

Reactive Oxygen Species Scavenging Nanozymes: Emerging Therapeutics for Acute Liver Injury Alleviation

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Abstract: Acute liver injury (ALI), a fatal clinical disease featured with a swift deterioration of hepatocyte functions in the short term, has emerged as a serious public health issues that warrants attention. However, the effectiveness of existing small molecular antioxidants and anti-inflammatory medications in alleviating ALI remains uncertain. The unique inherent structural characteristics of liver confer it a natural propensity for nanoparticle capture, which present an opportunity to exploit in the formulation of nanoscale therapeutic agents, enabling their selective accumulation in the liver and thereby facilitating targeted therapeutic interventions. Significantly increased reactive oxygen species (ROS) accumulation and inflammation response have been evidenced to play crucial roles in occurrence and development of ALI. Nanozymes with ROS-scavenging capacities have demonstrated considerable promise in ROS elimination and inflammation regulation, thereby offering an appealing therapeutic instrument for the management of acute liver injury. In this review, the mechanisms of different type of ALI were summarized. In addition, we provide a comprehensive summary and review of the available ROS-scavenging nanozymes, including transition metal-based nanozymes, noble metal nanozymes, carbon-based nanozymes, and some other nanozymes. Furthermore, the challenges still need to be solved in the field of ROS-scavenging nanozymes for ALI alleviation are also discussed.

Keywords: acute liver injury, nanozyme, ROS-scavenging, antioxidant, anti-inflammation

Introduction

Acute liver injury (ALI) is one of the main ongoing hot topics of medical research. Recently, the high incidence of acute liver injury triggered by coronavirus disease 2019 (COVID-19) infection and the overdose of antipyretic drugs have made ALI a serious clinical concern that warrants attention.¹ As an essential organ of the human body, the liver assumes an indispensable function in various physiological processes.² Accordingly, the liver exhibits a high susceptibility to numerous external factors and stimuli, and excessive transient stimulation or enduring chronic stimulation can readily induce acute liver injury or chronic liver diseases, such as hepatic fibrosis, liver cirrhosis, and liver cancer.³ ALI is distinguished by a swift deterioration of hepatocyte functions in the short term, especially jaundice and coagulation disorders, which generally arise from drug poisoning, alcohol abuse, virus infection, hepatic resection or transplantation surgery, etc.⁴⁻⁷ In the absence of prompt and efficacious intervention, ALI has the potential to advance into acute liver failure, ultimately culminating in a fatality.⁸ The prevalence of ALI exhibits a persistent upward trend, primarily attributed to substance abuse, unhealthy lifestyles, and environmental pollution, among others.⁹ The pathophysiological process of ALI is characterized by a multitude of intricate mechanisms, encompassing various intracellular and extracellular events.¹⁰ Recent studies have accumulated substantial evidence to support the pivotal involvement of oxidative stress and inflammation in various forms of liver injury.¹¹ N-acetyl cysteine (NAC) and glutathione (GSH), well-known small molecular reactive oxygen species (ROS) scavengers, have been extensively used as clinical antidotes against ALI.

Nevertheless, the narrow therapeutic window imposes limitations on their clinical application.¹² Therefore, it is imperative to explore novel methodologies that can provide more comprehensive safeguarding against ALI.

Nanozymes, a kind of nanomaterials with enzyme-like catalytic characteristics, have garnered extensive interest in the scientific community due to their high catalytic activity, good physiological stability, and cost-effectiveness in terms of manufacturing and storage.^{13,14} Among them, nanozymes with ROS-scavenging capacities have attracted increasing attention in the field of ALI alleviation for their advantages in many aspects. First of all, ROS-scavenging nanozymes possess the ability to persistently eliminate excess ROS in a catalytic manner and regulate inflammation rather than a simple consumption of ROS in those small molecular scavengers.^{11,15} Subsequently, compared with small molecular ROS scavengers, the nanozymes possess the characteristics of controllable nanoparticle size and diversified surface modifications, which have been proven to have the effect of prolongating blood circulation time and enhancing hepatic accumulation.¹⁶ The liver possesses inherent structural characteristics that confer it with a natural propensity for nanoparticle capture, such as the presence of the mononuclear phagocyte system, which harbors a substantial population of macrophages responsible for the internalization of nanoparticles.^{17–20} Additionally, the utilization of specific target molecule on nanoscale delivery systems probably mitigate the undesired distribution of the therapeutic agents to other organs, thereby reducing off-target effects and systemic toxicity.²¹ For example, glycyrrhetic acid is used as a hepatocyte-targeting ligand functionalized on the L-Se-methylselenocysteine nanoparticles. The further experiment showed that the resultant exhibit enhanced hepatocyte uptake and liver accumulation.²² These superior characteristics make ROS-scavenging nanozymes an excellent alternative for the treatment of ALI.

In this review, we focus on the developments of ROS-scavenging nanozymes and their applications in alleviation of acute liver injury in recent years (Figure 1). Firstly, we discuss the mechanisms of ROS-scavenging nanozymes to

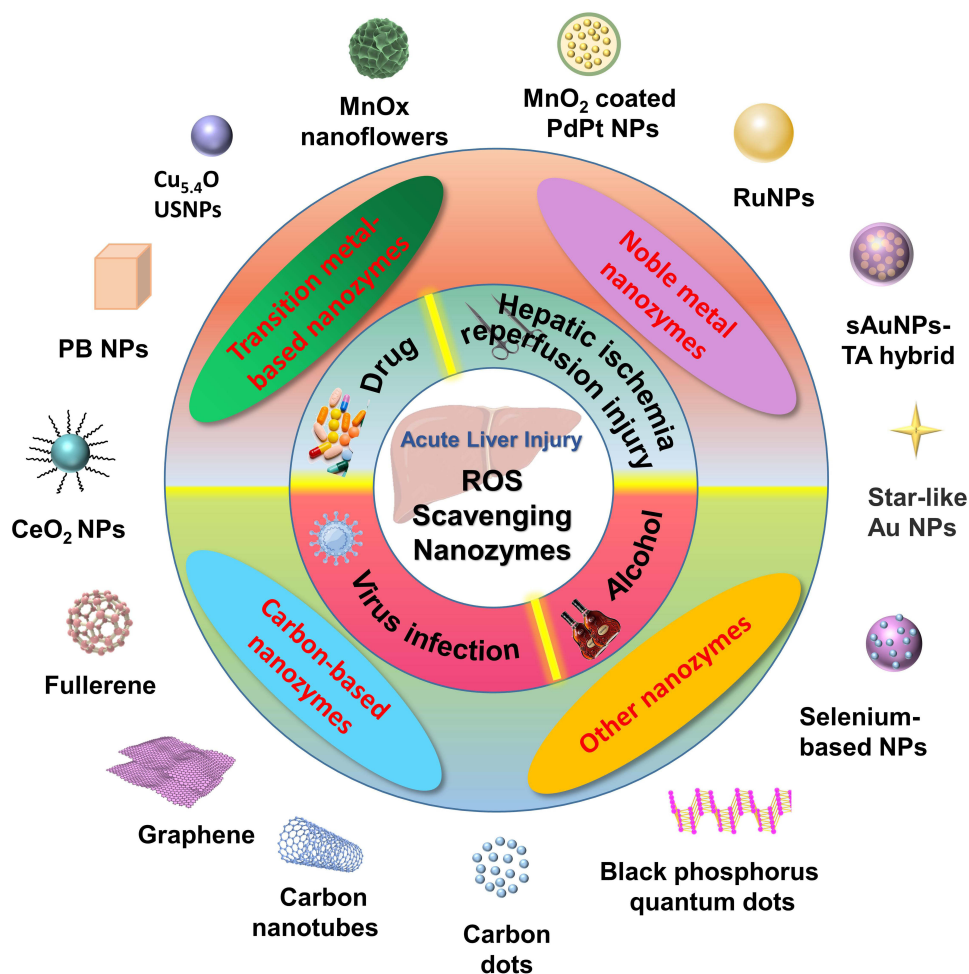


Figure 1 Schematic illustration of the cause of acute liver injury and ROS-scavenging nanozymes for alleviation of acute liver injury.

alleviate liver injury. Subsequently, we provide a comprehensive summary and review of the available ROS-scavenging nanozymes, including transition metal-based nanozymes, noble metal nanozymes, carbon-based nanozymes, and some other nanozymes. These antioxidant nanozymes exhibit a high level of efficacy and facilitate the alleviation of ALI. Finally, we critically examine the challenges and prospects in the field of ROS-scavenging nanozymes for ALI alleviation. We hope that this article will serve as a convenient reference for future endeavors in fundamental research and clinical application.

The Mechanisms of Different Type of Acute Liver Injury

When an acute liver injury occurs, excessive amounts of ROS are rapidly produced by the damaged mitochondria of hepatocytes, and inflammation-related immune cells. The representative ROS predominantly include hydrogen peroxide (H_2O_2), superoxide radical species ($\bullet O_2^-$), hydroxyl radicals ($\bullet OH$), and singlet oxygen (1O_2). Oxidative stress, which arises from an excessive accumulation of ROS, plays a significant role in various biological processes including aging, inflammation, and apoptosis.^{23,24} The aforementioned stresses give rise to detrimental effects on diverse cellular constituents, encompassing proteins, lipids, and DNA, which play crucial roles in maintaining redox reactions and signal transduction for homeostasis. Consequently, these impairments contribute to cellular malfunction, demise, and ultimately the onset of pathological conditions. It is worth noting that although the critical role of oxide stress is similar, the mechanisms of different ALIs differ due to the inducer. Table 1 provides a concise overview of the pathogenesis of different types of acute liver injury, which will be further elaborated as follows.

