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From liver fibrosis to hepatocarcinogenesis: Role of excessive liver H_2O_2 and targeting nanotherapeutics



Among various factors that cause liver fibrogenesis and HCC, reactive oxygen species (ROS) have attached much attentions in last decades, including superoxide anion $(O_2^{\bullet-})$, hydroxyl radical (OH•),

hydroxyl ion (OH⁻), hydrogen peroxide (H₂O₂), singlet oxygen (¹O₂),

and ozone (O₃) [11-13]. Enhanced levels or accelerated generation of

ROS has been demonstrated in the plasma of patients with liver disease

as well as animal models [14]. The elevated levels of ROS served as an

intracellular signaling mediator which significantly promotes HSC

activation and ECM synthesis during liver injuries (Fig. 1) [15]. Besides,

ROS activated oncogenic pathways like protein kinase B (Akt), extra-

cellular signal-regulated kinase (ERK), (hypoxia-inducible factor) HIF,

c-Jun N-terminal kinase (JNK), microtubule-associated protein kinase

(MAPK) and promoted cellular DNA mutations, which were significant

which limits ROS damage at a single cell scale [17]. The half -life period

and effective distance of different ROS in cells are: O_2^{\bullet} (1–4 µs, 30 nm);

¹O₂ (3 μs, 100 nm); HO• (1 μs, 1 nm); H₂O₂ (1 ms, 1 μm) [18]. H₂O₂ is a

kind of stable ROS and can freely diffuse into the interstitial areas sur-

rounding cell. As a result, diffused H2O2 causes damage to intracellular

Most kinds of ROS are extremely unstable with their high reactivity,

pathways that lead to hepatocarcinogenesis [16].

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ARTICLE INFO	A B S T R A C T
Keywords: Liver fibrosis Hepatocarcinogenesis Nanotherapeutics H ₂ O ₂ accumulation Oxidative stress	Liver fibrosis and hepatocellular carcinoma (HCC) have been worldwide threats nowadays. Liver fibrosis is reversible in early stages but will develop precancerosis of HCC in cirrhotic stage. In pathological liver, excessive H_2O_2 is generated and accumulated, which impacts the functionality of hepatocytes, Kupffer cells (KCS) and hepatic stellate cells (HSCs), leading to genesis of fibrosis and HCC. H_2O_2 accumulation is associated with overproduction of superoxide anion (O_2^{\bullet}) and abolished antioxidant enzyme systems. Plenty of therapeutics focused on H_2O_2 have shown satisfactory effects against liver fibrosis or HCC in different ways. This review summarized the reasons of liver H_2O_2 accumulation, and the role of H_2O_2 in genesis of liver fibrosis and HCC. Additionally, nanotherapeutics targeting H_2O_2 were summarized for further consideration of antifibrotic or

1. Introduction

Liver fibrosis has a high incidence and is usually happened with high fat diet, alcohol abuse, hepatitis B virus (HBV) or hepatitis C virus (HCV) infection [1]. Most hepatocellular carcinomas (HCC) are developed in the context of chronic inflammation induced liver fibrosis and cirrhosis [2]. Generally, liver fibrosis is gradual and reversible, but it will develop into irreversible cirrhosis [3], HCC and liver failure [4] without effective treatments. Liver fibrosis is associated with improved hepatic precancerous risk, and is regarded as a key factor to drive HCC immune escape [5]. Liver fibrosis presents hepatocytes injury, hepatic stellate cells (HSCs) activation, macrophage polarization and extracellular matrix (ECM) accumulation [6,7]. Chronic damage and inflammation in liver stimulate the precancerosis of HCC by disrupting cellular copying machinery or altering paracrine signaling [8]. ECM molecules, including collagen, fibronectin and laminin, can interact with HCC and stimulate tumor migration [9,10]. Besides, liver fibrosis is reported to elevate level of immune checkpoint molecules and promote hepatocarcinogenesis through reprogramming HCC cells and regulating immunosuppression [5] (see Tables 1 and 2).

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Table 1

Different nanotherapeutic systems for liver diseases treatment.

Treatments	Nanoparticles	Applications	Ref.
Nanozymes	Prussian blue	Incorporated with MSCs as a ROS scavenger to help MSCs survive in high oxidative stress environment.	[141]
	CeO ₂	Hepatoprotective activity by reducing ROS level and attenuating inflammatory response.	[143]
	MnO ₂	Mn ⁴⁺ receives electrons transferred from bacteria and catalyze H ₂ O ₂ decomposition to prevent the accumulation of lactic acid.	[154]
	Mn_3O_4	Eliminating nearly 75% $O_2^{\bullet-}$ and H_2O_2 .	[156]
	MoS_2	Attenuating electron transfer in cytochrome c/H_2O_2 to ameliorate antioxidant defense system	[175]
H ₂ O ₂ scavengers	DATS	Generating H ₂ S to increase intracellular GSH and suppress oxidative stress in mitochondria	[188]
	NAC	Precursor of GSH to prevent Fe ₃ O ₄ NPs-induced cell injury.	[<mark>192</mark>]
	GSH	GSH with thiol-reduced form can efficiently react with ROS to form GSSH.	[198]
H ₂ O ₂ -sensitive nanosystems	PBEM-co-DPA	ROS and pH dual-sensitive block polymer for polydatin responsively release.	[15]
	Diselenide bonds	ROS-responsive degradation to release TNF- α siRNA.	[<mark>193</mark>]
	POC	H_2O_2 oxidate peroxalate esters in POC	[194]
	RABA	Conjugating atRA and boronic acid for H_2O_2 and other ROS species scavenging.	[195]

Table 2 Nanotherapeutics for HCC treatment.

Classifications	Nanosystems	Applications	Ref.
Nanozymes	Porous PB loaded with sorafenib	PB catalyzed H ₂ O ₂ into O ₂ to release tumor hypoxia and exhibited good	[138]
	Hollow PB nanocage loaded with MCT4 siRNAs and LAP	photothermal effect. LAP induced H_2O_2 production and combined with PB to inhibit tumor	[142]
	CeO ₂ NPs	through Fenton reaction. CeO ₂ NPs selectively targeted hepatic tumor and induced excess ROS	[147]
	PEGylated Mn ₂ O ₃ NPs	degradation, Achieved effective imaging of liver metastatic by T1- contrast enhancement in tumor and T2-shortening in background	[159]
	Verteporfin loaded MnO ₂ nanocomposites	Mn^{2+} assisted reduction of energy gap between Verteporfin and triplet O ₂ , and generated O ₂ for PDT	[160]
	Fe-HMON-Tf loaded with DOX	DOX self-generated H_2O_2 and enhanced Fe^{2+}/Fe^{3+}	[164]
	Fe-TCPP MOFs with hypoxic prodrug TPZ	TCPP PDT exhausted O_2 generated by Fe ³⁺ and triggered activation of TPZ	[173]
H ₂ O ₂ scavengers	Rutin-loaded PLGA NPs	Rutin increased levels of antioxidant enzymes and downregulated proinflammatory cytokines in DEN-induced HCC.	[183]
	fluorinated chitosan assembled with TCPP- conjugated CAT	CAT catalyzed O ₂ generation helped to improve SDT therapeutic efficacy of TCPP	[186]
	Sorafenib-CAT-PLGA microspheres	CAT can improve tumor hypoxic micro-environment and enhance the function of	[187]
H ₂ O ₂ -sensitive nanosystems	ROS-responsive Gal- SLP for sorafenib and shUSP22	Sorafenib worked as an ROS inducer and triggered shUSP22 release to inhibit	[196]
	Solid lipid microparticle for GSH oral administration	HCC glycolysis. GSH-loaded NPs showed ROS scavenging activity in the presence of H-O.	[198]
	PEG-b-PBEMA integrated PA micelle	PA upregulate H_2O_2 and amplified oxidation damage against tumor cells.	[197]

macromolecules due to its lacking ionic charge. H_2O_2 is the most abundant ROS species due to its high chemical stability [19]. In the liver, O_2^{-} and H_2O_2 are continuously generated in various physiological processes [20,21]. It is notable that during respiring process, many spontaneous and enzymatically catalyzed reactions can overproduce O_2^{-} as an intermediate, including mitochondrial respiration, cytosol/plasma membranes-associated NADPH oxidases (NOX), xanthine oxidase, and cytochrome [22,23]. The intermediate O_2^{-} is unstable and is rapidly converted into H_2O_2 by superoxide dismutase (SOD), resulting in permeation of H_2O_2 in the liver (Fig. 2). Therefore, excessive H_2O_2 should be responsible for the oxidative stress in liver tissues.

