLS)	↑renal function, ↓pathological changes and oxidative stress	↑VPR2-CAMP-PKA-CREB pathway ↓senescence-related proteins	[175]
	Fangji Huangqi decoction(FJHQD)	↓RTEC apoptosis	↑PI3K/Akt signaling pathway	[176]
LPS-AKI	FangJiFuling decoction (FF)	↓inflammation, mitochondrial-mediated apoptosis ↑cell junction	Bax/Bcl-2 ratio ↓Cx43	[177]

Notes: ↓reduce or inhibit; ↑increase or activate.

Abbreviations: A&P, Astragalus propinquus Schischkin and Panax notoginseng; AKI, acute kidney injury; AKT, protein kinase B; α-SMA, alpha smooth muscle actin; ATP5D, ATP synthase subunit delta; BUN, blood urea nitrogen; Bad, Bcl-2 associated agonist of cell death; Bax, Bcl-2 associated X protein; Bcl-2, B-cell lymphoma-2; CAMP, cyclic adenosine monophosphate; CREB, cyclic-AMP response element binding protein; Cx43, connexin 43; H/R, Hypoxia/reoxygenation; iNOS, inducible nitric oxide synthase, IRI, ischemia reperfusion injury; JPYS, Jianpi Yishen Tang/Jian-Pi-Yi-Shen formula; LPS, lipopolysaccharide; LncRNA, long non-coding RNA; MCP-1, monocyte chemoattractant protein-1; NDUFA10, ubiquinone oxidoreductase subunit A10; Nrf2, nuclear factor-related factor 2; PKA, protein kinase A; PI3K, phosphoinositide 3-kinase; RTEC, renal tubular epithelial cell; SCr, serum creatinine; Sirt3, sirtuin 3; Syk, spleen tyrosine kinase, TUNEL, terminal deoxynucleotidyl transferase-mediated dUTP-biotin nick end labeling; VPR2, arginine vasopressin receptor 2.

CIS-AKI

Astragalus and Panax Notoginseng Compound (A&P)

The A&P compound, consisting of *Astragali Radix, Notoginseng Radix et Rhizoma, Angelicae Sinensis Radix, Achyranthis Bidentatae Radix, and Eckloniae Thallus*, has shown potent renoprotective effects in CIS-AKI mouse models. Its primary mechanism involves inhibition of the macrophage-inducible C-type lectin receptor (Mincle) signaling pathway. A&P significantly decreased mRNA expression levels of pro-inflammatory cytokines IL-1β, IL-6, TNF-α, and MCP-1 in renal tissues and serum. It also downregulated iNOS, a marker of M1 macrophages, and inhibited the Syk/NF-κB signaling pathway, both in vitro and in vivo.[166] A&P improved renal fibrosis in UUO mice by inhibiting LncRNA A33 and downregulating ferroptosis signaling.[167] It also reduced renal damage and inflammation in diabetic nephropathy primarily through the inhibition of the Mincle/Card9/NFκB pathway.[178]

Jianpi Yishen Tang or Jian-Pi-Yi-Shen Formula (JPYS)

JPYS, a traditional multi-herbal formulation composed of *Astragali Radix, Atractylodis Macrocephalae Rhizoma, Dioscoreae Rhizoma, Cistanches Herba, Amomi Fructus Rotundus, Salviae Miltiorrhizae Radix et Rhizoma, Rhei Radix et Rhizoma, and Glycyrrhizae Radix et Rhizoma Praeparata*, exerts renoprotective effects in mice with CIS-AKI by mitigating apoptosis and inflammation, primarily through suppression of NF-κB signaling. Treatment with JPYS reduced the number of TUNEL-positive apoptotic cells, downregulated the expression of pro-apoptotic proteins Bax,

Bad, and caspase-3, and upregulated Bcl-2 in kidney tissues. Additionally, JPYST suppressed serum and renal levels of inflammatory mediators, including TNF-α, IL-1β, and IL-6.[168] JPYS protects the kidney from cisplatin-induced AKI by regulating metabolic disorders. Key affected pathways include vitamin B6 metabolism, alanine/aspartate/glutamate metabolism, lysine biosynthesis, and butyrate metabolism.[169]

