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Antioxidant nanozymes in kidney injury: mechanism and application

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Excessive production of reactive oxygen species (ROS) in the kidneys is involved in the pathogenesis of kidney diseases, such as acute kidney injury (AKI) and diabetic kidney disease (DKD), and is the main reason for the progression of kidney injury. ROS can easily lead to lipid peroxidation and damage the tubular epithelial cell membrane, proteins and DNA, and other molecules, which can trigger cellular oxidative stress. Effective scavenging of ROS can delay or halt the progression of kidney injury by reducing inflammation and oxidative stress. With the development of nanotechnology and an improved understanding of nanomaterials, more researchers are applying nanomaterials with antioxidant activity to treat kidney injury. This article reviews the detailed mechanism between ROS and kidney injury, as well as the applications of nanozymes with antioxidant effects based on different materials for various kidney injuries. To better guide the applications of antioxidant nanozymes in kidney injury and other inflammatory diseases, at the end of this review we also summarize the aspects of nanozymes that need to be improved. An in-depth understanding of the role played by ROS in the occurrence and progression of kidney injury and the mechanism by which antioxidant nanozymes reduce oxidative stress is conducive to improving the therapeutic effect in kidney injury and inflammation-related diseases.

1. Introduction

The kidneys receive 20–25% of the blood supply of the entire body, and effectively scavenge metabolic waste and maintain the homeostasis of the body. Approximately 7% of the total oxygen in the human body is used for high solute exchange in renal tubules, so the oxygen demand is high. On the other hand, the kidneys are often exposed to high concentrations of hazardous substances, which makes them susceptible to hypoxia and injury. Various ischemia-hypoxic and toxic injuries can lead to kidney injury and cause inflammation and cell death, resulting in acute kidney injury (AKI).[1,2] AKI is a heterogeneous group of diseases associated with rapid kidney function decline within a short period (<7 days). AKI usually manifests in elevated serum creatinine concentrations and oliguria, and is part of acute kidney disease and disorders (AKD).[3–5] Several factors can cause AKI, and they are often related to sepsis, renal insufficiency, nephrotoxic drugs, and the perioperative period.[6] Infections and hypovolemic shock are often the main causes of AKI in low-income and middle-income countries. In high-income countries, AKI is mostly caused by sepsis or drugs in hospitalized older patients. Infection and trauma-related AKIs are frequent in all regions.[5] AKI accounts for 10–15% of all hospitalized patients, and its prevalence in patients admitted to the intensive care unit can exceed 50%. Major complications include volume overload, uremic complications, electrolyte disturbances, and drug toxicity.[3,4]

Kidney injury is also a major complication of diabetes, with approximately 50% of patients with type 2 diabetes mellitus developing diabetic kidney disease (DKD). DKD is also an important causative factor for end-stage renal disease (ESRD), which can significantly increase the mortality rate of diabetes. With the increasing incidence of diabetes, the total number of patients with diabetes globally is expected to increase from 382 million in 2013 to 592 million in 2035.[7,8] There are currently no drugs to effectively halt the progression of kidney injury, and kidney replacement therapy (KRT) may be the only option for patients with kidney disease currently. However, despite the use of KRT, the mortality rate in kidney injury is markedly higher than that in other critical illnesses despite kidney replacement therapy, which places a heavy burden on the medical system.[9,10] Therefore, it is necessary to find better strategies to delay and halt the progression of kidney injury.

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A study of the pathophysiological characteristics of various types of AKI showed that excess ROS are closely related to various types of kidney injury. Scavenging ROS is effective for treating kidney injury. ROS can act as messengers to regulate intracellular signaling pathway transduction and immune responses, and exert important effects on several signal transduction cascades. When ROS change, the functions of cells, organs, and organisms will be affected.[11] The specific relationship between ROS and kidney injury is described in the next section. Currently, traditional antioxidants and anti-inflammatory drugs have severe side effects and low renal targeting. The therapeutic effect is often unsatisfactory and aggravates kidney injury.[1] With the wide range of applications of nanozymes in the field of biomedicine, several nanomaterials have demonstrated the catalytic activities of natural enzymes such as peroxidase (POD), oxidase (OXD), superoxide dismutase (SOD), and catalase (CAT), among others. They can effectively replace the traditional enzymes for catalysis.[12] Given the antioxidant effects of several nanomaterials, several researchers have investigated the role and mechanism of nanozyme antioxidants in ROS-related diseases such as Alzheimer's disease, inflammation, and Parkinson's disease.[13,14] With the development of nanozymes and an improved understanding of nanozymes, several scholars have studied the therapeutic effects in kidney injury of antioxidant nanozymes based on various materials. As a new way to treat kidney injury, no scholars have reviewed this aspect at present. To allow relevant personnel to better understand this field and the therapeutic effect of antioxidant nanozymes on kidney injury, we reviewed the antioxidant effects of various nanozymes on kidney injury. This review explores the relationship between ROS and kidney injury and then introduces their antioxidant mechanisms and therapeutic effects on kidney injury according to different classifications of nanomaterials. Finally, the challenges and future development directions for the development of antioxidant nanozymes in the field of kidney injury treatment are discussed, and some design ideas for nanozymes are proposed to provide references for relevant personnel to carry out more extensive research.

2. Kidney injury and ROS

ROS are chemically active molecules, ions, or free radicals inevitably produced by organisms through enzymatic reactions and metabolic processes. They can be divided into two categories: non-free radicals and free radicals. Non-free radical ROS include hydrogen peroxide (H_2O_2), singlet molecular oxygen ($^1O_2$), and organic hydroperoxides (ROOH). The free radical ROS include superoxide anion radical ($O_2^{\bullet -}$), hydroxyl radical ($^{\bullet}OH$), and peroxygen radical ($ROO^{\bullet}$). ROS are mainly produced *via* oxygen metabolism through a series of electron transfers, and can also be produced when cells are stimulated by exogenous substances and cytokines.[15,16] Most ROS are produced by cells in a controlled manner by enzymatic systems such as nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, and participate in various physiological activities in the human body. ROS are mainly produced by mitochondria and NADPH oxidase (NOX). The kidney has a high mitochondrial density and oxygen consumption because it has high energy demands for reabsorption and excretion. Mitochondrial oxidative stress, ROS production, and inflammation exist in all pathological stages of kidney injury.[17] By studying the pathophysiology of sepsis-induced kidney injury, van der Slikke *et al.* found that sepsis resulted in the reduction of mitochondrial mass and nuclear and mitochondrial DNA oxidation in the kidneys.[18] In addition to mitochondria, ROS in normal and pathological kidneys are mainly derived from NADPH oxidase. When NADPH oxidases transfer electrons from NADPH, they react with oxygen to form superoxide. Superoxide releases Fe^{3+} from ferritin and promotes the production of additional ROS such as peroxides. The Fenton reaction of peroxide with Fe^{2+} tends to produce $^{\bullet}OH$, which can attack almost all cell components and produce extra free radicals.

ROS regulate cell homeostasis, and their production and clearance is always maintained in a dynamic balance. Under pathophysiological conditions, the antioxidant system is easily damaged, resulting in ROS imbalance and signal transduction disorders. Understanding the mechanism of oxidative stress and metabolic dysfunctionrelated diseases will help us find new and more effective treatments for related diseases. The progression of kidney injury goes in hand in hand with inflammation and oxidative stress, and lipid peroxidation has a marked impact on the progression of kidney injury. Lipid peroxidation can not only directly destroy phospholipids and mediate proinflammatory changes, but also acts as a cell death signal to induce programmed cell death.[19] In addition, excessive production of ROS may aggravate damage of the endoplasmic reticulum, lysosomes, and other organelles, leading to kidney injury. Among NADPH oxidase subtypes, NADPH oxidase 4 is highly expressed in the kidneys and is closely related to the pathological processes of several renal diseases. Superoxide produced by NADPH oxidase can also directly trigger mitochondrial ROS production, which promotes ROS-mediated apoptosis and aggravates kidney injury with inflammation.[20,21] Under the action of SOD, $O_2^{\bullet -}$ produced by mitochondria and NADPH will become H_2O_2 and aggravate the damage to the endoplasmic reticulum and lysosomes (Fig. 1). In addition, H_2O_2 can further generate higher toxic $^{\bullet}OH$ through the Fenton reaction, thus causing DNA damage and lipid peroxidation. The presence of enzymes such as catalase and glutathione peroxidase (GPx) can catalyze H_2O_2 to become non-toxic water.[16,22] Therefore, antioxidant enzymes such as superoxide dismutase, glutathione peroxidase, and catalase play an important role in the production and elimination of ROS, which is conducive to reducing kidney injury.

3. ROS-based antioxidative stress therapy for kidney injury

The antioxidant system in the human body can effectively scavenge and inhibit ROS, protect cells and biomolecules from

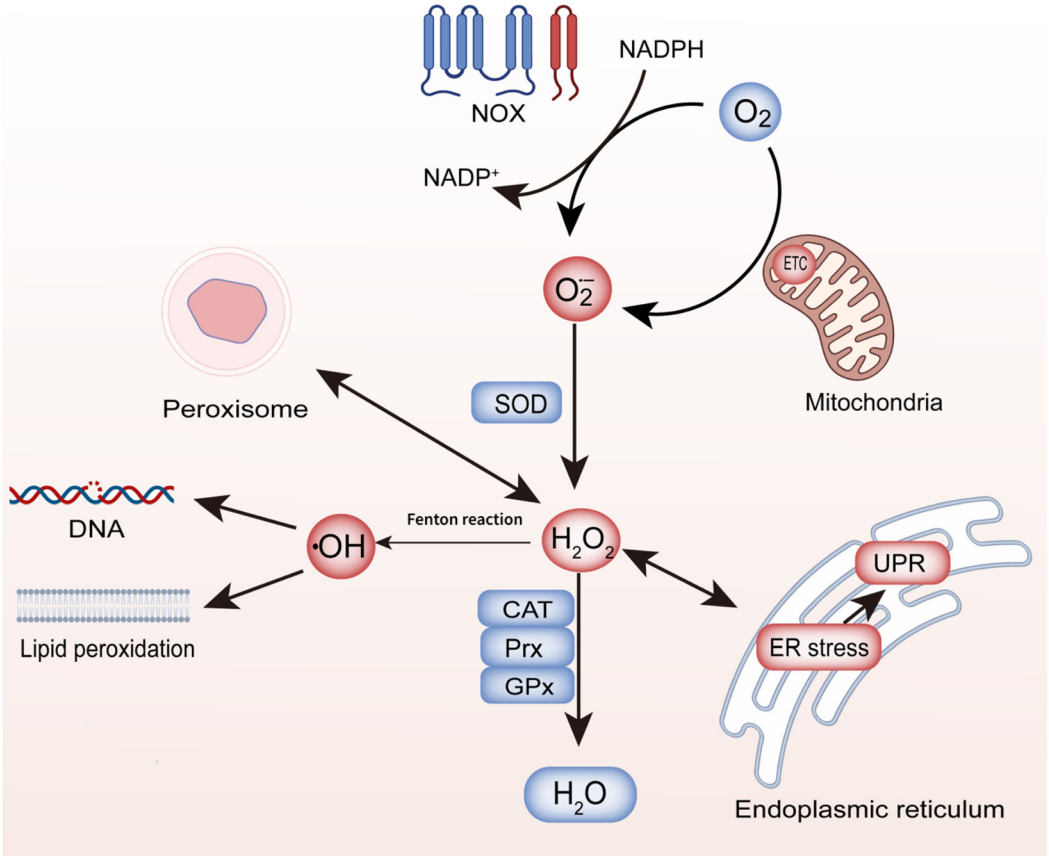

Fig. 1 Schematic illustration of the subcellular generation and destination of the main reactive oxygen species: H_2O_2, $O_2^{\cdot-}$, and $^{\cdot}OH$.

ROS damage, and maintain the dynamic balance of ROS. The antioxidant system is mainly composed of non-enzymatic antioxidants and natural enzymatic antioxidants. Vitamin E, ascorbic acid, reduced glutathione, and melanin are all non-enzymatic antioxidants that are effective in scavenging oxygen free radicals. Natural enzymatic antioxidants, including superoxide dismutase, glutathione peroxidase, and catalase, mainly act in synergy with antioxidant systems to catalyze free reactions to scavenge ROS.[23,24] To date, many scholars have made efforts in the treatment of kidney injury. Studies have found that the PINK1-PRKN/PARK2 pathway can mediate mitophagy and preserve mitochondrial mass, reduce ROS production and inhibit inflammation, and protect renal tubular epithelial cells.[25] Trehalose is a natural non-reducing disaccharide present in bacteria, fungi, and plants. It is a recently discovered inducer of autophagy and transcription factor EB (TFEB). Trehalose can activate TFEB-mediated autophagy in mice with kidney injury, attenuating mitochondrial dysfunction and kidney injury induced by cisplatin.[26]

In addition to scavenging ROS through mitochondrial phagocytosis to reduce kidney injury, researchers have also explored several other pathways that inhibit ROS production and oxidative stress (Fig. 2). ELABELA is a 32-residue hormone peptide that is abundant in the kidneys, and it attenuates kidney injury mediated by the NADPH oxidase/ROS/NLRP3 inflammatory response pathway. ELABELA inhibits NADPH oxidase activity and decreases ROS concentrations, thereby blocking the formation and activation of the NLRP3 inflammatory response.[27] MAResin1 (MAR1) is a lipid mediator with an anti-inflammatory effect that can inhibit the NOX4/ROS/NF-κB p65 signaling pathway. It can reduce renal inflammation, apoptosis, oxidative stress, and mitochondrial dysfunction, and has a protective effect on sepsis-related kidney injury.[28] Nuclear factor erythroid 2 related factor 2 (Nrf-2) is a significant regulator of the redox equilibrium, and can induce a series of cytoprotective genes to regulate oxidative stress and ameliorate kidney disease by eliminating ROS.[29] Astilbe can effectively promote the activation of Nrf-2 and the expression of antioxidant genes, inhibit the expression of TNF-α and the activation of NF-κB, and consequently reduce ROS accumulation and apoptosis of cells induced by cisplatin.[30] Dexmedetomidine (DEX) has also been found to significantly improve renal impairment by reducing apoptosis and oxidative stress and enhancing autophagy. DEX can inhibit the PI3K/Akt/mTOR pathway and ROS/JNK pathway, restore autophagy, and reduce oxidative stress and apoptosis.[31,32] Traditional natural enzymatic antioxidants have high catalytic efficiency; however, they have several limitations, such as high preparation costs, harsh reaction conditions, poor stability, easy oxidation, and low bioavailability. Therefore, finding and develop-