Nanotherapeutics have many advantages, such as more precise diagnosis, improved targeting efficiency, fewer side effects, and enhanced therapeutic monitoring [24]. Liver characteristics can be utilized to develop nanotherapeutics due to specific enrichment of nanoparticles (NPs) [25]. And nanotherapeutics targeting H_2O_2 have been proved to be effective in both anti-fibrosis therapy and HCC treatment [26,27]. It's necessary to discuss the pathogenicity mechanism of H_2O_2 in liver fibrosis/HCC, and develop appropriate treatments for medical staff. In this review, we summarized recent findings relevant to the association among H_2O_2 accumulation, liver fibrosis and consequent hepatocarcinogenesis. Meanwhile, we depicted typical nanotherapeutics that attenuated liver fibrosis and HCC through downregulating oxidative stress or H_2O_2 conversion. Targeting oxidative stress with these compounds will be a promising strategy in liver fibrosis and HCC treatment.

2. Accumulation of H₂O₂ in liver

Accumulation of H_2O_2 in liver has been frequently reported in last decades [19,28], which is mainly related to two aspects: increased H_2O_2 generation and decreased H_2O_2 elimination. In most conditions, H_2O_2 is

generated from O_2^{-} in mitochondrial electron transport chain, and is cleared by pathways involving antioxidant enzyme systems, such as catalase (CAT), ascorbate peroxidase (APX), glutathione peroxidase (GPX) and peroxiredoxins (PRDXs) [22,23]. In acute or chronic liver diseases, metabolism of H₂O₂ is out-of-balance with liver metabolic remodeling or CAT poisoning (Fig. 3) [29,30].

2.1. Increased H₂O₂ generation

As the major metabolic organ, liver controls macronutrient metabolism [31], lipid homeostasis [32], and ethanol/drug elimination [33], which require amounts of adenosine triphosphate (ATP) to keep normal function. Mitochondria, as the powerhouse of cells with respiratory chain, is the primary intracellular sites of oxygen consumption as well as the major source of ROS [34,35]. In mitochondria aerobic respiration, electrons flow along the respiratory chain and eventually culminate at complex IV, in which the molecular oxygen is reduced into water. As described in Fig. 4, superoxide is predominantly generated at complex I and complex III of the cytochrome chain during the process [36]. At M. Shao et al.



Fig. 1. Scheme of pathological changes of normal liver to the fibrosis owing to ROS stimuli. As illustrated above, high fat diet, alcohol, virus, drugs, ischemiareperfusion injury and other harmful substances make the hepatic tissues vulnerable to ROS related oxidative stress, which will trigger liver injury and lead to liver fibrosis, and further induce precancerosis of HCC.



Fig. 2. Role of H_2O_2 in liver fibrosis. Endogenous H_2O_2 sources include NADPH oxidases, peroxidase and the mitochondria electron transport. The excessive H_2O_2 accumulation leads to oxidative stress and oxidative damage of biomolecules, eventually induces the fibrosis and HCC.

first, most electrons were safely reacted with protons and oxygen molecules to form water at complex IV of the respiratory chain. The other electrons didn't react directly with oxygen at complex I and complex III, and were leaked from the respiratory chain to form $O_2^{\bullet-}$, which directly leaded to the formation of H_2O_2 [37].

Liver fibrosis is usually accompanied with high-fat/sucrose diet [38, 39], alcohol abuse [40], or ischemia-reperfusion injury (I/R injury) [41], resulting in overproduced H_2O_2 in liver. High-fat/sucrose diet decreases the reduced form of coenzyme Q (ubiquinol, CoQH₂), which is easy to be oxidized into ubiquinone (CoQ) or ubisemiquinone. While



Fig. 3. Different routes of H_2O_2 production and scavenging. The major sources of H_2O_2 are the NOXs and the mitochondrial respiratory chain, as well as a considerable number of oxidases in peroxisome. H_2O_2 is cleared by pathways involving antioxidant enzyme systems, such as CAT, APX, PRX and GPX. In non-enzymatic pathway, H_2O_2 is scavenged by ascorbate (AsA), glutathione (GSH). The generated H_2O_2 can further convert to OH• *via* Fenton reaction.

electrons are reversely transported from CoQH₂ to complex I for nicotinamide adenine dinucleotide (NADH) formation when CoQ pool is significantly reduced [42]. And a high NADH/NAD ⁺ ratio is responsible for the O₂⁻ production with direct formation of H₂O₂ [42]. Leverve et al. demonstrated that high-fat (HF) diet led to liver mitochondrial alterations. Quinone pools (CoQ9 and CoQ10) of mitochondria was lower and ratio of reduced CoQ9-to-oxidative CoQ9 was higher in HF diet treated rats, which corresponded to lower respiration rate and higher H₂O₂ production [38]. For high-sucrose diet, levels of reduced CoQ9 and CoQ10 were also significantly lower in mitochondria of sucrose-fed rats [39]. Additionally, high-fat/sucrose diet induces the accumulation of fat in liver and increases circulating free fatty acid. H₂O₂ is produced by peroxisomes as a byproduct of fatty acid oxidation by acyl-CoA oxidase, which directly transfers electrons to O₂ to form O₂⁻ [23].

Alcohol is one of the most abused hepatotoxic species, and alcoholic liver disease (ALD) has been a global heathy problem [43]. In 1992, chronic treatment of ethanol has been reported to significantly increase H_2O_2 generation by elevating peroxisomal β -oxidation of acyl-CoA compounds [44]. Apart from the toxic intermediate acetaldehyde, H₂O₂ was considered as a cornerstone for ethanol-mediated liver damage through inducing autophagy and programmed cell death [43]. ROS accumulation, especially H₂O₂ has been demonstrated to cause major injury during liver ischemia-reperfusion [45]. I/R injury involved interruption and restoration of blood supply, which resulted in acute hypoxia state of tissues [41]. For adaptive responses to acute hypoxia, a superoxide burst was produced with hypoxia activated mitochondrial Na⁺/Ca²⁺ exchanger in I/R injury [46]. Hernansanz-Agustín et al. indicated that oxygen depletion could trigger complex I deactivation transition (active/'deactive' transition), and electrons were reversely transported from CoQH₂ to NAD⁺, which implied high ROS production [47]. Tumor cells were regarded to obtain high metabolic activity and tumor mitochondria handled overproduction of different ROS [48]. To evade oxidative toxicity of oxygen free radicals, SOD was highly expressed in tumor cells to enhance conversion of free radicals into low toxic H₂O₂, which activated oncogenic and angiogenic pathway and helped cell invasion [22].