Pathogenesis of Various Forms of Acute Liver Injury

Drug-Induced Liver Injury

Drug-induced liver injury, a prevalent form of ALI, usually arises as a consequence of drug abuse or the undesirable side effects of a diverse range of pharmaceutical agents, encompassing anti-tumor chemotherapy drugs, anti-tuberculosis drugs, antipyretic and analgesic drugs, immunosuppressants, hypoglycemic and lipid-lowering drugs, as well as antibacterial, antifungal, and antiviral drugs, among others. Liver damage caused by acetaminophen (APAP) has become a leading cause of acute liver failure in many countries today because it is widely used as an antipyretic and analgesic.^{30–32} Take APAP-induced ALI as an example. Overdose of APAP produces an excessive amount of highly reactive intermediate metabolite

Table 1 Summary of Mechanisms for Different Types of Acute Liver Injury

Category	Injury Mechanism	Ref.
Drug-induced liver injury	Overdose of drugs produces an excessive amount of highly reactive intermediate metabolite N-acetyl-p-benzo-quinone imine (NAPQI) inside hepatocytes. Subsequently, the excessive NAPQI depletes glutathione in the cytosol and mitochondria, leading to oxidative stress, eg, the overexpression of ROS and lipid peroxidation (LPO).	[25,26]
Hepatic ischemia-reperfusion injury	Inadequate oxygen and blood supply followed by reperfusion lead to the generation of ROS, subsequently eliciting endothelial dysfunction, DNA damage, and inflammatory reactions, ultimately culminating in cellular demise. The over-accumulation of ROS induces oxidative damage of hepatocytes then apoptosis or necrosis and release of damage associated molecular patterns (DAMPs), thereby promoting inflammatory response, which in turn increases the level of ROS.	[27]
Virus infection-induced liver injury	Occurrence of an inflammatory cytokine storm	[28]
Alcohol-induced liver injury	Ethanol metabolite, acetaldehyde exerts hepatotoxic effects by directly affecting liver cells through its actions on mitochondria, microtubules, and plasma membranes. The acetaldehyde-protein complex further causes degeneration and necrosis of liver cells. Additionally, a metabolite of acetaldehyde, acetic acid, is converted to superoxides by xanthine oxidase, thereby inducing LPO, destroying cell membrane lipids and promoting liver damage.	[29]

N-acetyl-p-benzo-quinone imine (NAPQI) inside hepatocytes. Subsequently, the excessive NAPQI depletes glutathione in the cytosol and mitochondria, leading to oxidative stress, eg the overexpression of ROS and lipid peroxidation (LPO).^{25,26} The hepatocytes are prone to damage and necrosis due to the excessive accumulation of ROS and LPO in the liver, which is widely acknowledged as a primary causal factor.^{33,34} Therefore, therapeutic strategies focused on ROS scavenging are greatly demanded for drug-induced liver injury.

Hepatic Ischemia-Reperfusion Injury

Hepatic ischemia-reperfusion injury (HIRI) is a significant complication that arises as a result of different liver surgical procedures, such as liver resection and transplantation, and causes of hepatic dysfunction and failure.^{35–38} HIRI is characterized by a phenomenon of inadequate oxygen and blood supply followed by reperfusion in the liver, resulting in a pronounced inflammatory response and an increased level of oxidative stress.³⁹ The primary pathophysiological mechanism underlying hepatic ischemia-reperfusion injury entails the generation of ROS, which subsequently elicit endothelial dysfunction, DNA damage, and inflammatory reactions, ultimately culminating in cellular demise. The over-accumulation of ROS during HIRI induces oxidative damage of hepatocytes then apoptosis or necrosis and release of damage-associated molecular patterns, thereby promoting inflammatory response, which in turn increases the level of ROS.²⁷ Despite the abundance of evidence regarding the efficacy of antioxidants in the management of HIRI, the number of drugs approved by the Food and Drug Administration for HIRI treatment remains limited. Therefore, it is crucial to develop novel efficient antioxidants to eliminate the excess ROS with the aim of mitigating and preventing HIRI.

Virus Infection-Induced Liver Injury

Viral hepatitis is a major public health problem which may change to chronic, and eventually lead to end-stage liver disease and even hepatocellular carcinoma.^{40–42} At present, viral hepatitis has been identified as A, B, C, D and E, among which hepatitis A and E usually present with a self-limited course followed by complete recovery,^{43,44} hepatitis B and C often result in chronic infection and responsible for the most adverse consequences of this disease.^{45,46} Apart from the above hepatitis virus, some non-hepatotropic viruses such as cytomegalovirus, Epstein-Barr virus and other infections can also cause liver damage.^{47–49}

In recent years, with the outbreak of COVID-2019, virus infection-induced liver injury has attracted increasing attention.⁵ Multiple studies have substantiated the presence of liver injury in individuals afflicted with COVID-19,⁵⁰ with a higher propensity for severe cases to exhibit pronounced liver impairment in comparison to milder cases.⁵¹ Moreover, the occurrence of an inflammatory cytokine storm has been observed in severe cases of COVID-19, but further investigation is required to determine if it is the underlying factor contributing to liver injury. Besides, the excessive utilization of medications in the treatment of COVID-19 presents a potential risk factor for liver injury.²⁸ Therefore, it is imperative to not only address the primary disease resulting from coronavirus infection but also to closely monitor the incidence of liver injury and the administration of medications that have the potential to cause liver injury.^{52,53} Therefore, it is of great clinical significance to prevent liver injury through ROS-scavenging and inflammation regulation in coronavirus-infected patients.

Alcohol-Induced Liver Injury

Alcohol-induced liver injury is a common liver disease as a result of heavy drinking in many countries. Acute alcohol exposure can cause a “perfect storm” that favors inflammatory liver damage, including steatosis, dysregulated immunity response, and inflammation, thereby augmenting susceptibility to infection and increasing gastrointestinal tract permeability.^{54,55} Acetaldehyde, a metabolite of ethanol metabolism, exerts hepatotoxic effects by directly affecting liver cells through its actions on mitochondria, microtubules, and plasma membranes.²⁹ The formation of complexes between acetaldehyde and proteins contributes to the degeneration and necrosis of liver cells. Furthermore, acetic acid, a metabolite of acetaldehyde, is converted into superoxide by xanthine oxidase, leading to LPO, damage to cell membrane lipids, and the promotion of liver injury. Both processes have the potential to increase the recruitment of pro-inflammatory macrophages in the liver, as well as augment the production of cytotoxic cytokines and ROS, which further promote the deterioration of the liver injury induced by acute alcohol exposure.

Mechanism of ALI Alleviation by Using ROS-Scavenging Nanozymes

Nanozymes are a category of nanomaterials that demonstrate enzyme-like characteristics by facilitating the transformation of substrates into products under physiological circumstances, although they may deviate from the catalytic pathway observed in natural enzymes.⁵⁶ The past decade has witnessed the notable advancement of nanozymes, with the discovery of over 1200 distinct nanomaterials exhibiting various enzymatic activities. These nanomaterials encompass a wide range of compositions, such as noble-metal nanocrystals, transition metal-based nanomaterials, carbon-based nanomaterials, polymer-metal complexes, and metal-organic frameworks, etc.⁵⁷ These nanozymes can be classified as mimics of oxidoreductases and hydrolases, including oxidase (OXD), peroxidase (POD), catalase (CAT), superoxide dismutase (SOD), nuclease, phosphatase, and others. Among them, nanomaterials with simulated CAT and SOD activity, and hydroxyl radical antioxidant capacity (HORAC) activity can eliminate ROS and generate oxygen to ameliorate the inflammatory microenvironment, which is beneficial for the alleviation of inflammatory responses. During the ALI process, there are abundant inflammatory macrophages and significantly increased ROS levels in the injured liver. The utilization of ROS-scavenging nanozymes in the management of ALI probably eliminate the excess ROS and improve the inflammatory microenvironment. Meanwhile, compared with small molecular ROS scavengers, ROS-scavenging nanozymes possess longer blood circulation time and preferable hepatic accumulation capacity,¹⁶ which reasonably enhance the therapy efficacy via improving the bio-availability of therapeutic agents and decreasing the possible non-specific organ distribution.

ROS-Scavenging Nanozymes for ALI Alleviation

In order to better study the mechanism and treatment of acute liver injury, different kinds of acute liver injury animal models have been established, including drug-induced liver injury (eg APAP-induced liver injury,^{58–60} anthracycline-induced liver injury⁶¹), chemical-induced liver injury (eg CCl₄-induced liver injury^{62,63}), immune-induced liver injury (eg lipopolysaccharide (LPS)-induced liver injury,^{64,65} D-galactosamine-induced liver injury,⁶⁶ concanavalin A-induced liver injury^{67,68}), alcohol-induced liver injury,^{69,70} and hepatic ischemia-reperfusion injury.^{7,35,71}

Transition Metal-Based Nanozymes

Transition metal elements exhibit significant potential in the application of catalysis due to their variable valence state resulting from the incompletely filled valence d-orbitals.^{72,73} Many transition metal elements served as the active center of natural antioxidant enzymes, for instance, the active centers of SOD are mainly copper (Cu) and zinc (Zn) ions, or manganese (Mn) ions, or iron (Fe) ions.^{57,74} According to SOD with various metal centers were denoted as CuZn-SOD, Mn-SOD, and Fe-SOD, respectively. Transition metal elements-contained nanomaterials usually exhibit SOD-like activity due to their similar component with natural antioxidant enzymes. Transition metal-based nanozymes, such as transition metal-based oxides, sulfides, Prussian blue (PB), and Prussian blue analogues (PBA), as well as others, have been demonstrated to have significant ROS-scavenging capacity in a catalytic manner, showing promise for the alleviation of ROS-upregulated inflammation diseases, including ALI. A brief summary of transition metal-based antioxidant nanozymes for the alleviation of acute liver injury has been presented in Table 2, and a comprehensive examination of these nanozymes will be provided as follows.

Ce-Based Nanozymes

Ce-based nanoparticles, including CeO₂, CeO_{2-x}, and Ce₂O₃ nanoparticles, etc., exhibit multiple enzyme-like catalytic activity, such as SOD-like activity, CAT-like activity, and HORAC, which can efficiently convert •O₂⁻, H₂O₂, and •OH to harmless H₂O and O₂. The superior ROS-scavenging enzyme-like activities of Ce-based nanozymes (CeNZs) could be attributed to the rapid transfer between the Ce³⁺ and Ce⁴⁺ ions on the surface of Ce-based nanoparticles. Due to their excellent antioxidant properties, CeNZs have been widely used to downregulate oxidative stress for the alleviation of ROS-related diseases including ALI.⁸² For instance, the study conducted by Ni et al demonstrated that ceria nanoparticles possess the capability to effectively mitigate the clinical manifestations of HIRI through the process of scavenging ROS, as well as inhibiting the activation of Kupffer cells and monocyte/macrophage cells (Figure 2A).³⁵ The subsequent hepatic inflammatory response is mitigated by a substantial decrease in the release of pro-inflammatory cytokines and the limited recruitment and

Table 2 Summary of ROS-Scavenging Nanozymes for the Alleviation of Acute Liver Injury