QiShenYiQi Pills (QSYQ)

QSYQ, a widely used TCM prescription, composed of *Astragali Radix, Salviae Miltiorrhizae Radix et Rhizoma, Notoginseng Radix et Rhizoma, and Dalbergiae Odoriferae Lignum*, showed remarkable efficacy in alleviating CIS-AKI in mouse models. The therapeutic effects of QSYQ are associated with the preservation of mitochondrial function, reduction of oxidative stress, and inhibition of apoptosis. It significantly decreased SCr and BUN levels, while ameliorating histopathological damage such as tubular necrosis, protein casts, and epithelial desquamation. QSYQ also improved renal microcirculation, enhanced mitochondrial complex activity, and upregulated mitochondrial proteins such as NDUFA10 (NADH: ubiquinone oxidoreductase subunit A10), ATP5D, and Sirt3. Furthermore, it reduced levels of thiobarbituric acid-reactive substances (TBARS) and the expression of cleaved caspase-9 and cleaved caspase-3, key markers of mitochondrial apoptosis.[170]

San-Huang Decoction (SHD)

SHD, another multi-component herbal formulation, composed of *Astragali Radix, Rhei Radix et Rhizoma, and Notoginseng Radix et Rhizoma*, protects against CIS-AKI through both anti-inflammatory and anti-apoptotic mechanisms. It achieves this by suppressing the NF-κB signaling pathway and activating the PI3K/AKT pathway, which promotes cell survival. These combined effects help to mitigate cisplatin-induced damage to renal glomerular and tubular structures in experimental mice.[171]

Zhibai Dihuang Granule (ZDG)

ZDG, a traditional multi-herbal formulation composed of *Anemarrhenae Rhizoma, Phellodendri Chinensis Cortex, Rehmanniae Radix Praeparata, Corni Fructus, Dioscoreae Rhizoma, Moutan Cortex, Poria, and Alismatis Rhizoma*, exerts protective effects against CIS-AKI by modulating key apoptotic and inflammatory pathways. It downregulates caspase-3 and NF-κB p65 expression, regulates MAPK pathway-related proteins, and thereby reduces renal cell apoptosis and inflammation. These actions help preserve renal structure and function, highlighting ZDG's potential as a multi-target therapeutic agent for nephrotoxic injury.[172]

Qiong-Yu-Gao (QYG)

QYG, a traditional formula composed of *Rehmanniae Radix, Poria, and Ginseng Radix* (7:2:1), alleviates cisplatin-induced AKI by modulating gut microbiota and their metabolites. It increases beneficial SCFAs (eg, acetic and butyric acid), reduces uremic toxins (indoxyl sulfate, p-cresyl sulfate), and inhibits histone deacetylase activity. These effects collectively reduce renal fibrosis, inflammation, and apoptosis, highlighting QYG's potential as a gut–kidney axis-targeting therapy.[173]

Zhen-Wu-Tang (ZWT)

ZWT, is a classic formula composed of *Aconiti Lateralis Radix Praeparata, Paeoniae Radix Alba, Poria, Atractylodis Macrocephalae Rhizoma, and Zingiberis Rhizoma Recens*, exerts anti-fibrotic and anti-apoptotic effects in cisplatin-induced acute kidney injury (CIS-AKI). It improves renal histology, reduces abnormal collagen deposition, and lowers serum BUN and creatinine levels. ZWT downregulates pro-fibrotic markers TGF-β and Wnt, while upregulating protective factors Nrf2, PI3K, and Akt. It also reduces apoptosis and fibrosis by modulating caspase-3, Bax, and α-SMA expression, highlighting its potential as a multi-pathway therapeutic agent for CIS-AKI.[174]

IRI-AKI

Wuling San (WLS)