2.2. Decreased H_2O_2 elimination

Mammalian expression of CAT is most abundant in liver, kidney and



Fig. 4. Mitochondria-derived ROS generation and their elimination by the antioxidant system. O_2^{--} is generated predominantly at complex I, III of the respiratory chain. O_2^{--} is converted to H_2O_2 by two dismutases including SOD2 in mitochondrial matrix and SOD1 in mitochondrial intermembrane space. Under normal physiological conditions, the generated H_2O_2 is then eliminated by CAT, and PRDXs, GPXs. During the process of liver fibrosis, the harmful stimuli alter the balance between generation and scavenging of H_2O_2 due to high H_2O_2 production and low antioxidant capacity of mitochondria. Additionally, excessive free fatty acid can interfere with ETC through promoting the TCA cycle.

erythrocytes [49]. CAT is the central enzyme that regulates oxidative stress by catalyzing H₂O₂ into H₂O and oxygen [50]. Decreasing level of CAT suggests the presence of intracellular oxidative stress in liver tissue [51]. CAT expression can be diminished in different conditions. Peroxisome proliferator-activated receptor gamma (PPARy) is the well-known activator of CAT gene transcription [52], and inhibition of PPARy can stimulate the downregulation of CAT [53]. Reduced liver CAT activity or decreasing CAT level were reported in murine NASH (nonalcoholic steatohepatitis) models [54]. Dong et al. found that CAT decreased in liver fibrosis induced by carbon tetrachloride (CCl₄). Overexpression of CAT led to a decrease in the secretion of collagen 1 and angiopoietin 1 and inhibited activation of HSC-T6 cells [27]. Walid G. et al. administrated human recombinant TNF- α (tumor necrosis factor α) into rats and observed significant decrease in the CAT [55]. Additionally, due to the active heme center of CAT for H2O2 decomposition, chemicals that can tightly bind with heme iron (NO, CN, H2S) will inhibit the activity of CAT, thus inducing the increasing H_2O_2 concentration [29,56].

PRDX and GPX are main members of the mitochondrial antioxidant defense system [57]. PRDX3 is an efficient H_2O_2 -eliminating enzyme in mitochondria, which oxidize peroxidatic cysteine (CysP) into –SOH, then formed an intermolecular disulfide bond with a resolving cysteine (CysR) on the second subunit [58]. GPX mediates selenocysteine and H_2O_2 reaction to form selenol, which is subsequently resolved by two GSH [58]. These antioxidant enzymes are observed to be downregulated in many diseases. Han et al. reported that liver I/R impaired function of NADP⁺-dependent isocitrate dehydrogenase 2 (IDH2), which leading to the decreased level of NADPH (nicotinamide adenine dinucleotide

phosphate), decreased activity of GPX, and an increased H_2O_2 production [59]. Accumulation of bile acids has been proved to cause decreased PRDX3 expression through downregulation of nuclear respiratory factor 2 (Nrf2), and led to the impairment of mitochondrial antioxidant system [60].

GSH is a tripeptide, y-glutamylcysteinyl glycine, which is found in all mammalian tissues and is especially high concentrated in the liver [61]. GSH/GPX system controlled the redox balance in untransformed cells [62]. GSH depletion in liver is highly associated with different hepatopathies. Hepatic cirrhosis with decreased circulating GSH is apparently due to the decreased function of liver, which includes GSH transfer to plasma [63]. Shrestha, N. et al. found that GSH content was significantly depleted in the CCl4 induced liver fibrosis, but it was significantly restored by the treatment of glutamine as a major precursor of GSH synthesis [64]. And alcohol abuse produced amounts of toxic metabolite acetaldehyde in liver, which was reported to bind to GSH and inhibit its H₂O₂ scavenger function, resulting in aggravating oxidative stress and lipid peroxidation [65]. However, GSH in liver tumors was slightly lower compared with normal tissue and declared no significance [66]. Many researchers even have reported higher GSH level in different human cancers [67]. Tumor cells upregulated GSH synthesis and regeneration to antagonize high-level ROS that were toxic [67]. Furthermore, GSH was regarded as the main contributor to tumor growth, and blocking early synthesis of GSH blunted tumor proliferation [68].

3. Role of H₂O₂ in liver fibrosis and HCC

H₂O₂ impacts the functionality of several liver-specific cells, such as hepatocytes, Kupffer cells (KCs) and HSCs, leading to the generation and development of liver fibrosis [19]. Damaged hepatocytes will release fibrogenic mediators to stimulate HSCs activation, and induce the recruitment of leukocytes by inflammatory cells [69]. Activated HSCs also mediate a range of immunoregulatory effects by producing NOX enzymes, ROS, pro-inflammatory cytokines and chemokines [70]. As the liver resident macrophages, KCs are activated under oxidative stress, and activated KCs secreted different cytokines and released ROS, which were important in liver inflammation [71,72]. Additionally, the liver sinusoidal endothelial cells (LESCs) are also highly sensitive to oxidative stress delivered via the portal vein (Fig. 5) [71]. In turn, the released ROS from damaged hepatocytes or activated inflammatory cells was able to induce cellular activation, migration or chemotaxis, which have been reported to contribute to liver fibrogenesis [11]. HCC was known as "inflammatory cancer", which was derived from liver inflammation with ongoing released chemokines and ROS [73]. What's more, in chronic liver diseases, prolonged ROS accumulation oxidized DNA bases membrane and cellular lipid, which participates in

hepatocarcinogenesis [74].

3.1. Damage of hepatocytes

Hepatocytes involve cellular metabolism, iron homeostasis and detoxification process [75]. H₂O₂ can increase MAPK activity through oxidizing cysteine residues in protein tyrosine phosphatases, releasing and activating its binding partner MAPKKK5 (or apoptosis signal-regulating kinase 1, ASK1). Thereby it stimulated the cellular matrix genes expression and inflammatory molecules release, and promoted cellular apoptosis and necrosis [76,77]. Besides, in response to the oxidative stress caused by excessive H₂O₂, hepatocytes highly express poly (ADP-ribose) polymerase 1 (Parp1) and mediate translocation of high mobility group box 1 (HMGB1) from nuclear to cytoplasm, which triggers inflammatory response and liver damage [78]. In addition, H₂O₂ at non-toxic levels was reported to be responsible for ethanol induced hepatic damage rather than acetaldehyde through autophagy [43]. Mueller et al. concluded that ethanol induced upregulation of NOX4 and CYP2E1 (cytochrome P450 2E1) to overproduce H₂O₂ during ethanol metabolism, thus activated hepatocyte autophagy without the involvement of mTOR (mammalian target of rapamycin).



Fig. 5. Illustration of the effect of accumulated H_2O_2 on hepatocyte, HSCs, KCs, and LSECs during fibrogenesis. During the continuous H_2O_2 stimuli, the functionality of several liver-specific cells, such as hepatocytes, KCs and HSCs was impacted leading to the generation and development of liver fibrosis. The excess H_2O_2 induces apoptosis and necrosis of hepatocytes, promotes HSCs activation, exacerbates the inflammatory responses involved the activation of resident KCs, and induces the endothelial-to-mesenchymal transition (EndMT) process of LSECs, which contributing to liver fibrosis and eventually inducing HCC.

What's more, liver is the conductor of systemic iron balance. Under normal conditions, ferric iron binds to the transferrin (Trf) and forms a nontoxic complex for iron delivery. But in liver fibrosis or liver cirrhosis, reduced Trf levels and iron overloaded have been reported, and higher amounts of non-bound iron are transported into liver for clearance [79]. Presence of accumulated H₂O₂ and non-bound iron in liver leads to the production of dangerous OH• through Fenton reaction [80]. OH• is highly reactive for biomacromolecules, such as DNA, protein and lipid, leading to oxidative damage or lipid peroxidation [81]. Then, the decrease in reduced GSH level and GPX4 activity trigger the destruction of the cell membrane integrity. Peroxidized lipid couldn't be removed through the GSH/GPX system and finally induced ferroptosis of hepatocytes [82,83]. In addition, ROS increased the expression and synthesis of cytokines, including interleukin 1 β (IL-1 β), IL-8, and TNF- α , which caused apoptosis and necrosis of hepatocytes and relating to liver fibrosis [84].

As the by-product of hepatocytes, H₂O₂ could diffuse into nuclear and damage DNA in hepatocytes [74]. Once damaged, hepatocytes were initiated to the compensatory proliferation, and accumulated genetic mutations for carcinogenesis [85]. The formation of oxidative DNA marker, 8-Oxo-2'-deoxyguanosine (8-OHDG), was linked to epigenetic instability in HCC [86]. Wang et al. found that hepatocytes expressed 8-OHDG was increased during NASH diet due to NOX2-mediated DNA oxidative damage. NOX2 was encoded by cybb gene, and was regulated by TAZ (transcriptional co-activator with PDZ-binding motif), a transcriptional regulator that promote NASH to HCC [87]. What's more, Seo et al. found that alcohol damaged hepatocytes could excrete 8-OHDG enriched extracellular vesicles (EVs) and transfer them into HCC cells. 8-OHDG-enriched EVs subsequently activated oncogenic pathways, such as JNK, STAT3 (signal transducer and activator of transcription 3), BCL-2 (B cell lymphoma-2), and TAZ, thereby inducing hepatocarcinogenesis [88].

