

Salvianolic Acids and Their Pharmacological Promise in Kidney Diseases: A Narrative Review

Chi Chen^{1,2,*}, Yanyan Xiao^{1,2,*}, Weiqun Zhou^{3,*}, Yangyang Li^{1,2}, Liqi Hou⁴, Yi Ling See^{1,2}, Shengchun Liao⁵, Hui Huang^{1,2}, Yuan Chen⁶, Qi Chen⁷, Junfei Xu^{1,2}, Hao Lu^{1,2}

¹Department of Endocrinology, Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Shanghai, People's Republic of China; ²Shanghai Key Laboratory of Traditional Chinese Clinical Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai, People's Republic of China; ³Department of General Surgery, The 922nd Hospital of the Joint Logistics Support Force of the Chinese People's Liberation Army, Hengyang, People's Republic of China; ⁴Department of Shuguang Clinical Medical College, Shanghai University of Traditional Chinese Medicine, Shanghai, People's Republic of China; ⁵Department of Nephrology, Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Shanghai, People's Republic of China; ⁶Department of Traditional Chinese Medicine, Henan Provincial People's Hospital, Zhengzhou, People's Republic of China; ⁷Department of Endocrinology and Metabolism, Shanghai Tenth People's Hospital, Tongji University School of Medicine, Shanghai, People's Republic of China

*These authors contributed equally to this work

Correspondence: Hao Lu; Junfei Xu, Email luhao403@163.com; xujunfei_liuli@163.com

Abstract: Kidney disease is a major public health challenge, affecting millions of people worldwide. Conventional treatments often produce suboptimal outcomes and are associated with various adverse effects. Traditional Chinese Medicine has shown promising therapeutic potential, offering distinct advantages over conventional therapies for preventing and treating kidney diseases. Salvianolic acids, the principal bioactive constituents of *Salvia miltiorrhiza*, are widely used in the management of renal disorders. However, no dedicated review has systematically synthesized pharmacological evidence across different models of kidney disease. To advance both basic research and clinical applications, this review summarizes current knowledge on the therapeutic effects of salvianolic acids in acute kidney injury, diabetic kidney disease, and nephrotic syndrome. Their renoprotective actions arise from the modulation of multiple pathological processes, including inflammation, oxidative stress, apoptosis, mitochondrial dysfunction, endoplasmic reticulum stress, and autophagy dysregulation. Collectively, salvianolic acids hold promise as potential therapeutic agents for kidney diseases. Further studies are needed to confirm these molecular mechanisms and identify specific targets. Additionally, large-scale, long-term, multicenter clinical trials are crucial to evaluate the efficacy and safety of salvianolic acids in treating kidney diseases.

Keywords: salvianolic acids, acute kidney injury, diabetic kidney disease, nephrotic syndrome

Introduction

Kidney diseases, encompassing acute kidney injury (AKI) and chronic kidney disease (CKD), have diverse etiologies and represent a global public health challenge, characterized by substantial morbidity, mortality, and economic burden.¹ More than 850 million individuals worldwide were affected by kidney diseases, with approximately 5 million deaths attributed to these diseases each year.^{2,3} It is projected that CKD will become the fifth-leading cause of death globally by 2040.⁴ The pathological manifestations of kidney diseases are complex and varied, and the underlying mechanisms are not yet fully understood. Once kidney disease progresses to renal failure, it becomes irreversible. Current therapeutic strategies primarily focus on the active treatment of primary diseases and providing supportive care through immunosuppressants, hormonal therapies, antihypertensive agents, and antidiabetic medications.⁵ However, the effects of these treatments are unsatisfactory and often accompanied by adverse reactions, such as low immunity, obesity, and hypotension.⁶ Additionally, patients with end-stage renal disease are reliant on dialysis or kidney transplantation to prolong their lives.⁷ Therefore, patients with kidney diseases urgently need innovative treatment modalities. In this context, traditional Chinese medicines have gained recognition for their potential in preventing and treating kidney ailments, attributed to their natural sources and low toxicity.

Salvia miltiorrhiza Bunge (SM), a widely used herb in traditional Chinese medicine, has a long-standing history of clinical application.^{8,9} According to traditional Chinese medicine texts, SM is known for its ability to promote blood circulation and relieve stagnation, and hence, it is widely used in patients suffered from cardiovascular diseases.¹⁰ The composition of SM is both complex and diverse, with its active constituents broadly categorized into water-soluble and lipid-soluble compounds.¹¹ Salvianolic acids are the primary water-soluble compounds extracted from the roots of SM.¹² Notably, salvianolic acid A (SAA) and salvianolic acid B (SAB) are the most abundant among the salvianolic acids.

In recent years, increasing evidence has highlighted the anti-inflammatory, antiproteinuric, and renoprotective effects of salvianolic acids. These properties have positioned salvianolic acids as promising natural compounds for the treatment of kidney diseases. Nevertheless, despite the growing body of experimental and preclinical evidence, the existing literature remains fragmented, and an integrated overview of pharmacological findings across diverse models and pathological contexts of kidney diseases is still lacking. This review aims to provide a comprehensive and timely overview of the effects and pharmacological mechanisms regarding the use of salvianolic acids in the management of kidney diseases, including AKI, diabetic kidney disease (DKD), and nephrotic syndrome (NS). By summarizing the latest research, we sought to offer valuable insights for further basic research, drug development, and clinical application of salvianolic acids in preventing and treating renal diseases.

Treatment of Kidney Diseases

AKI

AKI is a major global health concern marked by a rapid and sudden deterioration in kidney function.¹³ The primary contributors include ischemia-reperfusion injury (IRI), exposure to nephrotoxic agents, and sepsis.¹⁴ AKI is associated with considerable morbidity and mortality.¹⁵ Additionally, it raises the likelihood of developing CKD and ESRD, as well as contributing to cardiovascular diseases, thereby posing a significant threat to overall health and well-being.¹⁶ Given its anti-inflammatory and antioxidant activities, the potential role of salvianolic acids has been extensively investigated in various models of AKI, including IRI and nephrotoxin-induced damage. The mechanisms underlying the protective effects involve the activation of key signaling pathways (Figure 1).

Renal Ischemic Reperfusion Injury

Preservation of Microvascular Integrity and Renal Hypoxia

Microvascular dysfunction and peritubular capillary (PTC) rarefaction are early and critical events in renal ischemia-reperfusion injury, leading to sustained tissue hypoxia and secondary tubular damage. SAA has been shown to significantly improve renal function and attenuate histological injury in rat models of renal IRI by preserving PTC integrity and improving renal oxygenation. Mechanistically, SAA inhibits platelet activation and upregulates Klotho and vascular endothelial growth factor A expression, thereby protecting endothelial structure and mitigating post-ischemic hypoxia.¹⁷ These findings highlight a prominent microvascular-protective role of SAA in ischemic AKI.

Attenuation of Oxidative Stress and Inflammatory Responses

Oxidative stress and inflammation are tightly coupled pathological processes during renal IRI. Salvianolic acids exert coordinated antioxidant and anti-inflammatory effects in this context. SAA treatment effectively mitigated kidney damage, evidenced by reduced plasma creatinine and blood urea nitrogen levels, as well as decreased apoptosis-positive tubular cells and oxidative stress. The protective mechanisms involved activation of key signaling pathways, including phosphorylation of protein kinase B (Akt) and mammalian target of rapamycin (mTOR). In hypoxia/reoxygenation injured proximal renal tubular cells, SAA significantly reduced reactive oxygen species (ROS) levels in a dose-dependent manner and increased phosphorylated-eukaryotic initiation factor 4E binding protein 1 (4EBP1) expression. Importantly, the cytoprotective effects of SAA were inhibited by specific inhibitors like LY294002 and rapamycin, highlighting its action through the Akt/mTOR/4EBP1 signaling pathway.¹⁸