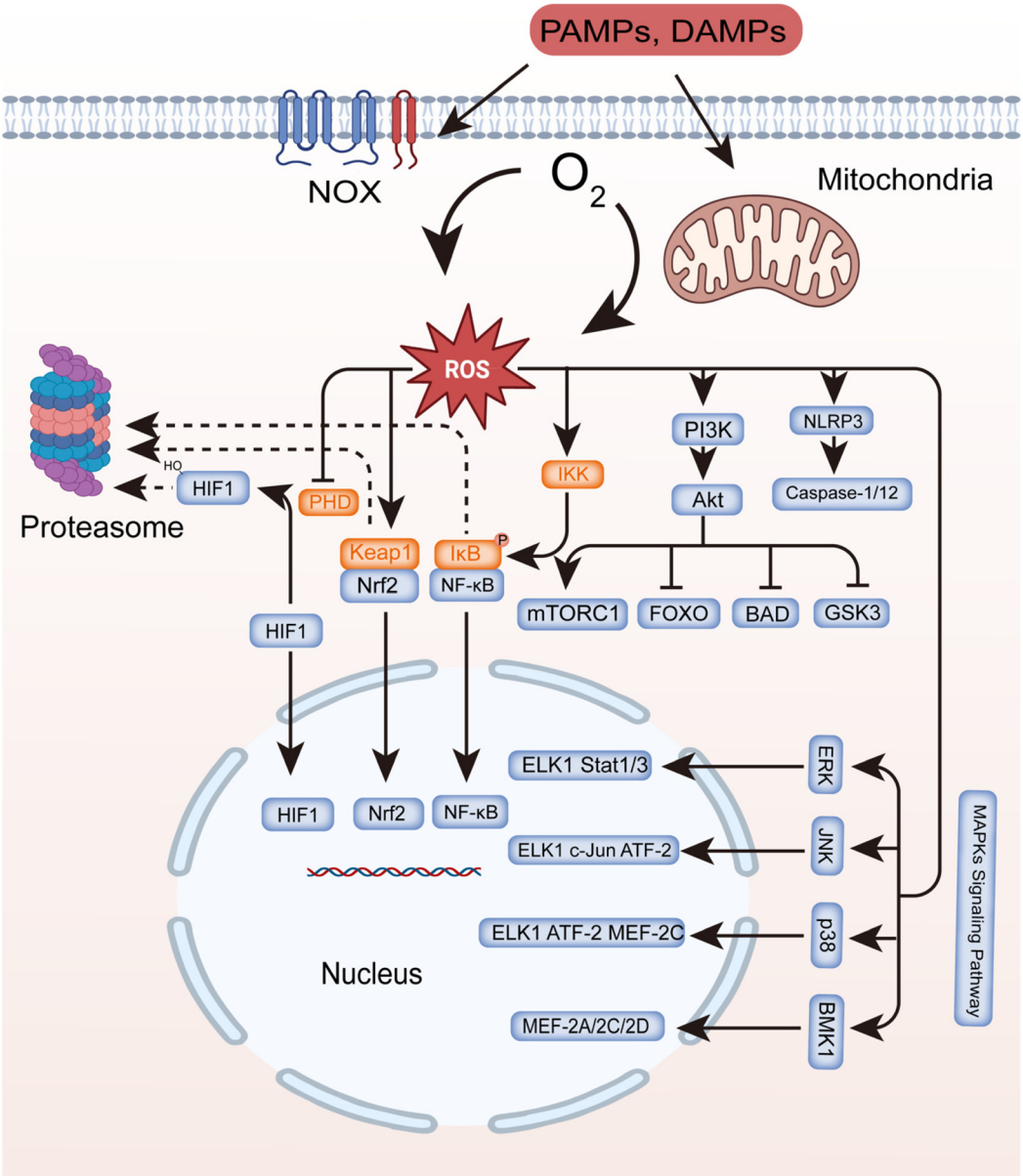

Fig. 2 Schematic illustration of reactive oxygen species regulating signaling pathways and gene expression.

ing a series of artificial enzymes with good physicochemical properties and biocatalytic activity to replace natural enzymes has become a research hotspot.[33]

4. Nanozymes and AKI

Since Gao *et al.* discovered Fe_3O_4 nanoparticles with peroxidase-like activity in 2007, people have broken with the traditional notion that inorganic materials have no biological activity.[34] After several years of rapid development of nanotechnology, biotechnology, and rapid development of catalytic medicine, several nanomaterials have been studied and found to demonstrate various enzyme-mimicking activities, which have been widely used in biomedical research. According to statistics, there have been more than 7500 papers on nanozymes, and about 300 different nanomaterials with enzyme activity have been reported, which are used in various fields such as molecular detection, cancer therapy, and environmental therapy.[35] Nanozymes usually refers to nanomaterials with enzymatic catalytic activity, and their sizes are usually between 1 and 100 nanometers. Artificial enzymes have unique characteristics such as high catalytic activity, low manufacturing cost, good stability, and adjustable catalytic activity, which underlie their marked application potential for various fields.[36] Nanozymes can be mainly classified as metal-based nanozymes (gold, platinum), metal oxide or metal sulfide nanozymes (cerium dioxide, iron sulfide), and carbon-based

nanozymes (graphene and carbon dots).[37] They can also be divided into the oxidoreductase family and the hydrolase families. The oxidoreductase family includes peroxidase, superoxide dismutase, oxidase, catalase, and nitrate reductase, and the hydrolase family includes esterase, nuclease, urease, phosphatase, and protease.[14] In addition, with the rapid development of nanoscience and technology, single-atom nanozymes have demonstrated higher nanozyme activity by simulating the highly evolved catalytic centers of natural enzymes, but this paper will not review them.[38]

Nanotechnology has facilitated the discovery of several multifunctional nanozymes with unique ROS generation, transition, or elimination functions. These ROS-regulating nanozymes can be used as exogenous interventions to regulate cellular redox status and treat various ROS-related diseases. Nanozymes with antioxidant enzyme activities, such as SOD and CAT, can scavenge ROS and reduce oxidative stress, and they have been extensively applied to the therapy of inflammatory diseases, cardiovascular diseases, and brain diseases.[13] By studying the pathophysiological mechanism underlying various types of kidney injury, it has been found that all types of kidney injury are closely related to ROS and oxidative stress. The persistence of ROS in the kidneys can lead to irreversible fibrosis and renal failure. Due to the disadvantages of traditional antioxidant drugs such as low targeting and marked side effects, several scholars are committed to exploring the therapeutic effect of antioxidation nanozymes in kidney injury.[1] This article reviews antioxidant nanozymes that have been used in the treatment of various types of kidney injury in recent years, focusing on their ability to scavenge ROS and inhibit oxidative stress. Classified based on the main elements of the nanozymes, the role of nanozymes synthesized from related elements with anti-inflammatory and antioxidant effects on kidney injury has been introduced (Table 1). At the end of the article, we also summarize the current limitations and challenges faced by antioxidant nanozymes, hoping that this review can provide a reference for more nanozyme models for kidney injury treatment in the future, and promote more scientific research to facilitate the development of treatments for kidney injury.

5. Application of antioxidant enzymes in AKI

5.1. Metal-based nanozymes

5.1.1 Ce-based nanozymes. Cerium-based nanozymes have been found to have a series of enzyme activities such as CAT, SOD, cytochrome C oxidase, and POD, and have been widely used in the biomedical field. Cerium is a rare-earth metal with two chemical states (Ce^{3+} and Ce^{4+}) when combined with oxygen. The reduced (Ce^{3+}) and oxidative (Ce^{4+}) states of cerium are related to the mechanism of enzyme reaction mediated by nanoparticles, and they affect the enzyme-like activity of cerium oxide nanoparticles. The presence of Ce^{3+} and Ce^{4+} and the transition of their chemical states have a crucial effect on ROS scavenging.[39,40] Studies have shown that a high Ce^{3+}/Ce^{4+} ratio is associated with a higher SOD-like activity of cerium oxide. By reducing the size of ceria nanoparticles and doping ceria with Zr/La atoms, more surface oxygen vacancies can be formed to ensure high Ce^{3+} and increase its SOD activity.[41] It was found that the CAT-mimicking activity of cerium dioxide (CeO_2) nanoparticles was also related to the +3 reduction of Ce. Studies show that low Ce^{3+}/Ce^{4+} ratios are associated with higher CAT activity, which can effectively catalyze H_2O_2 to H_2O and O_2.[42] By regulating the chemical state of Ce, ceria nanoparticles can show excellent SOD and CAT activities, selectively scavenge O_2^- and H_2O_2, and prevent cellular oxidative stress injury.

To date, cerium oxide nanoparticles have been applied in research for the treatment of several diseases, such as stroke,[43] liver diseases such as hepatic ischemia-perfusion injury,[44,45] wound healing,[46] and ulcerative colitis,[47] given their excellent anti-inflammatory and antioxidant properties. Since the progression of kidney injury is closely related to the activities of ROS and oxidative stress, several scholars have explored the therapeutic effects of cerium oxide nanoparticles on kidney injury. RIRI can easily result in kidney injury and is associated with several procedures such as nephrectomy, kidney transplantation, and nephrectomy. When renal ischemia-reperfusion restores aerobic metabolism, ROS are produced which damage cells and induce apoptosis. Cell injury and apoptosis can also cause inflammatory cell infiltration, which further aggravates kidney injury. Zhou *et al.* synthesized cerium nanoparticles (CNPs) with sizes of 118 nm and good biocompatibility by the thermal decomposition method for prophylaxis against RIRI. CNPs demonstrate SOD activities and a hydroxyl radical antioxidant capacity (HORAC), clear accumulated ROS in the kidneys, reduce the concentrations of pro-inflammatory cytokines and chemokines, and, in turn, protect the kidneys from RIRI and prevent renal fibrosis.[48] Hong *et al.* used a non-hydrolytic sol–gel reaction method with doped zirconia in CNPs to maintain a high Ce^{3+} concentration and improve the oxygen free radical-scavenging ability of the synthesized zirconia nanoparticles (CZNPs). Their study showed that CZNPs can block hypoxia-induced phosphorylation of JNK and p38, relieve intracellular oxidative stress, and alleviate RIRI-induced kidney injury. Compared with CNPs, CZNPs showed better stability and efficacy in protecting the renal structure and glomerular function.[49] Intra-abdominal infections can also cause kidney injury, which presents with significant renal tubule injury, brush margin loss, and glomerular capillary network disorder, mainly caused by systemic inflammatory response syndrome mediated by increased chemical stress. Manne *et al.* found that CeO_2 nanoparticles can improve the structure and function of the kidneys by clearing ROS, reducing the concentrations of caspase-3 and serum biomarkers for kidney injury, and preventing F-actin loss.[50] Yu *et al.* further studied the therapeutic effect of cerium nanoparticles on sepsis-induced AKI using an ICR male mice sepsis model induced by lipopolysaccharide. Cerium nanoparticles can reduce the progression of AKI by simulating CAT and SOD activities to scavenge ROS,

Table 1 Working mechanism and applications of antioxidant nanozymes in kidney injury

Category	NMs	Chemical approach	Characterization	Catalytic activity	Mechanism	Disease model	Treatment	Ref.
Ce based								
	CNPs	Synthesized by thermal decomposition method from $Ce(NO_3)_3{\cdot}6H_2O$, TOPO, ODE	Size: 46 nm, 81 nm, and 118 nm	SOD, HORAC	Scavenge ROS, reducing oxidative stress, reduce proinflammatory cytokines and chemokines	AKI: *In vitro*: HK-2, HUVEC, RAW264.7, RTEC, MAEC; *in vivo*: IR/contrast-induced AKI in C57BL/6J mice	*In vitro*: 20 μg ml^{-1}; *in vivo*: 1 mg kg^{-1}, intravenous injection	48
	PEG-CZNPs	Dope zirconia in CNPs by non-hydrolytic sol–gel reaction method	Size: 2 nm; surface modification: PEG	POD, CAT, SOD	Reduce mitochondrial injury and restore autophagy flux	RIRI: *in vitro*: HK2 cells; *in vivo*: RIRI in male BALB/c mice	*In vitro*: 5–40 μg ml^{-1}; *in vivo*: 10 mg kg^{-1}, intraperitoneal injection	49
	CeO_2 NPs	Purchased from US Research Nanomaterials Inc	Size: 10–40 nm	CAT, SOD	Scavenge ROS, reduce renal inflammation and renal apoptosis	AKI intra-abdominal infection-induced AKI in Sprague–Dawley rats	*In vivo*: 0.5 mg kg^{-1}, intraperitoneal injection	50
	Atv/PTP-TCeria NPs	Ceria nanoparticles modified with triphenylphosphine, and then coated with mPEG-TK-PLGA and loaded with atorvastatin	Size: 43.1 ± 7.50 nm; surface modification: triphenylphosphine, mPEG-TK-PLGA; load: atorvastatin	CAT, SOD	Target kidney and mitochondrial to scavenge ROS, synergistic with atorvastatin	AKI: *in vitro*: HUVEC; *in vivo*: LPS-induced AKI in ICR male mice	*In vitro*: 0.125–1.00 mM; *in vivo*: 1 mg kg^{-1}, intravenous injection	51
	CNPs	Synthesized by an improved reverse micelle method, and then modified by DSPE-PEG2K	Size: 9.7 nm; surface modification: DSPE-PEG2K	CAT, SOD	Use pH difference to clear ROS from the normal tissue without affecting the tumor	AKI: *in vitro*: HK-2 cells, ES-2 cells, OVCAR8, HepG2, A549, L02; *in vivo*: cisplatin-induced AKI in ICR mice	*In vitro*: 0–50 μM; *in vivo*: 0.5 or 1.5 mg kg^{-1}, intravenous injection	54
	Nanoceria (NC)	Purchased from Sigma-Aldrich, USA	Size: 287.6 ± 52 nm	CAT, SOD	Scavenge free radicals and reduce oxidative stress levels	Nephrotoxicity: cisplatin-induced nephrotoxicity in male Swiss albino mice	*In vivo*: 0.2 and 2 mg kg^{-1}, intraperitoneal injection	53
	CeO_2NPs	From the Faculty of Postgraduate Studies for Advanced Sciences, Beni-Suef University, Egypt	—	CAT, SOD	Scavenge ROS, up-regulate antioxidant-related genes and down-regulate apoptosis genes	Kidney injury: cadmium-induced kidney injury in male albino rats	*In vivo*: 0.1 and 0.5 mg kg^{-1}, intraperitoneal injection	56
	Ultrasmall ceria NPs	Prepared by a facile fabrication approach using citrate as a stabilizer at room temperature	Size: 3–4 nm Surface modification: citric acid	POD, CAT, SOD	Quickly accumulate in the kidneys and scavenge ROS	AKI: *in vitro*: HEK293T cells; *in vivo*: rhabdomyolysis-induced AKI mice model	*In vitro*: 0–200 μg mL^{-1}; *in vivo*: 2 mg ceria NPs in 150 μL PBS, intravenous injection	57
	LF-CONP	LF modified CONPs by physical adsorption	Surface modification: lactoferrin	—	Target kidney to inhibit pro-inflammatory cytokines levels and oxidative stress	Renal fibrosis: renal fibrosis male Swiss albino mice model	*In vivo*: 1 mg kg^{-1}, intravenous injection	58
	MET-HMSN-CeO_2	Dope cerium oxide in HMSN and use its hollow structure to load metformin	Size: 117 nm; surface modification: HMSN; load: MET	CAT, SOD	Scavenge free radicals	DKD: *in vitro*: NRK-52E cells; *in vivo*: STZ-induced DN in Sprague Dawley (SD) rats	*In vitro*: 10 μg mL^{-1}; *in vivo*: 10 mg kg^{-1}, intravenous injection	52