3.2. Inducing HSCs activation

 H_2O_2 is regarded to induce liver fibrosis *via* activating HSCs directly or indirectly. H_2O_2 accumulation promotes HSCs activation and *trans*differentiation into myofibroblast through regulating pro-angiogenic and pro-fibrogenic responses [89]. Mounting evidences pointed to a link between excessive H_2O_2 accumulation and HSC activation. For example, deficiency of enzymes that involved ROS generation catalyzing in mice decreased HSC activation and fibrogenesis [90–92]. Novo et al. showed that all effective stimuli for profibrogenic human HSC and myofibroblast-like cells (MFs) require intracellular generation of ROS as a common critical step for trigger chemotaxis through redox-sensitive activation of extracellular regulated JNK1/2 and ERK1/2 [11]. Inhibition of phosphorylated JNK and mitochondria interaction, or reduced mitochondrial ROS production could reduce HSC activation and liver injury [93].

H₂O₂ also displays an important role in fibrosis in conjunction with the TGF- β 1 (transforming growth factor-beta 1) signaling system [94]. TGF-B1 has been reported to present as a latent complex and deposited in the hepatic sinusoid at high concentration [95]. H₂O₂ can convert latent TGF- β 1 to the active form and promote activation of HSCs, and consequently triggered fibrogenesis [96]. Furthermore, H₂O₂ is capable of modifying different cellular pathways through DNA binding sites dysfunction of redox-sensitive transcription factors or by cysteine residues oxidation on these molecules, such as hypoxia-inducible factor-1 alpha (HIF-1 α) and nuclear factor kappa-B (NF- κ B) [97]. H₂O₂ generated from mitochondria can mediate stabilization and decrease degradation of HIF-1 α , which has been implicated in the development of hepatic fibrosis and immune response [98]. Furthermore, due to the hypoxia feature of fibrotic tissues, H2O2 was also an important factor released by hypoxic hepatocyte to regulate HSCs expression of matrix metalloproteinase 2 (MMP-2) through cell-cell interaction. MMP-2 produced by HSCs is involved in ECM remodeling and degrades

collagen IV around HSCs, therefore promoting the activation, proliferation, and migration of HSCs [99].

Activated HSCs was a major kind component in HCC and secreted ECM, growth factors and cytokines for HCC progression [100]. HSCs were converted into cancer-associated fibroblasts (CAFs), which implicated the chemotherapy resistance, angiogenesis, and stemness maintenance of HCC [101]. Besides, activated HSCs also mediated immunosuppression in liver and promoted HCC progression [102]. Liu et al. elucidated the interaction between HSCs and HCC through intrahepatic microbiota disturbances. They found higher *S.maltophilia* infection provoked senescence-associated secretory phenotype (SASP) activation of HSCs *via* TLR4/NF-κb pathway [103]. Activation of SASP in HSCs has been correlated with HCC development *via* excretion of inflammatory cytokines, chemokines, matrix-remodeling factors, and growth factors [104].

3.3. Inflammatory regulation

 H_2O_2 is not only a cellular key reactive oxygen species but also an important inflammatory cofactor [105]. Increased level of H_2O_2 can promote inflammatory responses through activation of several pro-inflammatory signal pathways, typically MAPK, NF-κB and Janus kinase (JAK)-STAT signal pathways, which lead to indirect enhancement of liver fibrosis [106,107]. ROS is related to the increased production of damage-associated molecular patterns (DAMPs). DMAPs are a kind of signaling molecules, which involved in inflammatory reactions, homeostasis restoration, and induced cofactors that promote liver fibrosis, ALD or NASH [89,108]. Upon liver damage, oxidant stress highly induces osteopontin, which is a matrix-bound protein emerged as a key DAMP in the pathogenesis of liver fibrosis by increasing HMGB1 and collagen type I expression in HSCs [109].

Innate immune responses involved the activation of resident KCs as well as the recruitment of leukocytes to the liver [110]. H₂O₂ is reported to activate KCs, and activated KCs are well-known sources of hepatic ROS. This process leads to a vicious cycle of ultimately fibrosis [111, 112]. Besides, recent studies have demonstrated that a fraction of LSECs may contribute to liver fibrosis directly via endothelial-mesenchymal transition (EMT) process, and ROS plays a key role in EMT [113]. Aberrant activation of EMT has been demonstrated to promote hypoxia, glycolysis, and subsequent fibrogenesis in different organs, including liver and kidney [114,115]. ROS production in endothelial cells has been shown to promote tissue fibrosis likely via EMT process, which pivoting LESCs into a myofibroblasts-like phenotype [116]. Luo et al. showed that H₂O₂ could disrupt mitochondrial function through evaluation the protein level of NOX2, and lead to defenestration in LSECs. Silence of NOX2 gene could rescue mitochondrial function and subsequently maintain LSECs fenestrae [117].

Liver inflammation was shown to be critical in chronic hepatitis associated hepatocarcinogenesis, and KCs were reported to be the HCCspecific tumor-associated macrophages (TAMs) [118]. Activation of KCs led to the release of different inflammatory cytokines and modulated HCC progression. In early phases of chronic inflammation, KCs were polarized into M1 phenotype and release TNF- α , IL-6, IL-1 β and iNOS (inducible nitric oxide synthase) [119]. During HCC progression, KCs were dynamically switched from M1 phenotype to TAMs (M2 phenotype) with IL-6 stimulation [120]. Kong et al. found that the development of HCC was promoted by macrophages secreted IL-6, which in turn enlisted leukocytes. IL-6-deficient mice showed lower infiltrated inflammatory cells in liver, and HCC tumor was much smaller in IL-6-knock out mice [118].

3.4. Tumor progression

ROS induced hepatic injury, including peroxidation of protein, DNA and lipid, inflammatory reaction, tended to initiate tumorigenesis.

Tumor cells obtained high level production of superoxide with major sources of NOXs [121], mitochondria [122], and peroxisome [123], which was rapidly converted to H_2O_2 via SOD. H_2O_2 accumulation in liver can induce chromosomal mutations and finally malignant transformation of proliferating hepatocytes [124]. Research has found that H_2O_2 could stimulate angiogenesis and mediate migration and invasion capacity in HCC cells via AKT activation [125,126]. Over 90% of HCC cased arise in chronic liver disease, which was the strongest risk factor for HCC [127]. Activated HSC was the key cell involved in chronic liver damage, which undergone phenotypic changes, synthesized extracellular matrix components and stimulated the migration of endothelial cells [128]. Previous findings showed that HCC almost always occurred with different degrees of fibrosis or hepatic inflammation [124].

Furthermore, H_2O_2 could regulate immunosuppressive tumor microenvironment (TME) and assist tumor immune escape. Excess ROS in TME was reported to reduce T cell activity through inhibiting mTOR pathway, which was important for T cell activation and proliferation [129]. It has been reported that H_2O_2 activated HSCs could mediate re-differentiation of CD14⁺HLA-DR^{-/low} monocyte into myeloid derived suppressor cells (MDSCs) in liver [130]. MDSCs were universal negative regulators of adaptive immunity and showed immunosuppressive activity to promote HCC proliferation [131]. Zhao et al. reported that HSCs increased levels of regulatory T cells (Tregs) and MDSCs in HCC microenvironment, and assisted the immune evasion of hepatoma cells [132].