Nanozymes Classification	Examples	Active Component	Size	Enzyme-like Activities	Liver Injury Model	Ref.
Ce-based nanozymes	Ceria nanoparticles	CeO _{2-x}	5–10 nm	CAT, SOD, HORAC	Hepatic ischemia-reperfusion injury	[35]
	Er ³⁺ -doped CeO _{2-x} Nanoprobes	Er-CeO _{2-x}	7.9 ± 0.4 nm	CAT	LPS-induced acute liver injury	[64]
	Ceria Nanozymes	CeO ₂	12 nm (hydrodynamic diameter)	CAT, SOD, HORAC	APAP-induced acute liver injury	[58]
	Ceria Nanozymes	CeO ₂	3 nm	CAT, SOD	APAP-induced acute liver injury	[59]
	CeO ₂ Nanoparticles	CeO ₂	Ambiguous	CAT, SOD, HORAC	Hepatic ischemia-reperfusion injury	[7]
	Mesoporous Hollow Manganese Doped Ceria Nanoparticles	MnO _x -CeO ₂	220 nm	HORAC	Hepatic ischemia-reperfusion injury	[71]
	BSA-functionalized cerium oxide and manganese oxide nanocomposites	CeO ₂ , MnO ₂	2 nm	CAT, SOD, HORAC	Hepatic ischemia-reperfusion injury	[75]
Fe-based nanozymes	Prussian blue nanozymes	PB	119 nm (hydrodynamic diameter)	SOD, CAT, POD, HORAC	Anthracycline-induced liver injury	[61]
	Prussian blue nanozyme impregnated mesenchymal stem cells	PB	34 ± 8 nm (hydrodynamic diameter)	SOD, CAT, POD	Hepatic ischemia-reperfusion injury	[76]
	Prussian blue nanozymes	PB	80.2 nm	CAT, POD, HORAC	Hepatic ischemia-reperfusion injury	[77]
	Prussian blue nanozymes	PB	39.8 ± 9.54 nm	CAT, SOD	APAP-induced liver injury	[60]
	Manganese Prussian blue nanozymes	Mn-PBA	122 nm (hydrodynamic diameter)	CAT, SOD	APAP-induced liver injury	[78]
	Biomimetic PB nanozymes	PB@MSCM	160 nm	SOD, CAT, POD	Radiation-induced hematopoietic injury	[79]
Cu-based nanozymes	Copper oxide nanozymes	Cu _{5,4} O	3.5–4.0 nm	SOD, CAT, HORAC, GPx	APAP-induced liver injury	[13]
	Cu NZs@PLGA nanofiber-reinforced dECM hydrogels	Cu _{5,4} O	4.0 nm	SOD, CAT, HORAC	CCl ₄ -induced liver injury	[62]
Mn-based nanozymes	Mesoporous Hollow Manganese Doped Ceria Nanoparticles	MnO _x -CeO ₂	220 nm	HORAC	Hepatic ischemia-reperfusion injury	[71]
	BSA-functionalized cerium oxide and manganese oxide nanocomposites	CeO ₂ , MnO ₂	2 nm	CAT, SOD, HORAC	Hepatic ischemia-reperfusion injury	[75]
	Platelet membrane-coated, tempol-grafted, Mn-doped mesoporous silica nanoparticles (TMSN@PM)	Mn-SiO ₂ , tempol	142 nm (hydrodynamic diameter)	CAT, SOD, HORAC	APAP-induced liver injury	[80]

(Continued)

Table 2 (Continued).

Nanozymes Classification	Examples	Active Component	Size	Enzyme-like Activities	Liver Injury Model	Ref.
Other transition metal-based nanozymes	Polyvinyl pyrrolidone modified tungsten disulfide (WS ₂ -PVP) nanoflower	WS ₂	500 nm	CAT, SOD, HORAC	CCl ₄ -induced liver injury	[63]
	MoS ₂ -PEG@BSA (MPB) nanosheets	MoS ₂	200 nm	CAT, SOD, HORAC, GPx	APAP-induced liver injury	[81]

infiltration of neutrophils. Li et al developed CeO₂ nanozymes for the detoxification and inflammatory regulation of drug-induced liver injury (DILI) (Figure 2B).⁵⁸ CeNZs can effectively eliminate ROS within compromised hepatocytes, thereby facilitating the process of detoxification. Meanwhile, the CAT-like activity of CeNZs promotes the production of abundant oxygen, which exhibits a distinct inhibitory effect on pro-inflammatory macrophages, resulting in the alleviation of inflammation. The concurrent detoxification and inflammatory regulation capacities of CeNZs enable a DILI alleviation option with a comparatively extended therapeutic time window in contrast to NAC. Based on the excellent therapeutic efficacy of CeNZs on ALI, they further developed a ROS-sensitive nanozyme-augmented photoacoustic nanoprobe RSPN for the early diagnosis and therapy of acute liver failure.⁵⁹ The CeNZs-mediated catalytic transformation of ROS into O₂ bubbles was employed to augment the photoacoustic efficiency of photoacoustic imaging contrast agent ZnPc for the early diagnosis of ALI.

The catalytic activity of CeNZs exhibits a strong positive correlation with both the specific surface area, the proportion of different valence states (Ce³⁺/Ce⁴⁺), and the concentration of oxygen vacancies (O_v). Doping is an effective strategy to increase the O_v concentration of Ce-based nanoparticles, which may lead to a substantial improvement in the catalytic efficiency of CeNZs. For example, Li et al designed Er³⁺-doped CeO_{2-x} (Er-CeO_{2-x}) NPs with multiple enzyme simulation activities for the treatment of LPS-induced acute liver injury.⁶⁴ Si et al successfully synthesized manganese-doped mesoporous hollow ceria nanoparticles (MnOx-CeO₂ NPs), and when the MnOx-CeO₂ NPs with 4% Mn doping ratio exhibited the best anti-oxidant capability (Figure 2C). After doping with Mn, the oxygen vacancy concentration and specific surface area were significantly increased, which was directly related to the elevated anti-oxidant effect in the EPR measurement. These nanoparticles were further investigated for their potential in vivo application for inhibiting HIRI.⁷¹ The administration of MnO_x-CeO₂ NPs led to a notable decline in serum levels of alanine transaminase (ALT) and aspartate transaminase (AST), a reduction in malondialdehyde (MDA) level, an elevation in superoxide dismutase (SOD) level in the liver, and a mitigation of the pathological alterations induced by HIRI.

Fe-Based Nanozymes

Ferrum (Fe)-based nanozymes have attracted extensive attention in the field of biomedicine due to their excellent magnetic and catalytic properties.⁸³⁻⁸⁵ Prussian blue (PB) and its analogs possess multiple enzyme-like activities, including CAT, SOD, and POD, showing great prospects in the field of anti-oxidation and anti-inflammation.⁸⁶ The antioxidant properties of PB nanozymes can be ascribed to the abundant variable valence states present within the structure of PB (such as Fe³⁺/Fe²⁺, [Fe(CN)₆]³⁻/[Fe(CN)₆]⁴⁻).⁸⁷ PB nanozymes have been used for the alleviation of diseases associated with ROS, especially the ALI, e.g., DILI and HIRI, etc. For example, Bai et al developed PB nanozymes to prevent anthracycline-induced liver injury by attenuating oxidative stress and regulating inflammation (Figure 3A).⁶¹ Huang et al used PB nanozymes to alleviate hepatic ischemia reperfusion injury by scavenging ROS in primary hepatocytes, reducing neutrophil infiltration and promoting macrophage polarization to the anti-inflammatory M2 type (Figure 3B).⁷⁷ Sahu et al integrated PB nanozymes into the mesenchymal stem cells (MSCs) in order to enhance the viability of MSCs under conditions of high oxidative stress, while also amplifying their paracrine effect and anti-inflammatory properties (Figure 3C).⁷⁶ This intervention led to a significant therapeutic outcome in the context of HIRI. Feng et al reports a simple and efficient one-step synthesis of Prussian blue (PB) nanozymes with multiple antioxidant enzymatic activities that effectively treat APAP-induced DILI (Figure 3D).⁶⁰ According to in vivo experimental studies,

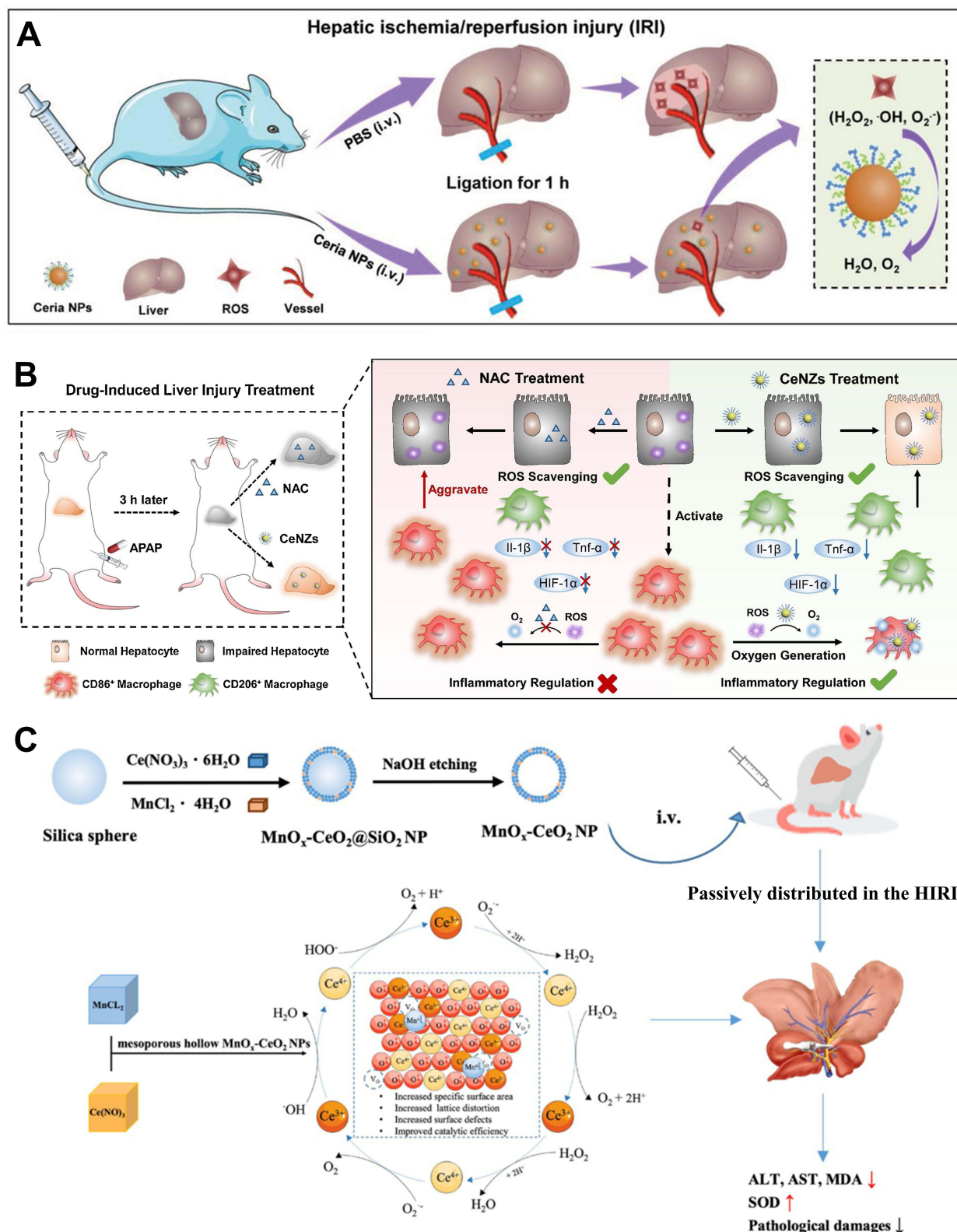


Figure 2 Ce-based nanozymes (CeNZs) for ALI alleviation. **(A)** Schematic illustration of preventing hepatic ischemia-reperfusion injury by ceria NPs. Reprinted from Ni D, Wei H, Chen W, et al. Ceria nanoparticles meet hepatic ischemia-reperfusion injury: the perfect imperfection. *Adv Mater.* 2019;31:1902956. © 2019 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.³⁵ **(B)** Schematic mechanism of ceria nanozymes for drug-induced liver injury therapy by dual detoxification and inflammatory regulation. Reprinted from *Nano Today*, 35, Li F, Qiu Y, Xia F, et al. Dual detoxification and inflammatory regulation by ceria nanozymes for drug-induced liver injury therapy. 100925, copyright 2020, with permission from Elsevier.⁵⁸ **(C)** Schematic illustration of the preparation of mesoporous hollow manganese doped ceria nanoparticle and application for effectively prevention of hepatic ischemia reperfusion injury. Reprinted from Dove Medical Press, Si PR, Lei JX, Yang C, et al. Mesoporous hollow manganese doped ceria nanoparticle for effectively prevention of hepatic ischemia reperfusion injury. *Int J Nanomedicine.* 2023;18:2225–2238.⁷¹