Wuling San (WLS), a classical formula for urological disorders, composed of *Poria, Polyporus, Alismatis Rhizoma, Atractylodis Macrocephalae Rhizoma, and Cinnamomi Ramulus*, shows renoprotective effects in IRI-AKI. WLS enhances AVPR2 expression and activates the AVPR2–cAMP–PKA–CREB signaling pathway, leading to improved

renal function, reduced oxidative stress, and amelioration of renal pathology. Additionally, it decreases the expression of cellular senescence-related proteins, supporting its potential role in mitigating renal injury and promoting recovery.[175]

Fangji Huangqi Decoction (FJHQD)

FJHQD, a classic formula for reducing edema composed of composed of *Stephaniae Tetrandrae Radix, Astragali Radix, Glycyrrhizae Radix et Rhizoma, Atractylodis Macrocephalae Rhizoma, Zingiberis Rhizoma Recens, and Jujubae Fructus*, alleviates renal I/R injury and H/R-induced damage in TCMK-1 cells by activating the PI3K-Akt signaling pathway. In both in vivo and in vitro models, FJHQD reduces renal injury and tubular epithelial cell apoptosis, highlighting its potential as a protective agent targeting survival pathways in IRI-AKI.[176]

LPS-AKI

FangJiFuling Decoction (FF)

FF, composed of composed of *Stephaniae Tetrandrae Radix, Poria, Astragali Radix, Cinnamomi Ramulus, and Glycyrrhizae Radix et Rhizoma*, exerts protective effects in LPS-induced acute kidney injury by suppressing inflammation and apoptosis. In treated mice, FF significantly reduced renal injury, and its effects may be mediated through the regulation of connexin 43 (Cx43), suggesting a potential role for FF in modulating intercellular communication and inflammatory signaling in septic AKI.[177]

Conclusion And Perspective

Characteristics of TCMs in the Treatment of AKI

The incidence of AKI among hospitalized patients remains relatively low, reported to be around 0.99%–2.3%,[179] and it predominantly occurs in critical care settings such as emergency departments and intensive care units. Consequently, the clinical involvement of TCM in AKI management is limited, leading to a lack of unified understanding regarding its etiology, pathogenesis, syndrome differentiation, and treatment within the TCM framework.

Despite this, TCM practitioners have begun exploring individualized treatment approaches based on the underlying cause and clinical symptoms of AKI. For instance, in AKI induced by infection or febrile illnesses, detoxifying and heat-clearing herbs such as Rheum palmatum (Dahuang), Coptis chinensis (Huanglian), Glycyrrhiza uralensis (Gancao), or Xuebijing injection are frequently used. For drug-induced AKI, herbs that invigorate kidney function and promote blood circulation, such as Astragalus membranaceus (Huangqi) and Salvia miltiorrhiza (Danshen), are commonly prescribed. In patients presenting with reduced urine output, gastrointestinal symptoms, or elevated SCr without overt symptoms, treatment often mirrors chronic renal failure management based on syndrome differentiation.

The author believes that the Chinese herbs mentioned in the text, such as licorice, salvia miltiorrhiza, astragalus, coptis, rhubarb and kudzu root, may be the most promising drugs for treating AKI. According to TCM theory, if these individual herbs are appropriately combined and formulated into various scenarios for use, there will definitely be a promising clinical application prospect.

Chinese Herbal Medicines are Effective for Both AKI and CKD?

Many Chinese herbal medicines used to manage CKD—including Astragalus, Licorice, Salvia miltiorrhiza, Rhizoma coptidis, and Rhubarb—have demonstrated efficacy in AKI experimental models, exhibiting anti-inflammatory, antioxidant, and anti-apoptotic effects, reducing SCr, and improving histopathological kidney damage. However, the translation of these findings to clinical application remains limited due to the absence of large-scale clinical trials, standardized formulations, and robust combination strategies. The inherent heterogeneity and rapid progression of AKI complicate clinical trial design, making it challenging to evaluate the efficacy of these interventions systematically. Further research is required to validate these promising findings in broader patient populations.