4. Nanotherapeutics strategies

Many different pharmacotherapeutic strategies aimed at reversal or prevention of fibrosis/cirrhosis progression and induction of HCC ablation have been considered, but the effect of these therapies is not satisfactory [77]. Due to the complex pathogenesis of hepatic fibrosis and HCC, specific effective drugs in clinical practice were still lacking [133]. Given the importance of H_2O_2 in liver fibrosis and HCC, oxidative stress targeted therapy has great potential in liver fibrosis and HCC. Besides, due to the superiority that nanoparticles circulated in blood was



Fig. 6. (a) Illustration of the POD-like activity of PB NPs. Adapted with permission [136]. Copyright 2016, American Chemical Society. (b) PB impregnated mesenchymal stem cells for hepatic I/R injury alleviation. Adapted with permission [141]. Copyright 2021, American Chemical Society. (c) Scheme illustrating the SP94-PB-SF-Cy5.5 NPs treatment regimen for HCC [138]. Copyright 2020, American Chemical Society.

mainly sequestered in liver, nanotherapeutics aimed at liver oxidative stress were effective in the treatment of liver diseases. Hence, the application of multifunctional nanotherapeutics involving H_2O_2 scavenging and efficient delivery of different cargos have been an evolved area of interest [134].

4.1. Nanozymes

Nanozyme is a kind of nanomaterials with enzyme-like capability, and has been included in the Encyclopedia of China and the textbook of enzyme engineering [135]. Nanozyme with catalytic activities, such as peroxidase (POD), CAT, SOD, and GPX has been demonstrated to ameliorate liver oxidative stress and fibrosis [136,137] and produce synergistic effects for HCC treatment [138].

4.1.1. Prussian blue (PB)

PB has been commonly used as a biocompatible contrast agent for magnetic resonance imaging (MRI), and has been approved by the Food and Drug Administration (FDA) as an antidote for thallium in 2010 [139]. Zhang et al., reported that PB NPs obtained multienzyme-like activity, including POD, CAT and SOD (Fig. 6a) [136]. Particularly, PB could efficiently scavenge $O_2^{\bullet-}$ and H_2O_2 without generation of the toxic byproduct OH•, showing that PB is of good biocompatibility for in vivo applications. Due to the proven biocompatibility and multifunctional nanozyme activity of PB, Sahu et al. incorporated PB nanozyme into mesenchymal stem cells (MSCs) to augment the function of MSCs for liver I/R injury alleviation. MSCs cell therapy is promising in protecting organs from I/R injury by mitochondrial transfer, macrovesicles and the paracrine effect [140]. But the harsh environment of I/R injury site limited the survival and engraftment of MSCs and impeded the therapeutic effect. Corporation of PB as a ROS scavenger didn't affect the stemness and differentiation potential of MSCs, and augmented the paracrine effect and anti-inflammatory properties of the MSCs (Fig. 6b) [141].

The CAT-like activity of PB is also used to relieve tumor hypoxia by decomposing excess H_2O_2 in TME to produce O_2 . Zhou et al., designed

HCC-targeted PB NPs loaded with sorafenib representing a valuable treatment option for HCC (Fig. 6c). The CAT-like ability and photothermal effect of PB-induced O_2 production, which greatly reprogram the hypoxic and immunosuppressive TME, alleviating tumor hypoxia and reducing M2 macrophages [138]. Wang et al. utilized β -lapachone (LAP) to initiate high-level H₂O₂ production and transferred MCT4 siRNA to mediate lactate blockade, therefore increasing tumor pH and triggering PB-mediated Fenton reaction for tumor treatment [142].

4.1.2. Cerium oxide (CeO₂)

CeO2 has been proven to be an effective H2O2 scavenger and displayed hepatoprotective activity against liver fibrosis [143]. The catalytic properties of CeO2 mainly depend on the formation of oxygen vacancies and electron transition between the oxidation state (Ce^{4+}) and reduction state (Ce^{3+}) [144]. Mitra et al. reported an aqueous-soluble nanoceria (GCCNP) with dominated Ce^{3+} that can scavenge the ROS, such as H₂O₂ and OH•, and inhibit neovascularization formation (Fig. 7a) [145]. Besides, Oró et al. demonstrated that liver was the major target of CeO₂ (4 nm) NPs in CCl₄ fibrotic rats (Fig. 7b). After intravenous injection for 8 weeks, CeO2 NPs were mainly located in the liver, which were intended to be used as a drug delivery vehicle [143]. CeO₂ NPs with antioxidant enzyme-mimetic activities, such as SOD activity, CAT activity, POD activity, have also been a new therapeutic tool in HCC [146]. Fernandez-Varo et al. consider CeO2 NPs could be an NP-based therapy platform in HCC. The authors found that CeO2 NPs can be adsorbed in human hepatocyte cancer cells and induce ROS degradation and tumor recession [147].

Evidences have shown a significant therapeutic potential of CeO_2 NPs in driving liver regeneration [148], reducing lipid peroxidation [149] and liver steatosis [143] in different experimental conditions. In 2019, Cordoba-Jover et al. firstly found the effects of CeO_2 on liver regeneration after partial hepatectomy (PHx) and acetaminophen (APAP)-induced liver injury in rats (Fig. 7c) [148]. Malondialdehyde (MDA) is the major lipid oxidation product in biological samples. Reduced level of MDA in plasma was detected in CCl₄ BALB/c mice treated with CeO₂, indicating that lipid peroxidation was reduced after



Fig. 7. (a) Free radical scavenging activity and autoregenerative properties of GCCNPs. Adapted with permission [145]. Copyright 2017, American Chemical Society. (b) Scheme illustrating the CeO₂NPs administration protecting against chronic liver injury by reducing liver steatosis and portal hypertension and markedly attenuating the intensity of the inflammatory response. Adapted with permission [143]. Copyright 2016, Elsevier. (c) CeO₂NPs treatment increased liver regeneration and cell proliferation. Adapted with permission [148]. Copyright 2019, Springer Nature.

CeO₂ treatment [149]. However, very high doses of CeO₂ (40 μ g/mL) may induce oxidative stress and decrease intracellular GSH in normal cells, therefore inducing cell apoptosis [150]. The application of CeO₂ is a double-edged sword, and clinical safety and efficacy studies should be more precisely considered in future works [151].

4.1.3. Manganese (Mn)-based nanomaterials

Mn is a necessary nontoxic element involved in physiological metabolism [152]. The multiple oxidation states of Mn (II, III, IV and VII) confers manganese oxide with superior redox capacity and anti-oxidant potential to scavenge ROS [153]. Higher-valent Mn-based nanomaterials, such as MnO₂, Mn₃O₄, have been applied as biodegradable nanozymes to catalyze H₂O₂ decomposition into O₂ (Fig. 8) [154–156]. Chen et al. modified MnO₂ nanoflowers on the surface of *Shewanella oneidensis* MR-1 and constructed a biohybrid Bac@MnO₂ [154]. The biohybrid could transfer electrons from lactate acid to Mn⁴⁺ for respiration in the absence of O₂, and meanwhile catalyze H₂O₂ decomposition. This process synergistically prevented the accumulation of lactic acid. Yao et al. reported Mn₃O₄ NPs possessed multiple enzyme mimicking activities of SOD and CAT, which could eliminate as much as 75% of O₂⁻⁻ and H₂O₂ [156].

 H_2O_2 with untimely clearance can be converted to OH•, which are extremely reactive and more toxic than other ROS [157]. On the other side, Mn ions (such as Mn^{3+} , Mn^{4+}) can be reduced into lower-valent Mn^{2+} by intracellular GSH ($Mn^{3+/4+}$ + GSH → Mn^{2+} + GSSG) [158]. Mn^{2+} exhibits the potential for contrast amplification as the relativity could be highly increased after binding with proteins [159]. Wang, Y., et al. developed an innovative MnO_2/BPD nanosystem to improve the survival rate of patients with unresectable HCC (Fig. 9a–c). MnO_2 was reduced to Mn^{2+} by high intracellular GSH, and self-assembled with verteporfin (BPD) to produce MnO_2/BPD . This process also generated O_2 to enhance the effects of photodynamic therapy (PDT) and deplete GSH, which prolonging the life of the ROS and amplified ROS damage [160].

