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Leveraging the dual role of ROS in liver diseases with nanomaterials: clearing and amplifying for therapy

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The dual role of reactive oxygen species (ROS) in various liver diseases leads to the potential of nanomaterials in addressing challenges related to liver conditions. Considering the pivotal role of ROS in liver disease progression, the design and application of nanomaterials need to align with distinct disease characteristics and the unique liver microenvironment. By reviewing the interaction between nanomaterials and ROS in liver diseases and their potential applications in liver disease treatment, this work discusses the multifaceted properties of nanomaterials and their high specificity and prospects in liver disease treatments.

Introduction

Liver disorders present substantial challenges to global healthcare because of the liver's vital function in detoxification and metabolism regulation. Being the main organ responsible for metabolizing various compounds, the liver produces reactive oxygen species (ROS) *via* numerous enzymatic processes during cellular metabolism.[1] Physiological processes maintain low-to-moderate levels of ROS.[2] However, excessive ROS production, resulting in oxidative stress, plays a pivotal role in the development and progression of various liver conditions, such as alcoholic liver disease (ALD), non-alcoholic fatty liver disease (NAFLD), drug-induced liver injury (DILI), hepatitis, cirrhosis, Wilson's disease, hemochromatosis, non-alcoholic steatohepatitis (NASH), and primary biliary cholangitis (PBC).[3] Nevertheless, ROS can have dual effects for therapy of liver diseases, acting both as detrimental agents that drive fibrosis and as therapeutic agents that can promote cancer cell death when elevated. The ability to precisely regulate ROS levels is crucial for developing effective treatments for conditions like liver fibrosis, hepatitis, and liver cancer.

Nanomaterials, recognized for their extremely small size and large surface-area-to-volume ratio, have opened up new opportunities in medicine, especially in targeted drug delivery and diagnostics. These materials, typically measuring between one and one hundred nanometers, exhibit distinct physicochemical characteristics that can be tailored for specific medical uses. By functionalizing their surfaces with ligands, nanomaterials can be directed to specific cells or tissues, improving drug therapy efficacy. In diagnostics, nanoparticles enhance the sensitivity and precision of imaging agents, allowing earlier detection of diseases.[4] The liver, as the body's central detoxifying organ, is naturally adept at filtering out substances from the bloodstream. Nanoparticles are primarily taken up by the liver through passive accumulation, driven by the phagocytic activity of liver sinusoidal endothelial cells and Kupffer cells. This passive liver targeting is beneficial for treat-

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ing liver conditions because it ensures that a higher concentration of therapeutic nanoparticles reaches the liver, enhancing local therapeutic effects, while minimizing systemic exposure and associated toxicity. Nanomaterials demonstrate significant potential in regulating ROS, either by scavenging excess ROS in inflammatory liver diseases or by increasing ROS levels to trigger apoptosis in liver cancer cells. This review introduces a comprehensive perspective on the dual role of ROS in liver diseases, followed by an examination of the potential of nanomaterials with catalytic activity for therapeutic applications. This work highlights both the detrimental and therapeutic roles of ROS in liver diseases, and illustrates how nanomaterials can mitigate liver damage through scavenging excess ROS and kill liver cancer cells through amplifying ROS production by utilizing their inherent catalytic properties. To lay the foundation for the development of next-generation ROS catalytic nanomaterials, this review also provides a thorough discussion regarding various nanomaterial strategies for liver therapy, detailing their mechanisms and potential clinical applications. This also fills the gap in the existing literature, by providing a detailed mechanistic discussion on how different types of catalytic nanomaterials interact with ROS in liver microenvironments. In the end, this review also uniquely emphasizes that standardized production, biosafety and regulatory considerations are critical gaps between the current research on nanocatalytic medicine and real application in the clinic (Fig. 1).

ROS in liver diseases: mechanisms and therapeutic roles

ROS generation mechanism

ROS are reactive molecules produced from the partial reduction of oxygen, primarily within mitochondria. They include superoxide anions ($O_2^{\bullet -}$), hydrogen peroxide (H_2O_2), hydroxyl radicals ($^{\bullet}OH$), and singlet oxygen ($^1O_2$) (reaction (1)).[5,6] At physiological levels, ROS serve as critical signaling molecules, regulating processes such as cell proliferation, differentiation, and immune responses. However, excessive ROS production leads to oxidative stress, which damages cellular components like DNA, proteins, and lipids, contributing to diseases such as cancer, neurodegenerative disorders, and cardiovascular diseases.

$$\begin{aligned} O_2 &\xrightarrow{+e^-} O_2^{\bullet -} \xrightarrow{+e^-(+2H^+)} H_2O_2 \\ &\xrightarrow{+e^-} {}^{\bullet}OH + OH^- \xrightarrow{+e^-(+2H^+)} 2H_2O \end{aligned} \quad (1)$$

The primary source of ROS is the mitochondrial electron transport chain (ETC), where electron leakage results in superoxide formation. Superoxide is converted to hydrogen peroxide by superoxide dismutase (SOD), and in the presence of transition metals, hydrogen peroxide can generate highly reactive hydroxyl radicals through Fenton reactions (reactions (2) and (3)).[7] ROS can also be produced by enzymes like NADPH oxidase and xanthine oxidase, or by external factors such as UV radiation and environmental toxins.