Key Issues and Considerations

The concept of early and active dialysis in AKI management has shown potential to improve short-term outcomes. However, while dialysis is life-saving, it does not address the underlying pathophysiology of AKI. Approximately 20%

of AKI cases progress to acute kidney disease (AKD), and, if unresolved, to CKD and eventually end-stage renal disease (ESRD). At this progression stage, TCM may offer unique therapeutic advantages. The authors note successful clinical treatment of three AKI cases following chemotherapy, in which renal function was fully restored with the use of tailored TCM compounds. Preventive TCM administration during subsequent chemotherapy courses helped maintain stable kidney function for at least six months post-treatment. These clinical experiences, though promising, underscore the urgent need for more rigorous evidence to support broader application.

Expanding Research Horizons in TCM-Based AKI Treatment

To advance TCM applications in AKI, it is essential to bridge traditional pathogenesis theories with modern pharmacological insights and AKI mechanisms. According to TCM principles, AKI is categorized as a critical illness and may benefit from potent herbs such as Aconitum carmichaelii (Fuzi), Rhubarb, Panax ginseng (Renshen), and Rehmannia glutinosa. Pharmacological studies have identified several herbs with properties aligned with AKI pathophysiology—namely anti-inflammatory, antioxidant, hemodynamic modulation, and tissue regeneration effects. These include Polygonatum sibiricum, Lycium barbarum (Goji),[180] Paeonia lactiflora,[181] Epimedium brevicornum, and Cuscuta chinensis.[182] In addition, classical TCM formulations have gained research interest in AKI treatment such as Zhenwu Decoction,[174] Buzhong Yiqi Decoction,[183] Shenfu Injection.[31] These compounds warrant further clinical and mechanistic exploration to confirm their therapeutic roles and to potentially integrate them into modern AKI management strategies.

In the future, potential directions for the development of Chinese Herbal Medicines (CHMs) in the intervention of Acute Kidney Injury (AKI) may include the following aspects:

① Identify the most effective CHMs for different etiologies and types of AKI. For example, in pre-renal failure or ischemia-reperfusion injury, are blood-activating and stasis-resolving herbs such as Astragalus and Salvia Miltiorrhiza more effective than heat-clearing and detoxifying herbs like Coptis and Rhubarb? Conversely, the opposite may be true for AKI induced by sepsis.

② Enhance the bioavailability of individual CHM components or modify their structures to improve clinical efficacy and biocompatibility. Research on carbon dots derived from CHMs represents a promising direction in this field.[184] Recent studies indicate that ultra-small, highly biocompatible carbon dots from natural plants can ameliorate AKI. For instance, carbon dots derived from Phellodendri Chinensis Cortex Carbonisata can protect against AKI induced by Deinagkistrodon acutus venom,[185] while natural carbon dots extracted from Ziziphi Spinosae can mitigate sepsis-related AKI.[186]

③ Deepen mechanistic research: Investigate the intervention and regenerative effects of CHMs on intrinsic kidney cells, particularly the repair and regeneration of renal tubular epithelial cells, along with the underlying mechanisms. Explore their influence on renal stem cells and assess their significance in AKI—whether they play a more critical role than previously recognized mechanisms such as anti-inflammatory, antioxidant, hemodynamic improvement, and modulation of autophagy or apoptosis.

④ Integrate disease and syndrome research: Establish AKI diagnostic and classification criteria that integrate both Traditional Chinese Medicine (TCM) and Western medicine perspectives, and develop biomarkers for TCM syndrome differentiation.

⑤ Conduct high-quality clinical research: Design multicenter, large-sample randomized controlled trials to evaluate the efficacy of TCM injections and enemas in severe AKI. Develop rapid, controllable formulations suitable for acute and critical conditions (eg, nano-formulations) and perform real-world studies to assess long-term medication safety.

⑥ Explore integrated treatment models: Investigate the adjunctive role of TCM during continuous renal replacement therapy (CRRT) and develop intervention strategies for the transition from AKI to Chronic Kidney Disease (CKD). Interdisciplinary research is expected to promote the standardized and international application of TCM in the prevention and treatment of AKI.

Finally, to clearly illustrate the current depth of research, the single herbs, herbal monomers, and compound formulas covered in this review have been systematically summarized and graded according to the animal models and clinical trial

designs employed. The evidence levels are defined as follows: "+" indicates support from only a single experimental study; "++" indicates multiple experimental studies; "+++" indicates clinical studies; and "++++" indicates evidence from both clinical and experimental studies. Detailed information is presented in Table 10 and Table 11. Additionally, the formulas mentioned in the article and their corresponding herbal compositions are summarized in Table 12.