Given the crucial role of the hypoxic TME in tumor progression and drug resistance, MnO₂ NPs have been developed as nanoscale oxygen delivery systems. Chang et al. report a NanoMnSor nanoparticle drug carrier which could codelivery of MnO₂ and sorafenib by synergistically inhibiting the progression of primary HCC (Fig. 9d). The catalytic effect of MnO₂ on oxygen generation by H₂O₂ alleviated tumor hypoxia, and thereby overcoming hypoxia-induced resistance to sorafenib [161]. Mn^{2+} could mediate Fenton-like reaction with H₂O₂ and generated toxic OH• ($Mn^{2+} + H_2O_2 \rightarrow Mn^{3+} + OH• + OH-$) for anti-tumor therapy, which might enlarge free radical damage toward normal liver tissues [162]. But fortunately, in normal cells or fibrotic liver cells, the level of GSH content is lower compared with tumor cells, and this side effect is negligible with low cytotoxicity on normal cells [162,163]. Even so, it's suggested to restrict the dosage of Mn-based nanomaterials and monitor the hepatic function indexes during the treatment.

4.1.4. Fe-based nanozymes

Fe-based nanozyme is another commonly used category, and has been widely applied in anti-tumor therapy. Fe-mediated Fenton reaction converted endogenous H_2O_2 into highly toxic hydroxyl radicals, which were efficient in inhibiting HCC progression [164]. As HCC cells overexpress transferrin receptors, Zhou et al. constructed a tumor-targeting theragnostic nanoplatform by incorporating transferrin with a mesoporous iron framework (Fe-HMON-Tf) to enhance specific HCC targeting. Doxorubicin (DOX) was further loaded in the framework to generate H_2O_2 in HCC cells, which was converted to OH• via Fe²⁺/Fe³⁺ from the Fenton reaction (Fig. 10a) [164]. Xie et al. found that iron oxide nanoparticles (IONPs) possessed an intrinsic and directed cytostatic efficiency for HCC (Fig. 10b). They found that Fe₂O₃@DMSA applied as autophagy intervention agents to directly suppress hepatoma with iron-retention-induced sustained ROS production [165].

To further improve the chemodynamic therapy (CDT) efficacy, self-enhancement of H_2O_2 was applied to amplify tumor death. Li et al.



Fig. 8. (a) Schematic illustration of tumor targeting of Bac@MnO₂ and its tumor inhibition mechanism. Adapted with permission [154]. Copyright 2020, Wiley-VCH. (b) Step-by-step synthesis of drug loaded hollow MnO₂ nanoparticles and (c) pH-responsive drug delivery and oxygen generation in H₂O₂ solution. Adapted with permission [155]. Copyright 2017, Springer Nature. (d) Mn₃O₄ scavenging of O_2^- compared with CeO₂ NPs, SOD and (e) reaction with H₂O₂ compared with CeO₂ NPs, CAT. Adapted with permission [156]. Copyright 2018, The Royal Society of Chemistry.



Fig. 9. (a-c) Illustration of MnO_2/BPD synthesis, reduction and self-assembly *in vivo*. O_2 was produced and supported PDT efficiency. Adapted with permission [160]. Copyright 2020, American Chemical Society. (d) Schematic representation of the mechanism by which NanoMnSor can serve as a theranostic anticancer agent. Adapted with permission [161]. Copyright 2020, American Chemical Society.



Fig. 10. (a) Synthesis and biomedical application of DOX@Fe-HMON-Tf NPs. Adapted with permission [164]. Copyright 2021, Springer Nature. (b) The carboxy-functional iron oxide nanoparticles ($Fe_2O_3@DMSA$) significantly impact on the iron transport system and promotes the retention of intracellular iron, resulting in excessive ROS-induced tumoricidal autophagy. Adapted with permission [165]. Copyright 2021, Springer Nature.

design a Vitamin c (Vc) loaded biodegradable mesoporous magnetic nanocubes (MMNCs) with phasechange materials (PCM). Vc served as an original source of H_2O_2 , and cooperated with MMNCs to mediate Fenton reagent-like activity in an acidic environment [166]. Fan et al. designed a H_2O_2 -generation engineered bacterium and covalently loaded magnetic Fe_3O_4 NPs to enhance tumor in-situ CDT [167]. *Escherichia coli MG1655* was overexpressed with respiratory chain enzyme II (NDH-2), which transferred electrons in respiratory chain to oxygen molecules and generated H_2O_2 continuously to provide reagent of Fenton reaction.

However, Fe-based nanozymes were not suggested for treatment of liver fibrosis. Firstly, many liver diseases, such as ALD and hereditary hemochromatosis, have been reported to induce iron accumulation in liver and cause iron metabolism disorders [80,168]. Externally administrated iron was mainly stored in liver and aggravated iron overload disorders, leading to cellular ferroptosis, hepatic function damage and biliary excretion limitation [169]. Secondly, Fe-based materials have a risk in catalyzing H_2O_2 to generate OH• through Fe²⁺-mediated Fenton reaction, which would result in DNA damage, lipid and protein oxidation and carcinogenesis [29]. Liu et al. explored chronic iron overload induced liver injury through dietary feeding ferrocene [170]. They found that iron overload mainly caused cell damage in liver with iron initiated oxidative stress. Wu et al. reported that iron overload promoted heme oxygenase 1 (HO-1) expression and induced liver injury accompanied with fibroblast growth factor 21 (FGF21) upregulation [171]. FGF21 could in turn protect hepatocytes from iron-induced ferroptosis by promoting HO-1 ubiquitination and degradation.

4.1.5. Metal-organic frameworks (MOFs)

MOFs were porous supramolecular crystal with numerous

catalytically active site, and multifunctional modifications further extended their applications [172]. MOFs mimicked catalytic activity of CAT, PRDX and SOD, therefore converting H₂O₂ into OH• or O₂. Pan et al. designed a nanoscale MOF of Fe-meso-tetra(4-carboxyphenyl) porphyrin (TCPP) to load hypoxic sensitive tirapazamine (TPZ) (PFTT), which was further coated with tumor cell membrane to evade immune clearance and enhance homologous targeting [173]. PFTT was decomposed in lysosomes and released Fe³⁺ to catalyze H₂O₂ into oxygen, which was exhausted by PDT and triggered activation of TPZ for cancer treatment (Fig. 11a). Recently, researchers found that endogenous H₂O₂ in tumor was not sufficient for highly efficient PDT or CDT. Ding et al. anchored Au NPs on the surface of a Fe-TCPP MOF through in situ growth. Au NPs acted as glucose oxidase to catalyze glucose and elevated cellular H₂O₂ level for enhanced CDT [174]. As shown in Fig. 11b, porous FeMOFs were loaded with chemotherapeutic camptothecin (CPT) and acted burst release under phosphate ions stimulation. Simultaneously, FeMOF and Au NPs combined a cascade catalytic system, which significantly improved antitumor efficiency.

4.1.6. Other nanozymes

Apart from the nanozymes mentioned above, there are some nanomaterials newly discovered to obtain catalytic capability. Zhou et al. demonstrated that molybdenum disulfide (MoS₂) nanozymes exhibit activities of four major cellular cascade antioxidant enzymes (including SOD, CAT, POD, and GPX), and play a role as a self-cascade platform for cellular ROS scavenging and hepatic fibrosis therapy (Fig. 12a) [175]. Other CAT-like nanozymes containing rare metal oxide-based nanomaterials, such as iridium (Ir), Ruthenium (Ru) and Platinum (Pt)-based nanozymes, have shown high CAT-like activity, which could immediately convert H_2O_2 to O_2 and alleviate oxidative stress for biomedical applications (Fig. 12b) [176–178].