Table 1 *(Contd.)*

Category	NMs	Chemical approach	Characterization	Catalytic activity	Mechanism	Disease model	Treatment	Ref.
Gold based								
	AuNPs	Purchased from PlasmaChem GmbH, Germany	Size: 20 nm	CAT, SOD	Enhance Nrf-2 signal transduction and inhibit Keap-1	Renal injury: *in vitro*: MCF-7 cells; *in vivo*: 5-fluorouracil-induced renal injury in Sprague Dawley rats	*In vitro*: 0–25 μg mL^{-1}; *in vivo*: 70 μg kg^{-1}, intraperitoneal injection	59
	AuNPs	Synthesized by chemical reduction and loaded with FIG leaf extract	Size: 20 nm; load: FIG leaf extract	—	Increase the renal targeting of FIG leaf extract and synergistic antioxidant	AKI: cisplatin-induced AKI in male albino rats	*In vivo*: AuNPs 1 mg kg^{-1}, orally	65
	PEG-AuNPs	Synthesized by the reduction of $HAuCl_4$ with sodium citrate, and then coated with PEG	Size: 16–25 nm; surface modification: PEG	SOD, GPx	Active AMPK-Nrf-2 pathway	DKD: STZ-induced DN in male BALB/c mice	*In vivo*: 40, 150, and 400 μg kg^{-1}, intravenous injection	66
	Au NCs-NAC	Ultrasmall gold nanoclusters capped with NAC	Size: 2 nm; surface modification: NAC	CAT, SOD, POD	Scavenge ROS, reduce the release of inflammatory cytokines, synergistic antioxidant	AKI: *in vitro*: 293T cells, RAW264.7 cells; *in vivo*: glycerol-induced AKI mice model	*In vitro*: 100 μg mL^{-1}; *in vivo*: 2 mg mL^{-1}, 100 μL, intravenous injection	67
	NA2-AuNPs	NA-2 coated gold nanoparticles	Size:10–90 nm; surface modification: NA-2	—	Decrease COX-2 gene expression, antioxidant and anti-inflammatory	AKI: glycerol-induced AKI in male BALB/c mice	*In vivo*: 30 mg kg^{-1}, intraperitoneal injection	68
Zinc based								
	ZnONPs	Purchased from Sigma-Aldrich	Size: <100 nm	—	Increase antioxidant enzyme activity, inhibit oxidative stress and renal fibrosis	DKD: STZ-induced DN in male Wistar rats	*In vivo*: 2.5 mg kg^{-1}, intraperitoneal injection	74
	ZnONPs	Purchased from Sigma-Aldrich, USA	Size: ≤40 nm	—	Anti-inflammatory, antioxidant, anti-apoptotic effects	AKI: cisplatin-induced AKI in male Sprague–Dawley rats	*In vivo*: 5 mg kg^{-1}, intraperitoneal injection	75
	ZnONPs	Combination therapy of FA and ZnONPs	—	—	Inhibit the production of ROS, enhance antioxidant activity	RIRI: RIRI in male Sprague Dawley rats	*In vivo*: 5 mg kg^{-1}, intraperitoneal injection; FA (100 mg kg^{-1}) *via* gastric gavage	76
Mn based								
	PTC-M	dMn_3O_4 NPs was synthesized by coprecipitation method and then loaded by PTC	Size: 18.0 ± 0.6 nm; surface modification: PTC and 1-dodecanethiol	CAT	Target kidney, scavenge ROS, reduce inflammation and apoptosis	RIRI: *in vitro*: HK-2 cells; *in vivo*: RIRI in male C57BL6 mice	*In vitro*: /; *in vivo*: 0.5 mg kg^{-1}, intravenous injection	78
	Mn_3O_4 Nfs	Synthesis from $KMnO_4$ and oleic acid	Size: 110 ± 8 nm	CAT, SOD, HORAC	Scavenge ROS and cfDNA	AKI: *in vitro*: HK-2 cells; *in vivo*: cisplatin/ischemia-reperfusion induced AKI mouse models	*In vitro*: 10 μg mL^{-1}; *in vivo*: 10 mg kg^{-1}, intravenous injection	79
Other metal based								
	$Cu_{5.4}O$ USNPs	Synthesized by green, fast and cost-effective method from Cu^{2+} and L-ascorbic acid (AA)	Size: 3.5–4.0 nm	CAT, SOD, GPx	Excellent ROS scavenging ability, increase the expression of antioxidant genes	AKI: *in vitro*: HEK293 cells; *in vivo*: glycerol/cisplatin-induced AKI in female BALB/c mice	*In vitro*: 0–50 ng mL^{-1}; *in vivo*: 4 μg kg^{-1}, intravenous injection	91

Table 1 *(Contd.)*

Category	NMs	Chemical approach	Characterization	Catalytic activity	Mechanism	Disease model	Treatment	Ref.
	Ir NPs-PVP	Synthesized by alcohol reduction from $IrCl_3$ and PVP	Size: 1–2 nm; surface modification: PVP	CAT, SOD, POD	Effectively scavenge ROS	AKI: *in vitro*: HEK293T cells; *in vivo*: rhabdomyolysis/ cisplatin-induced AKI in female BALB/c mice	*In vitro*: 0–200 μg mL^{-1}; *in vivo*: 500 μg Ir NPs-PVP in 150 μL PBS, intravenous injection	92
	RuO_2NPs	Synthesized by solvothermal method from $RuCl_3{\cdot}3H_2O$ and CS	Size: ~2 nm	CAT, SOD, POD, GPx	Multi-enzyme activity, anti-oxidation and anti-apoptosis	AKI: *in vitro*: HEK293 cells; *in vivo*: glycerol-induced AKI in female ICR mice	*In vitro*: 20 μg mL^{-1}; *in vivo*: 5 mg kg^{-1}, intravenous injection	94
	POM nanoclusters	Synthesized by $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$, NaH_2PO_4, L-ascorbic acid, *etc.* through a one-pot approach	Size: 1 nm	CAT, SOD, HORAC	Scavenge ROS and inhibit ROS-induced cell damage	AKI: *in vitro*: HEK293 cells; *in vivo*: glycerol/ cisplatin-induced AKI in female ICR mice	*In vitro*: 0–200 μg mL^{-1}; *in vivo*: 1 mg in 100 μL PBS, intravenous injection	95
	TWNDs	Prepared by reducing phosphotungstic acid with tannic acid under alkaline conditions	Size: 2–4 nm; surface modification: tannic acids	CAT, SOD, HORAC	Promote mitophagy, reduce ROS and inflammatory cell infiltration	AKI *In vitro*: HK-2 cells, RAW264.7 cells; *in vivo*: glycerol/ cisplatin-induced AKI in female ICR mice	*In vitro*: 5–100 μg mL^{-1}; *in vivo*: 4, 8 and 16 mg kg^{-1}, intravenous injection	96
PB based								
	Ultrasmall PB NZs	Synthesis ultrasmall PB NZs with CS	Size: ~4 nm	CAT, SOD, POD	Excellent RONS scavenging ability and renal accumulation	AKI: glycerol/cisplatin-induced AKI in female BALB/c mice	*In vivo*: 100 μg in 100 μL PBS, intravenous injection	86
Se based								
	SeNPs	Sodium selenite is reduced with the reduced form of glutathione in the presence of BSA	Size: 10–80 nm	—	Increase levels of antioxidants	AKI: glycerol-induced AKI in Wistar male albino rats	*In vivo*: 0.1 mg kg^{-1}, orally	107
	Lyc-SeNPS	Obtained by the reaction of Na_2SeO_3 with LYC	Size: <130 nm; surface modification: LYC	—	Significantly scavenge free radicals and enhance endogenous antioxidant system	AKI: glycerol-induced AKI in Wistar male albino rats	*In vivo*: 0.5 mg kg^{-1}, orally	108
	SeNPs	Prepared with selenium oxide, citric acid, ascorbic acid	—	—	Inhibit oxidative stress and partially restore insulin release in diabetic rats	DKD: STZ-induced diabetes during pregnancy in female Wistar albino rats	*In vivo*: 2.5 mg kg^{-1}, orally	109
	Ch-SeNPs	Synthesis with Na_2SeO_3 and CS	Surface modification: CS	—	Inhibit oxidative stress and renal fibrosis	DKD: STZ-induced DN in male Sprague–Dawley rats	*In vivo*: 2 mg Se per kg b.wt., orally	110
	$Se@SiO_2$	Coat silica on Se quantum dots by orthosilicate hydrolysis and then coated by PVP	Size: ~55 nm; surface modification: PVP	—	Effectively scavenge ROS, maintain GSH levels, and inhibit inflammatory factor signaling pathways	AKI: *in vitro*: HK-2 cells; *in vivo*: I/R-induced AKI in male C57bl/6 mice	*In vitro*: 40 μg mL^{-1}; *in vivo*: 1 mg kg^{-1}, intraperitoneal injection	111
	$Se@SiO_2$	Se quantum dots were coated with hydrolyzed silica to synthesize $Se@SiO_2$ and then coated with PVP	Size: 47–59 nm; surface modification: PVP	—	Activate Sirt1, protect renal cells and inhibit cell apoptosis	AKI: *in vitro*: HK-2 cells; *in vivo*: cisplatin-induced AKI in C57BL/6 mice	*In vitro*: 0–640 μg mL^{-1}; *in vivo*: 200 μl, 2 mg ml^{-1}, intravenous injection	112

Table 1 *(Contd.)*

Category	NMs	Chemical approach	Characterization	Catalytic activity	Mechanism	Disease model	Treatment	Ref.
	Se@BSA	Prepared with sodium selenate, ascorbic acid and BSA	Size: ~80 nm	—	Upregulate the level of GPx-1 and inhibit the activation of the NLRP3 inflammasome	AKI: *in vitro*: HK-2 cells; *in vivo*: I/R-induced AKI in male C57 mice	*In vitro*: 50 μg mL^{-1}; *in vivo*: 20.1, 0.5, and 1 mg kg^{-1}, intravenous injection	113
Melanin based								
	MMPP nanoparticles	Mn^{2+} chelated melanin nanoparticles are prepared through simple matching and self-assembly methods, and further combined with PEG	Size: ~4.5 nm; surface modification: PVP and PEG	CAT, SOD, HORAC	Scavenge a variety of toxic ROS, inhibit oxidative stress	AKI: *in vitro*: HEK293 cells; *in vivo*: glycerol-induced AKI mice model	*In vitro*: 25/100 μg mL^{-1}; *in vivo*: 200/500 μg melanin per mouse, intravenous injection	119
	GMP nanoparticles	PJ34 was loaded by anti-GPR97-conjugate melanin nanoparticles	Size: 117 nm; surface modification: PEG and anti-GRP97; load: PJ34	CAT, SOD, HORAC	Scavenge multiple toxic ROS, anti-apoptotic and anti-inflammatory	AKI: *in vitro*: NRK-52E cells; *in vivo*: glycerol-induced AKI in male ICR mice	*In vitro*: 0–50 μg mL^{-1}; *in vivo*: 3 mg mL^{-1}, 200 μL, intravenous injection	120
Carbon based								
	h-GQDs	Obtained from the reduction of c-GQDs by $NaBH_4$	Size: 4.4–4.8 nm; surface modification: PEG	Phenol-like antioxidant	Mimic the antioxidant activity of phenols and efficiently scavenge ROS	AKI: *in vitro*: HEK-293T cells; *in vivo*: rhabdomyolysis-induced AKI in Balb/c mice	*In vitro*: 5–20 μg mL^{-1}; *in vivo*: 10 mg kg^{-1}, intravenous injection	123
	SeCQDs	Doping selenium in carbon quantum dots	Size: ~40 nm; surface modification: DFO	CAT, SOD, HORAC	Broad-spectrum ROS clearance and good renal accumulation	AKI: *in vitro*: HEK293 cells; *in vivo*: cisplatin/rhabdomyolysis-induced AKI in female ICR mice	*In vitro*: 0–100 μg mL^{-1}; *in vivo*: 50 μg in 200 μL PBS, intravenous injection	125
	C60	Combination therapy of C60 and curcumin	—	CAT, GST	Scavenge ROS, antioxidant, anti-inflammatory	DKD: STZ-induced DN in Wistar albino breed rats	*In vivo*: 1.0 mg kg^{-1}, orally	124
	PDA-CNDs	Synthesized from *m*-phenylenediamine and CNDs	Size: ~4.92 nm	CAT, SOD, HORAC	Scavenge ROS and inhibit oxidative stress	AKI: *in vitro*:HK-2 cells; *in vivo*: cisplatin/IRI induced AKI in male ICR mice	*In vitro*: 0–30 μg mL^{-1}; *in vivo*: 1 mg in 100 μL PBS, intravenous injection	126