Table 10 Clinical and Experimental Studies on the Intervention of AKI with TCM Compound

TCM Compound	IRI/H/R	SEP/LPS	CIS/CIN	CON	ICU/MOF	A ON C	NS	CS	VA/GM
Clinical Research									
Shenkang injection(SKI)	++++	+++	+		+++		+++		
Xuebijing injection(XBJI)		++++						+++	
Danhong injection(DHI)				+++					
Shenfu injection(SFI)	+++								
Chuan Huang Fang(CHF)						++++			
Astragalus injection(ASI)	+++	+	+						
Qishen Huoxue Granules(QHG)					+++				
Compound glycyrrhizin									+++
Experimental Study									
Astragalus propinquus Schischkin and Panax notoginseng (A&P)			++						
Jian-Pi-Yi-Shen (JPYS)			++						
QiShenYiQi Pills (QSYQ)			+						
San-Huang decoction (SHD)			+						
Qiong-Yu-Gao (QYG)			+						
Zhibai Dihaung Granule(ZDG)			+						
Zhen-Wu-Tang (ZWT)			+						
Wuling San (WLS)	+								
Fangji Huangqi decoction(FJHQD)	+								
FangJiFuling decoction(FF)		+							

Notes: +: Single Experimental Study; ++: Multiple Experimental Studies; +++: Clinical Research; ++++: Clinical research + experimental Study.
Abbreviations: A ON C, AKI on CKD, CIN, contrast-induced nephropathy; CIS, cisplatin-induced AKI; CON, contrast-induced AKI; CS, crush syndrome; GM, gentamicin, H/R, hypoxia/reoxygenation; ICU, intensive care unit, IRI, ischemia reperfusion injury; LPS, lipopolysaccharide; MOF, multiple organ failure; NS, nephrotic syndrome; SEP, sepsis; VA, vancomycin.

Table 11 Studies on the Intervention of Single Herb or TCM Monomers in AKI

Single Herb/TCM Monomer		IRI/H/R	SEP/LPS	CIS/CIN	CON	VA/GM	FA	Lead/CdCl	DOX	MTX/CCl4	AA
Huangqi	Astragaloside IV (AS-IV)	++	++	++							
	Astragalus polysaccharide (APS)		+	++							
Gancao	Licorice							+			
	Glycyrrhizin	++	++	+							
	Glabridin	+									
	Glycyrol						+				
	Glycyrrhisoflavone								+		
	Liquiritigenin						+				
	Licochalcone A		+								
	Licochalcone B								+		
	Isoliquiritigenin			++					+		
Danshen	Salvia Miltiorrhiza			++							
	Total tanshinones		+								
	Tanshinone IIA (Tan IIA)	++	++	+	+		++				
	Salvianolate	+									
	Salvianolic acid A(SAA)	++	+			+					
	Salvianolic acid B (SAB)	++			++						+

(*Continued*)

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Table 11 (Continued).

Single Herb/TCM Monomer		IRI/H/R	SEP/LPS	CIS/CIN	CON	VA/GM	FA	Lead/CdCl	DOX	MTX/CCl4	AA
	Salvianolic acid C(SAC)			+							
	Magnesium lithospermate B (MLB)	+		+							
Dahuang	Rhubarb extract	+									
	Rhein		++								
	Emodin	++	++	+		++			+		
	Chrysophanol	+		+							
Huanglian	Berberine	++	++	++	++	++	+	+	++		+
	Rhizoma coptidis extracts(RCE)		+	+							
Gegen	Pueraria	+	++					++			
Huangqin	Scutellaria baicalensis			+		+					+
	Baicalin	++	++	++	+	+	++	+	++		+
	Wogonin			++							
	Oroxylin A	+		+							
	Skullcapflavone II										+

Notes: +: Single Experimental Study; ++: Multiple Experimental Studies.
Abbreviations: AA, aristolochic acid; CCl4, carbon tetrachloride; CdCl, cadmium chloride; CIN, contrast-induced nephropathy; CIS, cisplatin-induced AKI; CON, contrast-induced AKI; CS, crush syndrome; DOX, doxorubicin; FA, folic acid; GM, gentamicin; H/R, hypoxia/reoxygenation; IRI, ischemia reperfusion injury; LPS, lipopolysaccharide; MTX, methotrexate; SEP, sepsis; VA, vancomycin.