4.2. H₂O₂ scavengers

The utilization of free radical scavenging mechanisms for the treatment of liver fibrosis is also an effective antioxidative therapy targeting oxidative-stress microenvironment. H_2O_2 scavengers, containing endogenous antioxidant species (e.g., Vitamins C, carotenoids, flavonoids, AsA, GSH, etc.) and exogenous antioxidant enzymes (e.g., CAT, GPX, etc.), have been served to prevent or repair damage caused by free radicals [179]. Diethylnitrosamine (DEN)-induced HCC model was achieved with increased ROS production and disturbed cellular endogenous redox balance. Natural products, such as R-phycoerythrin-rich protein [180], Silibinin [181] and Rutin [182], have been reported to be strong antioxidants and free-radical scavengers in HCC treatment. To improve the biopharmaceutical and preclinical performance against HCC, Pandey et al. designed a novel Rutin (RT)-loaded PLGA NPs (RT-PLGA-NP) for HCC treatment. RT-PLGA-NP increased levels of SOD, CAT, GSH and GPx compared with DEN control group, which could be used for improving the biopharmaceutical and preclinical performance against HCC (Fig. 13a) [183]. Sameem et al. also targeted the biosynthesis of silver nanoparticles. The synthesized nanoformulation loaded with biomolecules present in *Ziziphus mauritiana* extract effectively inhibited the growth of hepatic cancer via reducing oxidative stress (Fig. 13b) [184].

In tumor hypoxia, tumor macrophage was polarized from M1 phenotype to M2 phenotype, which protected tumor cells from immune system attack [185]. CAT, as a major antioxidant enzyme, could remove overexpressed H₂O₂ in tumor tissue and promote tumor oxygenation. To enhance the combined therapeutic efficacy, Liu et al. synthesized fluorinated chitosan as a highly effective non-toxic transmucosal delivery carrier and assembled with TCPP-conjugated CAT to form nanoparticles [186]. CAT catalyzed O₂ generation helped to improve therapeutic efficacy of sonodynamic therapy (SDT). Chao et al. utilize liposome drug delivery system to load CAT, lyso-targeted NIR photosensitizer (MBDP) and Dox simultaneously for synergistic chem-PDT and immunosuppressive TME reversion [185]. Furthermore, CAT could improve tumor hypoxic microenvironment and enhance the function of sorafenib (SOR) in inhibiting tumor angiogenesis. Li et al. constructed PLGA microspheres (SOR-CAT-PLGA MSs) encapsulating SOR and CAT. The SOR-CAT-PLGA MSs could significantly improve the therapeutic effect on rabbit liver tumors [187].

Zhang et al. found that the primary organosulfur compound in garlic, Diallyl trisulfide (DATS), could produce hydrogen sulfide (H₂S) *in vivo* and suppress oxidative stress-induced HSCs activation. Study showed that DATS decreased the intracellular lipid peroxide levels and increased the levels of GSH in H₂O₂-treated HSCs with generation of H₂S [188]. Another example is N-acetylcysteine (NAC). As a precursor of GSH, NAC has been examined with potent hepatoprotective activity [189]. NAC is an organosulfur compound derived from Allium plants, which has strong clearance capability of free radicals. Notably, NAC is the only FDA-approved antioxidant for treatment of acetaminophen-induced hepatotoxicity [190]. NAC has been reported to protect liver against CCl_4 and TAA induced chronic liver injury through decreasing oxidative stress by regenerating antioxidant enzymes and GSH levels [191]. Co-delivery of NAC with iron oxide NPs has been demonstrated to



Fig. 11. (a) Schematic illustration of the cancer-cell membrane-coated self-assembled nanocomposites for multimodal synergistic breast cancer therapy. Adapted with permission [173]. Copyright 2022, Elsevier. (b) Schematic illustrating the chemical structures, synthetic route and application of the hybrid nanomedicine PEG-Au/FeMOF@CPT. Adapted with permission [174]. Copyright 2020, Wiley-VCH.



Fig. 12. (a) Schematic illustration of the cellular cascade process of MoS_2 for ROS scavenging. Adapted with permission [175]. Copyright 2021, The Royal Society of Chemistry. (b) Schematic illustrating the synthetic route and application of multifunctional RuO2@BSA@IR-808-Br2. Adapted with permission [176]. Copyright 2020, The Royal Society of Chemistry. (c) Schematic illustration of enhanced radiotherapy using porous Pt NPs. Adapted with permission [178]. Copyright 2019, Elsevier.

mitigate the oxidative toxicity in hypoxia/reoxygenation cardiomyocytes (Fig. 13c) [192].

4.3. H₂O₂-sensitive nanosystems

Overproduction of H₂O₂ causes oxidative stress and becomes the hallmark of profibrotic/pro-tumor microenvironment. In response to the oxidative stress, Lin et al. developed a ROS and pH dual-sensitive block polymer PEG-P(PBEM-co-DPA) based polydatin-loaded micelle (PD-MC) for liver fibrosis amelioration (Fig. 14a). PBEM-co-DPA can responsively release polydatin upon ROS stimulation, which has been demonstrated hepatoprotective and antifibrotic capacities. PD-MC significantly improves utilization of polydatin and holds great potential in clinical application of polydatin against liver fibrosis [15]. Zhang et al. utilized a ROS-degradable tumor necrosis factor-α (TNF-α) siRNA delivery system for treatment of acute liver failure (ALF) (Fig. 14b). TNF- α siRNA was compensated by the Man-COOH of Se-PEI polymer via electrostatic interaction. The ROS-responsive polyetheleneimine with diselenide bonds could degrade into small segments and potentiate gene knockdown efficiency in inflammatory microphages, which provided a new modality for the anti-inflammatory therapy of ALF [193].

 H_2O_2 -activatable nanodrugs are efficient due to synergistic targeted drug release and H_2O_2 scavenging capacity. Curcumin is a major active phenolic component of turmeric with antioxidant and antiinflammatory activity, but its therapeutic potential is limited by poor solubility and stability. Lee et al. reported a H_2O_2 -reactive poly(oxalateco-curcumin) (POC) prodrug to scavenge H_2O_2 and released curcumin in a H_2O_2 -triggered manner (Fig. 14c) [194]. Additionally, peroxalate esters in POC can be oxidated by H_2O_2 and generate CO₂ bubble, which can serve as a platform for ultrasound imaging of H_2O_2 accumulation site in liver diseases. In 2022, Lee's group further designed a self-assembling all-trans retinoic acid-based (atRA) hybrid prodrug (RABA) for hepatic I/R injury (Fig. 14d) [195]. RABA nanoassemblies can react with the massive H_2O_2 generated during I/R injury and responsively release atRA, which exhibits significantly synergistic therapeutic efficacy.

For anti-tumor therapy, intertumoral ROS levels were improved to amplify the oxidative stress and accelerate drug release from ROSresponsive delivery systems. Sorafenib was the first-line treatment for unresectable HCC with approximately 40% available rate. To improve therapeutic efficiency, Xu et al. chose an ROS-responsive galactosedecorated lipopolyplex (Gal-SLP) to codelivery sorafenib and shUSP22. Sorafenib worked as an ROS inducer and triggered shUSP22 release to silence USP22, which inhibited HCC glycolysis and enhanced efficiency of sorafenib (Fig. 15a) [196]. Yin et al. applied palmitoyl ascorbate (PA) to generate H_2O_2 in tumor site, and a H_2O_2 -sensitive amphiphilic block copolymer PEG-*b*-PBEMA was utilized to construct micelles. With H_2O_2 generation, the micelle was broken up and release quinone methide (QM) for GSH depletion, therefore amplifying oxidation damage against tumor cells (Fig. 15b) [197,198].

4.4. Challenges of nanotherapeutics application

Despite the application of nanotherapeutics are highly promising, there are also negative-effect reports of the increased exposure of nanomaterials, especially nondegradable inorganic NPs, including oxidative stress leading to liver dysfunction, non-biodegradability and biopersistance of NPs, and their interactions with critical biomolecules [199]. 30–99% of exogenously administered nanoparticles were collected and accumulated in liver [200]. However, hepatic processing and biliary excretion of nanoparticles were usually slow and might take months [201]. Long-term usage of inorganic NPs increased the chronic liver toxicity with their prolonged retention time resulted from relatively slow clearance pathways in liver [199]. Yun et al. found that extensive systemic distribution of Ag originating from the Ag NPs resulted in increases of serum ALP and calcium. Daily oral dosing of Ag NPs exerted increased lymphocyte infiltration in liver, which caused rising possibility of liver toxicity [202].