NPs: nanoparticles; TOPO: trioctylphosphine oxide; ODE: 1-octadecene; SOD: superoxide dismutase; HORAC: hydroxyl radical antioxidant capacity; ROS: reactive oxygen species; AKI: acute kidney injury; HK-2: human renal tubular epithelial cells; HUVEC: human umbilical vein endothelial cells; RTEC: renal tubular epithelial cells; MAEC: mouse aortic endothelial cells; IR: ischemia-reperfusion; PEG: polyethylene glycol; POD: peroxidase; CAT: catalase; RIRI: renal ischemia-reperfusion injury; CeO_2: cerium oxide; mPEG: methoxypolyethylene glycols; PLGA: polylactic acid-glycolic acid copolymer; ICR: Institute of Cancer Research; DSPE-PEG2K: 1,2-distearoyl-*sn-glycero*-3-phosphoethanolamine-*N*-[methoxy (polyethylene glycol)-2000]; ES-2: human ovarian cells; OVCAR8: ovarian carcinoma cell line; hepatocellular carcinoma cell line; A549: lung carcinoma cell line; L02: normal hepatocytes; HEK293T: human embryonic kidney 293 T; PBS: phosphate buffered saline; LF: lactoferrin; HMSN: hollow mesoporous silica nanocomposite; MET: metformin; Nrf-2: nuclear factor erythroid 2-related factor 2; Keap-1: Kelch-like ECH-associated protein 1; MCF-7: breast cancer cell line; FIG: *Ficus carica* L; GPx: glutathione peroxidase; AMPK: adenosine 5′ monophosphate-activated protein kinase; DKD: diabetic kidney disease; STZ: streptozotocin; DN: diabetic nephropathy; NAC: *N*-acetylcysteine; NA-2: *N*-(2-hydroxyphenyl)acetamide; COX-2: cyclooxygenase-2; PTC: (PEG)-stearamine (C18) conjugate; cfDNA: cell-free DNA; USNPs: ultrasmall nanoparticles; PVP: polyvinyl pyrrolidone; CS: chitosan; POM: polyoxometalate; TWNDs: ultra-small tungsten-based nanodots; PB NZs: Prussian blue nanozymes; LYC: lycopene; BSA: bovine serum albumin; NRK-52E: renal tubular duct epithelial cells of rats; DFO: deferoxamine; GST: glutathione *S*-transferase; CNDs: carbon nanodots.

but they have limitations. For example, ultra-small cerium nanoparticles guarantee high bionic enzyme activities but have the disadvantage of a short half-life in circulation. Ordinary cerium nanoparticles cannot selectively target mitochondria, which are the key sites for ROS production. The authors synthesized triphenylphosphine-modified cerium oxide nanoparticles with ROS-responsive shells and atorvastatin loaded (Atv/PTP-TCeria NPs). Atv/PTP-TCeria NPs with particle sizes of 43.1 ± 7.50 nm can effectively target the kidneys and release atorvastatin in a high ROS environment. Compared with ordinary ceria NPs, Atv/PTP-TCeria NPs have higher stability and biocompatibility and can target mitochondrial scavenging of excess ROS. Loading atorvastatin can reduce the amount of ceria and reduce their toxicity, which yields antioxidant and antioxidant effects.[51] Based on the role played by hyperglycemia and oxidative stress in diabetic nephropathy, Tong *et al.* also constructed a synergistic nanocomposite MET-HMSN-CeO_2 with good biocompatibility.[52] They used hollow mesoporous silica nanocomposites (HMSN) with good biocompatibility as the carriers, by doping trace cerium dioxide and loaded metformin, to facilitate free radical scavenging *in vivo*. The loading capacity of MET-HMSN-CeO_2 was 15.57%, and more than 40% of the drug could be released within 24 h. In the streptozotocin-induced kidney injury rat model, MET-HMSN-CeO_2 reduced the blood glucose concentration by inhibiting oxidative stress and cell apoptosis, thus protecting against diabetic nephropathy and significantly improving kidney injury.

Chemotherapy is one of the primary types of cancer treatment. When chemotherapy drugs are used to treat kidney cancer, they can destroy the structure and function of kidney cells and cause kidney injury by producing ROS. As a chemotherapy drug, cisplatin (CP) is widely used to treat various cancers, including testicular cancer, bladder cancer, ovarian cancer, and other solid cancers, due to its high curative effect and high cure rate. The production of highly reactive free radicals leads to renal tubular dysfunction and kidney injury, which limits the clinical application of cisplatin. Nanoceria has a protective effect against CP-induced kidney injury.[53] It can effectively scavenge free radicals, reduce the concentrations of plasma markers of kidney injury and pro-inflammatory factors, and improve oxidative stress by increasing the concentrations of endogenous antioxidants. Currently, several antioxidant nanomaterials are extensively applied to the treatment of ROS-related diseases, but the scavenging of ROS often promotes the growth and metastasis of tumor tissues. Weng *et al.* obtained cerium oxide nanoparticles (CNPs) with adjustable catalytic activity by using the pH difference between normal and tumor tissues.[54] CNPs showed SOD-like activity in both neutral and acidic conditions and catalyzed superoxide radical ($^{\bullet}O_2^-$) disproportionation to produce H_2O_2. H_2O_2 can be decomposed by CNPs under neutral conditions; however, a high concentration of H^+ destroys the active catalytic sites, and the blocking of the antioxidant cycle inhibits the CAT-like activity of CNPs in an acidic tumor microenvironment. The results showed that CNPs can reduce kidney injury caused by chemotherapy drugs without interfering with the efficacy of chemotherapy drugs (Fig. 3). Cadmium is a naturally heavy metal that can accumulate in the human body through the food chain, mainly in the liver and kidneys. The kidneys are highly sensitive to cadmium exposure. Cadmium can increase the production of ROS and induce renal inflammation by activating the NLRP3 inflammatory body through the ROS/MAPK/NF-κB signaling pathway.[55] CeO_2 NPs have good biocompatibility and can prevent cadmium-induced kidney injury by clearing ROS, downregulating apoptotic genes, and upregulating antioxidation-related genes.[56]

Targeting the kidneys with nanoparticles has been a challenging task. Previous studies have shown that nanomaterials with sizes below the renal filtration threshold (5.5 nm) can effectively accumulate in the kidneys through the glomeruli. Zhang *et al.* constructed ultrasmall ceria nanoparticles with good SOD and CAT activities. They have good biocompatibility and diameters of only 3–4 nm.[57] *In vitro* and *in vivo* experiments have shown that the ultrasmall ceria NPs had good biocompatibility and renal accumulation, and can alleviate AKI by scavenging $^{\bullet}OH$, $^{\bullet}O_2^-$, and other ROS. In addition to reducing the diameters of ceria nanoparticles to passively target the kidneys, modifying the surface of nanoparticles is also a way to target the kidneys. Aslam *et al.* used lactoferrin (Lf)-modified cerium oxide nanoparticles (Lf-CONP) targeting kidneys to treat renal fibrosis.[58] As a typical pathological phenomenon of chronic kidney disease, renal fibrosis is caused by oxidative stress secondary to the persistent injury of renal cells. Lactoferrin has a protective effect on the kidneys, which are rich in lactoferrin receptors. Lf-CONP has good anti-inflammatory and antioxidant effects. It can significantly inhibit the leukocyte level of proinflammatory cytokines and has a stronger anti-fibrosis effect than cerium oxide nanoparticles alone.

5.1.2 Gold-based nanozymes. Gold is a biocompatible metal with low cytotoxicity and anti-inflammatory and antioxidant properties. However, gold compounds are complex and easily inactivated *in vivo*, limiting their application in the biomedical field.[59] Studies have shown that gold nanoparticles (AuNPs) have good physical and chemical properties, high water solubility, good stability, and high catalytic activity, and they have been applied in several fields such as oncology,[60,61] ophthalmology, and bone tissue engineering.[62,63] AuNPs are promising antioxidant nanozymes that can scavenge free radicals and inhibit ROS production to increase the antioxidant defense enzyme in the body.[64] Currently, the anti-inflammatory and antioxidant effects of AuNPs are also being explored for the treatment of AKI. The Nrf-2 pathway is a significant approach for cell resistance to oxidative stress, and its downstream heme oxygenase 1 (HO-1) and γ-glutamyl cysteine synthase are important for promoting the scavenging of ROS. Keap-1 is a cytoplasmic inhibitor of Nrf-2. Mohamed El-Sherbiny *et al.* reported that AuNPs significantly increased the tissue and gene expression of Nrf-2, HO-1, and γ-glutamyl cysteine synthase, as well as decreased Keap-1 and protected against 5-FU-induced kidney injury.[59] A study reported that AuNPs also preserved renal function as a carrier loaded with a

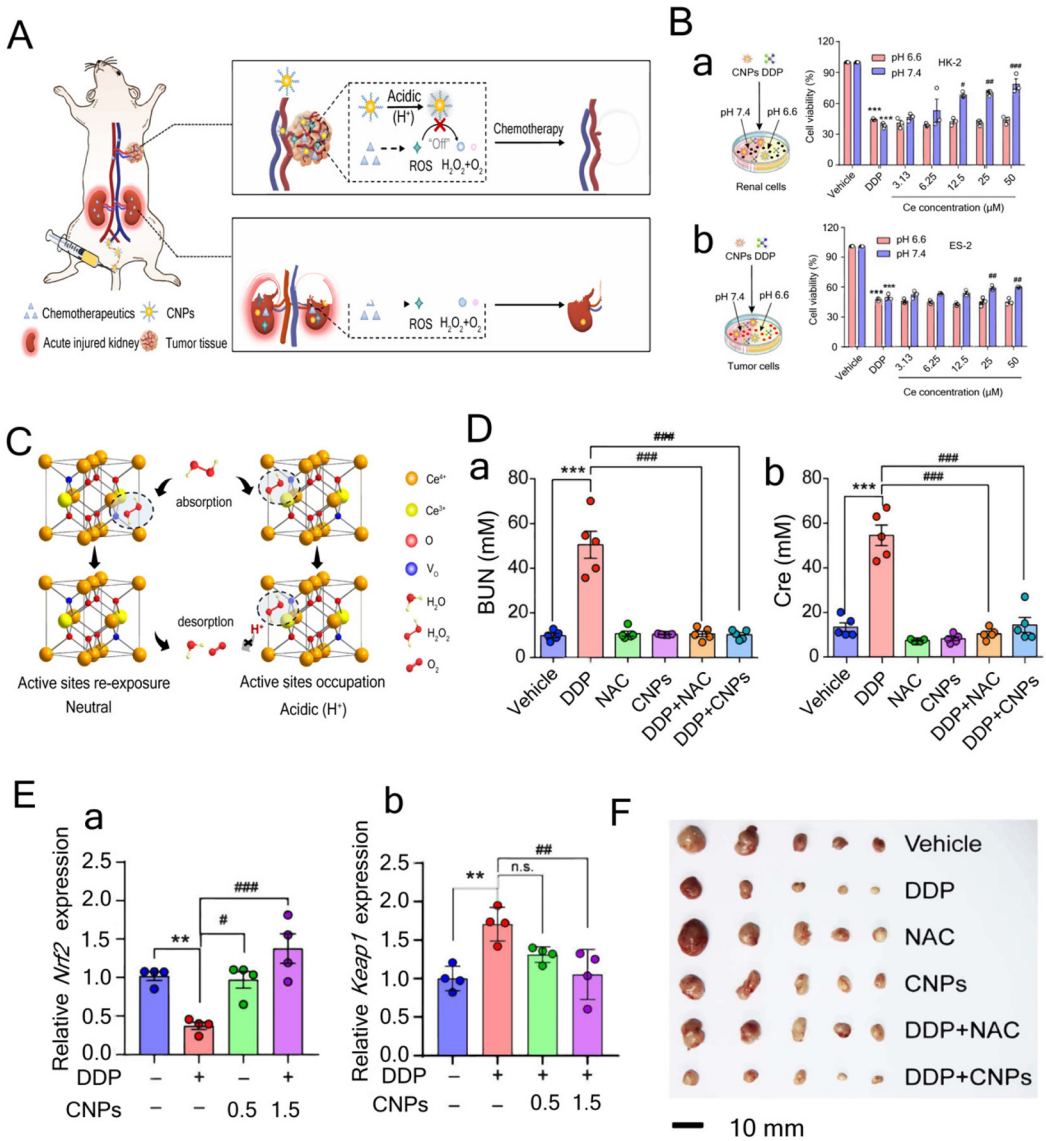

Fig. 3 Catalytic mechanisms of CNPs. A. Schematic illustration of catalytic activity tunable CNPs with context-dependent cytoprotective activities for AKI prevention during chemotherapy. B. The survival rate of HK-2 cells (a) and ES-2 cells (b) upon treatments with 10. C. Schematic illustration of the context-dependent catalase-like activity of CNPs under different pH conditions. D. Serum BUN (a) and Cre (b) levels of nude mice. E. Relative mRNA expressions of Nrf2 (a), Keap1 (b) in the renal cortex from each group. F. Images of the dissected tumors from groups of nude mice fed with sterile water after treatment. Reprinted with permission from ref. 54. Copyright (2021) *Nature Communications*.