Table 12 Summary of Herbal Formulas and Medicinal Preparations

Name	Herbal Compositions	Reference
Shenkang injection(SKI)	Rhei Radix et Rhizoma (Dahuang), Salviae Miltiorrhizae Radix et Rhizoma (Danshen), Carthami Flos (Honghua), Astragali Radix (Huangqi)	[27]
Xuebijing injection(XBJI)	Paeoniae Radix Rubra (Chishao), Chuanxiong Rhizoma (Chuanxiong), Angelicae Sinensis Radix (Danggui)	[20]
Danhong injection(DHI)	Salviae Miltiorrhizae Radix et Rhizoma (Danshen), Carthami Flos (Honghua)	[21]
Shenfu injection(SFI)	Ginseng Radix et Rhizoma Rubra (Hongshen), Aconiti Lateralis Radix Praeparata (Fupian)	[16]
Chuan Huang Fang(CHF)	Rhei Radix et Rhizoma (Dahuang), Aconiti Lateralis Radix Praeparata (Fuzi), Codonopsis Radix (Dangshen), Salviae Miltiorrhizae Radix et Rhizoma (Danshen), Coptidis Rhizoma (Huanglian), Smilacis Glabrae Rhizoma (Tufuling), Pinelliae Rhizoma Praeparatum (Zhibanxia), Citri Reticulatae Pericarpium (Chenpi), Cordyceps Mycelium (Chongcaojunsi)	[23]
Astragalus injection(ASI)	Astragali Radix (Huangqi)	[24]
Qishen Huoxue Granules(QHG)	Radix Astragali (Huangqi), Salvia miltiorrhiza (Danshen), Radix Paeoniae Rubra (Chishao), Flos Carthami (Honghua), Radix Angelicae Sinensis (Danggui)	[25]
Compound glycyrrhizin	Licorice (Gancao)	[26]
Astragalus propinquus Schischkin and Panax notoginseng (A&P)	Astragali Radix (Huangqi), Notoginseng Radix et Rhizoma (Sanqi), Angelicae Sinensis Radix (Danggui), Achyranthis Bidentatae Radix (Niuxi), Eckloniae Thallus (Kunbu)	[166]
Jian-Pi-Yi-Shen (JPYS)	Astragali Radix (Huangqi), Atractylodis Macrocephalae Rhizoma (Baizhu), Dioscoreae Rhizoma (Shanyao), Cistanches Herba (Roucongrong), Amomi Fructus Rotundus (Kouren), Salviae Miltiorrhizae Radix et Rhizoma (Danshen), Rhei Radix et Rhizoma (Dahuang), Glycyrrhizae Radix et Rhizoma Praeparata (Zhi Gancao)	[168]
QiShenYiQi Pills (QSYQ)	Astragali Radix (Huangqi), Salviae Miltiorrhizae Radix et Rhizoma (Danshen), Notoginseng Radix et Rhizoma (Sanqi), Dalbergiae Odoriferae Lignum (Jiangxiang)	[170]
San-Huang decoction (SHD)	Astragali Radix (Huangqi), Rhei Radix et Rhizoma (Dahuang), Notoginseng Radix et Rhizoma (Sanqi)	[171]
Zhibai Dihaung Granule(ZDG)	Anemarrhenae Rhizoma (Zhimu), Phellodendri Chinensis Cortex (Huangbai), Rehmanniae Radix Praeparata (Shudihuang), Corni Fructus (Shanzhuyu), Dioscoreae Rhizoma (Shanyao), Moutan Cortex (Mudanpi), Poria (Fuling), Alismatis Rhizoma (Zexie)	[172]
Qiong-Yu-Gao (QYG)	Rehmanniae Radix (Shudihuang), Poria (Fuling), Ginseng Radix (Renshen)	[173]
Zhen-Wu-Tang (ZWT)	Aconiti Lateralis Radix Praeparata (Fuzi), Paeoniae Radix Alba (Shaoyao), Poria (Fuling), Atractylodis Macrocephalae Rhizoma (Baizhu), Zingiberis Rhizoma Recens (Shengjiang)	[174]

(*Continued*)

Table 12 (Continued).