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + {}^{\bullet}OH + OH^- \quad (2)$$

$$Fe^{3+} + H_2O_2 \rightarrow Fe^{2+} + OH^- + HO^{\bullet}{}_2 \quad (3)$$

Cells counterbalance ROS through antioxidant defenses, including enzymes like superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), along with non-enzymatic antioxidants like vitamins C and E. Disruption of this balance leads to oxidative stress and cell damage. Understanding the mechanisms of ROS generation and regulation is essential for developing therapeutic strategies aimed at either reducing ROS or enhancing antioxidant defenses to restore cellular homeostasis. In the treatment of liver diseases, ROS can be either amplified for targeting tumour cells or scavenged for decelerating the progression of diseases such as hepatitis and cirrhosis, highlighting the complex role of ROS in liver diseases.

The dual role of ROS in liver disease treatment

In liver disease treatment, ROS play a complex dual role, where excessive levels can cause damage, while controlled increases can serve therapeutic purposes. Hepatocytes, which make up 80% of all liver cells, are sensitive to ROS-induced injury.[8] ROS-mediated peroxidation of mitochondrial lipids in hepatocytes aggravates oxidative stress by impairing the electro transport chain, and contributes to the initiation and progression of chronic liver diseases.[9,10] Oxidative stress also promotes calcium influx and calcium accumulation in mitochondria, triggering apoptosis and necrosis of hepatocytes.[11] The release of pro-apoptotic factors and damage-associated molecular patterns (DAMPs) from injured hepatocytes can contribute to the death of hepatocytes and other liver cells, and activate hepatic stellate cells (HSCs), Kupffer cells (KCs), and other recruited immune cells to produce inflammatory and fibrogenic factors.[12,13] HSCs have progenitor cell-like properties, and quiescent HSCs control vitamin A homeostasis, ECM turnover, immunoregulation and liver development.[14] Under the circumstance of ROS and lipid peroxidation, HSCs are activated and transdifferentiate into proliferative and contractile myofibroblasts, synthesizing and releasing ECM components within the liver and initiating liver fibrosis, which could further turn into cirrhosis and hepatocellular carcinoma (HCC).[15,16] Thus, restoring redox homeostasis through antioxidant therapy is a practical option for these liver diseases. Flavonoid dihydromyricetin is hepatoprotective by improving mitochondrial redox homeostasis in fatty liver mouse.[17] Curcumin can increase the activities of SOD, CAT, and GPx through Nrf2 signaling, and it protects rats from ethanol-induced liver injury.[18,19] S217879, which triggers antioxidant responses by disrupting the interaction between KEAP1 and Nrf2, also inhibits liver fibrosis progression in mice.[20]

ROS activates differently at different stages of HCC, which could be ROS-driven HCC development and oxidative stress-induced cell death. DNA damage and genetic instability caused by ROS can lead to HCC initiation and progression.[21]