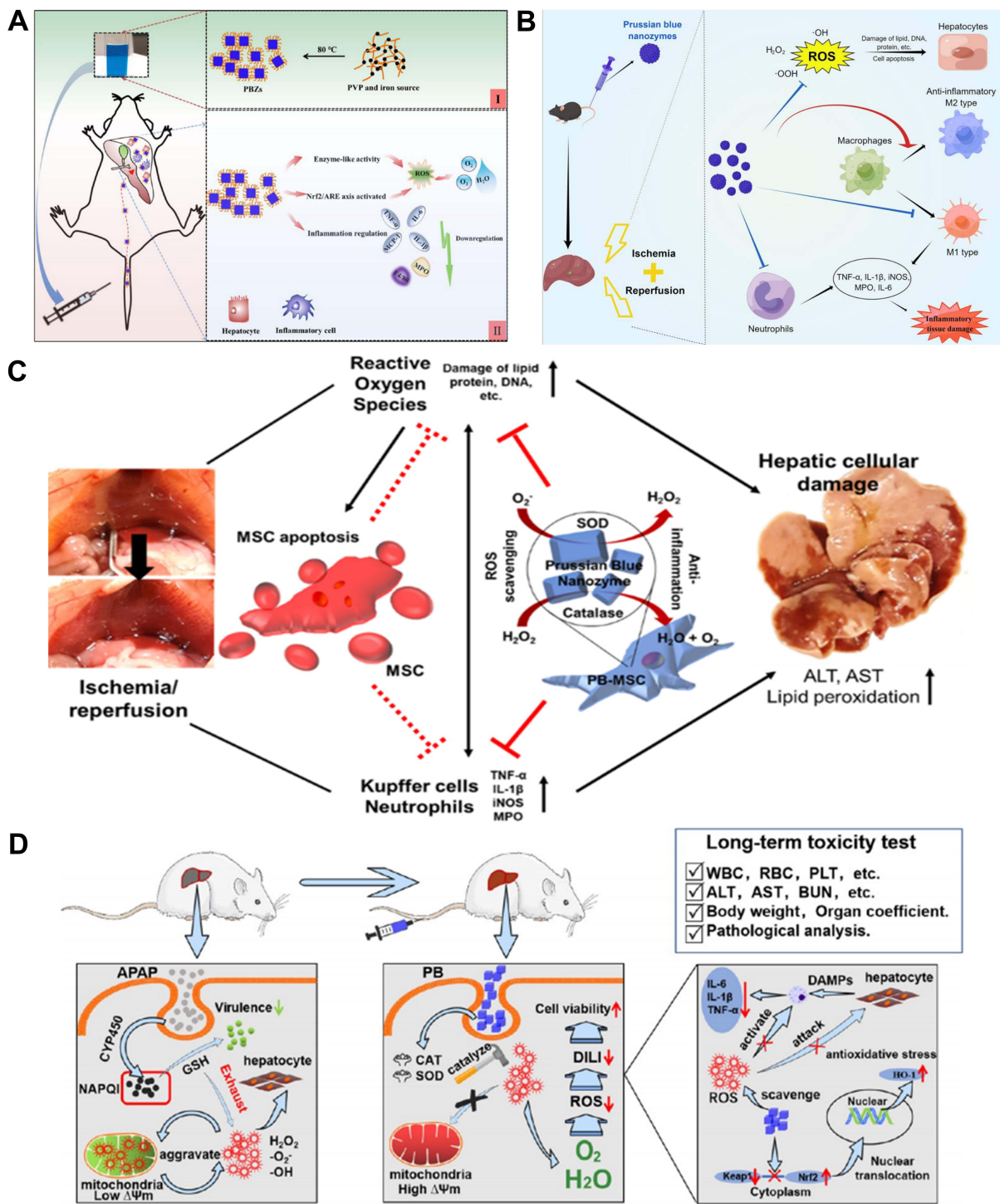


Figure 3 Fe-based nanozymes for ALI alleviation. **(A)** Schematic illustrations of PB nanozymes preventing anthracycline-induced liver injury by attenuating oxidative stress and regulating inflammation. Bai H, Kong F, Feng K, et al. Prussian blue nanozymes prevent anthracycline-induced liver injury by attenuating oxidative stress and regulating inflammation. *ACS Appl Mater Interfaces*. 2021;13:42382–42395. Copyright © 2021 American Chemical Society.⁶¹ **(B)** Schematic diagram of the mechanisms of PB scavengers protect against hepatic ischemia reperfusion injury. Huang YX, Xu QY, Zhang J, et al. Prussian blue scavenger ameliorates hepatic ischemia-reperfusion injury by inhibiting inflammation and reducing oxidative stress. *Front Immunol*. 2022;13:891351.⁷⁷ This is an open-access article distributed under the terms of the Creative Commons CC BY license, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. **(C)** Schematic illustrations of PB nanozyme impregnated mesenchymal stem cells for hepatic ischemia-reperfusion injury alleviation. Reprinted from Sahu A, Jeon J, Lee MS, et al. Nanozyme impregnated mesenchymal stem cells for hepatic ischemia-reperfusion injury alleviation. *ACS Appl Mater Interfaces*. 2021;13:25649–25662. Copyright © 2021 American Chemical Society.⁷⁶ **(D)** Schematic illustrations of PB nanozymes preventing APAP-induced liver injury by scavenging ROS, relieving oxidative stress, and regulating the inflammatory response. Feng Q, Xu H, Pan X, et al. Antioxidation and anti-inflammatory activity of Prussian blue nanozymes to alleviate acetaminophen-induced acute liver injury. *ACS Appl Nano Mater*. 2023;6:8468–8481. Copyright © 2023 American Chemical Society.⁶⁰

the levels of serum biochemical indicators and histopathological examination of DILI mice livers showed that 12.5 mg/kg PB nanozymes could effectively inhibit liver necrosis and 25 mg/kg PB nanozymes achieved the same therapeutic effect as 300 mg/kg NAC. It is well-established that the substitution of iron with transition metals, including cobalt, nickel, manganese, copper, and zinc, enables the synthesis of diverse Prussian blue analogs (PBA) exhibiting distinct chemical compositions yet sharing similar crystal structures.⁸⁸ These element substitutions probably facilitate the acquisition of novel traits in PBA, such as the alteration of multiple enzymatic activities. Moreover, Chen et al have successfully prepared multi-functional manganese Prussian blue nanozymes (MPBZs) with excellent ROS-scavenging capacity for the efficient treatment of APAP-induced liver injury by undergoing sequential processes ranging from antioxidation to anti-inflammation, including Nrf2 signaling pathway activation, inhibition of mitochondrial-induced oxidative stress and inflammation regulation.⁷⁸

Cu-Based Nanozymes

Copper (Cu) plays a crucial role as a vital trace element within the human body, contributing significantly to both structural composition and physiological functions.⁸⁹ Cu-dependent natural antioxidant enzymes, like Cu-Zn SOD, tyrosinase, and ceruloplasmin are organisms' essential components to effectively eliminate ROS under oxidative stress.⁹⁰ In the realm of ROS-scavenging and anti-inflammation, Cu-based nanozymes have garnered significant interest as of late. For example, Lin et al designed a copper-tannic acid coordination nanosheets (CuTA) nanozyme that combined copper ion and tannic acid.⁹¹ CuTA nanozyme exhibited superior SOD-like activity, CAT-like activity, and HORAC, serving as a powerful antioxidant for the regulation of inflammation. Deng et al developed ultrasmall Cu₂O and Cu hybrid nanozymes (Cu_{5.4}O nanozymes) with broader-spectrum enzymatic catalytic properties and antioxidant activities for inflammatory diseases therapeutic interventions and preventive measures, including ALI, acute kidney injury, and diabetic wound healing (Figure 4A).¹³ Jin et al further fabricated a synergistic therapeutic platform (HLCs/Cu NZs@fiber/dECM) consisting of Cu_{5.4}O nanozymes-loaded PLGA nanofibers and decellularized extracellular matrix hydrogels for the alleviation of ALI and preventing the deterioration of hepatocytes necrosis (Figure 4B).⁶²

Mn-Based Nanozymes

Manganese (Mn) is a multivalent transition metal element, the transformation of various valence states makes manganese exhibits superior catalytic activity, and thus various manganese-based nanozymes have emerged. Meanwhile, another essential trace element in the human body, manganese is the main active component of some metalloenzymes and participates in many physiological activities, which makes manganese-based nanomaterials get important applications in the biomedical field. For example, manganese is the active center of Mn-SOD, which is an important antioxidant enzyme in mitochondria and plays a critical role in the protection of cells from oxidative damage. Inspired by the natural Mn-SOD, some Mn-based nanozymes with antioxidant activities have been designed and used for ROS-scavenging and anti-inflammation. For example, Yao et al synthesized Mn₃O₄ nanoparticles with remarkable ROS-scavenging activities for ROS-induced ear-inflammation treatment.⁹² The Mn₃O₄ NPs could be used not only to eliminate •O₂⁻, but also catalyze the scavenging of H₂O₂ and •OH. Owing to its superior antioxidant activities, Mn-based nanozymes have also been involved in the alleviation of ALI. Deng et al developed a platelet membrane (PM)-coated, Mn-doped, and tempol-grafted mesoporous silica nanoparticles (TMSN@PM) (Figure 5A and B) with excellent ROS-scavenging, oxygen production, and MRI capacity for the ameliorating and therapy monitoring of inflammation, including ALI and acute pancreatitis (Figure 5C).⁸⁰ Manganese-based composite nanozymes, such as mesoporous hollow doped ceria nanoparticles (MnOx-CeO₂ NPs) and BSA-functionalized CeO₂ and MnO₂ composite nanoparticles (CM NCs), also have been developed to alleviate the hepatic ischemia-reperfusion injury (Figures 2C).^{71,75} The CM NCs can scavenge and eliminate •O₂⁻, H₂O₂, and •OH during the reperfusion process, subsequently suppressing the activation of Kupffer cells and neutrophils, and reducing the secretion of inflammatory factors.