FIG leaf extract in cisplatin-induced AKI mouse models.[65] The FIG leaf extract was rich in flavonoids and phenolic compounds with antioxidant activity, and loading AuNPs improved its renal targeting, resulting in synergistic antioxidant effects. The surface modification of AuNPs can change the physical and chemical properties of nanoparticles to improve their biological activities. Saleh *et al.* modified AuNPs with polyethylene glycol (PEG) to increase the blood stability and solubility of AuNPs and reduce their biotoxicity.[66] PEG-AuNPs protect against RIRI in diabetic mice by activating the AMPK-Nrf2 pathway and AMPK/PI3K/AKT pathway, inhibiting excessive production of mitochondrial ROS, and inhibiting oxidative stress and the inflammatory response.

Gold nanoclusters (Au NCs) also have high stability and excellent biocompatibility, catalytic activity, and physicochemical properties. They have also been confirmed to demonstrate multi-enzyme activity which can target various ROS. Zhang *et al.* further explored the direct anti-inflammatory and antioxidant effects of Au NCs on AKI.[67] They used *N*-acetylcysteine (NAC) as a reducing agent and a blocking agent to synthesize ultrasmall gold nanoclusters (Au NCs-NAC) with diameters of 1–2 nm and excellent biocompatibility, that can be targeted to the kidneys and be quickly cleared by the human body. Au NCs-NAC had good water solubility and stability and high bioavailability, and demonstrated multi-enzyme-mimicking activities. Since NAC also has anti-inflammatory

and antioxidant effects, Au NCs-NAC can clear excess ROS, reduce the concentration of pro-inflammatory cytokines, and yield stronger antioxidant protection and anti-inflammatory effects (Fig. 4). Another anti-inflammatory, *N*-(2-hydroxyphenyl)acetamide (NA-2) was used to prepare NA-2-AuNPs by coating gold nanoparticles.[68] The combination of NA-2 and gold nanoparticles significantly improved its anti-inflammatory and antioxidant activities, alleviated the injury of the microvilli on the brush edge of the renal tubules, and protected the renal tubules by changing the inflammation and oxidation processes.

5.1.3 Zinc-based nanozymes. Zinc oxide nanoparticles (ZnONPs), as a new type of nanomaterial, can produce ROS and induce cell apoptosis and have excellent anti-cancer and antibacterial properties.[69,70] In addition, ZnONPs can improve insulin sensitivity, inhibit α-amylase and α-glucosidase, and

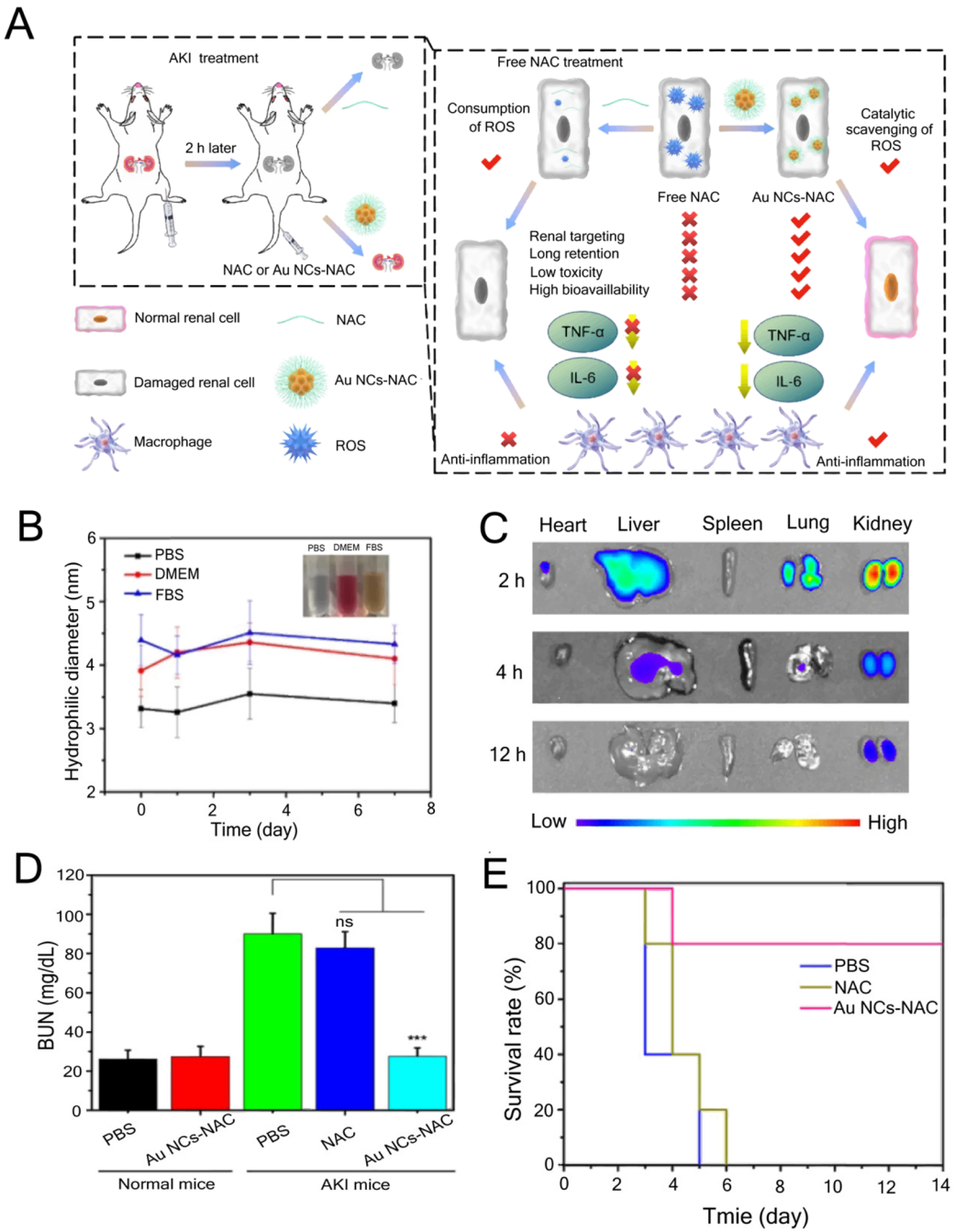

Fig. 4 Catalytic mechanisms of Au NCs-NAC. A. Schematic illustration of broad-spectrum antioxidant and anti-inflammatory activities of ultrasmall Au NCs-NAC for AKI alleviation as compared with NAC. B. Hydrophilic diameter of Au NCs-NAC in PBS, DMEM, and FBS. C. *Ex vivo* fluorescence imaging of Au NCs-NAC in the major organs of AKI mice. D. The levels of BUN in serum under different conditions. E. Survival curves of AKI mice after treated with PBS, free NAC or Au NCs-NAC. Reprinted with permission from ref. 67. Copyright (2021) *Theranostics*.

promote insulin release and glucose uptake to reduce blood glucose.[71,72] Zinc, as an important trace element in the human body, also plays a significant role in enhancing antioxidant defense. Different from anti-cancer and antibacterial activities, small doses of ZnONPs can also improve the activities of antioxidant enzymes, scavenge free radicals, and reduce lipid peroxidation concentration.[72,73] Given the hypoglycemic, anti-inflammatory, and antioxidant properties of ZnONPs, Alomari *et al.* found that ZnONPs can alleviate the progression of diabetic nephropathy by improving the activities of SOD, CAT, and GP_X, inhibiting oxidative stress, and reducing renal fibrosis.[74] The anti-inflammatory and antioxidant effects of ZnONPs also have a therapeutic effect on cisplatin-induced kidney injury; they can reverse the decrease in the concentrations of antioxidant enzymes caused by cisplatin and reduce the proportion of apoptotic and necrotic cells, which can effectively prevent renal dysfunction during cancer treatment.[75] As a phenolic plant component, ferulic acid (FA) can inhibit the enzyme that catalyzes ROS production and enhance the enzyme activity of ROS scavenging, which indicates its marked antioxidant activity. Amira *et al.* found that the combination of FA and ZnONPs in treating rats with RIRI significantly increased the activity of antioxidant enzymes and up-regulated Nrf-2 and HO-1 expressions. Their combination had stronger anti-inflammatory and antioxidant effects on I/R-induced kidney injury than FA or ZnONPs alone.[76]

5.1.4 Mn-based nanozymes. Mn_3O_4 nanoparticles have SOD and CAT-mimicking activities, and the level of scavenging of ROS is higher than that of traditional CeO_2 nanozymes, which can be used for the treatment of inflammation *in vivo*.[77] Hong *et al.* synthesized 1-dodecyl mercaptan-stabilized hydrophobic dMn_3O_4 nanoparticles by the co-precipitation method, stably loaded them into ROS-sensitive nanoparticles (PTC), and developed a multifunctional nano-platform (PTC-M) that could inhibit inflammation and scavenge ROS.[78] PTC can improve the stability, solubility, and biocompatibility of dMn_3O_4. PTC-M can be passively targeted at the kidneys, and PTC is decomposed under the action of ROS to enhance the internalization of nanoparticles and accelerate intracellular release. It also inhibits ROS-induced apoptosis of renal tubular epithelial cells and protects human renal tubular epithelial cells from H_2O_2-induced injury. Studies have shown that serum cell-free DNA (cfDNA) levels are elevated in AKI and can lead to acute inflammation and aggravate kidney injury. Therefore, Meng *et al.* constructed a nanoflower-structured Mn_3O_4 (Mn_3O_4 Nfs) with dual capabilities of ROS scavenging and cfDNA adsorption for treating kidney injury.[79] On the one hand, Mn_3O_4 Nfs have good biocompatibility; demonstrate SOD, CAT, and other enzyme-mimicking activities; and exhibit excellent ROS scavenging ability *in vitro* and *in vivo* experiments. On the other hand, Mn_3O_4 Nfs can effectively eliminate cfDNA and reduce the inflammatory response. The combination of these two effects underlies the significant therapeutic effects in both cisplatin/ischemia-reperfusion-induced AKI mouse models (Fig. 5).

5.1.5 PB-based nanozymes. Prussian blue nanoparticles mimic the activities of several antioxidant enzymes to effectively scavenge multiple ROS.[80] ROS-induced oxidative stress injury and cell apoptosis are involved in several inflammatory diseases, and PBNPs may be effective for controlling ROS-induced cell injury. Prussian blue nanozymes are promising for various oxidative stress-related diseases, including ischemic stroke,[81] colitis,[82] acute pancreatitis,[83] liver injury,[84] and Parkinson's disease.[85] Zhang *et al.* synthesized ultrasmall Prussian blue nanozymes (PB NZs) with chitosan to improve their biocompatibility.[86] Studies have shown that they demonstrate various activities of CAT, POD, and SOD, and satisfactorily scavenge reactive oxygen/nitrogen species (RONS). *In vitro*, PB NZs can protect HEK293T cells from H_2O_2-induced injury. In clinically relevant AKI models, MRI/PA dual-mode imaging has demonstrated that they rapidly accumulate in the kidneys, protect the kidneys and prevent the progression of AKI (Fig. 6).

5.1.6 Other metal-based nanozymes. Copper-based nanomaterials demonstrate POD-mimicking activity and can generate harmful ROS, and they are used for antibacterial, antifungal, and tumor therapy.[87–89] On the other hand, several metal-based and metal oxide-based nanozymes have been used to replace traditional antioxidants for the treatment of inflammation because of their good stability, biocompatibility, and ROS-scavenging ability.[90] Some studies have developed ultrasmall $Cu_{5.4}O$ nanoparticles ($Cu_{5.4}O$ USNPs) with an average hydrodynamic diameter of approximately 4.5 nm, which is smaller than the renal filtration threshold and has good biocompatibility and filtration.[91] $Cu_{5.4}O$ USNPs also have GPx, SOD, CAT, and other enzyme-mimicking activities and can effectively scavenge ROS; inhibit MAPK signaling pathways; significantly reduce the serum and tissue concentrations of inflammatory factors such as TNF-α and IL-1β; improve the levels of mRNA expressions of antioxidant genes; and effectively protect the kidneys and delay the progression of AKI. In animal experiments, $Cu_{5.4}O$ USNPs also facilitated the treatment of acute liver injury and wound healing. A study has reported the therapeutic effect of ultrasmall PVP-modified Iridium nanoparticles (Ir NPs-PVP) on AKI.[92] The hydrodynamic size of Ir NPs-PVP is 3–4 nm, and they can quickly be cleared from the kidneys through urine, which shows their good biocompatibility. Ir NPs-PVP also demonstrate multi-enzyme-mimicking activities; therefore, they can effectively scavenge H_2O_2, O_2^-, OH and other ROS, and play protective roles against H_2O_2-induced oxidative injury of HEK293T cells and rhabdomyolysis/cisplatin-induced AKI.