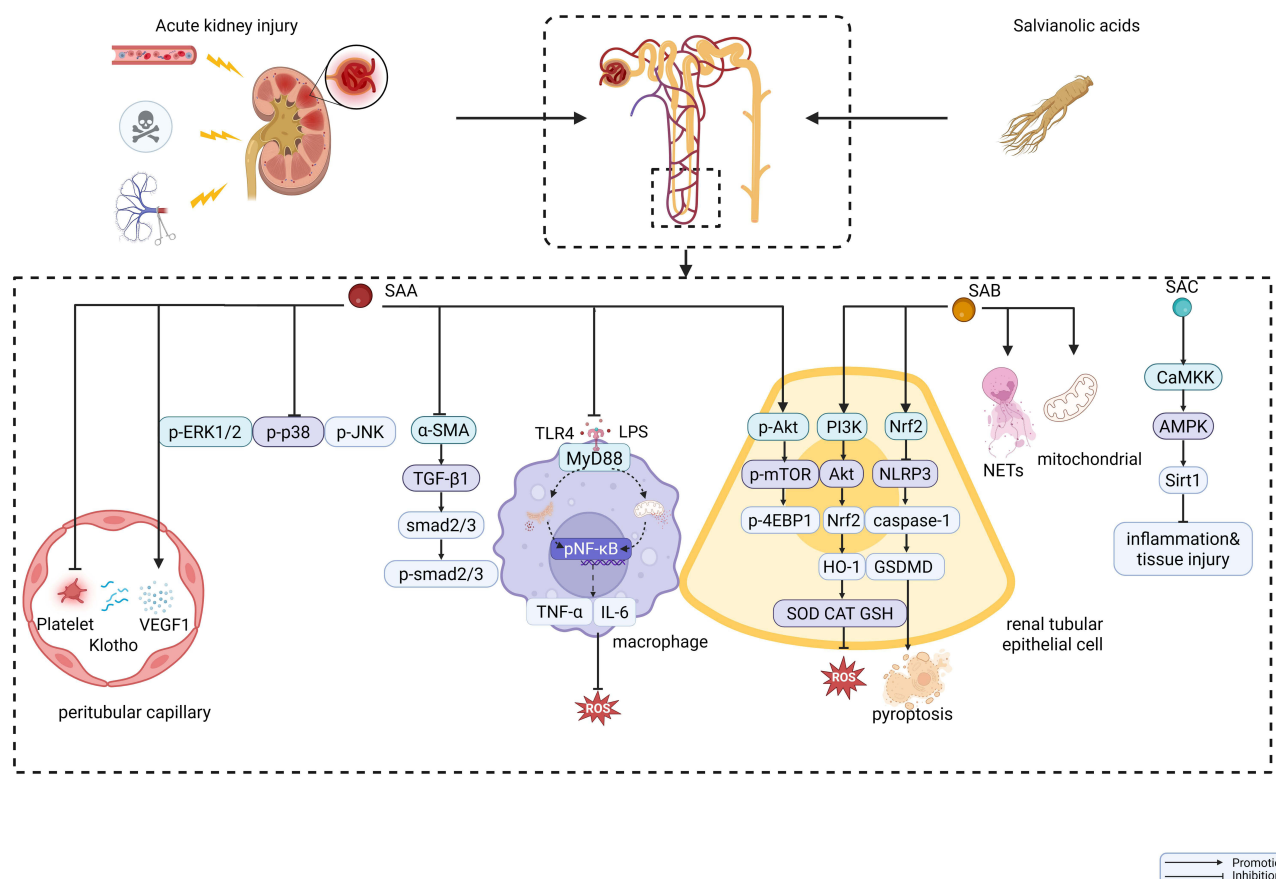


Figure 1 The potential mechanisms of salvianolic acid in the treating acute kidney injury. SAA could inhibit platelet activation, elevate Klotho protein expression and up-regulate vascular endothelial growth factor A expression in peritubular capillary. SAA could activate the Akt/mTOR/4EBP1 pathway in HK-2 cell, and SAA that bound to TLR4 was able to reduce ER stress and ROS generation in macrophage. SAA could regulate the MAPKs and TGF- β /smads signaling pathways. SAB could decrease the level of oxidative stress by activating PI3K/Akt/Nrf2 pathway in HK-2 cell. SAB can inhibit caspase-1/GSDMD-mediated pyroptosis by activating Nrf2/NLRP3 signaling pathway. SAB could improve the mitochondrial function and antibacterial effects via NETs. SAC can provide potent anti-inflammatory and antioxidant effects by inhibiting the CaMKK-AMPK-Sirt1-associated signaling axes.

SAB exhibits similarly robust protective effects against oxidative stress-driven inflammation in renal IRI. In rat IRI models, pretreatment with SAB significantly reduces malondialdehyde levels, enhances endogenous antioxidant capacity, and suppresses inflammatory cytokine production through activation of the PI3K/Akt signaling pathway.¹⁹

Another study also demonstrated that SAB effectively ameliorated renal damage by significantly reducing oxidative stress markers and inflammatory cytokine levels. SAB treatment reversed the upregulation of NLRP3 inflammasome components, including caspase-1, gasdermin D (GSDMD), and interleukin-1 β , all of which were elevated in kidney tissues subjected to IRI. Further investigations revealed that SAB pretreatment enhanced the nuclear accumulation of nuclear factor erythroid 2-related factor 2 (Nrf2), leading to the suppression of oxidative stress and pyroptosis, ultimately alleviating renal IRI.²⁰

Protection Against Severe Ischemic Stress Through Mitochondrial and Endothelial Stabilization

Beyond classical IRI models, the cytoprotective effects of salvianolic acids extend to severe ischemic stress conditions. In a crush syndrome-associated AKI model, SAB administration significantly improved survival rates and renal function while attenuating systemic inflammation. These benefits were attributed to mitigation of mitochondrial dysfunction, reduction of endothelial injury, and modulation of neutrophil extracellular trap-associated inflammatory responses.²¹ This evidence further supports the role of SAB as broad-spectrum cytoprotective agents under acute ischemic conditions.

Collectively, salvianolic acids represent a promising avenue for therapeutic intervention in the management of renal IRI, highlighting their potential role in improving outcomes for patients suffering from ARI. Further research into their mechanisms and clinical applications will be essential in realizing their full potential in renal IRI management.

Nephrotoxic Agents

Various nephrotoxic agents, such as anticancer drugs, contrast agents, and antibiotics, are common causes of drug-induced kidney injury, which makes up 20% of AKI cases.²² Salvianolic acids have emerged as promising candidates for the prevention and management of AKI due to their multifaceted protective mechanisms against nephrotoxicity.

Suppression of Inflammation and Oxidative Stress to Attenuate Tubular Injury

Inflammation and oxidative stress are closely associated pathological features of nephrotoxic AKI, and salvianolic acids have been shown to attenuate both processes across multiple experimental models. In lipopolysaccharide (LPS)-challenged AKI, SAA significantly improved renal function and mitigated histological injury while reducing inflammatory cytokine release and macrophage infiltration. Mechanistically, SAA directly targets Toll-like receptor 4 (TLR4), thereby suppressing downstream inflammatory signaling, alleviating endoplasmic reticulum stress, and limiting ROS generation.²³ Another study also revealed that SAA exhibited protective effects in AKI models induced by gentamicin. SAA significantly enhanced kidney function while demonstrating anti-inflammatory and antioxidant effects by lowering cytokines IL-6 and IL-12, decreasing MDA, and increasing superoxide dismutase (SOD) activity. Furthermore, SAA regulated mitogen-activated protein kinases (MAPK) and TGF- β 1/Smad signaling pathways, reducing phosphorylation of ERK1/2, p38, JNK, and Smad2/3, and the expression of TLR-4 and Smad7.²⁴ These findings collectively highlight the potential of SAA as a therapeutic agent for preventing AKI induced by nephrotoxic agents.

Similarly, SAB demonstrated significant protective effects against contrast-induced acute renal injury (CI-AKI), a common cause of hospital-acquired acute renal failure. The study revealed that intravenous SAB pretreatment notably reduced serum creatinine levels and mitigated histological renal tubular injuries.²⁵ Additionally, SAB decreased the number of apoptosis-positive tubular cells, activated the Nrf2 pathway, and lowered renal oxidative stress induced by iodinated contrast media. Importantly, the protective effects of SAB were found to be mediated through the PI3K/Akt/Nrf2 signaling pathway, as evidenced by the abolishment of renoprotection in the presence of the PI3K inhibitor wortmannin. These findings underscore the potential of SAB as an effective prophylactic agent against CI-AKI.²⁵

Sirt1-Dependent Regulation of Stress Responses and Anti-Apoptotic Protection

Cisplatin is a potent chemotherapy agent for a wide variety of solid tumors, but its use is limited due to significant nephrotoxic effects.²⁶ There are currently no approved medications available to address the side effect. Recently, it is reported that salvianolic acid C (SAC) effectively protected against cisplatin-induced AKI in a mouse model. SAC administration significantly improved kidney function and mitigated renal histological damage. Furthermore, SAC decreased MDA levels while increasing glutathione levels, and simultaneously reduced the expression of inflammatory mediators such as iNOS, cyclooxygenase-2, and NF- κ B, along with the activation of MAPK in renal tissues. Additionally, SAC diminished TLR-4 expression and enhanced the activity of various antioxidative enzymes. The protective effects of SAC were reversed by Sirtuin 1 inhibition, underscoring its potential as a therapeutic agent in alleviating oxidative stress and inflammation associated with cisplatin-induced nephrotoxicity.²⁷

Hence, salvianolic acids offer a promising strategy for managing AKI caused by different nephrotoxic agents. By addressing critical pathways associated with oxidative stress, inflammation, and cellular apoptosis, SAA, SAB, and SAC collectively demonstrate significant therapeutic potential in nephrotoxic AKI treatment. These findings highlight the need for further research and clinical exploration of these compounds.

Diabetic Kidney Disease

DKD is one of the most prevalent microvascular complications of diabetes mellitus.²⁸ Nowadays, with the rising prevalence of diabetes, DKD has become a severe global public health issue and predominant cause of ESRD.²⁹ Various pathologic mechanisms drive the development of DKD, including disturbances in glucose and lipid metabolism,

abnormal hemodynamics, oxidative stress, inflammation, fibrosis, autophagy, and alterations in intestinal flora.^{30,31} However, despite these complex pathogeneses, current treatment options for DKD remain limited.