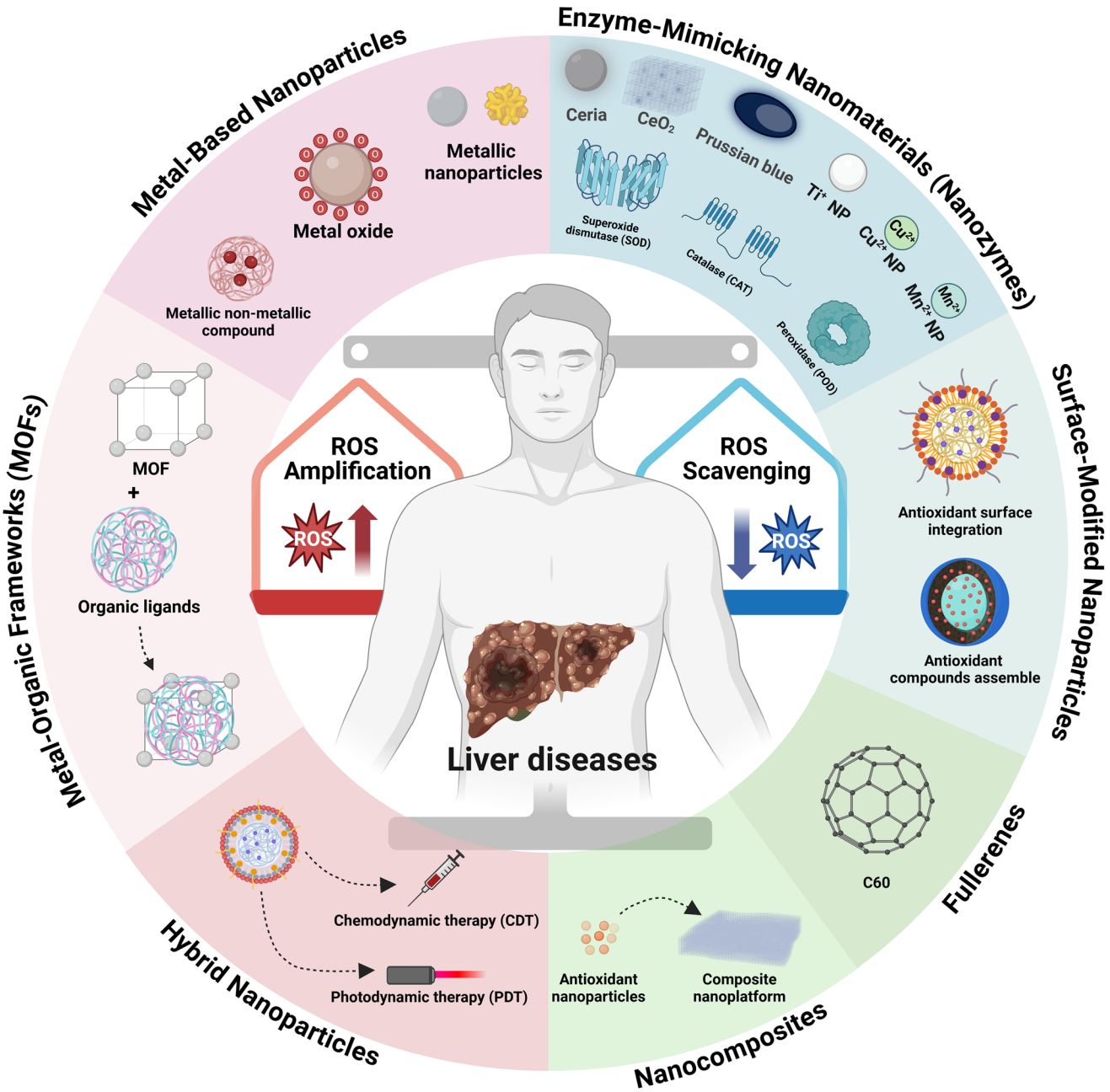

Fig. 1 This review systematically illustrates the dual role of reactive oxygen species (ROS) liver disease treatment. It elaborates how nanomaterials can be utilized to either amplify or scavenge ROS for therapeutic purposes, highlighting the potential of ROS-targeting nanomaterials in enhancing liver disease treatment strategies. This figure offers new perspectives on the development of innovative therapies aimed at modulating ROS levels to optimize therapeutic outcomes.

Mitochondrial DNA is more vulnerable to ROS because it lacks histones, and mitochondrial dysfunction leads to proto-oncogene activation and HCC advancement.[22,23] The hyperactivation of Nrf2 signaling, whose original function is to protect cells from oxidative stress, enhances the survival and chemotherapy resistance of HCC.[24,25] A key option for effective HCC therapy is triggering the apoptosis of HCC cells by further enhancing oxidative stress. Cisplatin induces intracellular ROS production and accelerates senescence of HCC.[26] In Hep3B cells, coptisine promotes autophagy by ROS-induced mitochondrial dysfunction and PI3K/AKT/mTOR signaling inhibition.[27] Koumine inhibits proliferation and promotes apoptosis of HCC cells by promoting ROS generation and suppressing ERK/p38 MAPK pathways.[28] Artesunate also elevates the ROS level in HCC cells, enhancing Bax/Bcl-2 and triggering apoptosis.[29]

Elevated ROS levels induce oxidative stress, which promotes the activation of hepatic stellate cells, which contribute to col-

lagen deposition and tissue scarring hepatocyte damage, leading to inflammation, and fibrosis in liver fibrosis and hepatitis. Conversely, they can be beneficial for liver cancer therapy by inducing apoptosis to damage macromolecules in tumor cells, including proteins, DNA, and lipids, activating anti-inflammatory responses. Therefore, designed targeted drugs could achieve the anti-neoplastic goal selectively by increasing the ROS level to reach or exceed the cytotoxic threshold for oxidative stress-mediated tumor cell death.

Nanomaterial-based strategies for ROS scavenging in oxidative stress

Enzyme-mimicking nanomaterials (nanozymes) for ROS decomposition

Certain types of tiny particles, specifically cerium oxide nanoparticles (also known as nanoceria) and molybdenum-based nanomaterials, possess inherent catalytic properties that enable them to act as antioxidants (Fig. 2). These nanomaterials can mimic the actions of antioxidant enzymes such as SOD and CAT. Ceria nanoparticles serve as representative nanoantioxidants, effectively mitigating hepatic injury by scavenging ROS, inhibiting immune cell activation, and reducing pro-inflammatory cytokines.[30,31] Their antioxidant ability is provided by their physicochemical properties, including relatively larger Ce^{3+} content, owing to the high surface-to-volume ratio, and redox reactions achieved by Ce^{3+}/Ce^{4+} cycles.[32–36] Platinum nanoparticles could markedly suppress the production of H_2O_2, $^{\bullet}OH$, the alpha,alpha-diphenyl-beta-picrylhydrazyl radical and nitric oxide, thus protecting hepatic cells from oxidative damage.[37] These catalytic activities of platinum nanoparticles are attributed to the switch between different oxidation states, d-orbitals that enable electron transfer reactions, the large amount of active surface atoms given by the high surface-to-volume ratio, and their high binding affinity to oxygen-containing species.[38–41]