Ruthenium is also used in the treatment of kidney injury. Jiang *et al.* prepared ultrafine ruthenium nanoparticles (C3N4-Ru) with obvious peroxidase-like activity in the absence of a reducing agent.[93] Ultrasmall RuO_2 nanoparticles (RuO_2NPs) have also been used to treat kidney injury due to their multi-enzyme-mimicking activity and ROS scavenging ability.[94] RuO_2NPs have several enzyme activities, including GPx, CAT, SOD, and POD activities. RuO_2NPs can protect HEK293 cells from ROS injury *in vitro* with good biocompatibility and stability. The ROS-scavenging ability and anti-apoptotic ability of

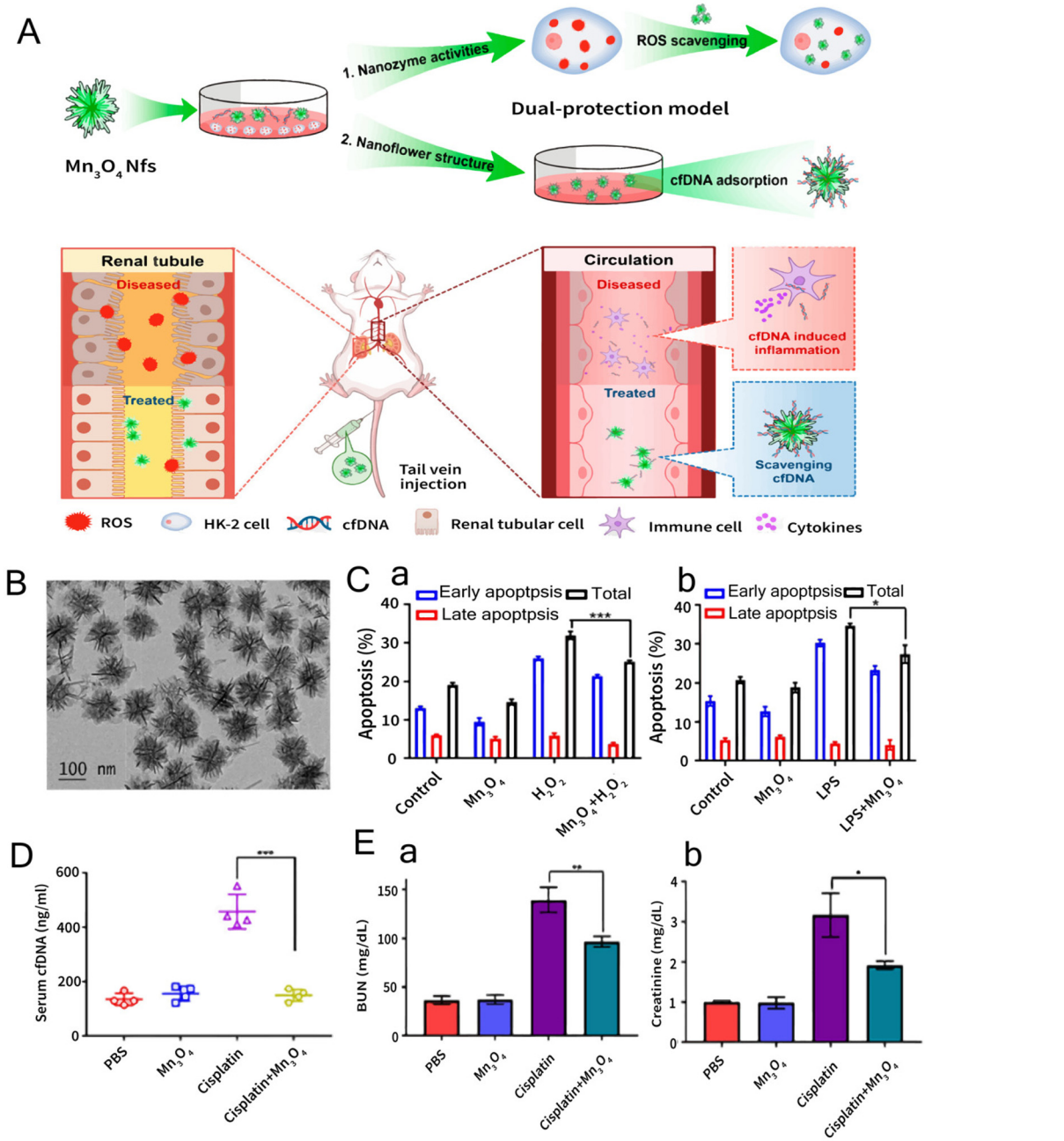

Fig. 5 Catalytic mechanisms of Mn_3O_4 Nfs. A. Schematic representation of the therapeutic mechanism of Mn_3O_4 Nfs to AKI. B. TEM image of Mn_3O_4 Nfs. C. Quantification of apoptosis in H_2O_2 (a) and LPS (b) models. D. cfDNA-scavenging activities of Mn_3O_4 Nfs *in vivo*. E. Blood urea nitrogen (a) and serum creatinine (b) measurement. Reprinted with permission from ref. 79. Copyright (2022) *ACS Applied Materials & Interfaces*.

RuO_2NPs have been confirmed in mice; it is a potential drug for the prevention of kidney injury. A molybdenum-based polyoxometalate (POM) nanocluster, another ultrasmall-size metal-based nanozyme, also acts as an antioxidant to prevent ROS-mediated kidney injury in a mouse model.[95] The ultrasmall Mo-based POM nanoclusters are preferentially taken up by the kidneys and demonstrate antioxidant activity against H_2O_2, $O_2^{\bullet-}$, and $^{\bullet}OH$; in turn, they inhibit oxidative stress and lipid peroxidation, and have a good therapeutic effect on ROS-induced kidney injury (Fig. 7). Huang *et al.* synthesized ultrasmall tungsten-based nanodots (TWNDs) that could reach the renal tubule through the glomeruli and passively target the mitochondria of renal tubule epithelial cells.[96] TWNDs can promote mitophagy and reduce ROS concentrations to preserve mitochondrial function and reduce necrosis of the renal tubules. In addition, TWNDs can also reduce the aggregation of macrophages and other inflammatory cells, effectively relieve the oxidative stress in renal tubules, and provide a new approach for targeted mitochondrial and kidney injury therapy.

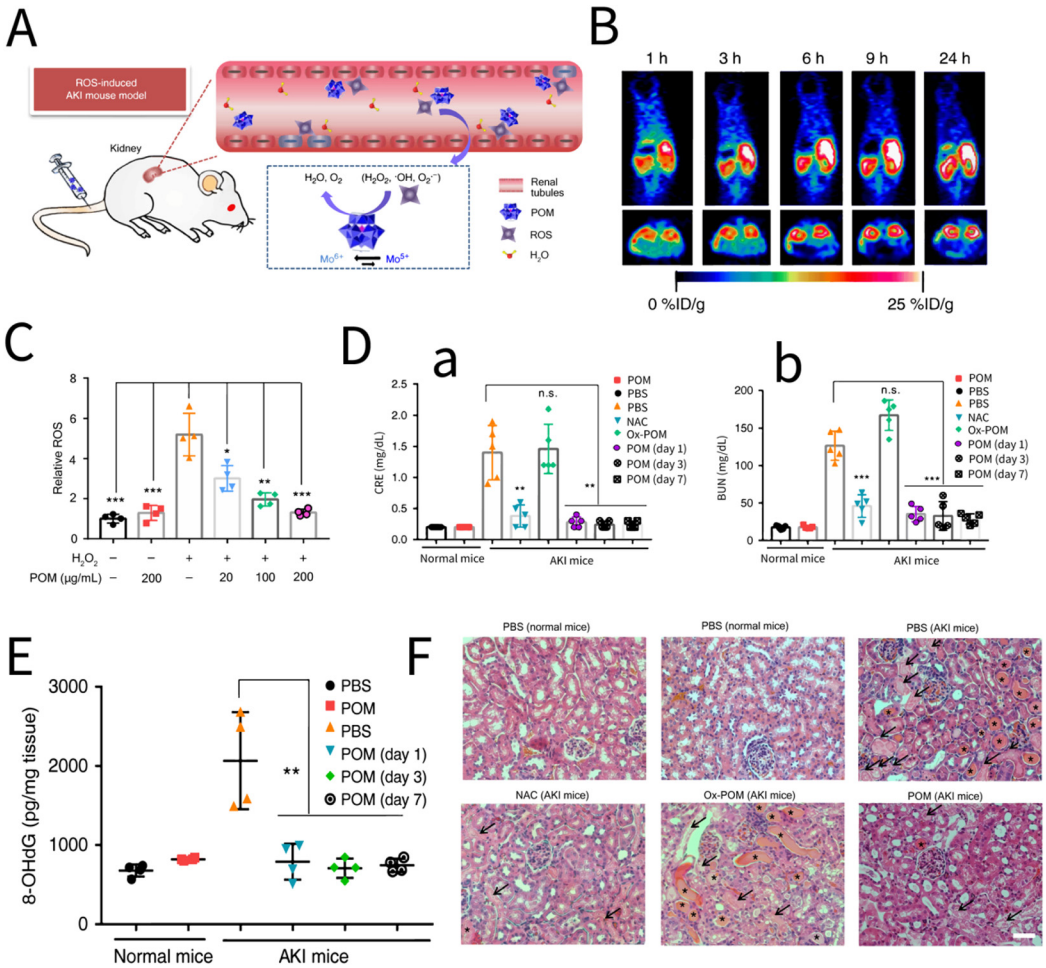

Fig. 6 Catalytic mechanisms of POM nanoclusters. A. Schematic of AKI treatment using POM nanoclusters and characterization. B. Representative longitudinal PET imaging of ^{89}Zr-POM in mice with AKI. C. ROS levels in untreated and POM-treated HEK293 cells incubated with 0.25 mM H_2O_2. D. CRE (a) and BUN (b) levels in the blood serum from each group. E. Measurement of DNA damage (8-OHdG) in renal tissue homogenates from each group. F. H&E staining of kidney tissues from each group. Reprinted with permission from ref. 95. Copyright (2018) *Nature Communications*.

5.2 Nonmetal-based nanozymes

5.2.1 Se-based nanozymes. Selenium is an essential trace element for human health. Selenium cysteine is usually formed with cysteine in the human body, and is involved in the synthesis of selenium proteins with antioxidant effects, and the activity of selenium proteins depends on the presence of selenium. Selenium has a narrow therapeutic window, and excessive intake of organic and inorganic selenium often leads to toxicity. Selenium nanoparticles (SeNPs) have lower toxicity and higher biocompatibility than organic or inorganic selenium compounds.[97,98] So far, SeNPs have been widely used for the treatment of cancer,[99] Alzheimer's disease,[100] arthritis,[101] diabetes,[102] and wound healing[103] due to their excellent anti-cancer, antibacterial, anti-inflammatory, and immunomodulatory properties. Selenium plays a significant role in the antioxidant defense system of the liver and is an essential component of glutathione peroxidase, which can improve the concentration of enzymes such as GP_X and reduce cell injury caused by free radicals.[104,105] Selenium has been shown to protect against kidney tissue injury by inhibiting oxidative stress and apoptosis.[106] The dual antioxidant and anti-inflammatory effects of SeNPs have also been leveraged for renal injury mediated by oxidative stress and inflammation. AlBasher *et al.* found that SeNPs can scavenge ROS by increasing the concentrations of antioxidants such as glutathione and GPx in a glycerol-induced AKI model, thereby inhibiting oxidative stress injury in the kidneys.[107] Ashraf Al-Brakati *et al.* further coated the SeNPs with lycopene (LYC), a natural carotenoid with significant antioxidant capacity, to improve stability, bioactivity, and bioavailability.[108] The synthesized LYC-SeNPs improved the endogenous antioxidant system and reversed oxidative stress to protect against AKI *via* anti-oxidation, anti-inflammation, and anti-apoptosis.

SeNPs were also found to reduce ROS produced in rats with gestational diabetes mellitus, partially restore insulin release, and reduce diabetic nephrotoxicity in diabetic rats.[109] To improve the stability, biocompatibility, bioavailability, and antioxidant properties of SeNPs, Khater *et al.* synthesized chitosan sodium selenium particles (Ch-SeNPs).[110] Ch-SeNPs

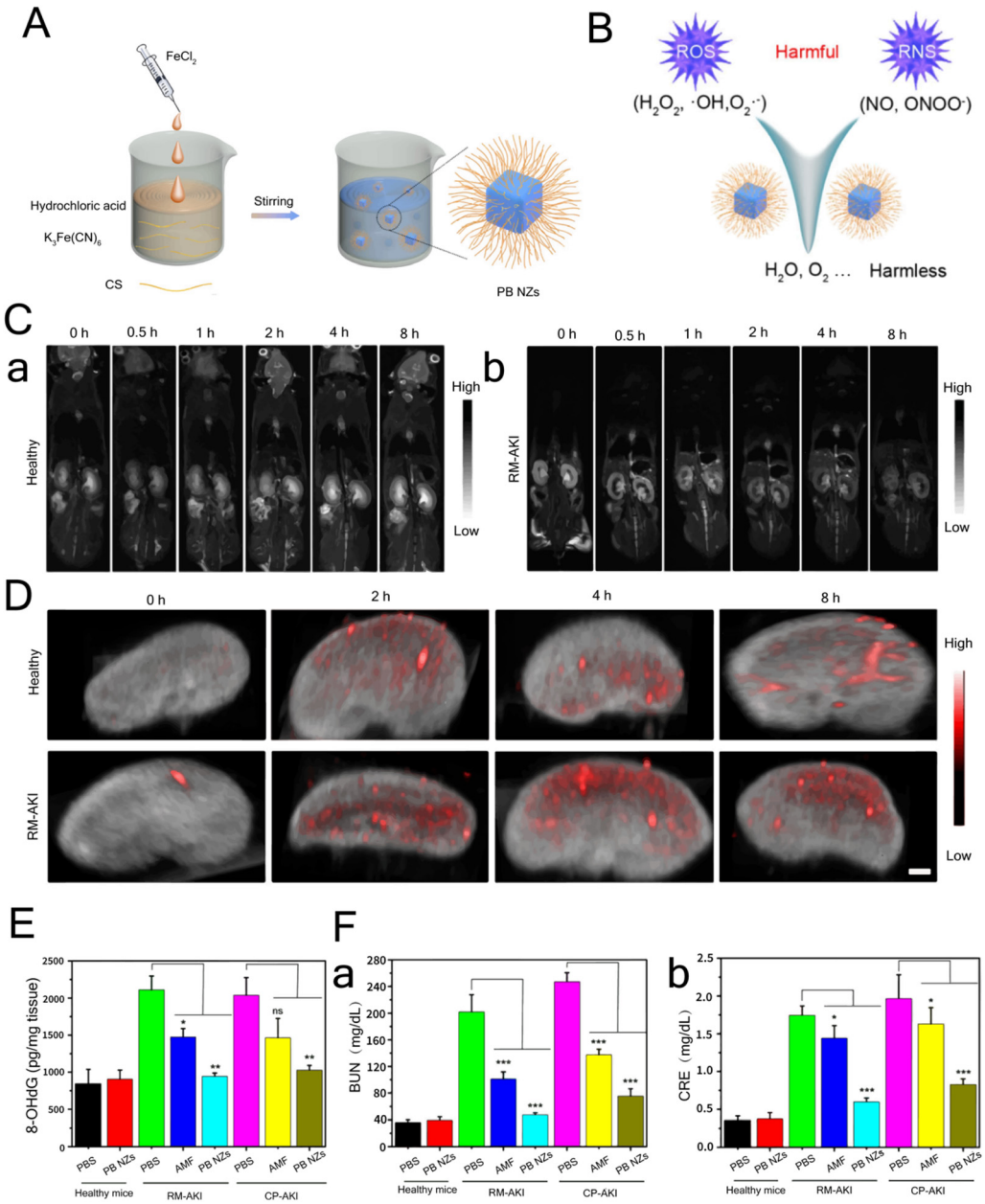

Fig. 7 Catalytic mechanisms of PB NZs. A. Schematic illustration of the preparation of PB NZs. B. Illustration of RONS scavenging by PB NZs. C. *T*2-Weighted MR images of PB NZs in healthy (a) and RM-AKI (b) mice at pre-injection (0 h) and different post-injection time points. D. Three-dimensional (3D) photoacoustic (PA) images in the kidneys of healthy and RM-AKI mice at different time points following i.v. injection of PB NZs. E. DNA damage measured in kidney tissue homogenates collected from each group. F. BUN (a) and CRE (b) in healthy mice and RM-AKI and CP-AKI mice treated with PBS, AMF or PB NZs. Reprinted with permission from ref. 86. Copyright (2021) *Journal of Nanobiotechnology*.