In recent years, the potential of TCM in the treatment of DKD has garnered increasing attention.³² In particular, SM, known for its rich active compounds and pharmacological properties, has gained attention for its protective effects against DKD. A meta-analysis of nine randomized controlled trials (RCTs) involving 723 participants assessed the effectiveness and safety of SM injection for DKD, which indicated that the combination of SM injection was more effective than Western medicine alone, leading to a higher total effective rate and a reduction in 24-h urinary protein, urinary albumin excretion rate, blood urea nitrogen, and $\beta 2$ microglobulin.³³ Among the key active components of SM, salvianolic acids show promise as viable therapeutic agents for DKD through various signaling pathways (Figure 2).

Preservation of Glomerular Endothelial Function and Attenuation of AGE–RAGE Signaling

SAA has emerged as a potential modulator of various pathological processes involved in DKD. Advanced glycation end products (AGEs) are a group of reactive compounds formed through irreversible non-enzymatic reactions between reducing sugars, such as glucose, fructose, and pentose, and the amino groups of proteins, lipids, and nucleic acids.³⁴ AGEs can contribute to kidney damage through both a direct receptor-independent pathway and an indirect cascade mediated by the receptor for advanced glycation end products (RAGE).³⁵ Hou et al³⁶ found that SAA significantly inhibited the formation of AGEs and reduced their accumulation, thereby ameliorating glomerular endothelial dysfunction. The study revealed that SAA effectively restored glomerular permeability by preventing cytoskeletal rearrangement

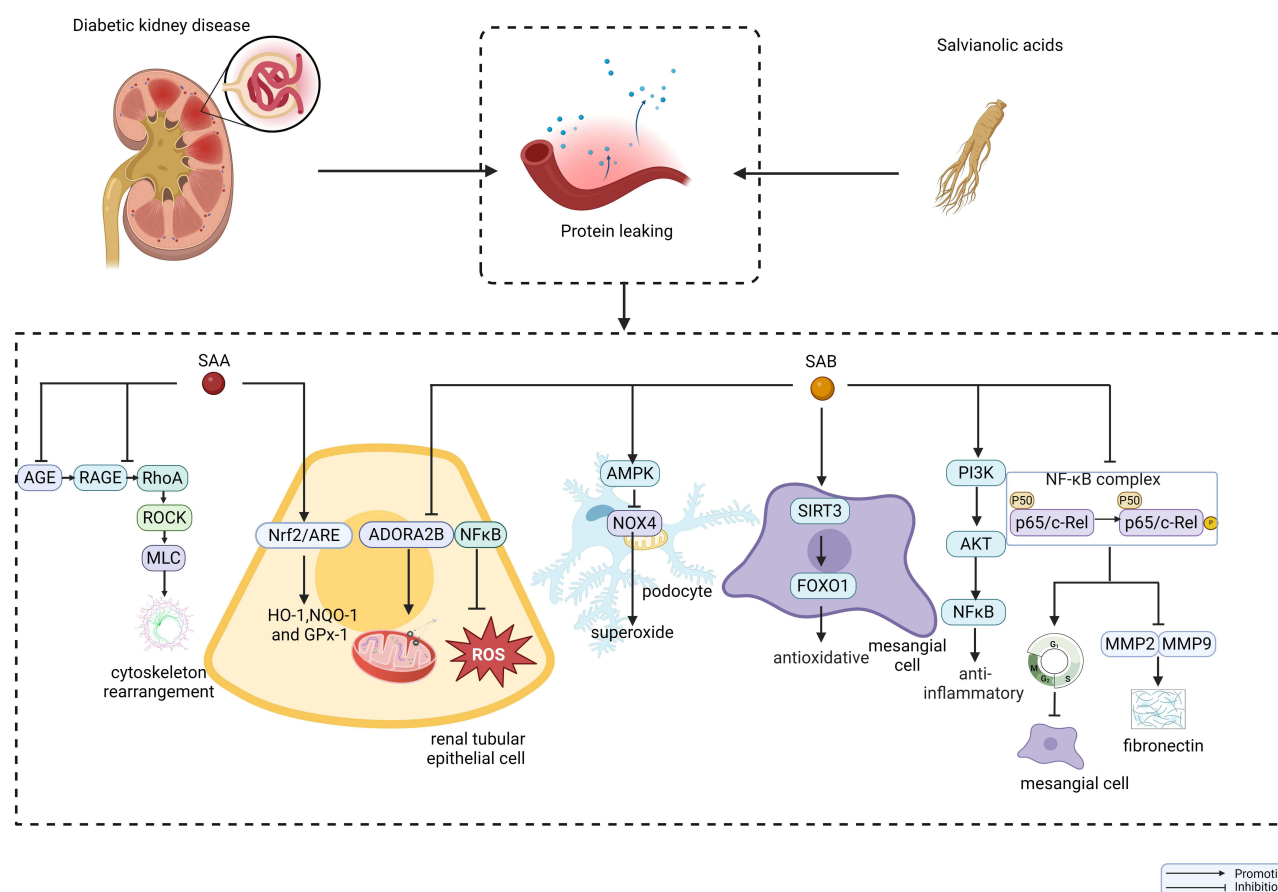


Figure 2 The potential mechanisms of salvianolic acid in the treating diabetic kidney disease. SAA could inhibit AGE-RAGE-RhoA/ ROCK pathway to suppress rearrangement of actin cytoskeleton, and activate the Nrf2/ARE pathway to up-regulate anti-oxidative enzymes (HO-1, NQO-1 and GPx-1). SAB could increase mitochondrial membrane potential and alleviate intracellular ROS generation via inhibiting ADORA2B, NALP3, and NF- κ B activity. SAB could also block mitochondrial NOX4 derived superoxide generation in human podocytes. SAB could activate the SIRT3/FOXO1-mediated signaling pathway to attenuate oxidative stress, and regulate PI3K/Akt/NF- κ B signaling pathway to attenuate inflammation response. SAB could release G1 phase arrest and delay S phase progression to inhibit cell proliferation and modulate MMP-2 and MMP-9 activities to reduce fibronectin secretion through suppressing NF- κ B activation.

induced by the AGE-RAGE-RhoA/ROCK signaling pathway, which was associated with decreased urinary albumin excretion and improved renal function, suggesting that SAA can counteract renal structural deterioration and preserve glomerular endothelial function.³⁶

Suppression of Oxidative Stress and Inflammatory Signaling

Oxidative stress and chronic inflammation are closely linked pathological features of DKD and contribute to progressive renal injury. Salvianolic acids have demonstrated consistent efficacy in attenuating these processes across multiple experimental DKD models.

SAA has been shown to effectively reduce oxidative stress in diabetic kidneys, leading to a decrease in NF- κ B p65 expression and increased levels of Nrf2-responsive antioxidant enzymes, such as heme oxygenase-1 (HO-1), NAD(P)H dehydrogenase (quinone) 1 (NQO-1), and glutathione peroxidase-1 (GPx-1). Furthermore, its combination with metformin enhanced the protective effects against renal injuries, which suggests a synergistic potential of SAA when used alongside other hypoglycemic drugs.³⁷

In parallel, salvianolic acid B (SAB) has demonstrated robust antioxidant and anti-inflammatory actions in DKD. A recent network pharmacology and molecular docking study showed that SAB exhibited more stable binding to potential DKD-related targets compared to tanshinone IIA.³⁸ Luo et al³⁹ demonstrated that SAB significantly inhibited high glucose-induced mesangial cell proliferation and extracellular matrix production in a dose-dependent manner. The underlying mechanism involved the modulation of cell-cycle progression and matrix metalloproteinases (MMP-2 and MMP-9) activity, primarily through the suppression of NF- κ B activation.³⁹ In another study by Liang et al,⁴⁰ salvianolate demonstrated renoprotective effects comparable to the NOX1/NOX4 inhibitor GKT137831, as evidenced by reduced albuminuria, decreased podocyte loss, and diminished mesangial matrix accumulation. Additionally, in human podocytes, SAB inhibited high glucose-induced mitochondrial NOX4-derived superoxide production, leading to a reduction in podocyte apoptosis through AMPK signaling.⁴⁰

Further evidence supports a broader antioxidative role of SAB in DKD progression. In high glucose-induced DKD rats, SAB significantly improved kidney histopathology and function, reducing cell apoptosis and enhancing the activity of antioxidant enzymes, such as GPx and SOD, while decreasing levels of ROS and MDA. Additionally, SAB also exhibited anti-inflammatory properties by suppressing pro-inflammatory cytokines, including IL-1 β , IL-6, MCP-1, and TNF- α , as well as reducing the expression of extracellular matrix components like collagen IV and fibronectin in rat mesangial cells (HBZY-1). Moreover, the ability of SAB to activate the SIRT3/FOXO1 signaling pathway has been proposed as a novel mechanism underlying its protective effects.⁴¹

Modulation of Mitochondrial Dysfunction and Inflammasome Activation

In high glucose-induced HK-2 cells, SAB treatment lead to significant downregulation of the adenosine A2B receptor (ADORA2B) and NALP3 inflammasome components, correlating with improved mitochondrial membrane potential and reduced ROS levels.⁴² In diabetic db/db mice, treatment with SAB contributed to body weight reduction, alleviation of hyperglycemia and hyperlipidemia, and improvements in kidney function.⁴² Additionally, the combination of SAB with tanshinone IIA has demonstrated synergistic improved kidney function and reduced inflammation in early-stage DKD through modulation of the PI3K/Akt/NF- κ B signaling pathway,⁴³ which further underscores the promising potential of salvianolic acids in the management of DKD.