Also, the polyvalency of transition metallic elements, such as manganese (Mn), ferrum (Fe), and molybdenum (Mo),[42,43] empowers the enzyme-like capabilities of these nanomaterials, suggesting their potential to eliminate ROS. Liu *et al.*[44] utilized the multi-nanozyme activities of Mn_3O_4 nanoparticles to protect liver cells from apoptosis and severe inflammatory reactions in acute liver injury therapy. When a nanomaterial incorporates multiple oxidation states of metals, it can demonstrate various enzymatic activities simultaneously. Prussian Blue could possess CAT, peroxidase (POD) and SOD activities, as Fe(III) mimics CAT and POD by decomposing hydrogen peroxide like CAT. Consequently, anthracycline-induced liver injury was effectively inhibited by Prussian Blue nanozymes.[45] Zhang *et al.* synthesized MoS_2-PEG@bovine serum albumin (BSA) nanosheets, which can scavenge different types of ROS by the participation of the Mo element in the redox reaction.[46] Modification by BSA improved the biocompatibility of the

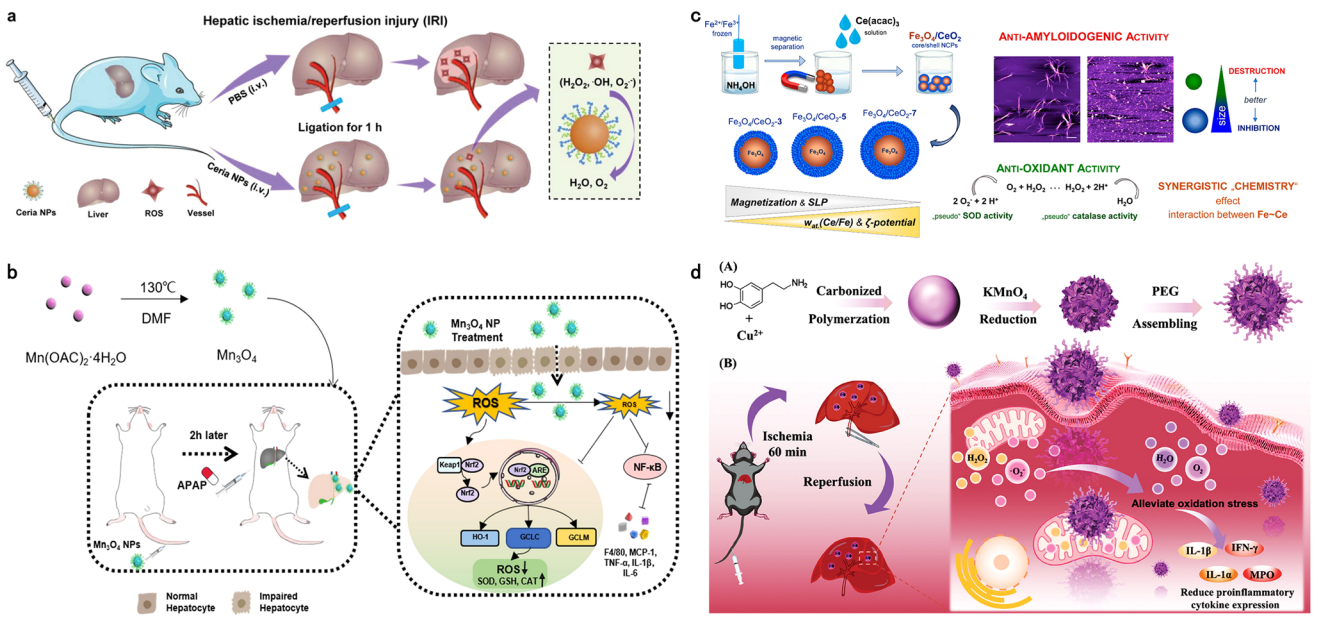

Fig. 2 (a) A schematic treatment of hepatic ischemia/reperfusion injury using ceria nanoparticles and their reactive oxygen species scavenging performance. Reproduced from ref. 31 with permission from Wiley-VCH GmbH, copyright 2019. (b) Schematic illustrations of the synthesis of Mn_3O_4 nanozymes and illustrations of Mn_3O_4 nanozymes preventing acetaminophen-induced acute liver injury by attenuating oxidative stress and counteracting inflammation. Reproduced from ref. 44 with permission from Elsevier, copyright 2024. (c) Schematic illustrations depicting Fe_3O_4/CeO_2 'core/shell' nanocomposites, which harness magnetic heating and robust antioxidant properties to enhance antioxidant and anti-amyloidogenic therapies for liver diseases. Reproduced from ref. 50 with permission from American Chemical Society, copyright 2023. (d) Schematic diagram of hepatic ischemia/reperfusion injury treatment with Cu_{us}-pC@MnO_2@PEG NPs. Reproduced from ref. 51 with permission from Wiley-VCH GmbH, copyright 2024.

nanosheet, and the CAT, SOD and GPx mimicking capabilities of the nanosheet ameliorated liver apoptosis and necrosis in acute liver injury mice. CAT- and SOD-like ultrasmall gold nanoparticles (AuNPs) can effectively alleviate acetaminophen-induced liver injury by scavenging excessive ROS and regulating inflammation.[47] Furthermore, CeO_2 NPs act as scavengers for ROS and NOS, displaying multi-enzyme mimetic capabilities, such as SOD, CAT, and POD, which are beneficial for NAFLD.[48] Notably, unlike conventional antioxidants, CeO_2 NPs exhibit activity exclusively when exposed to pathological levels of ROS, remaining inert and harmless in healthy cells.[49]

Moreover, the combination of metallic elements and metal oxides may generate a synergistic effect, potentially increasing the number and accessibility of active sites. This facilitates the adsorption and catalysis of free radicals or oxidizing agents, thereby enhancing antioxidant activity. MnO_x–CeO_2 nanoparticles containing 0.40% doped manganese displayed the highest capacity for scavenging ROS, likely attributable to the amplified specific surface area and elevated concentration of surface oxygen, which effectively prevent hepatic ischemia reperfusion injury. Expanding on these findings, "core/shell" nanocomposites, such as integrating magnetic Fe_3O_4 with redox-active CeO_2 nanoparticles and ultra-small copper nanoparticles (Cu_{us}-pC) with MnO_2, exhibiting enhanced ROS clearance by leveraging a synergistic catalytic mechanism,[50,51] hold promise for potential application in liver injury therapy.