effectively protect kidney cells from diabetic injury by inhibiting oxidative stress and renal fibrosis. Combining them with metformin has a significant synergistic therapeutic effect on the treatment of diabetic nephropathy. Porous Se@SiO_2 nanospheres are a novel type of nanomaterial prepared using nanotechnology. Their porous structure has a controlled-release effect and reduces the toxicity of selenium. Zheng *et al.* found that Se@SiO_2 can effectively clear ROS, maintain glutathione concentrations, inhibit inflammatory factor activation pathways, and protect against renal ischemia-reperfusion-induced oxidative stress injury.[111] Silencing information regulator 2-related enzyme 1 (Sirt1) is involved in important physiological processes such as stress response, inflammation, and apoptosis. Li *et al.* found that porous Se@SiO_2 nanospheres can protect kidney cells by activating Sirt1, inhibiting apoptosis, and alleviating cisplatin-induced acute kidney injury.[112] Using sodium selenate and biocompatible bovine serum albumin (BSA) as raw materials, Wang *et al.* synthesized Se@BSA nano-

particles for the treatment of AKI.[113] Se@BSA NPs can up-regulate the concentration of GP_X-1 in renal tubular epithelial cells. GPx-1 is mainly expressed in the kidneys and plays an important role in almost all renal GP_X activities. The regulation of the GPx-1/NLRP3/caspase-1 pathway inhibited the activation of the NLRP3 inflammasome, reduced the concentration of proinflammatory cytokines, and inhibited IRI-induced AKI and renal fibrosis (Fig. 8).

5.2.2 Melanin-based nanozymes. Melanin is a biopolymer that exists in several organisms, and several precursors are involved in biosynthesis. Melanin's physical and chemical properties are related to the ratio of 5,6-dihydroxyindole and 5,6-dihydroxyindole 2-carboxylic acid. DHICA is less concentrated and stable and is more likely to react with ROS through the transfer of the H atom; it also has free radical scavenging and antioxidant activities.[114] In 2017, Liu *et al.* found that melanin nanoparticles (MeNPs) demonstrate multi-enzyme activities, which can scavenge O_2^-, H_2O_2, OH, NO, and $ONOO^-$, among others.[115] Its potent RONS scavenging ability protects against ischemic stroke through multiple antioxidant and anti-inflammatory activities. Kwon *et al.* found that melanin-like nanoparticles (MNPs) also have good biocompatibility and ROS-targeted scavenging ability, and have strong antioxidant properties, which can be applied to the treatment of age-related macular degeneration. In addition,[116] MeNPs have good therapeutic effects on oxidative stress and inflammation-related diseases, such as osteoarthritis and myocardial infarction.[117,118] Sun *et al.* prepared Mn^{2+}-chelated melanin nanoparticles by simple self-assembly and combined them with polyethylene glycol to obtain MMPP nanoparticles with hydrodynamic diameters of only 4.5 nm.[119] MMPP nanoparticles have good kidney accumulation and protect HEK293 cells from harmful oxidative stress *in vitro*. The biocompatible MMPP nanoparticles can scavenge all types of toxic ROS and inhibit ROS-induced oxidative stress, effectively alleviating AKI in mice (Fig. 9). ROS-mediated oxidative stress often leads to DNA fragmentation and poly-ADP-ribose polymerase-1 (PARP-1) activation, further releasing pro-apoptotic proteins and causing

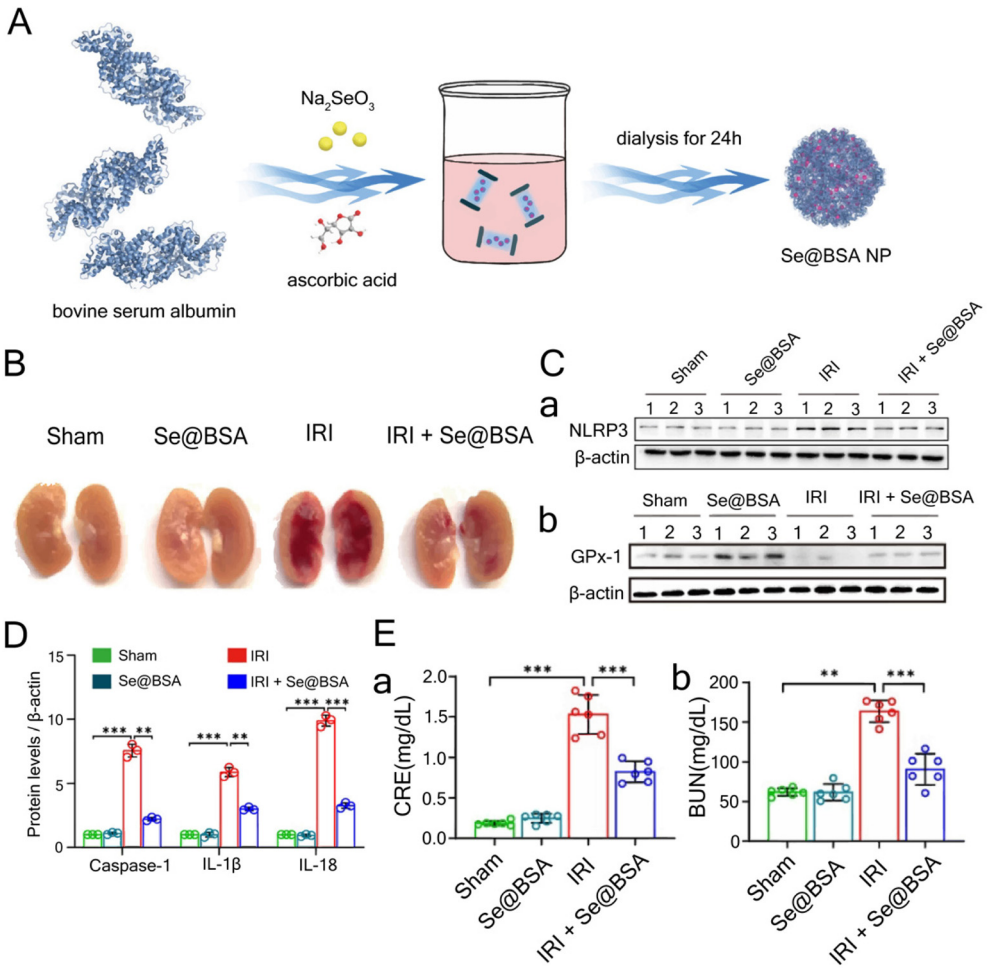

Fig. 8 Catalytic mechanisms of Se@BSA NPs. A. Diagram depicting the preparation of Se@BSA NPs. B. Pictures of different mouse kidneys. C. Western blotting detecting the NLRP3 (a) and GPx-1 (b) expression in the kidneys. β-Actin was used as the reference. D. Western blotting detecting the IL-1β, IL-18, and caspase-1 expression in the kidneys. β-Actin was used as the reference. E. Determination of CRE (a) and BUN (b) contents in IRI-AKI mice at 2 weeks after Se@BSA NP treatment. Reprinted with permission from ref. 113. Copyright (2022) *Theranostics*.

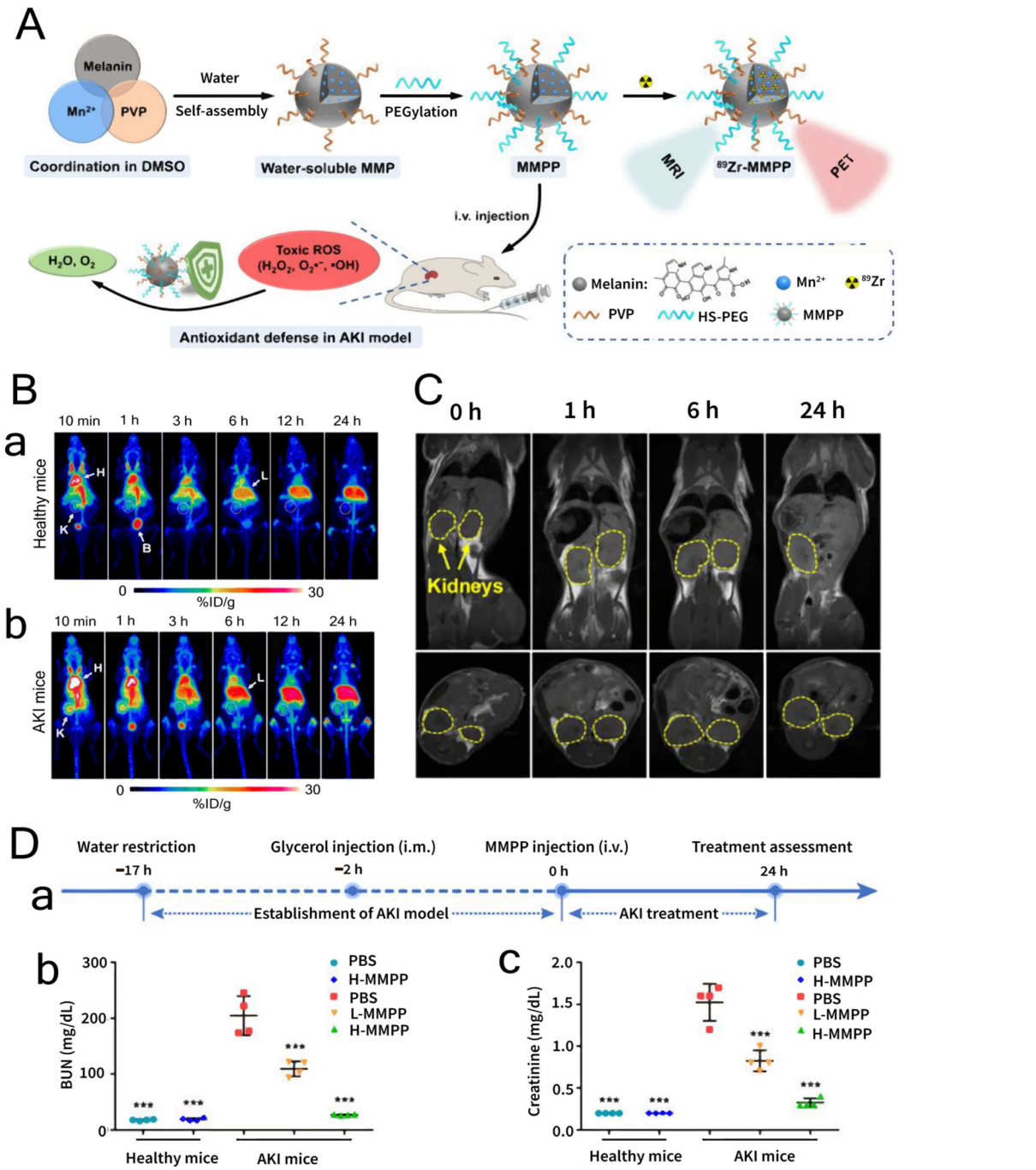

Fig. 9 Catalytic mechanisms of MMPP nanoparticles. A. Schematic illustration of the MMPP nanoparticle synthesis process and their activity as a naturally antioxidative platform for PET/MR bimodal imaging-guided AKI therapy. B. Representative maximum intensity projection (MIP) PET imaging of ^{89}Zr-MMPP in (a) healthy and (b) AKI mice. C. *T*1 weighted MR imaging of MMPP nanoparticles in AKI mice at pre-injection (0 h) and different post-injection time points. D. Formation of the AKI model and its treatment with MMPP nanoparticles. (a) Schematic illustration of the establishment of an AKI model in mice and their treatment with MMPP nanoparticles. Reprinted with permission from ref. 119. Copyright (2019) *Advanced Functional Materials*.

mitochondrial dysfunction. As an inhibitor of PARP-L, PJ34 hydrochloride has the advantages of high potency and specificity, but it is still limited in the treatment of kidney injury due to its short circulation time and low specificity. Zhao *et al.* used anti-GPR97-conjugated melanin nanoparticles as a carrier to load PJ34 and obtained a targeted nano-drug sustained-release platform (GMP nanoparticles) with PA imaging ability and triple therapeutic effects of anti-oxidation, anti-apoptosis, and anti-inflammation.[120] Since the GRP97 protein was significantly overexpressed on the renal tubular

epithelial membrane during AKI, PA imaging confirmed that anti-GPR97 enhanced the renal targeting of GMP. GMP nanoparticles have good dispersibility, solubility, and biocompatibility; have anti-inflammatory and anti-apoptotic properties; and can scavenge various toxic ROS and effectively treat rhabdomyolysis-induced AKI.