Nephrotic Syndrome

NS is a complex disorder characterized by heavy proteinuria (>3.5 g/d), hypoalbuminemia (serum albumin <2.5 g/dL), edema and hypercholesterolemia. Immunosuppression therapy is the most important treatment for NS, however, many patients may relapse or resistant after the therapy.⁴⁴ Furthermore, these therapies also cause many adverse effects including infection, osteoporosis, suppression of bone marrow and liver damage.⁴⁵ Traditional Chinese herbal medicines are commonly used in the treatment of NS in China, which could increase the remission rate and reduce the adverse effect.⁴⁶ Accumulating evidence has gradually revealed the potential of salvianolic acids in managing various forms of NS, showcasing their multifaceted therapeutic properties (Figure 3).

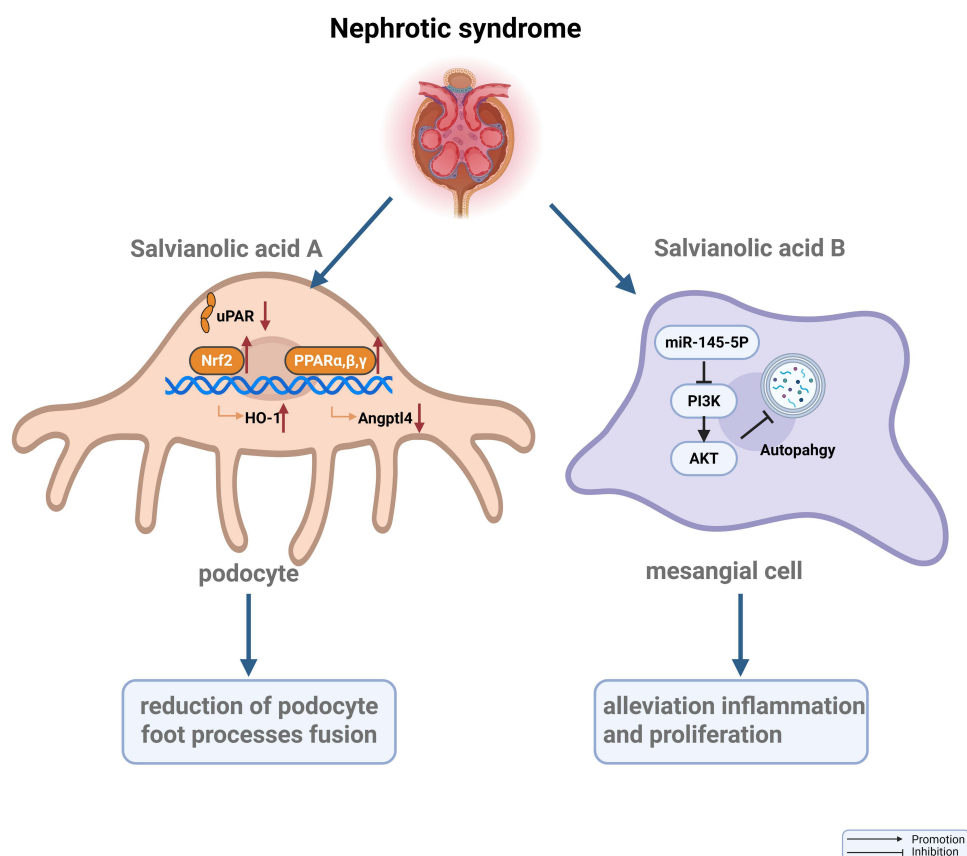


Figure 3 The potential mechanisms of salvianolic acid in the treating nephrotic syndrome. SAA in combined with low-dose prednisone effectively ameliorated the podocyte injury as indicated by the reduction of podocyte foot processes fusion by activation of the Nrf2/HO-1 and PPAR γ /Angptl4 pathways. SAA attenuates steroid resistant nephrotic syndrome by the reduction of podocytes apoptosis through suPAR/uPAR- $\alpha\beta$ 3 signaling inhibition. SAB attenuates renal autophagy to reduce cell proliferation and inflammation of membranous nephropathy, which was mediated by microRNA-145-5p to inhibit PI3K/Akt pathway.

Attenuation of Inflammation-Associated Podocyte Injury and Proteinuria

SAA has been shown to exert robust podocyte-protective effects across different experimental NS models. In a doxorubicin-induced nephropathy model, SAA significantly reduced proteinuria and hyperlipidemia while ameliorating histological renal damage. These benefits were associated with suppression of oxidative stress and inflammatory responses, as evidenced by downregulation of NF- κ B p65 and phosphorylated I κ B α , along with restoration of podocin expression, a key structural protein essential for podocyte integrity.⁴⁷

Consistent with these findings, SAA also exerted marked renoprotective effects in a rat model of adriamycin-induced minimal change disease. Treatment with SAA, particularly in combination with low-dose prednisone, significantly reduced urinary protein excretion and improved biochemical parameters, such as serum total protein, albumin, triglycerides, and creatinine. This combination therapy not only ameliorated pathological kidney lesions but also demonstrated a potent anti-proteinuric effect. Additionally, SAA contributed to the preservation of podocyte foot processes and regulated synaptopodin and desmin levels, which are critical for podocyte function. The protective effects of SAA were linked to the activation of the Nrf2/HO-1 and PPAR γ /Angptl4 signaling pathways.⁴⁸

To address the challenge of steroid-resistant nephrotic syndrome (SRNS), Li et al⁴⁹ investigated the role of SAA in targeting the soluble urokinase plasminogen activator receptor (suPAR) / urokinase-type plasminogen activator receptor (uPAR)- $\alpha\beta$ 3 signaling pathway. The study revealed elevated suPAR levels in serum and urine from SRNS patients, correlating with renal tissue uPAR expression. In vitro experiments demonstrated that SAA effectively reduced podocyte apoptosis and modulated the expression of suPAR/uPAR, leading to enhanced Nephlin expression, crucial for maintaining podocyte function. These results indicate that SAA has the potential to improve glucocorticoid resistance in podocytes, representing a promising therapeutic approach for SRNS.⁴⁹

Modulation of Autophagy and Mesangial Cell Proliferation

SAB has also shown potential in managing NS, particularly in cases of membranous nephropathy (MN). A study by Chen et al⁵⁰ highlighted the efficacy of SAB in improving kidney function in MN. The treatment resulted in significant reductions in proteinuria and serum creatinine levels while mitigating pathological changes in renal tissue. The therapeutic effects of SAB are attributed to its ability to inhibit mesangial cell proliferation and reduce inflammatory responses. Moreover, SAB was shown to activate renal autophagy through the modulation of microRNA-145-5p, which inhibited the PI3K/Akt signaling pathway. These findings position SAB as a promising therapeutic agent for alleviating MN by enhancing autophagy and reducing mesangial cell proliferation and inflammation.⁵⁰

Collectively, salvianolic acids mitigate NS progression by targeting inflammation-associated podocyte injury and proteinuria, while also modulating autophagy and cellular proliferation in specific pathological contexts. These multi-target actions underscore the therapeutic potential of salvianolic acids in diverse forms of NS.

Pharmacokinetics, Safety, and Toxicity

Pharmacokinetics

Absorption and Oral Bioavailability

SAA and SAB are both strongly hydrophilic and largely ionized at physiological pH, which limits passive diffusion across intestinal epithelium. In rats, the absolute oral bioavailability of SAA was reported to be only 0.39–0.52% following oral doses of 5–20 mg/kg.⁵¹ Similarly, SAB demonstrates an oral bioavailability of approximately 2–3% in rats and 1% in dogs, consistent with its highly hydrophilic structure and efflux-transporter susceptibility.⁵²

Tissue Distribution

After oral administration of SAA in rats, tissue distribution studies demonstrate that the highest concentrations are found in the stomach, followed by the small intestine and liver, with lower yet measurable levels detected in the kidney, lung, heart, and even brain homogenates.⁵¹ In humans, intravenously administered SAA exhibits a terminal half-life of approximately 1.6 to 2.9 hours and a large apparent volume of distribution ranging from 69 to 162 liters. This extensive distribution is attributable to active hepatic uptake mediated by organic anion-transporting polypeptide 1B1 and subsequent biliary efflux facilitated by P-glycoprotein.⁵³

For SAB, multiple preclinical studies demonstrate broad distribution to highly perfused organs. In rats receiving depside salts from *Salvia miltiorrhiza* intravenously, the main active component SAB reached the highest tissue levels in kidney, lung and liver.⁵⁴ In humans, SAB injection displays a biphasic plasma concentration–time profile with relatively large apparent distribution volumes and rapid decline in plasma concentrations, consistent with extensive extravascular distribution.⁵⁵