Besides metal-based nanomaterials, graphene-family nanomaterials also have distinctive electronic properties and high catalytic activities.[52] Among them, graphene oxide quantum dots (GOQDs) are more biocompatible compared with graphene oxide and pristine graphene because of their faster degradation and excretion, and the smaller size could also endow GOQDs with a stronger catalytic activity as nanozymes because of the large edge effects, high charge density, and quantum confinement.[53,54] In buffalo rat liver cells treated with ethanol, GOQDs not only acted as antioxidant nanozymes, but also promoted the transformation of toxic intermediates like aldehydes and enhanced lipid metabolism against alcohol intoxication.[55]

Surface-modified nanoparticles for ROS neutralization

Surface treatment of nanoparticles involves integrating them with compounds that possess antioxidant properties. This enhancement can be achieved by enveloping the nanoparticles with naturally occurring antioxidants, such as polyphenols, flavonoids, herbal medicines or vitamin E, through a process of binding or coating. For example, resveratrol, a polyphenol found in plants, offers protective effects of sirtuin 1 (Sirt1), thereby reducing ROS generation.[56,57] Teng *et al.* utilizes lysozyme micelles coated with galactose-conjugated oxidized starch to develop a liver-targeted system for delivering resveratrol in the treatment of NAFLD.[58] Reduction of $AgNO_3$ using leaf extract from *Brassica oleracea* generates Ag NPs with good ROS scavenging capability.[59]

Besides the integration of antioxidant compounds into nanoparticles, antioxidant compounds themselves may assemble into nanoparticles and still keep the capability of ROS neutralization. Inspired by the finding that antioxidant compounds rich in phenolic groups are effective in preventing the onset of non-alcoholic fatty liver disease, polydopamine that is rich in phenolic groups is assembled into nanoparticles.[60] These nanoparticles maintain high antioxidant power, counteract the hallmarks of hepatic steatosis and reduce the oxidative stress level.

Fullerenes for direct ROS scavenging

Fullerenes, characterized by their exceptional ability to directly neutralize free radicals, leverage their conjugated carbon structure and high electron affinity to stabilize and absorb free radicals through electron transfer. Their spherical shape provides multiple reactive sites, allowing fullerenes to effectively quench ROS and other free radicals.[61] This unique combination of reactivity and stability makes fullerene a powerful and reusable antioxidant. In rat liver primary hepatocytes exposed to ethanol, water-soluble fullerenes reduced alcoholic liver damage through excellent ROS scavenging capability and suppressing tumor necrosis factor expression.[62] C_{60} nanoparticles covered by hydrophilic 2-hydroxypropyl-β-cyclodextrin (HP-β-CD) scavenged not only free radicals but also ROS, alleviating liver injury induced by an overdose of acetaminophen. Additionally, metal atoms can be encapsulated within carbon cages or attached to surfaces through metal-containing functional groups, forming metallofullerenes (MF). The incorporation of metal atoms significantly enhances the reactivity of MF. These molecules retain the antioxidant properties of fullerenes while also exhibiting additional catalytic or magnetic characteristics, depending on the type of metal enclosed. Ferroferric oxide endohedral fullerenes ($Fe_3O_4@C_{60}(OH)_n$) in combination with static magnetic and electric fields has been shown to further enhance ROS clearance and demonstrate promising results in the alleviation of ALD.[63]

Nanocomposites for antioxidant ability improvement

Nanoparticles have the potential to be integrated into composite materials, serving as antioxidants. An example of this is embedding nanoparticles in polymers or various other matrices, which enhances the material's total antioxidant ability.

A multimodal tetrahedral DNA nanoplatform (TDN) has been identified as a promising system for liver therapies. A TDN, constructed by incorporating tumor necrosis factor-α siRNA (siTNF-α) *via* DNA hybridization and antioxidant manganese porphyrin (MnP4) through a π–π stacking interaction with G-quadruplex (G4), demonstrated effective therapeutic outcomes for acute liver failure.[64] Also, MXene, an emerging ultrathin two-dimensional material with intriguing physicochemical properties, continues to be extensively investigated. MXene–$Ti_3C_2T_x$ nanosheets showed an ability to scavenge free radicals on the liver cells *in vitro*.[65]

Moreover, nanoparticles can exhibit dual characteristics, as both antioxidants and camouflage, as the liver's own components, ensuring efficient liver distribution while combating oxidative stress.