Other Transition Metal-Based Nanozymes

Besides Ce, Fe, Mn, and Cu-based nanozymes, other transition metal-based nanoparticles, such as zinc-based (Zn-based), nickel-based (Ni-based), molybdenum-based (Mo-based) and tungsten-based (W-based) nanoparticles, also show the enzyme catalytic activities of scavenging ROS due to their diversity of valence states and adjustability of crystal defects.

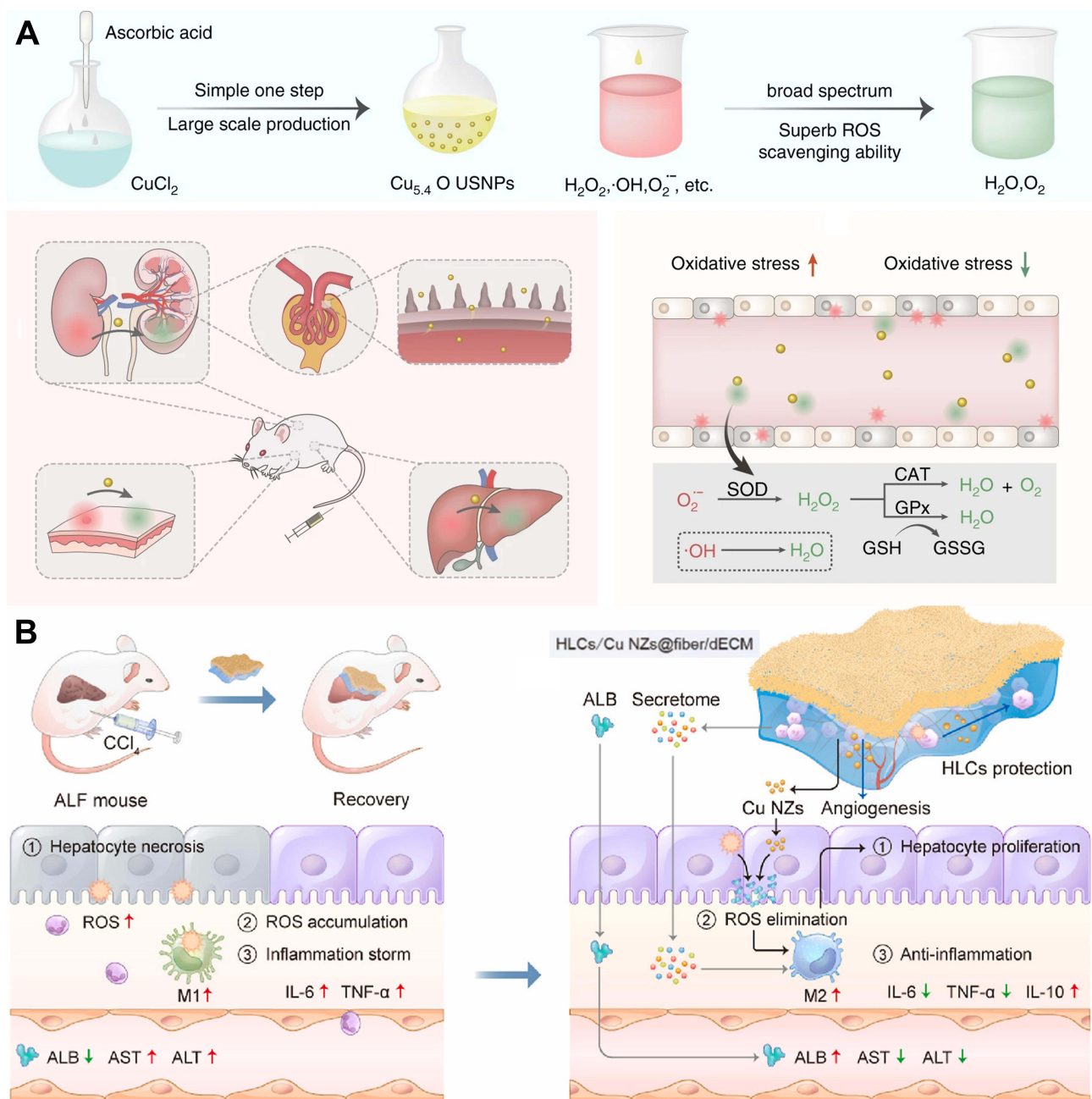


Figure 4 Cu-based nanozymes for ALI alleviation. **(A)** Schematic illustration of $\text{Cu}_{5,4}\text{O}$ ultrasmall nanoparticles (USNPs) as a broad-spectrum ROS scavenging agent in the treatment of ROS-related diseases, including ALI, acute kidney injury and diabetic wound healing. Liu T, Xiao B, Xiang F, et al. Ultrasmall copper-based nanoparticles for reactive oxygen species scavenging and alleviation of inflammation related diseases. *Nat Commun.* 2020;11:2788.¹³ This is an open-access article distributed under the terms of the Creative Commons CC BY license, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. **(B)** Schematic illustration of the HLCs/Cu NZs@fiber/dECM for CCl_4 -induced acute liver failure through the effects of ROS elimination, angiogenesis promotion, anti-inflammation, hepatocyte-related functions, and facilitating liver regeneration. Reprinted from *Bioact Mater*, 28, Jin Y, Zhang J, Xu Y, et al. Stem cell-derived hepatocyte therapy using versatile biomimetic nanozyme incorporated nanofiber-reinforced decellularized extracellular matrix hydrogels for the treatment of acute liver failure. 112–131, Copyright 2023.⁶² This is an open-access article distributed under the terms of the Creative Commons CC BY license, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

These transition metal-based nanozymes have also emerged as novel antioxidants for the management of ALI. For example, Wu et al developed ZnO-NiO@COOH particles with increased surface area and oxygen vacancy active sites, which can efficiently adsorb and eliminate ROS to block the generation of inflammatory storms and promote the alleviation of ALI.⁸ Zhang et al prepared $\text{MoS}_2\text{-PEG@BSA}$ nanosheets that exhibit remarkable biocompatibility and

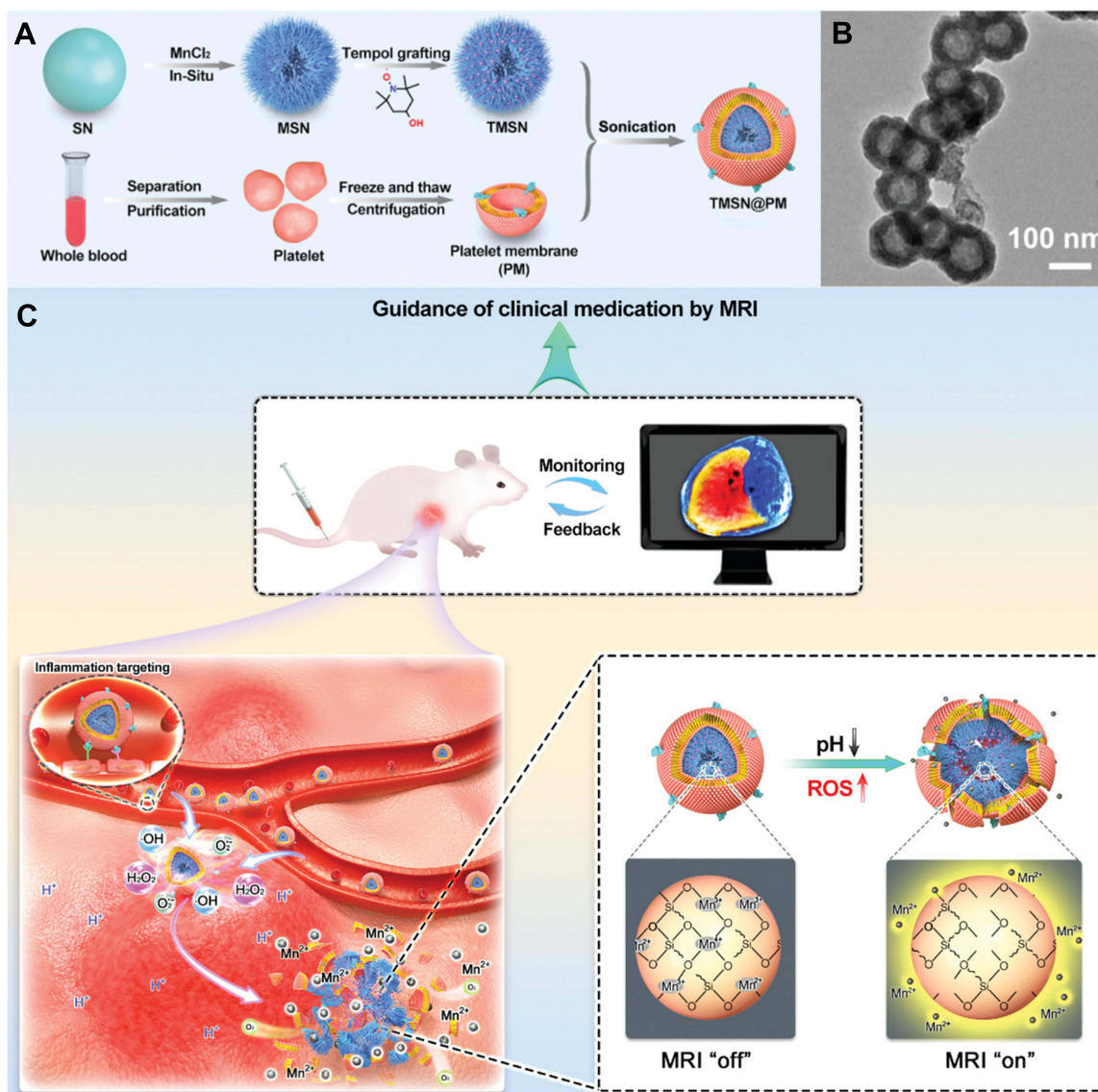


Figure 5 Mn-based nanozymes for ALI alleviation. (A) Schematic illustration of the preparation of TMSN@PM. (B) TEM image of TMSN@PM. (C) Schematic illustration of the in vivo MRI-guided real-time monitoring of the treatment process of inflammatory diseases using TMSN@PM. Reproduced with permission from Li X, Liu Y, Qi X, et al. Sensitive activatable nanoprobe for real-time ratiometric magnetic resonance imaging of reactive oxygen species and ameliorating inflammation in vivo. *Adv Mater.* 2022;34:e2109004. © 2022 Wiley-VCH GmbH.⁸⁰

enzymatic activity for the therapeutic intervention of ALI, showing promise in the therapy of ROS-related diseases.⁸¹ Xu et al synthesized a polyvinyl pyrrolidone modified tungsten disulfide (WS₂-PVP) nanoflowers with CAT, SOD, and glutathione peroxidase (GPx) enzymes activities for the scavenging of ROS (Figure 6A and B).⁶³ The WS₂-PVP nanoflowers exhibited excellent cell protection and significantly improved treatment outcomes on ALI (Figure 6C).