Metabolism

Both SAA and SAB undergo extensive biotransformation characterized predominantly by Phase II conjugation, with SAB exhibiting additional layers of structural modification. In humans, SAA is cleared mainly through hepatobiliary excretion of its conjugated metabolites, exhibiting a short terminal half-life and showing no evidence of systemic accumulation with repeated twice-daily infusion.⁵³ In contrast, SAB undergoes even more complex metabolic processing. Structural identification studies have shown that SAB is converted into more than ten metabolites through sequential reactions involving ester-bond cleavage, five-membered ring opening, decarboxylation, methylation, sulfonation, and glucuronidation, many of which circulate as secondary conjugates rather than as the parent compound.⁵⁶ Additionally, SAB is also a substrate for catechol-O-methyltransferase, and O-methylation constitutes a significant metabolic route contributing to its rapid disappearance from plasma.⁵⁷

Excretion

Quantitative excretion data further indicate extensive biotransformation, with only trace amounts of unchanged drug recovered in excreta. In rats, following oral administration of SAA, less than one percent of the administered dose was recovered as the parent compound in feces, bile, and urine, measured at 0.775%, 0.0037%, and 0.0025% respectively. These findings demonstrate that the vast majority of absorbed SAA undergoes metabolic conversion before elimination.⁵¹

In humans, SAA is cleared predominantly through hepatobiliary excretion of its conjugated metabolites and shows a short terminal half-life without meaningful accumulation after twice-daily infusion.⁵³

For SAB administered intravenously as deposite salts from *S. miltiorrhiza*, Li et al⁵⁴ reported that 86% of the dose was excreted in bile within 6 h, with only a minor fraction appearing unchanged in urine. Clinically, a randomized Phase I trial of SAB injection in healthy Chinese volunteers showed dose-proportional increases in peak exposure and overall systemic exposure across the 75 to 300 mg range, along with a short elimination half-life and no evidence of accumulation after five days of repeated administration, consistent with rapid systemic clearance.⁵⁵

Safety and Toxicity

Although salvianolic acids are widely recognized for their therapeutic potential, a careful assessment of their safety and toxicity profile is essential for clinical translation. Preclinical studies in models of AKI, DKD, and NS have consistently reported good tolerability at doses that exert robust renoprotective effects. Across these models, SAA is typically administered at 2.5–60 mg/kg and SAB at 10–200 mg/kg via intravenous, intragastric, or oral routes over treatment periods ranging from several days to up to 18 weeks. Within these dose ranges, improvements in renal function and histopathology are observed without evidence of treatment-related hepatotoxicity, hematologic abnormalities, or increased mortality beyond the underlying disease pathology, and histological examinations of major organs are generally unremarkable.

Beyond these disease-specific settings, recent non-clinical toxicology studies have provided a systematic assessment of SAA. In acute toxicity evaluations, the median lethal dose in mice was 1,161.2 mg/kg following a single intravenous injection. In Beagle dogs, the minimal lethal dose and maximal non-lethal dose were 682 mg/kg and 455 mg/kg, respectively, indicating a comparatively broad safety margin. A four-week repeated-dose study in Beagle dogs established a no observed adverse effect level of 20 mg/kg per day, whereas higher doses of 80 or 300 mg/kg produced only transient and fully reversible thymic atrophy and mild hepatic or renal tubular alterations, all of which resolved completely upon treatment cessation. Moreover, SAA exhibited no mutagenic activity in standard bacterial reverse-mutation assays or mouse micronucleus tests.⁵⁸

Early clinical data are also available. A first-in-human, randomized, double-blind, placebo-controlled single- and multiple-ascending-dose study in 116 healthy Chinese volunteers evaluated intravenous SAA over a single-dose range of 10–300 mg and multiple doses of 60–200 mg. SAA was well tolerated at all dose levels, with a low incidence of treatment-emergent adverse events that did not increase with dose, and no dose-limiting toxicities, clinically meaningful changes in vital signs, electrocardiograms, or clinical laboratory parameters.⁵³ Similarly, a phase I randomized, double-blind, placebo-controlled trial of SAB injection in healthy Chinese volunteers found that single doses up to 300 mg and 5-day repeated doses up to 250 mg were well tolerated, with no serious adverse events and no clinically significant abnormalities in hematologic indices or hepatic and renal function tests.⁵⁵

In addition, salvianolate injection, an injectable preparation enriched in salvianolic acids, has accumulated substantial post-marketing clinical experience in cardiovascular settings. A systematic review of its clinical application reported that serious adverse drug reactions were rare, and that the events observed, such as rash, dizziness, or mild gastrointestinal discomfort, occurred infrequently and were generally mild in severity.⁵⁹ A recent meta-analysis of randomized controlled trials in acute myocardial infarction further demonstrated that salvianolate injection improved clinical outcomes without increasing the overall incidence of adverse events when compared with standard therapy.⁶⁰ Taken together, evidence from both preclinical investigations and clinical practice supports the view that salvianolic acids exhibit a favorable safety profile at therapeutic exposures, while highlighting the need for more extensive long-term evaluations and kidney disease-specific safety assessments.

Conclusions and Future Perspectives

In recent years, kidney diseases have received widespread attention and become major public health problem worldwide. As valuable sources for developing novel drugs, natural medicines are gradually recognized worldwide because of their good therapeutic efficacy and low side effects. Salvianolic acids, the important bioactive component of SM, have received increasing attention for its potential pharmacological effects on the prevention and treatment of kidney diseases, including AKI, DKD, and NS. Here, we have provided a comprehensive overview of the therapeutic effects of salvianolic acids on kidney diseases in vivo (Table 1) and in vitro (Table 2). Possible mechanisms include modulation of oxidative stress, inflammatory response,

Table 1 Pharmacological Activities of Salvianolic Acids for Treating Kidney Diseases Under in vivo Models

Disease	Compound	Model	Interventions	Effects	Mechanisms	Reference
AKI	SAA	I/R-induced AKI in rats	SAA (2.5, 5 and 10 mg/kg, i.v.) was given daily for 5 consecutive days before I/R induction	Improved renal function Reduced histopathologic damage of kidney	Preventing Peritubular capillary (PTC) endothelium damages and preserving PTC integrity to improve the renal hypoxia	[17]
	SAA	I/R-induced AKI in rats	SAA (40 mg/kg, i.v.) was given 30 m before I/R induction	Improved renal function	Attenuation of oxidative stress and renal apoptosis Via activating Akt/ mTOR/4EBP1 signaling pathway	[18]
	SAB	I/R-induced AKI in rats	SAB (20 and 40 mg/kg, i.p.) was given daily for 7 consecutive days before I/R induction	Improved renal function	Alleviation of oxidative stress and inflammatory response via activating PI3K/Akt signaling pathway	[19]
	SAB	I/R-induced AKI in rats	SAB (50, 100 and 200 mg/kg, i.g.) was given daily for 7 consecutive days before I/R induction	Improved renal function	Attenuation of oxidative stress and inflammatory response via inhibiting caspase-1/GSDMD-mediated CaMKK by activating Nrf2/NLRP3 signaling pathway	[20]
	SAB	C/R-induced AKI in rats	SAB (10, 20 and 50 mg/kg, i.v.) was given once after decompression	Improved renal function and the survival rate	Attenuation of inflammation response and endothelial dysfunction by improving the mitochondrial function and through antibacterial effects via NETs.	[21]
	SAA	LPS-induced AKI in rats	SAA (60 mg/kg, i.g.) was given 1h before LPS induction	Improved renal function	Attenuation of inflammatory response via decreasing the release of serum inflammatory cytokines and blocking macrophage infiltration in damaged renal tissue.	[23]
	SAA	Gentamicin induced AKI	SAA (10, 20 and 40 mg/kg, i.g.) was given 6 h after gentamicin injury for 7 consecutive days	Improved renal function	Attenuation of oxidative stress and inflammatory response via regulating the MAPKs and TGF-1/smads signaling pathways	[24]
	SA-B	Iodinated contrast media-induced AKI in rats	SA-B (50 mg/kg, i.v.) was given 5 m before the intravenous injection of iohexol	Improved renal function Reduced histopathologic damage of kidney	Alleviation of oxidative stress via activating PI3K/Akt/Nrf2 Pathway	[25]
	SAC	Cisplatin-induced AKI in rats	SAC (5, 10 and 20 mg/kg, i.p.) was given for 10 consecutive days and then cisplatin was administered on day 7	Improved renal function	Attenuation of oxidative stress, inflammatory response and Apoptotic Effects via activating the CaMKK-AMPK-Sirt1-Associated Signaling Pathway	[27]
DKD	SAA	STZ-induced DKD in rats	SAA (3 mg/kg, o.g.) was given after DKD induction for 18 weeks	Improved renal function Reduced histopathologic damage of kidney	Attenuation of oxidative stress via activating the Nrf2/ARE pathway to up-regulate anti-oxidative enzymes (HO-1, NQO-1, GPx-1)	[37]
	SAA	HF diet and STZ-induced DKD in rats	SAA (1 mg/kg, p.o.) was given after DKD induction for 8 weeks	Improved renal function	Restoration of glomerular endothelial function and Attenuation of renal structural deterioration via inhibiting AGE-RAGE signaling pathway	[36]
	SAB	HG and HF diet combined with STZ-induced DKD	SAB (50, 100 and 200 mg/kg, p.o.) was given daily after DKD induction for 6 weeks	Improved renal function Reduced histopathologic damage of kidney	Attenuation of oxidative stress via activating the SIRT3/FOXO1-mediated signaling pathway.	[41]
	SAB+TanIIA	HG and HF diet combined with STZ-induced DKD	SAB (68.43 and 136.86 mg/kg, i.g.) and TanIIA (0.11, 0.22, 5.12 and 10.24 mg/kg, i.g.) was given daily after DKD induction for 14 days	Improved renal function	Attenuation of inflammation response via regulating PI3K/Akt/NF-κB signaling pathway	[43]
	SAB	Diabetic db/db mice (6-week-old)	SAB (50 mg/kg, p.o.) was given daily for 6 weeks	Improved renal function	Inhibiting the activation of ADORA2B, NALP3 and NFκB	[42]