Since albumin is produced by the liver, linking nanoparticles to albumin may enhance recognition by Kupffer cells. The cross-linking of nanoparticles with albumin facilitates rapid liver accumulation and uptake by Kupffer cells, enhancing the accumulation of exogenous nanomedicine. Edaravone, a potent antioxidant effective against ROS, has been encapsulated in disulfide cross-linked albumin nanoparticles (EeNA) for hepatitis therapy, as developed by Yasuda *et al.*[66]

Nanomaterial-driven ROS amplification for anticancer therapies

Metal-based nanoparticles for ROS-induced apoptosis in cancer cells

Metal nanoparticles, such as gold and silver nanoparticles, generate ROS through Fenton and Fenton-like reactions, leading to oxidative stress and apoptosis in liver cancer cells. These nanoparticles can deactivate intracellular enzymes and disrupt mitochondrial respiration, resulting in excessive ROS production (Fig. 3). Additionally, nanoparticles could modulate genes related to oxidative stress, such as soxS and met9, thereby accelerating intracellular ROS generation.[67] For instance, 30 nm silver nanoparticles exhibit potent anticancer effects on human hepatocellular carcinoma G2 (HepG2) cells by inducing ROS species, altering cysteoaspartic enzyme activity, and upregulating pro-apoptotic factors like Bax, ultimately driving apoptosis in HepG2 cells.[68]

In addition to utilizing the intrinsic properties of metals to generate ROS, metal oxide nanomaterials—primarily composed of silica, titanium dioxide, zinc oxide, and iron oxide—also play a significant role in triggering ROS generation. Nano-TiO_2, for example, exacerbates ROS generation under photocatalytic conditions, while UVA or nano-TiO_2 alone has minimal impact on cellular metabolism. This highlights the potential of titanium dioxide particles for precise liver cancer treatment. Upon UVA exposure, TiO_2 nanoparticles increase intracellular ROS, activate the TGF-β/Smad pathway, arrest the cell cycle in the G1 phase, inhibit cell growth, and induce apoptosis in liver cancer cells. In contrast, these nanoparticles have a minimal effect on cell growth, apoptosis, and cell cycle distribution in normal liver cells.[69] Leveraging the differential behavior of zinc oxide (ZnO_2) between liver cancer cells and normal hepatocytes, nanomaterials can be designed to selectively kill tumor cells. For example, catalase, primarily found in the liver, functions by decomposing H_2O_2 to water. When ZnO_2 is exposed to a microenvironment enriched with iron and copper ions in the liver, it triggers Fenton and Fenton-like reactions, releasing H_2O_2. Normal hepatocytes, rich in catalase, can decompose excess H_2O_2, while hepatocellular carcinoma cells, deficient in catalase, fail to neutralize H_2O_2, leading to apoptotic cascades.[70] Fe_3O_4 nanoparticles, which possess peroxidase-like catalytic activity, not only convert endogenous H_2O_2 into highly cytotoxic $^{\bullet}OH$, but also raise intracellular calcium levels and increase cleaved caspase-3 expression, inducing apoptosis in hepatocellular carcinoma cells.[71,72]

Moreover, combining metallic nanoparticles with non-metallic components enhances their stability and biocompatibility, improving their ability to regulate ROS accumulation and increase therapeutic efficacy. In the acidic tumor microenvironment (TME), ZnS@BSA nanoclusters could release zinc ions, amplifying the cyclic guanosine monophosphate–adenosine monophosphate synthase/interferon gene stimulator (cGAS/STING) pathway and fostering intracellular ROS generation by selectively inhibiting catalase *via* H_2S gas in hepatocellular carcinoma cells.[73]

Metal–organic frameworks (MOFs) for ROS amplification in the tumor microenvironment

Metal–organic frameworks (MOFs) are highly porous materials composed of metal ions coordinated to organic ligands. Their tunable structures and high surface areas make them versatile for biomedical applications, particularly in enhancing anticancer therapies by generating ROS within the TME. Fe-MOF NPs (MIL-101(Fe) NPs) serve as ROS generators by catalyzing substances within the TME, enabling microwave-enhanced dynamic therapy (MEDT).[76] MIL-101(Fe) nanozymes catalyze H_2O_2 in tumors to produce $^{\bullet}OH$. Under MW irradiation, this process noninvasively generates abundant $^{\bullet}OH$, facilitating MEDT. MIL-101@BSA-AuNCs NPs, formed *via* rapid assembly, allow for MRI and FI, monitoring MIL-101(Fe) dynamics and tumor diagnosis. With a porous structure, IL@MIL-101(Fe)@BSA-AuNCs NPs, serving as thermal sensitizers, achieve synergetic MTT and MEDT, while showing potential for clinical use combining therapy and imaging.

Similarly, the activation of NPs in the TME exerts synergistic therapeutic effects with chemotherapy. A study proposed a MIL-100-based NP system, coated with polydopamine (PDA) and NH(2)-PEGTK-COOH, then loaded with oxaliplatin.[77] Oxa@MIL-PDA-PEGTK is activated in the TME, generating ROS *via* the Fenton reaction, while the loaded oxaliplatin is released to perform its chemotherapeutic function. This strategy enhances drug delivery efficiency and allows for more precise target activation of chemotherapeutic agents.