Noble Metal Nanozymes

Noble metal (Au, Ag, Pt, Pd, Ru, Rh, Os, and Ir) nanomaterials, including simple substances, alloys, and noble metal-containing composites, have been used extensively in the field of catalysis, electronics, and healthcare due to their unique optical, electrical, and catalytic properties. A great number of noble metal nanomaterials have been demonstrated with multi-enzymatic catalytic activities, such as OXD-like, POD-like, CAT-like, and SOD-like activity, etc.^{93–96} The enzyme-like catalytic activity of noble metal nanozymes could be regulated by altering their size, morphology, composition, surface modification and so on. Owing to their superior physicochemical properties and antioxidant enzyme-like activities, noble metal nanozymes have attracted

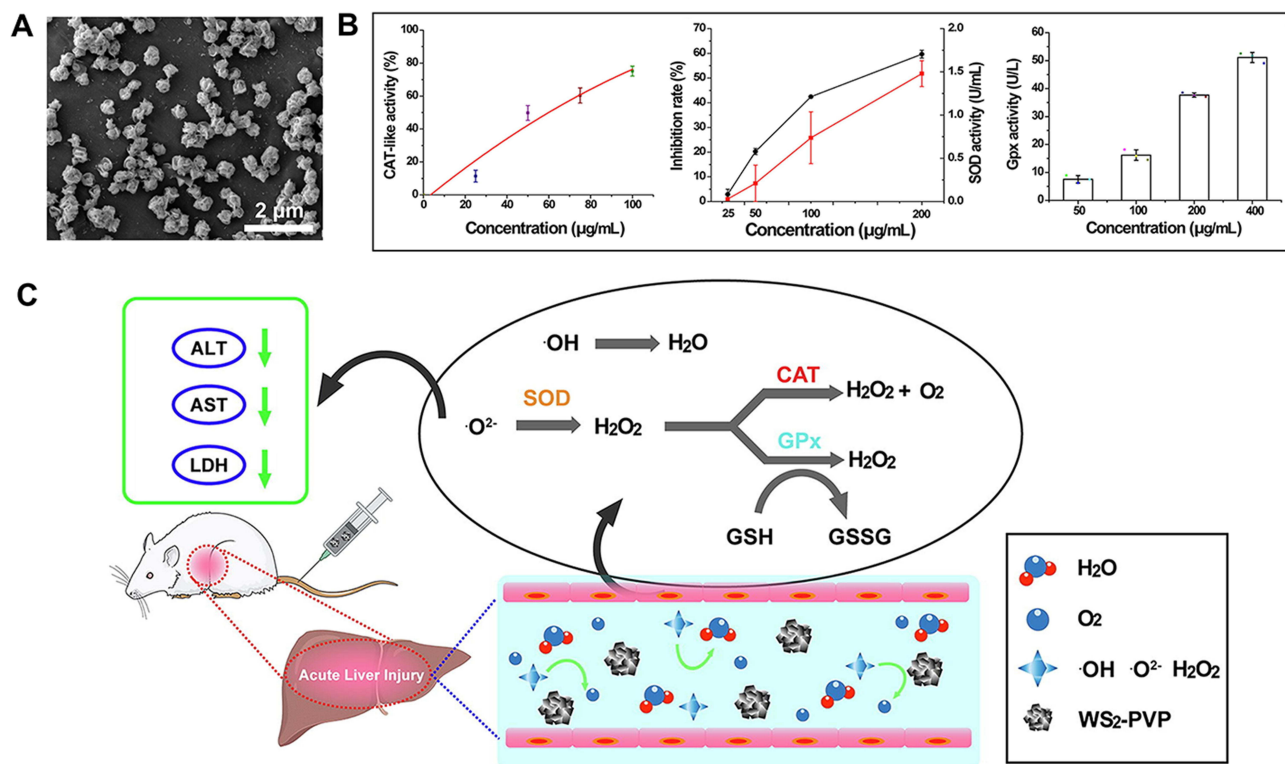


Figure 6 Other transition metal-based nanozymes for ALI alleviation. **(A)** FESEM image of WS₂-PVP nanoflowers. **(B)** CAT-like activity, SOD-like activity and GPx-like activity of WS₂-PVP nanoflowers. **(C)** Schematic diagram of ALI treatment with WS₂-PVP nanoflowers. Reprinted from *J Colloid Interf Sci*, 625, Xu H, Zhang ZR, Zhang LY, et al. Tungsten disulfide nanoflowers with multi-nanoenzyme activities for the treatment of acute liver injury. 544–554, Copyright 2022, with permission from Elsevier.⁶³

increasing attention within the realm of biomedical applications, such as the therapy of malignant tumors, antibacterial treatment, and the alleviation of ROS-related inflammation diseases.^{74,97–100} For example, Lu et al developed a carvedilol-loaded gold star-like nanozyme with ROS-scavenging and autophagy-inhibiting capacity for the therapy of hepatic fibrosis.¹⁰¹ Xia et al prepared an ultrasmall oxidized ruthenium (sRuNP) nanozymes with improved antioxidant enzyme-like activity and regulatory T cells upregulation function for the highly efficient therapy of APAP-induced ALI (Figure 7A).¹⁰² Zhang et al developed Pt nanoparticles and carbon nanodots integrated nanozyme (Pt@CNDs) with boosted cascade SOD and CAT activities for antioxidant therapy of acute inflammation, including tetrachloromethane (CCl₄)-induced ALI and phorbol 12-myristate 13-acetate (PMA)-induced ear inflammation (Figure 7B).¹⁰³ Lu et al reported a MnO₂-coated mesoporous PdPt alloy nanozyme with enhanced ROS-scavenging ability for the amelioration of APAP-induced ALI.¹⁰⁴ With the rapid progress of nanotechnology, nanomedicines with self-propulsion capability have garnered increasing attention due to their active drug delivery and deeper penetration ability.¹⁰⁵ However, most currently available ROS-scavenging nanozymes cannot actively eliminate ROS because they passively diffuse rather than self-charged propulsion. The exploration of actively ROS-scavenging nanozymes is highly desirable. In our recent work, we developed a self-propelled silica-supported ultrasmall AuNPs-tannic acid hybrid nanozyme (SAuPTB) to relieve and possibly even prevent APAP-induced ALI. In this work, SiO₂ nanoparticles were used as the carrier for ultrasmall AuNPs loading, and which could produce large amount of O₂ under H₂O₂, endowing the hybrid nanozyme with self-propelling properties. Moreover, tannic acid, a ubiquitous natural polyphenol with SOD and CAT-like activities was chelated on the surface of the synthesized nanoparticles to compensate for the lack of •OH scavenging properties of us-AuNPs and providing an approach to reduce nanomaterial biotoxicity and ensure biocompatibility (Figure 7C).¹⁰⁶ The in vivo studies show that SAuPTB can accumulate at inflammatory sites in mouse liver, resulting in the decrease of alanine aminotransferase, aspartate aminotransferase, and ROS, reduction in pro-inflammatory cytokines and chemokines, hence reduced hepatocyte necrosis, liver injury, and mortality. Furthermore, SAuPTB activates the nuclear erythroid 2-related factor 2 pathway to upregulate antioxidative genes and reduce oxidative stress.

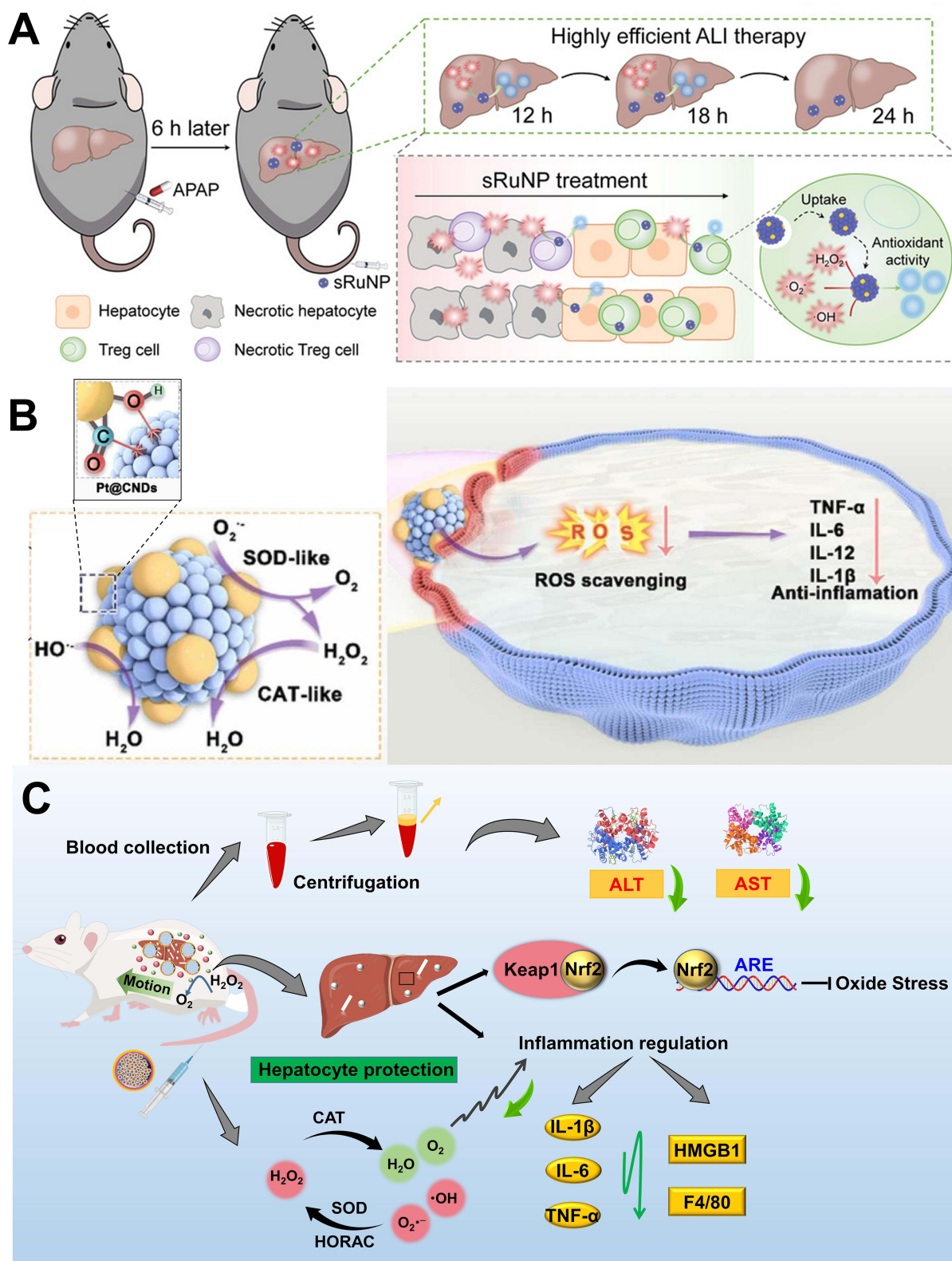


Figure 7 Noble metal nanozymes for ALI alleviation. **(A)** Schematic illustration of tuning the size of RuNPs to boost their antioxidant activity and the application for sRuNP for highly efficient ALI therapy. Reprinted from Xia F, Hu X, Zhang B, et al. Ultrasmall ruthenium nanoparticles with boosted antioxidant activity upregulate regulatory T cells for highly efficient liver injury therapy. *Small*. 2022;18:2201558. © 2022 Wiley-VCH GmbH.¹⁰² **(B)** Schematic illustration of synthesis of Pt@CNDs with cascade superoxide dismutase-catalase activities and applications in eliminating intracellular ROS. Reprinted from *Nano Today*, 49, Zhang Y, Gao W, Ma Y, et al. Integrating Pt nanoparticles with carbon nanodots to achieve robust cascade superoxide dismutase-catalase nanozyme for antioxidant therapy. 101768, Copyright 2023, with permission from Elsevier.¹⁰³ **(C)** Schematic representation of SAuPTB nanozymes relieves APAP-induced ALI by attenuating ROS and regulating inflammation. Reprinted from Zhou C, Zhang L, Xu Z, et al. Self-Propelled Ultrasmall AuNPs-tannic acid hybrid nanozyme with ROS-scavenging and anti-inflammatory activity for drug-induced liver injury alleviation. *Small*. 2023;19:2206408. Copyright © 2023 Wiley-VCH GmbH.¹⁰⁶