NS	SAL	Diabetic db/db mice (8-week-old)	SAL (80 mg/kg, i.p.) was given three times a week for 16 weeks	Improved renal function	Attenuation of oxidative stress and podocyte injury via blockading mitochondrial NOX4 mediated ROS generation	[40]
	SAA	Doxorubicin-induced nephropathy in rats	SAA (2.5, 5 and 10 mg/kg, i.v.) was given daily after Doxorubicin-induction for 21 consecutive days	Improved renal function	Attenuation of oxidative stress and inflammatory response via inhibiting NF- κ B activation and regulating podocin expression.	[47]
	SAA	ADR-induced minimal change disease (MCD) in rats	SAA (10 mg/kg, i.v.) was given daily after ADR induction for 3 weeks	Improved renal function Reduced histopathologic damage of kidney	Activating the Nrf2/HO-1 and PPAR γ /Angptl4 pathways	[48]
	SAB	Cationic bovine serum albumin-induced membranous nephropathy	SAB (100 mg/kg, p.o.) was given daily for 2 weeks	Improved renal function	Activation of renal autophagy to reduce cell proliferation and inflammation response via inhibiting PI3K/AKT signaling pathway by mediating microRNA-145-5p	[50]

Abbreviations: ADR, adriamycin; AGEs, advanced glycation end products; AKI, acute kidney injury; Akt, protein kinase B; C/R, compression/reperfusion; DKD, diabetic kidney disease; GPx-1, glutathione peroxidase-1; HF, high-fat; HG, high glucose; HO-1, heme oxygenase-1; I/R, ischemia/reperfusion; LPS, lipopolysaccharide; NQO-1, NAD(P)H dehydrogenase (quinone) 1; Nrf2, nuclear factor erythroid 2-related factor 2; NS, nephrotic syndrome; RAGE, receptor for advanced glycation end products; ROS, reactive oxygen species; SAA, salvanolic acid A; SAB, salvanolic acid B; SAC, salvanolic Acid C; SAL, salvanolate; STZ, streptozocin; TanIIA, tanshinone IIA.

Table 2 Pharmacological Activities of Salvianolic Acids for Treating Kidney Diseases Under in vitro Models

Disease	Compound	Model	Interventions	Effects	Mechanisms	Reference
AKI	SAA	Ischemic buffer and H/R-induced injury in HK-2 cells	SAA (40 μ M) was added to the cell culture 1h before treated with the Hypoxia/Reoxygenation condition	Improved cell survival	Reducing the levels of reactive oxygen species via activating Akt/mTOR/4EBP1 signaling pathway	[18]
	SAB	H ₂ O ₂ -induced injury in HK-2 cells	SAB (50 μ M) was added to the cell culture 1h before H ₂ O ₂ treatment	Improved cell viability	Activating Nrf2, and decreasing the levels of oxidative stress	[25]
	SAB	H/R-induced injury in HK-2 cells	Cells were incubated with SAB (20, 40 and 80 μ M) for 24h before H/R	Improved cell viability Decreased pyroptosis Decreased LDH release	Inhibiting caspase-1/GSDMD-mediated pyroptosis by activating Nrf2/NLRP3 signaling pathway	[20]
	SAA	LPS-induced injury in macrophages	SAA (10 μ M) was added to the cell culture 1h before LPS treatment	N/A	Decreasing inflammatory factors releases by blocking TLR4/MyD88 pathway Suppressing PERK-eIF2 α -CHOP ER stress pathway and ROS generation Suppressing LPS-stimulated JNK1/2 activation and blocking NF- κ B/p65 translocation	[23]
DKD	SAA	HG-Induced injury in HUVECs and HK-2 cells	HUVECs cells were treated with SAA (5 μ M) for 48h after HG HK-2 cells were treated with SAA (5 μ M) for 12, 24or 48 h after HG	N/A	Reducing intracellular ROS level and the expression of NF- κ B and α -SMA via up-regulating antioxidant enzyme HO-1 level mediated by Nrf2/ARE pathway	[37]
	SAB	HG-Induced injury in human mesangial cells	HMC were pretreated with SAB (0.1, 1 and 10 mM) for 24h before HG	Inhibiting mesangial cells proliferation and extracellular matrix production	Modulating the cell-cycle progress and MMP-2 and MMP-9 activities via suppressing NF- κ B activation	[39]
	SAB	HG-induced injury in HBZY-1 cells	HBZY-1 cells were pretreated with SAB (0.1, 1 and 10 μ M) for 24h before HG	Restoring the cell viability	Reducing oxidative stress and inflammatory response via the SIRT3/FOXO1 signaling pathway	[41]
	SAB	HG-induced injury in HK-2 cells	Treated with SAB (20 μ mol/L) for 24h after HG	N/A	Increasing mitochondrial membrane potential and alleviates intracellular ROS generation via Inhibiting the activation of ADORA2B, NALP3and NF κ B	[42]
	SAB	HG-induced injury in human Podocyte Cells	Treated with SAB (50 and 200 μ M) 24h after HG	Ameliorating podocyte apoptosis	Blockade of mitochondrial NOX4 mediated ROS generation	[40]
NS	SAA	ADR-induced injury in MPC5	Treated with SAA (50 μ mol/l) for 24h after ADR	Alleviating podocyte injury	Activating PPAR γ /Angptl4 pathway	[48]
	SAA	TNF- α and IFN- γ induced steroid resistant, ADR induced further injury in podocytes	Treated with SAA (12.5, 25 and 50 μ mol/L) for 24h before TNF- α , IFN- γ and ADR induced injury	Reducing the apoptosis of podocytes	Improving glucocorticoids resistance of podocyte which can be attributed in part to regulate the suPAR/uPAR- α v β 3 signaling pathway.	[49]
	SAB	LPS-induced injury in human mesangial cells	Treated with SAB for 24h after LPS	Inhibited mesangial cells proliferation	Promoting mesangial cell autophagy and reducing inflammation via inhibiting PI3K/Akt pathway regulated by miR-145-5p	[50]

Abbreviations: AKI, acute kidney injury; Akt, protein kinase B; DKD, diabetic kidney disease; GSDMD, gasdermin D; HG, high glucose; HMC, human mesangial cells; HUVECs, human umbilical vein endothelial cells; NS, nephrotic syndrome; ROS, reactive oxygen species; SAA, salvianolic acid A; SAB, salvianolic acid B; suPAR, soluble urokinase plasminogen activator receptor; uPAR, urokinase-type plasminogen activator receptor.

mitochondrial dysfunction, ferroptosis and apoptosis through pathways such as PI3K/Akt, AGE-RAGE-RhoA/ROCK, SIRT3/FOXO1, TGF- β /Smad and NF- κ B.

Despite the promising potential of salvianolic acids in the treatment of kidney diseases, further research is warranted to fully elucidate their exact mechanisms of action and clinical applications. First, common rodent models such as cisplatin-induced nephrotoxicity, ischemia–reperfusion injury, and db/db-driven diabetic models reproduce key pathological features but do not fully reflect the clinical complexity of human AKI or CKD. While current findings provide important proof-of-concept evidence, improving translational relevance will require the use of complementary and comorbidity-bearing models, and the integration of human-derived systems such as primary renal cells or organoids. Second, except the injection of SM preparation, clinical studies on salvianolic acids for kidney disease management are scarce, particularly large-scale, well-designed randomized controlled trials. It should be noted that the doses used in animal models are primarily intended to demonstrate pharmacological activity and elucidate mechanistic pathways, rather than to define therapeutic doses for humans. Owing to substantial interspecies differences in metabolism, bioavailability, and exposure–response relationships, these experimental doses cannot be directly extrapolated to clinical dosing. Future dedicated clinical research should focus on determining optimal dosing regimens and assessing the long-term efficacy and safety of salvianolic acid treatments. Third, exploring the potential synergistic effects of salvianolic acids in combination with other established kidney disease therapies—such as angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, SGLT2 inhibitors, and immunosuppressants—could provide valuable insights for developing more comprehensive treatment strategies.

Beyond these considerations, the intrinsically low oral bioavailability of salvianolic acids represents another key challenge for their clinical translation. Because only a small fraction of the orally administered dose reaches systemic circulation, most current applications continue to rely on injectable formulations to achieve adequate exposure. Encouragingly, formulation engineering has shown meaningful progress in addressing this limitation. Phospholipid-complex nanoparticles significantly improved the oral absorption and relative bioavailability of salvianolic acid B in rats,⁶¹ and additional enhancement was achieved using extra-virgin-olive-oil-based phospholipid-complex and self-microemulsifying systems, which increased permeability and reduced presystemic metabolism.⁶² Furthermore, other nanocarriers, including polymeric nanoparticles, liposomes, and solid lipid nanoparticles, have demonstrated the ability to protect salvianolic acids from rapid metabolic degradation and improve their intestinal absorption and tissue distribution.⁵² These advances indicate that optimized nanoformulations may support the development of more effective and patient-friendly oral preparations of salvianolic acids.