Hybrid nanoparticles for photodynamic and chemodynamic therapies

Metal nanoparticles exhibit the ability to convert light energy into heat under near-infrared (NIR) light, enabling the targeted destruction of tumor cells. For instance, under NIR illumination and microelectric fields, Au-based nanoparticles exhibit cytotoxicity by inducing ROS production.[74,75] Compared to a single metal nanoparticle, hybrid nanoparticles are multifunctional platforms that combine various therapeutic strategies to enhance the efficacy of cancer treatments. Specifically, photodynamic therapy (PDT) and chemodynamic therapy (CDT) have emerged as promising approaches due to their ability to selectively generate ROS in the TME. Hybrid nanoparticles can integrate both PDT and CDT into a single platform, utilizing their complementary mechanisms to amplify ROS production and induce oxidative damage in cancer cells.

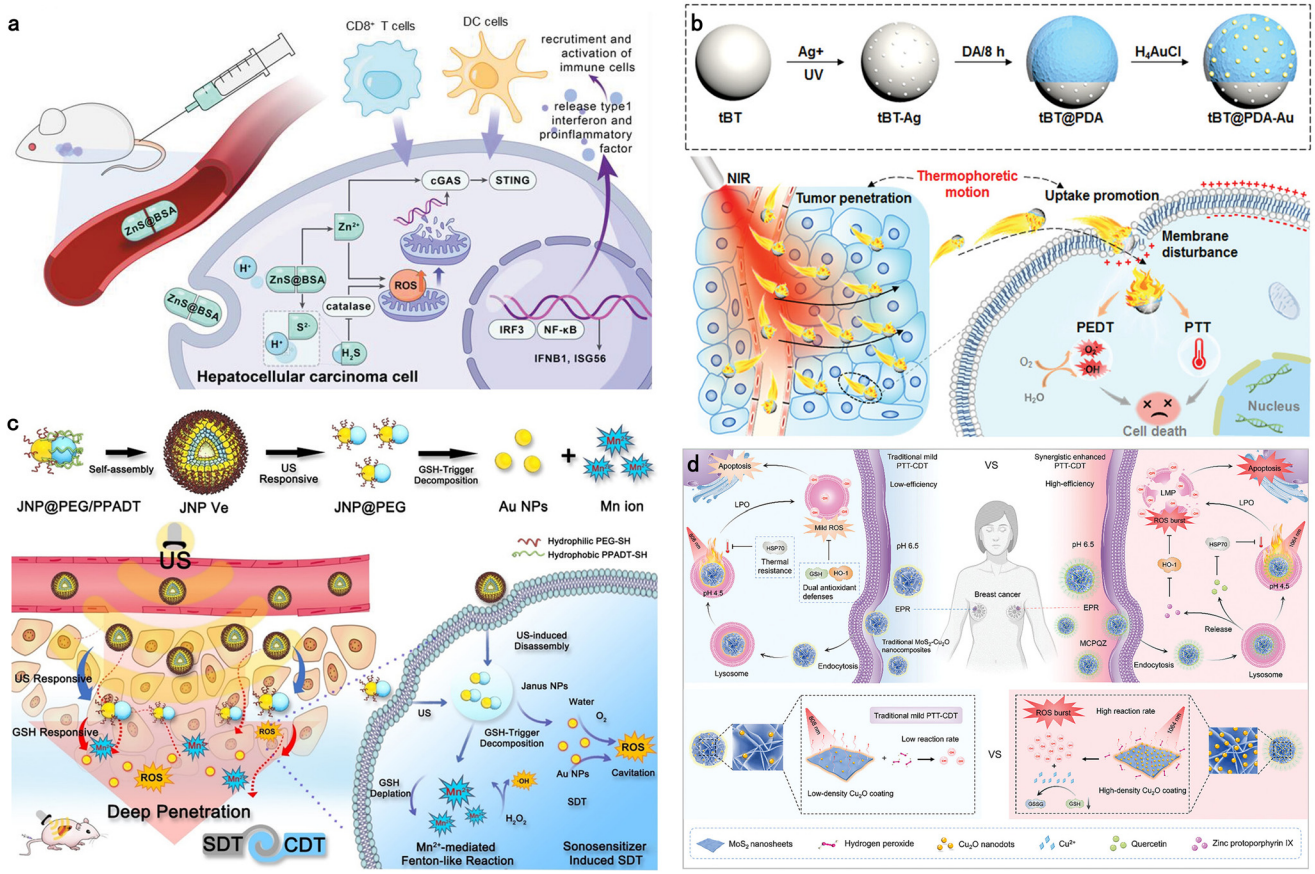

Fig. 3 (a) Schematic of the characteristics of ZnS@bovine serum albumin nanoclusters and the therapeutic process of ZnS@bovine serum albumin nanoclusters. Reproduced from ref. 73 with permission from Wiley-VCH GmbH, copyright 2019. (b) Near infrared illumination of nanoparticles generates a thermophoresis-driven motion and a built-in pyroelectric field to enhance tumor accumulation and diffusion and tumor cell internalization of nanoparticles, followed by integral photothermal therapy/pyroelectric dynamic therapy of tumors. Reproduced from ref. 75 with permission from Wiley-VCH GmbH, copyright 2019. (c) Illustration of the self-assembly of amphiphilic Janus Au–MnO nanoparticles into functional vesicles and (b) their sequential ultrasound and glutathione-induced disassembly into small Janus Au–MnO nanoparticles with deep tumor penetration for synergistic sonodynamic therapy/chemodynamic therapy. Reproduced from ref. 79 with permission from Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, copyright 2020. (d) Schematic illustration for the anticancer-mechanisms of multifunctional nanoplatform-mediated synergistic photothermal-chemodynamic cancer therapy. Reproduced from ref. 81 with permission from Wiley-VCH GmbH, copyright 2023.