Carbon-Based Nanozymes

The aforementioned ROS-scavenging nanozymes were almost developed through the utilization of the variable valence states of metal centers or the metal-mediated specific adsorption/desorption. These metal-contained nanozymes probably suffer from *in vivo* biosafety concerns, such the undesirable metal ions leakage or metabolic residues. Differ from metal-containing nanozymes, carbon-based nanomaterials, such as carbon dots, graphene, graphene quantum dots, fullerenes, carbon nanotubes, and carbon nanospheres et al, have been widely developed to mimic the enzyme-like activity due to their metal-free characteristics, good biocompatibility, and well-defined electronic and geometric structures.^{107,108} Previous studies have demonstrated that carbon-based nanozymes exhibit the OXD-, CAT-, POD-, SOD-, and GPx-like catalytic activities stemming from their unique catalytic centers, eg, C=O groups, etc.¹⁰⁹ Carbon-based nanozymes, being a group of highly advanced nanomaterials, have exhibited significant promise in various biomedical domains such as biosensing, disease detection, and therapeutic interventions. Based on the CAT- or SOD-like catalytic activities, carbon-based nanozymes can be used to eliminate excess ROS for inflammation alleviation. In recent years, carbon-based nanomaterials also have attracted great research interest in the alleviation of ALI as a result of their excellent catalytic ROS-scavenging capacities and liver target ability. For example, Umezaki et al prepared hydrophilic C₆₀(OH)₁₀ nanoparticles with ROS-scavenging properties for the treatment of an APAP-induced liver injury.¹¹⁰ Zhou et al developed biocompatible [60]/[70] fullerenols with superior ROS-scavenging ability for the alleviation of hepatotoxicity induced by doxorubicin chemotherapy (Figure 8B).¹¹¹ Long et al developed hydrophilic carbohydrate-derived nanoparticles with good colloidal stability and blood circulation lifetime, effective liver delivery ability, and excellent ROS scavenging capability to prevent the mice from hepatic ischemia-reperfusion injury (Figure 8E).¹¹² Xu et al developed an esterase-responsive carbon quantum dot-dexamethasone (CD-Dex) nanodrug for liver fibrosis therapy to simultaneously target pathological microstructures, scavenge ROS, and suppress inflammation (Figure 8A).¹¹³ Composition adjusting via element doping or surface integrating is an effective strategy to improve the catalytic performance of carbon-based nanozymes. For instance, Chen et al prepared nitrogen-doped carbon dots for HIRI alleviation (Figure 8D).¹¹⁴ Bai et al fabricated a lecithin-encapsulated selenium-doped carbon dots nanoparticles that exhibit a significant propensity for hepatic accumulation and effective scavenging capacity of ROS and inhibition of the release of inflammatory cytokines, thereby manifesting a favorable therapeutic effect beneficial therapeutic efficacy on HIRI (Figure 8C).¹¹⁵ Zhang et al constructed a Pt@CDs nanocomposite by integrating carbon dots with Pt NPs, which demonstrates promising potential as a highly efficient cascade antioxidant nanozyme, capable of safeguarding biological systems against damages caused by ROS, such as the ALI and acute ear inflammation (Figure 7B).¹⁰³

Other Nanozymes

Apart from the above-mentioned transmit-metal nanozymes, noble metal nanozymes, and carbon-based nanozymes, there are some other nanozymes with similar antioxidant enzymatic activities that have been used for the therapeutic intervention of various ALI, such as phosphorus-based nanoparticles, selenium-based nanoparticles, and some natural antioxidant enzyme-containing nanoparticles. For example, Ge et al developed black phosphorus quantum dots (BPQDs) with second near-infrared window (NIR-II) fluorescence imaging and ROS-scavenging capacity (Figure 9A).¹¹⁶ BPQDs have been found to be effective in providing protection to tissues against damage caused by ROS in cases of acute kidney and liver injury, which could be monitored by the responsive NIR-II FI. Lee et al have developed natural SOD-containing nanoparticles (d-HA/SOD/USCaP), which consist of multiple Cu-Zn SOD molecules embedded in a hydrophilic hyaluronic acid (HA) network decorated with ultrasmall calcium phosphate (USCaP).¹¹⁷ The d-HA/SOD/USCaP nanoparticles can effectively deliver the Cu-Zn SOD to hepatocytes, escape from the endosome after the cellular uptake, and retain its catalytic function both in the bloodstream and within the cytoplasm. The d-HA/SOD/USCaP exhibits superior therapeutic effects on the APAP-induced ALI via eliminating the excess ROS inside the liver (Figure 9B). Besides nanozymes, other nanoparticles with ROS-scavenging capacity also can be used as the therapeutic agents for the alleviation of ALI, such as polydopamine, melanin nanoparticles, etc.^{22,118,119} Although there has developed numerous antioxidants for the alleviation of ALI, the unclear long-term *in vivo* biosafety and degradation mechanism may hinder their translational application. Therefore, it still remains challenging to develop more efficient antioxidant nanozymes with excellent ROS scavenging capacity and negligible toxicity.

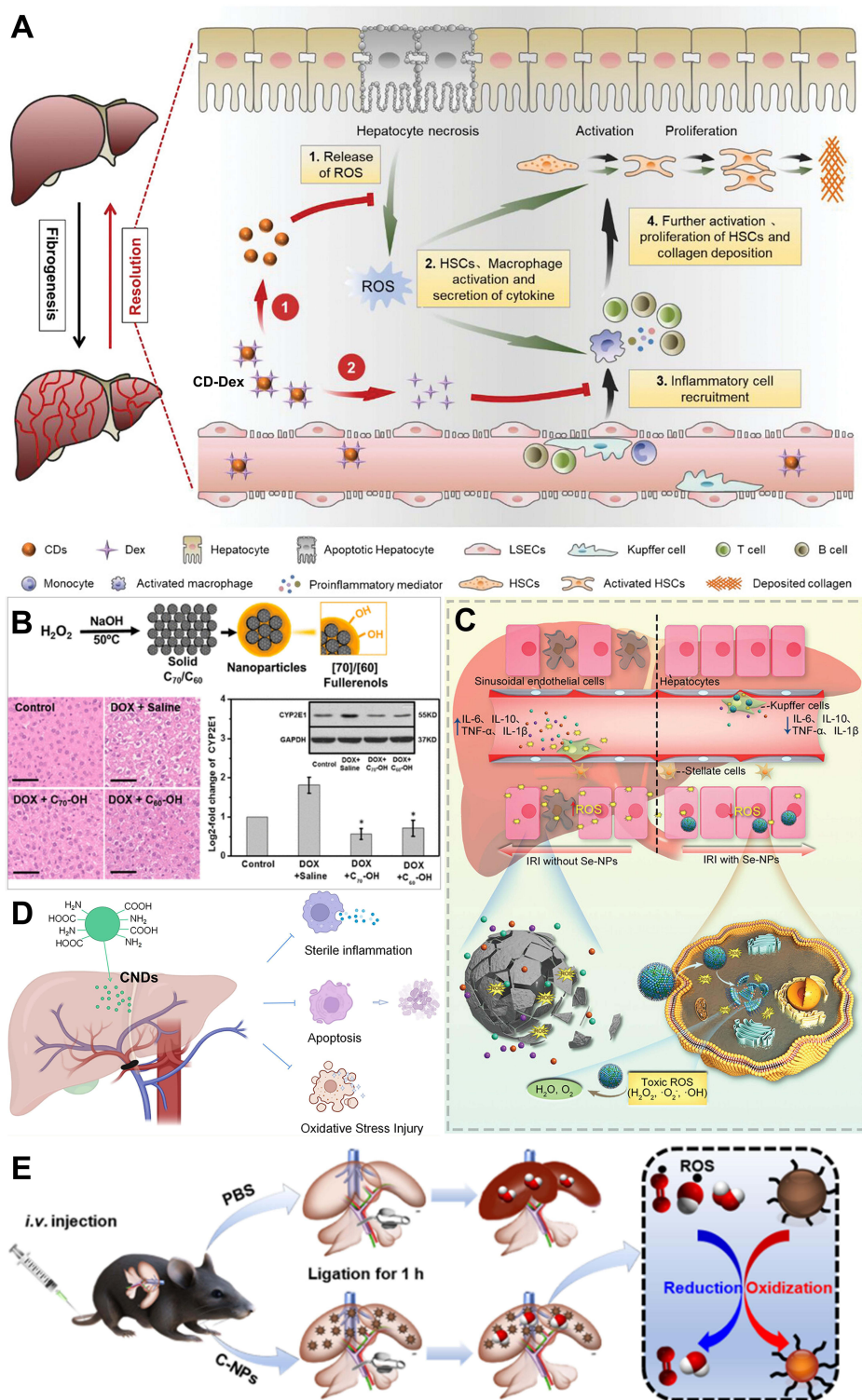


Figure 8 Carbon-based nanozymes for ALI alleviation. **(A)** Schematic illustration of esterase-responsive CD-Dex with ROS elimination and inflammation suppression capabilities for liver fibrosis therapy. Reprinted from Xu YC, Chen J, Jiang W, et al. Multiplexing nanodrug ameliorates liver fibrosis via ROS elimination and inflammation suppression. *Small*. 2022;18:2102848. Copyright © 2021 Wiley-VCH GmbH.¹¹³ **(B)** Schematic illustration of [70]/[60] fullerene nanoparticles against oxidative injury induced by reduplicative chemotherapy. Reprinted from Zhou Y, Li J, Ma HJ, et al. Biocompatible [60] / [70] fullerenols: potent defense against oxidative injury induced by reduplicative chemotherapy. *ACS Appl Mater Interfaces*. 2017;9:35539–35547. Copyright © 2017 American Chemical Society.¹¹¹ **(C)** Schematic illustration of the mechanism of self-assembled selenium-doped carbon quantum dots as antioxidants for HIRI management. Bai B, Qi S, Yang K, et al. Self-assembly of selenium-doped carbon quantum dots as antioxidants for hepatic ischemia-reperfusion injury management. *Small*. 2023;19:2300217. Copyright © 2023 Wiley-VCH GmbH.¹¹⁵ **(D)** Schematic illustration of nitrogen-doped carbon dots (CNDs) for reactive oxygen species scavenging on HIRI. Reprinted from Chen D, Wang CQ, Yu HJ, et al. Nitrogen-doped carbon dots with oxidation stress protective effects for reactive oxygen species scavenging on hepatic ischemia-reperfusion injury. *ACS Appl Nano Mater*. 2023. Copyright © 2023 American Chemical Society.¹¹⁴ **(E)** Schematic of carbohydrate-derived nanoparticles (C-NPs) for Hepatic ischemia-reperfusion injury treatment. Reprinted from Long Y, Wei H, Li J, et al. Prevention of hepatic ischemia-reperfusion injury by carbohydrate-derived nanoantioxidants. *Nano Lett*. 2020;20:6510–6519. Copyright © 2020 American Chemical Society.¹¹²