Future research should also prioritize the rational design of clinical trials to facilitate the translation of salvianolic acids into therapeutic applications. Early-stage indications such as postoperative AKI, nephrotoxin-associated AKI, and early DKD may be especially suitable for proof-of-concept studies. Clinical endpoints should include changes in estimated glomerular filtration rate, albuminuria, and validated biomarkers of tubular injury such as kidney injury molecule-1 and neutrophil gelatinase-associated lipocalin. Furthermore, although salvianolic acids have demonstrated favorable short-term safety in both preclinical and early clinical studies, long-term toxicology data remain insufficient. Comprehensive chronic toxicity studies, including reproductive and developmental evaluations as well as assessments in comorbidity-bearing animal models, are needed to establish the safety margins required for chronic use in CKD populations.

In conclusion, salvianolic acids are promising agents for treating kidney disease. Well-designed, large-scale, long-term, and multicenter clinical trials are necessary to thoroughly evaluate their efficacy and safety for the treatment of kidney diseases. Additionally, more pharmacological studies are required to further elucidate the molecular mechanisms and specific targets in the treatment of kidney diseases.

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References

1. Bello AK, Okpechi IG, Levin A, et al. An update on the global disparities in kidney disease burden and care across world countries and regions. *Lancet Glob Health*. 2024;12(3):e382–e395. doi:10.1016/s2214-109x(23)00570-3
2. Jager KJ, Kovesdy C, Langham R, Rosenberg M, Jha V, Zoccali C. A single number for advocacy and communication-worldwide more than 850 million individuals have kidney diseases. *Kidney Int*. 2019;96(5):1048–1050. doi:10.1016/j.kint.2019.07.012
3. Luyckx VA, Al-Aly Z, Bello AK, et al. Sustainable development goals relevant to kidney health: an update on progress. *Nat Rev Nephrol*. 2021;17(1):15–32. doi:10.1038/s41581-020-00363-6
4. Foreman KJ, Marquez N, Dolgert A, et al. Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: reference and alternative scenarios for 2016–40 for 195 countries and territories. *Lancet*. 2018;392(10159):2052–2090. doi:10.1016/s0140-6736(18)31694-5
5. Ruiz-Ortega M, Rayego-Mateos S, Lamas S, Ortiz A, Rodrigues-Diez RR. Targeting the progression of chronic kidney disease. *Nat Rev Nephrol*. 2020;16(5):269–288. doi:10.1038/s41581-019-0248-y
6. Shi Y, Shi X, Zhao M, Ma S, Zhang Y. Pharmacological potential of Astragali Radix for the treatment of kidney diseases. *Phytomedicine*. 2024;123:155196. doi:10.1016/j.phymed.2023.155196
7. Thurlow JS, Joshi M, Yan G, et al. Global epidemiology of end-stage kidney disease and disparities in kidney replacement therapy. *Am J Nephrol*. 2021;52(2):98–107. doi:10.1159/000514550
8. Su CY, Ming QL, Rahman K, Han T, Qin LP. Salvia miltiorrhiza: traditional medicinal uses, chemistry, and pharmacology. *Chin J Nat Med*. 2015;13(3):163–182. doi:10.1016/s1875-5364(15)30002-9
9. Zhang J, Zhang Q, Liu G, Zhang N. Therapeutic potentials and mechanisms of the Chinese traditional medicine Danshensu. *Eur J Pharmacol*. 2019;864:172710. doi:10.1016/j.ejphar.2019.172710
10. Ho JH, Hong CY. Salvianolic acids: small compounds with multiple mechanisms for cardiovascular protection. *J Biomed Sci*. 2011;18(1):30. doi:10.1186/1423-0127-18-30
11. Chen X, Guo J, Bao J, Lu J, Wang Y. The anticancer properties of Salvia miltiorrhiza Bunge (Danshen): a systematic review. *Med Res Rev*. 2014;34(4):768–794. doi:10.1002/med.21304
12. Jiang Y, Cai Y, Han R, Xu Y, Xia Z, Xia W. Salvianolic acids and its potential for cardio-protection against myocardial ischemic reperfusion injury in diabetes. *Front Endocrinol*. 2023;14:1322474. doi:10.3389/fendo.2023.1322474
13. Kellum JA, Romagnani P, Ashuntantang G, Ronco C, Zarbock A, Anders HJ. Acute kidney injury. *Nat Rev Dis Primers*. 2021;7(1):52. doi:10.1038/s41572-021-00284-z
14. Liu J, Han X, Zhou J, Leng Y. Molecular mechanisms of ferroptosis and their involvement in acute kidney injury. *J Inflamm Res*. 2023;16:4941–4951. doi:10.2147/jir.S427505
15. Hoste EAJ, Kellum JA, Selby NM, et al. Global epidemiology and outcomes of acute kidney injury. *Nat Rev Nephrol*. 2018;14(10):607–625. doi:10.1038/s41581-018-0052-0
16. Ikizler TA, Parikh CR, Himmelfarb J, et al. A prospective cohort study of acute kidney injury and kidney outcomes, cardiovascular events, and death. *Kidney Int*. 2021;99(2):456–465. doi:10.1016/j.kint.2020.06.032
17. Zhang Z, Qi D, Wang X, et al. Protective effect of Salvianolic acid A on ischaemia-reperfusion acute kidney injury in rats through protecting against peritubular capillary endothelium damages. *Phytother Res*. 2018;32(1):103–114. doi:10.1002/ptr.5954
18. Song Y, Liu W, Ding Y, et al. Salvianolic acid A ameliorates renal ischemia/reperfusion injury by activating Akt/mTOR/4EBP1 signaling pathway. *Am J Physiol Renal Physiol*. 2018;315(2):F254–F262. doi:10.1152/ajprenal.00508.2017
19. Ma ZG, Xia HQ, Cui SL, Yu J. Attenuation of renal ischemic reperfusion injury by salvianolic acid B via suppressing oxidative stress and inflammation through PI3K/Akt signaling pathway. *Braz J Med Biol Res*. 2017;50(6):e5954. doi:10.1590/1414-431x20175954
20. Pang Y, Zhang PC, Lu RR, et al. Andrade-Oliveira salvianolic Acid B modulates Caspase-1-Mediated pyroptosis in renal ischemia-reperfusion injury via Nrf2 pathway. *Front Pharmacol*. 2020;11:541426. doi:10.3389/fphar.2020.541426
21. Murata I, Sugai T, Murakawa Y, et al. Salvianolic acid B improves the survival rate, acute kidney dysfunction, inflammation and NETosis-mediated antibacterial action in a crush syndrome rat model. *Exp Ther Med*. 2022;23(5):320. doi:10.3892/etm.2022.11249
22. Hosohata K. Role of oxidative stress in drug-induced kidney injury. *Int J Mol Sci*. 2016;17(11). doi:10.3390/ijms17111826
23. Zeng X, Chen X, Qin H, et al. Preventive effects of a natural anti-inflammatory agent Salvianolic acid A on acute kidney injury in mice. *Food Chem Toxicol*. 2020;135:110901. doi:10.1016/j.fct.2019.110901
24. Diao HY, Zhu W, Liu J, Yin S, Wang JH, Li CL. Salvianolic acid A improves rat kidney injury by regulating MAPKs and TGF- β 1/Smads signaling pathways. *Molecules*. 2023;28(8). doi:10.3390/molecules28083630
25. Tongqiang L, Shaopeng L, Xiaofang Y, et al. Salvianolic Acid B prevents iodinated contrast media-induced acute renal injury in rats via the PI3K/Akt/Nrf2 pathway. *Oxid Med Cell Longev*. 2016;2016:7079487. doi:10.1155/2016/7079487
26. Pushpan CK, Kresock DF, Ingersoll MA, et al. Repurposing AZD5368 and dabrafenib for cisplatin-induced AKI. *J Am Soc Nephrol*. 2024;35(1):22–40. doi:10.1681/asn.0000000000000261
27. Chien LH, Wu CT, Deng JS, Jiang WP, Huang WC, Huang GJ. Salvianolic acid C protects against cisplatin-induced acute kidney injury through attenuation of inflammation, oxidative stress and apoptotic effects and activation of the CaMKK-AMPK-Sirt1-Associated signaling pathway in mouse models. *Antioxidants*. 2021;10(10). doi:10.3390/antiox10101620
28. Chen C, Chen Y, Zhai H, et al. Iodine nutrition status and its association with microvascular complications in urban dwellers with type 2 diabetes. *Nutr Metab*. 2020;17:70. doi:10.1186/s12986-020-00493-5
29. Alicic RZ, Rooney MT, Tuttle KR. Diabetic kidney disease: challenges, progress, and possibilities. *Clin J Am Soc Nephrol*. 2017;12(12):2032–2045. doi:10.2215/cjn.11491116