Au-decorated, poly(ethylene glycol)-coated zinc oxide nanorods (Au@P-ZnO NRs) have demonstrated an innovative piezocatalytic process, efficiently producing ROS upon ultrasound (US) exposure for precise cancer therapy.[78] When exposed to US, thermally activated electrons and holes in ZnO NRs accumulate at the surface through piezoelectric polarization, initiating ROS production for targeted cancer treatment. This effect is further amplified by Au nanoparticles acting as Fenton-like catalysts on the surface of P-ZnO NRs.

Likewise, under US exposure, the vesicles disintegrated into smaller Janus Au-MnO NPs with improved penetration capabilities; following this, GSH-triggered degradation of MnO released smaller Au NPs, which served as numerous cavitation sites, and liberated Mn^{2+} ions for CDT, leading to heightened ROS production.[79]

As for PDT, a versatile bioinspired protein corona strategy through assembling BSA protected Raman tag DTTC-conjugated Ag-hybrid hollow Au nanoshells (hollow AgAu-DTTC-BSA), in which their silver ion release and ROS generation were significantly suppressed, enabling no damage to normal cells and tissues, but could be reactivated on demand under laser-irradiation at the tumor site.[80] These nanoshells could also produce strong localized surface plasmon resonance for an efficient stable photothermal effect and enhanced SERS activity under laser irradiation. Another study developed a multifunctional nanoplatform with high-density cuprous (Cu_2O) supported molybdenum disulfide (MoS_2) nanoflowers (MC NFs). Such platforms could generate a potent ROS storm at the tumour site irradiated by NIR-II light for a short period of time, thus killing the tumor effectively.[81]

Conclusions

The intricate landscape of liver diseases is closely linked to the liver's essential roles in metabolic balance and detoxification.

Leveraging the liver's natural tendency to accumulate nanoparticles offers significant potential for targeted therapeutic benefits, while minimizing systemic toxicity. Although excessive ROS contribute to various liver-related pathologies, their dual role as both harmful agents and potential antitumorigenic factors presents promising therapeutic opportunities. Nanomaterials, with their precise targeting capabilities and unique physicochemical properties, represent a novel frontier in biomedical applications, particularly for liver-related treatments. This exploration of nanoparticle interactions with ROS provides valuable insights into advancing liver research and therapeutic interventions.

However, the clinical application of nanomaterials faces severe challenges as the biosafety and toxicity of nanomaterials are far from well understood. Thus, materials scientists are devoted to the scalable manufacture of nanomaterials with consistent quality and functionality. Tremendous amounts of biosafety data collected by following good laboratory practice guidance are needed for a comprehensive evaluation of nanomaterials. At the same time, the regulatory agencies should get involved and communicate with nanomaterial researchers to formulate relevant regulations. These regulations will serve as guidance when materials scientists are establishing standardized production and quality control systems for nanomaterials, and tell them what kind of research data regarding the effectiveness and biosafety of nanomaterials are persuasive to regulatory agencies.

Concern regarding the biosafety of nanomaterials also arises from the complex interactions between the nanomaterials and biological systems. With a specific emphasis on leveraging nanocatalytic therapies in treating oxidative stress-related hepatic diseases, this complexity is partially brought about by the wonders of the human body. ROS mediate proliferation, metabolism and other cellular events through not only their concentration, but also their subtype, compartmentalization and time of exposure. Currently, we have gained a certain ability to fine-tune the general catalytic capability of nanomaterials in intracellular redox metabolism. However, the specificity of these nanomaterials is far from that desired. In this situation, even though some therapeutic benefits can be achieved, the unwanted clearance of a certain ROS subtype in a specific intracellular compartment at a specific time point can trigger adverse effects during the application of nanocatalytic therapies. The overall lack of specificity in ROS scavenging caused by nanomaterials also makes giving a convincing explanation of the "mechanism of action" to regulatory agencies very difficult. Thus, improving the catalytic specificity of nanomaterials should be an important research direction. Nowadays, catalytic sites are exposed on most of these nanomaterials, lacking precise environment control for substrate binding, interaction and catalysis. Incorporation of appropriate ligands and morphology may help with specific substrate recognition. During the development of nanomaterials with catalytic capability, density functional theory helps to explain their catalytic reactions. Considering the success of machine learning and deep learning on interpreting the relationship between the structure and function of proteins, adopting these technologies may help to create novel catalytic nanomaterials with potent efficacy and high specificity.

Author contributions

Conceptualization, Z.L., S.W. and Z.T.; literature review, Z.L., Z. Y. and H.Y.; visualization, Z.L.; funding acquisition, Z.Y. and S. W.; writing – original draft, Z.L.; writing – review and editing, H.Y. and Z.T.; supervision, Z.T. All authors have read and agreed to the published version of the manuscript.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

Conflicts of interest

There are no conflicts to declare.

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