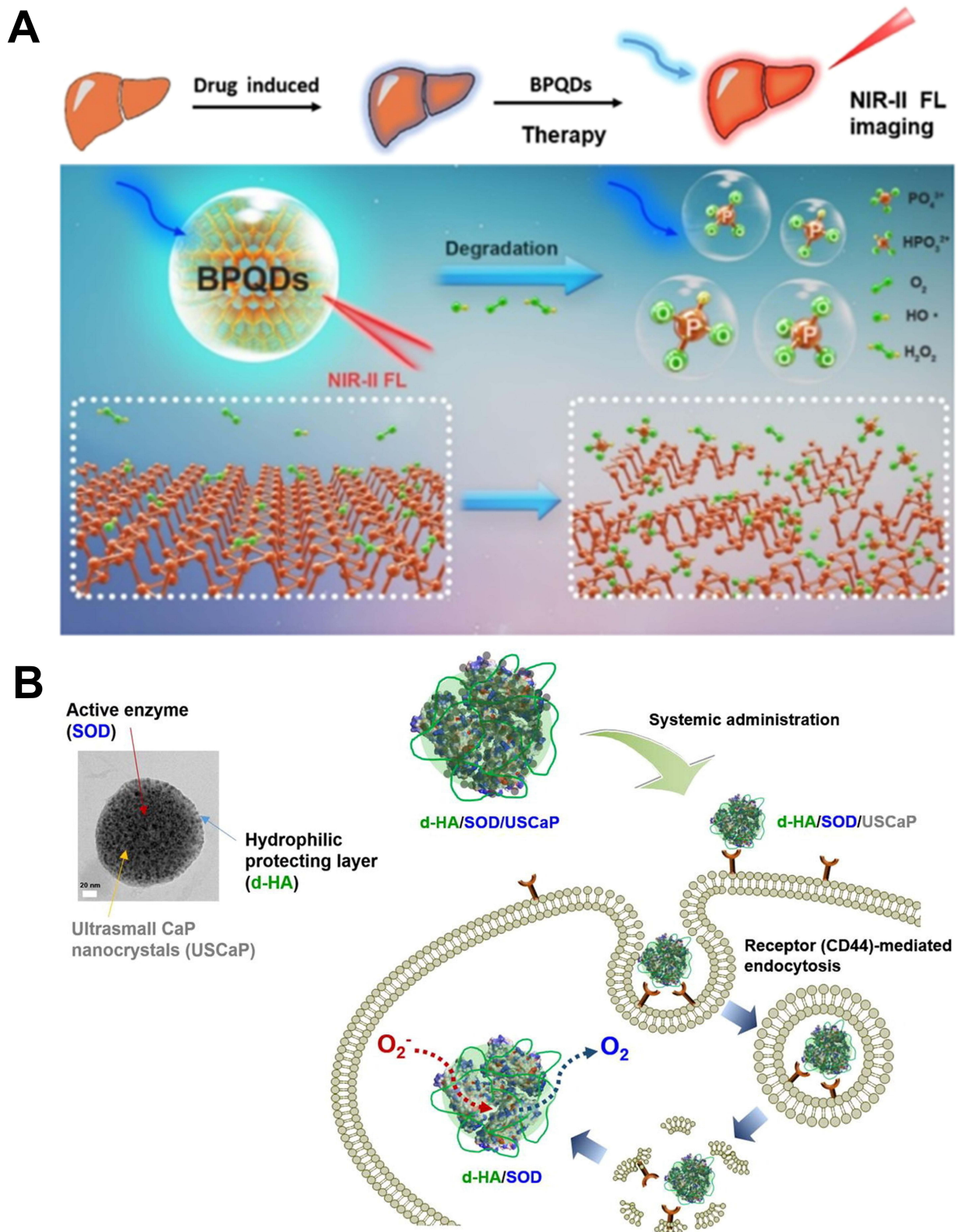


Figure 9 Carbon-based nanozymes for ALI alleviation. **(A)** Schematic illustration of NIR-II fluorescent biodegradable black phosphorus quantum dots (BPQDs) for precise acute liver injury imaging and therapy. Ge X, Su L, Yang L, et al. NIR-II fluorescent biodegradable nanoprobes for precise acute kidney/liver injury imaging and therapy. *Anal Chem.* 2021;93:13893–13903. Copyright © 2021 American Chemical Society.¹¹⁶ **(B)** Schematic illustration of targeted cellular delivery of robust d-HA/SOD/USCaP enzyme nanoparticles for the treatment of drug-induced liver injury. Reprinted from *Acta Biomater.* 81, Lee MS, Kim NW, Lee JE, et al. Targeted cellular delivery of robust enzyme nanoparticles for the treatment of drug-induced hepatotoxicity and liver injury. 231–241, Copyright 2018, with permission from Elsevier.¹¹⁷

Conclusion and Outlook

With the rapid development nanoscience and nanotechnology, its application in biomedicine has opened up a wide range of research interests. As one of the emerging research frontiers, nanozymes exhibit great prospects for disease therapy. Herein, we have summarized recent advancements in ROS-scavenging nanozymes and their applications in acute liver injury alleviation in recent years. We provide a comprehensive review of the available ROS-scavenging nanozymes, including transition metal-based nanozymes, noble metal nanozymes, carbon-based nanozymes, and some other nanozymes. The advancements presented provide compelling evidence to support the application of ROS-scavenging nanozymes in the therapeutic intervention of ROS-related inflammation, especially confirming the feasibility of constructing antioxidant nanozymes for mitigating liver injury. Although nanozymes have significant advantages in the application of biomaterials, there are still some key issues and challenges that need to be considered. (1) The ROS-scavenging efficiency of most nanozymes should be further improved. At present, most ROS-nanozymes employed in liver injury treatment required relatively high doses, which may cause long-term biotoxicity. Developing ROS-scavenging nanozymes with more efficient ROS-scavenging capacity possibly reduces the dosage of therapeutic nanozymes and improves biosafety. Incorporation of natural enzyme structural properties into the rational design of artificial antioxidant nanozymes probably be a highly promising strategy for enhancing catalytic performance. In addition, the introduction of the single metal atoms and rational design of cascade nanozymes may also provide promising approaches to improve the catalytic efficiency. (2) The stability and consistency of performance *in vitro* and *in vivo* should be verified. Nanozymes cannot avoid interactions with biomolecules after entering the blood circulation and cells, the adsorbed biomolecules certainly affect the active sites' exposure and substances affinity, which probably alter their catalytic performance. Investigation of the stability and consistency of ROS-scavenging activities of nanozymes shows an important impact. (3) The long-term *in vivo* metabolic pathway of the ROS-scavenging nanozymes should be further investigated. As an endogenous agent, ROS-scavenging nanozymes probably possess long-term toxicity on undesired tissues due to their nonspecific distribution and cellular uptake. The absence of toxicity studies investigating systemic biodistribution, tolerance threshold, degradation, and clearance rate hinders the determination of long-term effects of potential toxicity on animals. Consequently, there is an urgent need to undertake more extensive assessments encompassing physical and chemical properties, nanoscience, and biosafety toxicity in order to evaluate the potential risks associated with ROS-scavenging nanozymes, so that to promote its clinical transformation. (4) The natural targeting or the targeted modification of nanozymes should be further explored. As we known, there are many special biomarkers in the injury site. Such biomarkers could be used to identify liver injury, or exclude injury, early in the disease process. Moreover, they would allow therapy to be targeted to patients at high risk of adverse outcomes or allow early, safe discharge of well patients. Ai et al recently revealed that negatively charged melanin nanozymes could naturally targeted to inflammation sites in the colon through electrostatic interactions and bind at the lesion site for more than 72 h after oral administration.¹²⁰ The long-lasting characteristics of melanin nanozymes show super therapeutic effect on inflammatory bowel disease. Therefore, the natural targeting or the targeted modification of nanozymes could further improve and enhance the diagnosis and treatment of nanozymes.

Abbreviations

ALI, acute liver injury; ROS, reactive oxygen species; NAC, N-acetyl cysteine; GSH, glutathione; H₂O₂, hydrogen peroxide; •O₂⁻, superoxide radical; •OH, hydroxyl radical; ¹O₂, singlet oxygen; APAP, acetaminophen; NAPQI, N-acetyl-p-benzo-quinone imine; LPO, lipid peroxidation; HIRI, hepatic ischemia-reperfusion injury; DAMPs, damage-associated molecular patterns; OXD, oxidase; POD, peroxidase; CAT, catalase; SOD, superoxide dismutase; HORAC, hydroxyl radical antioxidant capacity; PB, Prussian blue; PBA, Prussian blue analogues; CeNZs, Ce-based nanozymes; DILI, drug-induced liver injury; O_v, oxygen vacancies; LPS, lipopolysaccharide; USNPs, ultrasmall nanoparticles; Plt, platelets; Mn, Manganese; MSCs, mesenchymal stem cells; Zn-based, zinc-based; Ni-based, nickel-based; Mo-based, molybdenum-based; W-based, tungsten-based; WS₂-PVP, polyvinyl pyrrolidone modified tungsten disulfide; CCl₄, tetrachloromethane; PMA, phorbol 12-myristate 13-acetate; SAuPTB, ultrasmall AuNPs-tannic acid hybrid nanozyme; PPM, MnO₂ coated mesoporous PdPt alloy nanozymes; BPQDs, black phosphorus quantum dots; NIR-II, second near-infrared window; HA, hyaluronic acid; USCaP, ultrasmall calcium phosphate.

Consent for Publication

The authors confirm that the details of any images can be published.

Acknowledgments

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Author Contributions

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

Disclosure

The authors report no conflicts of interest in this work.

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