Name	Herbal Compositions	Reference
Wuling San (WLS)	Poria (Fuling), Polyporus (Zhuling), Alismatis Rhizoma (Zexie), Atractylodis Macrocephalae Rhizoma (Baizhu), Cinnamomi Ramulus (Guizhi)	[175]
Fangji Huangqi decoction(FJHQD)	Stephaniae Tetrandrae Radix (Fangji), Astragali Radix (Huangqi), Glycyrrhizae Radix et Rhizoma (Gancao), Atractylodis Macrocephalae Rhizoma (Baizhu), Zingiberis Rhizoma Recens (Shengjiang), Jujubae Fructus (Dazao)	[176]
FangJiFuling decoction (FF)	Stephaniae Tetrandrae Radix (Fangji), Poria (Fuling), Astragali Radix (Huangqi), Cinnamomi Ramulus (Guizhi), Glycyrrhizae Radix et Rhizoma (Gancao)	[177]
Buzhong Yiqi Decoction	Astragali Radix (Huangqi), Codonopsis Radix (Dangshen), Atractylodis Macrocephalae Rhizoma (Baizhu), Angelicae Sinensis Radix (Danggui), Cimicifugae Rhizoma (Shengma), Bupleuri Radix (Chaihu), Citri Reticulatae Pericarpium (Chenpi), Glycyrrhizae Radix et Rhizoma Praeparata (Zhi Gancao)	[183]

Abbreviations

AA, aristolochic acid; AKI, Acute kidney injury; A ON C, AKI on CKD; APS, Astragalus polysaccharide; AS-IV, Astragaloside IV; A&P, Astragalus propinquus Schischkin and Panax notoginseng; BUN, Blood urea nitrogen; CCl4, carbon tetrachloride; CdCl, cadmium chloride; CHMs, Chinese herbal medicines; CIN, contrast-induced nephropathy; CIS, cisplatin; CKD, chronic kidney disease; CLP, cecal ligation and puncture; CHMs, Chinese herbal medicines; CON, contrast; Con-AKI, Contrast-induced AKI; CPB, cardiopulmonary bypass; CPR, cardiopulmonary resuscitation; CS, crush syndrome; DOX, doxorubicin; ERS, endoplasmic reticulum stress; FA, folic acid; GM, Gentamicin; H/R, Hypoxia/reoxygenation; IRI, ischemia reperfusion injury; ICU, intensive care unit; JPYS, Jianpi Yishen Tang/Jian-Pi-Yi-Shen formula; MOF, multiple organ failure; MTX, methotrexate; MLB, Magnesium lithospermate B; NIBV, nephropathogenic infectious bronchitis virus; OX, oxidative stress; RCE, Rhizoma coptidis extracts; RTEC, renal tubular epithelial cells; SAA/B/C, Salvianolic acid A/B/C; SCr, serum creatinine; Tan IIA, Tanshinone IIA; UUO, unilateral ureteral obstruction; VA, vancomycin; SKI, Shenkang injection; XBJI, Xuebijing injection; DHI, Danhong injection; SFI, Shenfu injection; CHF, Chuan Huang Fang; ASI, Astragalus injection; QHG, Qishen Huoxue Granules; QSYQ, QiShenYiQi Pills; SHD, San-Huang decoction; QYG, Qiong-Yu-Gao; ZDG, Zhibai Dihaung Granule; ZWT, Zhen-Wu-Tang; WLS, Wuling San; FJHQD, Fangji Huangqi decoction; FF, FangJiFuling decoction.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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