30. Tuttle KR, Agarwal R, Alpers CE, et al. Molecular mechanisms and therapeutic targets for diabetic kidney disease. *Kidney Int.* **2022**;102(2):248–260. doi:10.1016/j.kint.2022.05.012
31. Linh HT, Iwata Y, Senda Y, et al. Intestinal bacterial translocation contributes to diabetic kidney disease. *J Am Soc Nephrol.* **2022**;33(6):1105–1119. doi:10.1681/asn.2021060843
32. Shen S, Zhong H, Zhou X, et al. Advances in Traditional Chinese Medicine research in diabetic kidney disease treatment. *Pharm Biol.* **2024**;62(1):222–232. doi:10.1080/13880209.2024.2314705
33. Cai L, Chen Y, Xue H, et al. Effect and pharmacological mechanism of Salvia miltiorrhiza and its characteristic extracts on diabetic nephropathy. *J Ethnopharmacol.* **2024**;319(Pt 3):117354. doi:10.1016/j.jep.2023.117354
34. Zeng C, Li Y, Ma J, Niu L, Tay FR. Clinical/Translational aspects of advanced glycation end-products. *Trend Endocrinol Metabol.* **2019**;30(12):959–973. doi:10.1016/j.tem.2019.08.005
35. Yuan Y, Sun H, Sun Z. Advanced glycation end products (AGEs) increase renal lipid accumulation: a pathogenic factor of diabetic nephropathy (DN). *Lipids Health Dis.* **2017**;16(1):126. doi:10.1186/s12944-017-0522-6
36. Hou B, Qiang G, Zhao Y, et al. Salvianolic acid A protects against diabetic nephropathy through ameliorating glomerular endothelial dysfunction via inhibiting AGE-RAGE signaling. *Cell Physiol Biochem.* **2017**;44(6):2378–2394. doi:10.1159/000486154
37. Wu P, Yan Y, Ma LL, et al. Effects of the Nrf2 protein modulator salvianolic acid A alone or combined with metformin on diabetes-associated macrovascular and renal injury. *J Biol Chem.* **2016**;291(42):22288–22301. doi:10.1074/jbc.M115.712703
38. Zhang L, Han L, Wang X, et al. Exploring the mechanisms underlying the therapeutic effect of Salvia miltiorrhiza in diabetic nephropathy using network pharmacology and molecular docking. *Biosci Rep.* **2021**;41(6). doi:10.1042/bsr20203520
39. Luo P, Tan Z, Zhang Z, Li H, Mo Z. Inhibitory effects of salvianolic acid B on the high glucose-induced mesangial proliferation via NF-kappaB-dependent pathway. *Biol Pharm Bull.* **2008**;31(7):1381–1386. doi:10.1248/bpb.31.1381
40. Liang Y, Liu H, Fang Y, et al. Salvianolate ameliorates oxidative stress and podocyte injury through modulation of NOX4 activity in db/db mice. *J Cell Mol Med.* **2021**;25(2):1012–1023. doi:10.1111/jcmm.16165
41. Wen F, Zhang S, Sun L, Qian M, Xu H. Salvianolic acid B inhibits oxidative stress in glomerular mesangial cells alleviating diabetic nephropathy by regulating SIRT3/FOXO1 signaling. *Kidney Blood Press Res.* **2023**;48(1):738–751. doi:10.1159/000534832
42. Wang Y, Chang J, Qiao S, et al. Salvianolic acid B attenuates diabetic nephropathy through alleviating ADORA2B, NALP3 in inflammasome, and NFkB activity. *Can J Physiol Pharmacol.* **2024**;102(5):318–330. doi:10.1139/cjpp-2023-0089
43. Xu Z, Cai K, Su SL, Zhu Y, Liu F, Duan JA. Salvianolic acid B and tanshinone IIA synergistically improve early diabetic nephropathy through regulating PI3K/Akt/NF-kB signaling pathway. *J Ethnopharmacol.* **2024**;319(Pt 3):117356. doi:10.1016/j.jep.2023.117356
44. Feng M, Yuan W, Zhang R, Fu P, Wu T. Chinese herbal medicine Huangqi type formulations for nephrotic syndrome. *Cochrane Database Syst Rev.* **2013**;2013(6):CD006335. doi:10.1002/14651858.CD006335.pub3
45. Vivarelli M, Gibson K, Sinha A, Boyer O. Childhood nephrotic syndrome. *Lancet.* **2023**;402(10404):809–824. doi:10.1016/s0140-6736(23)01051-6
46. Wang XQ, Wang L, Tu YC, Zhang YC. Traditional Chinese medicine for refractory nephrotic syndrome: strategies and promising treatments. *Evid Based Complement Alternat Med.* **2018**;2018:8746349. doi:10.1155/2018/8746349
47. Fan HY, Yang MY, Qi D, et al. Salvianolic acid A as a multifunctional agent ameliorates doxorubicin-induced nephropathy in rats. *Sci Rep.* **2015**;5:12273. doi:10.1038/srep12273
48. Wang X, Qi D, Fu F, et al. Therapeutic and antiproteinuric effects of salvianolic acid A in combined with low-dose prednisone in minimal change disease rats: involvement of PPARγ/Angpt4 and Nrf2/HO-1 pathways. *Eur J Pharmacol.* **2019**;858:172342. doi:10.1016/j.ejphar.2019.04.023
49. Li X, Qi D, Wang MY, et al. Salvianolic acid A attenuates steroid resistant nephrotic syndrome through suPAR/uPAR-αβ3 signaling Inhibition. *J Ethnopharmacol.* **2021**;279:114351. doi:10.1016/j.jep.2021.114351
50. Chen J, Hu Q, Luo Y, et al. Salvianolic acid B attenuates membranous nephropathy by activating renal autophagy via microRNA-145-5p/phosphatidylinositol 3-kinase/AKT pathway. *Bioengineered.* **2022**;13(5):13956–13969. doi:10.1080/21655979.2022.2083822
51. Sun J, Song J, Zhang W, et al. Some pharmacokinetic parameters of salvianolic acid A following single-dose oral administration to rats. *Pharm Biol.* **2018**;56(1):399–406. doi:10.1080/13880209.2018.1491998
52. He G, Chen G, Liu W, et al. Salvianolic acid B: a review of pharmacological effects, safety, combination therapy, new dosage forms, and novel drug delivery routes. *Pharmaceutics.* **2023**;15(9). doi:10.3390/pharmaceutics15092235
53. Chen J, Ruan Z, Lou H, et al. First-in-human study to investigate the safety and pharmacokinetics of salvianolic acid A and pharmacokinetic simulation using a physiologically based pharmacokinetic model. *Front Pharmacol.* **2022**;13:907208. doi:10.3389/fphar.2022.907208
54. Li X, Yu C, Lu Y, et al. Pharmacokinetics, tissue distribution, metabolism, and excretion of depside salts from Salvia miltiorrhiza in rats. *Drug Metab Dispos.* **2007**;35(2):234–239. doi:10.1124/dmd.106.013045
55. Cheng J, Long J, Zhang J, et al. Safety, tolerance, and pharmacokinetics of salvianolic acid B in healthy Chinese volunteers: a randomized, double-blind, placebo-controlled Phase 1 clinical trial. *Front Pharmacol.* **2023**;14:1146309. doi:10.3389/fphar.2023.1146309
56. Xu M, Guo H, Han J, et al. Structural characterization of metabolites of salvianolic acid B from Salvia miltiorrhiza in normal and antibiotic-treated rats by liquid chromatography-mass spectrometry. *J Chromatogr B Analyt Technol Biomed Life Sci.* **2007**;858(1–2):184–198. doi:10.1016/j.jchromb.2007.08.032
57. Kobayashi H, Fukuyama K, Ohno A, et al. The Chinese herb component salvianolic acid B induces copper-mediated reactive oxygen species generation and oxidative DNA damage. *Genes Environ.* **2025**;47(1):20. doi:10.1186/s41021-025-00344-w
58. Yang MY, Song ZY, Gan HL, et al. Non-clinical safety evaluation of salvianolic acid A: acute, 4-week intravenous toxicities and genotoxicity evaluations. *BMC Pharmacol Toxicol.* **2022**;23(1):83. doi:10.1186/s40360-022-00622-1
59. Chen ZW, Xie YM, Liao X, Wang GQ. Systematic review on safety of Salvianolate injection. *Zhongguo Zhong Yao Za Zhi.* **2016**;41(19):3686–3695. doi:10.4268/cjcm20161931
60. Chen P, Zhang H, Gao Z, Shi D, Zhang J. Efficacy and safety of salvianolate injection in treating acute myocardial infarction: a meta-analysis and systematic literature review. *Front Pharmacol.* **2024**;15:1478558. doi:10.3389/fphar.2024.1478558
61. Peng Q, Gong T, Zuo J, Liu J, Zhao D, Zhang Z. Enhanced oral bioavailability of salvianolic acid B by phospholipid complex loaded nanoparticles. *Pharmazie.* **2008**;63(9):661–666.
62. Wang Y, Huang J, Wang Z, et al. Extra virgin olive oil-based phospholipid complex/self-microemulsion enhances oral absorption of salvianolic acid B through inhibition of catechol-O-methyltransferase-mediated metabolism. *Int J Pharm.* **2022**;611:121330. doi:10.1016/j.ijpharm.2021.121330

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