5.2.3 Carbon-based nanozymes. Carbon-based nanomaterials have unique monadic structures, high catalytic centers, and high porosity related to their mechanical properties. They have been found to have POD, CAT, and SOD mimetic activities, and have been used in biomedical fields.[41,42] Nanographene oxide (GO) possesses a two-dimensional honeycomb structure as a graphene derivative. It is hydrophilic due to its several hydroxyl groups on its surface, has a small size and large surface area, and is easy to use; it has been used as a drug carrier for the treatment of AKI.[121,122] Inspired by natural antioxidant polyphenols, Wang *et al.* constructed phenol-like group functionalized graphene quantum

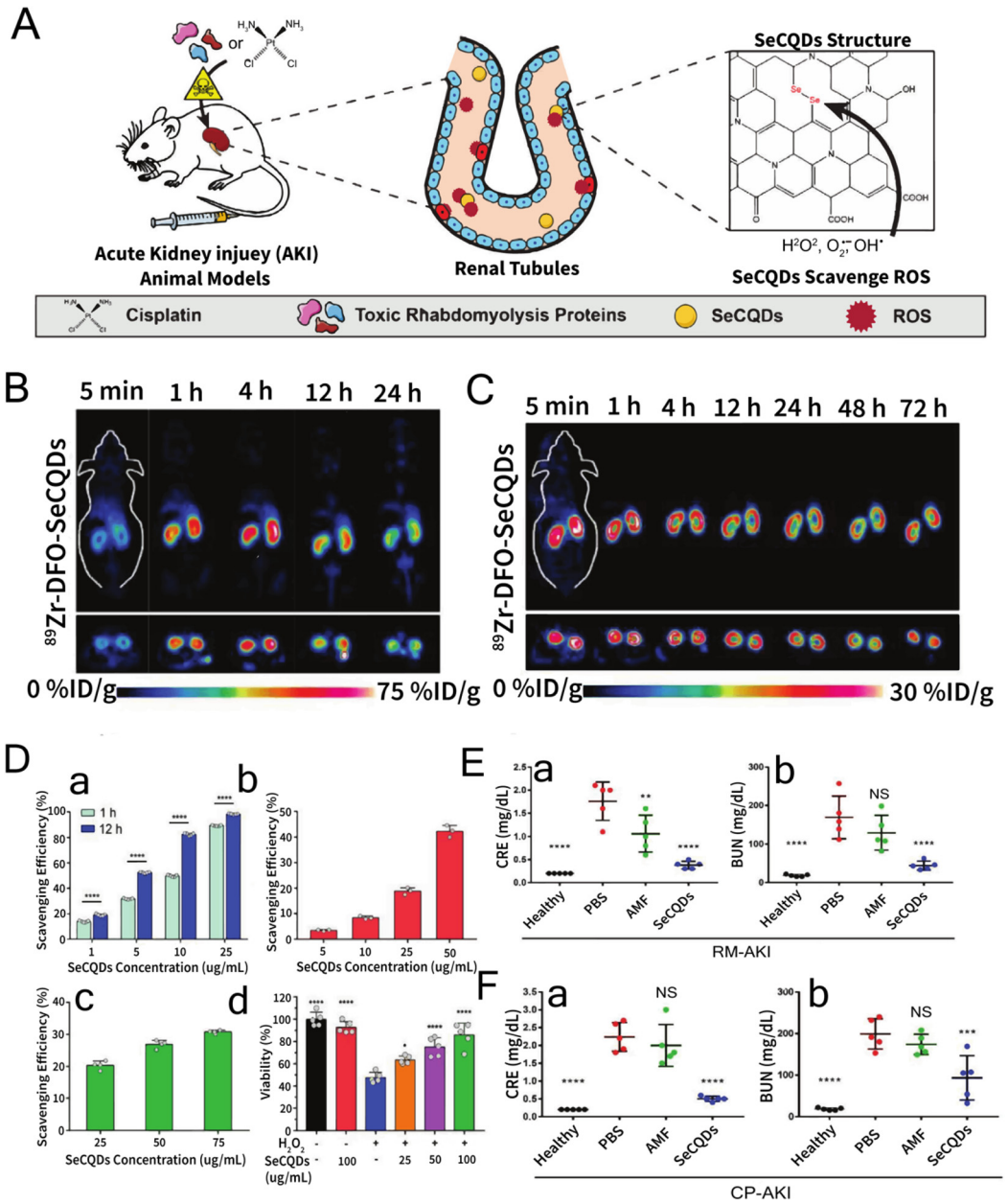

Fig. 10 Catalytic mechanisms of SeCQDs. A. Scheme showing the specific renal accumulation of SeCQDs allows the prevention and treatment of AKI of different origins. B. Coronal and axial slices of PET images after administering ^{89}Zr-DFO-SeCQDs in RM-AKI model. C. Coronal and axial slices of PET images after administering ^{89}Zr-DFO-SeCQDs in CP-AKI model. D. ROS scavenging efficiencies were evaluated for ABTS free radicals (a), $^{\bullet}OH$ (b), and $O_2^{\bullet-}$ (c). Cell viability assay (d). E. CRE (a) and BUN (b) serum concentrations of groups in the RM-AKI animal model. F. CRE (a) and BUN (b) serum concentrations of groups in the CP-AKI animal model. Reprinted with permission from ref. [125]. Copyright (2020) *Advanced Science*.

dots (h-GQDs) and exploited their antioxidant effects for the treatment of AKI.[123] h-GQDs have antioxidant activity due to abundant phenol-like functionalities on the surface, and can preferentially accumulate in the kidneys and effectively scavenge ROS. In addition, adjacent phenol-like groups have a synergistic antioxidant effect, and only one-sixteenth of the dose of the NAC can exert a similar effect to protect the kidneys from oxidative injury. C60 fullerene (C60) is a spherical carbon molecule that has been shown to have strong antioxidant properties. Demir *et al.* found that the combination of C60 with curcumin can be used to treat diabetic nephropathy.[124] The combination of curcumin and C60 can reduce the level of oxidative stress, protect against oxidative injury caused by ROS, and delay the progression of diabetes. Carbon quantum dots (CQDs) are easy to synthesize and have low costs and high biocompatibility, and they can effectively accumulate in the kidneys to treat kidney diseases. Therefore, some researchers constructed selenium-doped carbon quantum dots (SeCQDs) for the treatment of kidney injury.[125] SeCQDs showed significant renal accumulation and antioxidant properties in AKI mice, and they can scavenge ROS such as H_2O_2, $O_2^{\bullet-}$, and $^{\bullet}OH$, and have good therapeutic effects in two clinically relevant kidney injury models (Fig. 10). Based on the free radical scavenging effect of carbon nanodots (CNDs) *in vitro*, Gao *et al.* constructed *m*-phenylenediamine (PDA)-based carbon nanodots (PDA-CNDs) to explore their role in kidney injury.[126] PDA-CNDs, with an average diameter of less than 5 nm, can rapidly accumulate in the kidneys. They also have ROS scavenging abilities and anti-inflammatory properties *in vitro* and *in vivo*, and can effectively be used to treat IR injury and cisplatin-induced AKI.

6. Conclusion and perspectives

As described above, nanomaterial-based nanozymes have emerged as a novel agent for treating antioxidant-mediated kidney injury. As shown in the review, the chemical design represents an important achievement for the treatment of several kidney diseases *via* the modulation of the antioxidant activity of nanomaterials; effective attenuation of oxidative stress; and improvement of renal targeting, bioavailability, and renal clearance, among others. Despite the remarkable progress related to using these antioxidant nanozymes for treating kidney injury, these antioxidant nanozymes still have several limitations for the treatment of kidney injury.

First of all, the size, shape, surface charge and surface groups of nanozymes not only determine their activity to a large extent, but also are closely related to the glomerular filtration system and cell uptake. In addition, charge, coating, doping and loading also affect the properties and functions of nanozymes. Therefore, it is very important to understand the structure–function relationship. Among the nanozymes applied in kidney injury, they are different in size, shape, and surface modification. In addition to low efficacy, nanozymes without targeting may be potentially toxic to humans in long-term treatment. Being smaller than the renal filtration threshold facilitates their clearance by the body, but it also means that their half-life is shorter and they are more likely to aggravate injury caused by particle agglomeration. Nanozymes larger than the renal filtration threshold cannot be completely removed, so whether these nanozymes exacerbate kidney injury through other mechanisms remains a question. Although these nanozymes have the activity of natural antioxidant enzymes, their catalytic capacity may be different, so their catalytic activity still has great room for improvement. In addition, nanozymes with multiple enzyme-mimicking properties can catalyze a variety of substrates, which is conducive to enhancing antioxidant capacity. However, it raises several issues related to the catalytic specificity and substrate selectivity of nanozymes, and makes the synergistic activity of multiple nanozymes more difficult to control. Therefore, researchers should aim to obtain the optimal selection of basic parameters through standardized screening and evaluate the biocompatibility and long-term safety of nanozymes through strictly defined criteria. There is interest in transforming nanozymes from the current empirical science to a science built on theory and solid foundations and providing valuable guidance for the development of nanozymes for application in the treatment of kidney injury. Secondly, the preparation of antioxidant nanomaterials often involves organic reagents and metal ions and complicated steps for purification. These antioxidant nanomaterials may have unpredictable side effects in the human body and place marked stress on the environment. Therefore, the use of green methods to extract and synthesize nanozymes with excellent stability and antioxidant capacity may be more beneficial for the treatment of kidney injury. Besides, these studies involved rodent models, and there is a marked difference between healthy and unhealthy kidneys in rodents and humans. The mitochondrial and capillary density of mouse kidneys is much higher than that of humans, and the metabolic rate is nearly seven times more than in humans. Accordingly, mouse models of kidney injury cannot reflect the characteristics of patients with kidney injury well. Since mouse kidneys may be exposed to higher concentrations of ROS and more severe oxidative stress, multidimensional efficacy validation using different renal injury models is more conducive to promoting clinical transformation.

Research on the use of antioxidant enzymes for kidney injury is still within the initial stage of exploration; not many nanozymes are used to treat kidney injury through antioxidants. The transition from animal models to clinical applications requires a lot of effort from different disciplines. For example, nanozymes have a lot of room for improvement. Nanotechnology can continuously be improved. The current kidney injury animal model can also be improved to fully reflect human kidney injury. This review provides some valuable references for scholars engaged in related research in the future, helps to develop more efficient nanozymes, contributes to promoting the progress of the treatment of kidney injury, and is expected to promote the development of research in other oxidative stress-related diseases.

Abbreviations

ROS	Reactive oxygen species
AKI	Acute kidney injury
DKD	Diabetic kidney disease
AKD	Acute kidney disease
CKD	Chronic kidney disease
ESKD	End-stage kidney disease
KRT	Kidney replacement therapy
POD	Peroxidase
OXD	Oxidase
SOD	Superoxide dismutase
CAT	Catalase
H_2O_2	Hydrogen peroxide
$^1O_2$	Singlet molecular oxygen
ROOH	Organic hydroperoxides
$O_2^{\bullet -}$	Superoxide anion radical
$^{\bullet}OH$	Hydroxyl radical
$ROO^{\bullet}$	Peroxygen radical
NADPH	Nicotinamide adenine dinucleotide phosphate
ECM	Extracellular matrix
NOX	NADPH oxidase
IPC	Ischemic preconditioning
RIRI	Renal ischemia-reperfusion injury
GPx	Glutathione peroxidase
NLRP3	Nod-like receptor protein 3
TFEB	Ranscription factor EB
MAR1	MAResin1
Nrf-2	Nuclear factor erythroid 2 related factor 2
DEX	Dexmedetomidine
CeO_2	Cerium dioxide
CNPs	Cerium nanoparticles
HORAC	Hydroxyl radical antioxidant capacity
CZNPs	Zirconia attached CNPs
TCeria NPs	Triphenylphosphine modified ceria nanoparticles
Atv	Atorvastatin
PTP	mPEG-TK-PLGA
mPEG	Methoxypolyethylene glycols
MET	Metformin
HMSN	Hollow mesoporous silica nanocomposites
CP	Cisplatin
NPs	Nanoparticles
Lf-CONP	Lactoferrin-modified cerium oxide nanoparticles
AuNPs	Gold nanoparticles
HO-1	Heme oxygenase 1
Keap-1	Kelch-like ECH-associated protein 1
PEG	Polyethylene glycol
Au NCs	Gold nanoclusters
NAC	*N*-Acetylcysteine
NA-2	*N*-(2-Hydropxyphenyl)acetamide
ZnONPs	Zinc oxide nanoparticles
FA	Ferulic acid
PTC	(PEG)-stearamine (C18) conjugate
PTC-M	dMn_3O_4 nanoparticles with PTC
cfDNA	Cell-free DNA
Mn_3O_4 Nfs	Nanoflower-structured Mn_3O_4
$Cu_{5.4}O$ USNPs	Ultrasmall $Cu_{5.4}O$ nanoparticles
Ir NPs-PVP	Ultrasmall PVP-modified iridium nanoparticles
PVP	Polyvinyl pyrrolidone
RuO_2NPs	Ultrasmall RuO_2 nanoparticles
POM	Polyoxometalate
TWNDs	Ultra-small tungsten-based nanodots
PB	Prussian blue
NZs	Nanozymes
RONS	Reactive oxygen/nitrogen species
SeNPs	Selenium nanoparticles
LYC	Lycopene
Ch-SeNPs	Chitosan sodium selenium particles
Sirt1	Silencing information regulates 2-related enzyme 1
BSA	Bovine serum albumin
MeNPs	Melanin nanoparticles
MNPs	Melanin-like nanoparticles
PARP-1	Poly-ADP-ribose polymerase-1
GMP nanoparticles	Anti-GPR97-conjugated melanin nanoparticles load PJ34
GO	Nanographene oxide
h-GQDs	Phenol-like group functionalized graphene quantum dots
C60	C60 fullerene
CQDs	Carbon quantum dots
SeCQDs	Selenium-doped carbon quantum dots
CNDs	Carbon nanodots
PDA	*m*-Phenylenediamine

Author contributions

Jian Wu and Haojie Shang wrote the original draft. An Zhang, Yu He, and Yonghua Tong completed the recombination and arrangement of figures. Qiu Huang, Xiao Liu collected information and organized materials. Zhiqiang Chen and Kun Tang came up with the overall structure of the manuscript. All authors reviewed and edited this manuscript.

Conflicts of interest

There are no conflicts to declare.

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