Additionally, nanomaterials with ROS-generating capabilities could initiate cytotoxicity through direct NP-DNA interaction or cellular oxidative stress. NPs degradation induced ROS and ROS mediated detrimental effects, such as DNA damage, mRNA degradation, gene perturbation, etc., were toxic to cell activity [203]. After exerting expected therapeutic functions, the increased ROS level might also impair ambient normal tissues. Besides, ROS-generating functions of insufficient degraded nanomaterials might still exist sustained oxidative damage [204]. More recent advances in the field of nanomaterials development have not been extensively tested in preclinical models of liver fibrosis until today. Specifically targeting crucial cell types of the liver and to deliver potent anti-inflammatory or anti-fibrotic drugs with low systemic toxicity remained to be defined in the future [205]. Therefore, the application of these nanotherapeutics for liver fibrosis and HCC is still challenging, and biodegradable or biocompatible nanosystems were preferably recommended.

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Table 4. The effect of polymeric nanoparticles of rutin (PLGA-RT-NPs) on antioxidant parameters in the diethylnitrosamine-induced hepatocellular carcinoma rats.

Serial number	Antioxidant parameter	Groups						
		NC	NC + RT (50 mg/kg)	DEN	DEN + RT (5 mg/kg)	DEN + RT (50 mg/kg)	DEN + RT-PLGA-NP	
1	MDA (nmol/mg protein)	$\textbf{0.68} \pm \textbf{0.04}$	$\textbf{0.69} \pm \textbf{0.02}$	0.89 ± 0.06	$0.83\pm0.04^{\star}$	$0.74\pm0.05^{\ddagger}$	$0.72\pm0.03^{\S}$	
2	P-carbonyl (nmol/mg protein)	$\textbf{0.90} \pm \textbf{0.02}$	0.89 ± 0.04	1.98 ± 0.87	$1.65\pm0.67^{\ddagger}$	$1.34\pm0.73^{\$}$	$1.11\pm0.54^{\$}$	
3	GPx (U/g protein)	$\textbf{8.34} \pm \textbf{1.28}$	8.32 ± 1.64	$\textbf{1.54} \pm \textbf{0.97}$	$3.63 \pm 1.47^{\ddagger}$	$\textbf{5.96} \pm \textbf{2.68}^{\S}$	$\textbf{7.63} \pm \textbf{1.37}^{\S}$	
4	GST (U/mg protein)	$\textbf{18.23} \pm \textbf{2.34}$	$\textbf{18.21} \pm \textbf{3.45}$	$\textbf{24.75} \pm \textbf{3.53}$	$\textbf{23.84} \pm \textbf{2.21}^{\star}$	$21.98\pm2.76^{\ddagger}$	$20.12\pm1.93^{\$}$	
5	GSH (nmol/mg protein)	$\textbf{55.32} \pm \textbf{6.54}$	$\textbf{56.32} \pm \textbf{5.98}$	$\textbf{75.64} \pm \textbf{6.43}$	$70.32\pm5.78^\ddagger$	$64.32\pm6.54^{\S}$	$\textbf{58.32} \pm \textbf{7.65}^{\$}$	
6	MPO (U/mg protein)	$\textbf{19.21} \pm \textbf{1.82}$	$\textbf{20.01} \pm \textbf{1.94}$	$\textbf{34.32} \pm \textbf{2.54}$	$31.98 \pm 3.43^{\ddagger}$	$\textbf{26.32} \pm \textbf{2.84}^{\S}$	$\textbf{22.73} \pm \textbf{1.93}^{\$}$	
7	SOD (U/mg protein)	$\textbf{7.04} \pm \textbf{1.12}$	$\textbf{7.06} \pm \textbf{1.82}$	$\textbf{4.84} \pm \textbf{1.34}$	$5.26 \pm 1.49^{\ddagger}$	$5.99 \pm 1.37^{\S}$	$6.85\pm1.93^{\S}$	
8	CAT (unit/mg protein)	118.2 ± 7.86	119 ± 6.76	98.2 ± 8.23	$99.8\pm6.97^{\dagger}$	$108.4 \pm 5.67^{\$}$	$114.3\pm7.93^{\$}$	

All values correspond to mean \pm standard error of the mean.

[†]p < 0.05.

[‡]p < 0.01.

§p < 0.001; ANOVA, followed by Dunnett's multiple comparison test.</p>

*Non significant.

CAT: Catalase; DEN: Diethylnitrosamine; GPx: Glutathione peroxidase; GSH: Glutathione; GST: Glutathione S-transferase; HCC: Hepatocellular carcinoma; MDA: Malondialdehyde; MPO: Myeloperoxidase; NC: Normal control; PLGA: Poly(lactic co-glycolic acid); RT: Rutin; SOD: Superoxide dismutase.



Fig. 13. (a) The effect of polymeric nanoparticles of rutin (PLGA-RT-NPs) on antioxidant parameters in the diethylnitrosamine-induced hepatocellular carcinoma rats. Adapted with permission [183]. Copyright 2018, Future Medicine. (b) Scheme illustrating the biosynthesis of silver nanoparticles loaded with biomolecules presented in *Ziziphus mauritiana* extract with anticancer activity evaluation against hepatic cancer. Adapted with permission [184]. Copyright 2022, Elsevier. (c) Schematic diagram of synthesis of M-MSN@NAC. Adapted with permission [192]. Copyright 2019, Dovepress.

5. Conclusions and future perspectives

Liver fibrosis was the major causes of morbidity and mortality of patients with chronic liver disease, and eventually developed into HCC without effective therapy. At this stage, the research on the mechanism of liver fibrosis has been relatively adequate. The role of oxidative stress in liver fibrosis pathobiology is complex. ROS, especially H_2O_2 , has typically been considered as a main incentive in the pathogenesis of liver fibrosis. To our knowledge, NOXs, peroxisome and mitochondria electron transport chain are the major source of H_2O_2 in hepatic metabolic disorders. H_2O_2 induces liver fibrosis *via* activating HSC, injuring hepatic parenchymal cells and regulating immunocytes. What's more, H_2O_2 could diffuse into nuclear and cause DNA oxidative damage and lipid peroxidation, thereby inducing hepatocarcinogenesis. Thus, alleviation of H_2O_2 accumulation to avoid oxidative damage should be a potential approach for liver fibrosis and HCC therapy.

Specific pharmacological approaches that selectively target oxidative pathways for liver fibrosis treatment are still lacking, and numerous challenges remain to be overcame [23]. Due to the unique characteristics of liver, various kinds of nanomaterials were designed to specifically accumulated in liver. Nanotherapeutics integrated multiple antioxidant functions and drug-controlled release to obtain synergistic efficacy. But only few nanodrugs have entered clinical trials with approved pharmaceutical ingredients and liposomal or polymer carrier, and these commercial vehicles have the advantage of controllable costs [25,206]. The nanotherapeutics discussed above, especially non-biodegradable inorganic materials-based nanodrugs, were facing challenges of *in vivo* metabolism, long-term accumulation induced toxicity and costly synthesis process [25]. Even through, the development of nanotherapeutics against liver fibrosis provided more treatment options, and intensive investigation in this direction will be critical to making key discoveries that will ultimately find novel therapeutic approaches.

CRediT authorship contribution statement

Mengyun Peng and Gang Cao conceptualized the study and approved it for publication; Yifan Wang, Hongyan Dong and Xiaoqing Zhang selected articles and collected data; Xin Han, Xianan Sang and Yini Bao provided professional assistance during the manuscript writing; Meiyu Shao and Mengyun Peng wrote this manuscript. Lu



Fig. 14. (a) Schematic illustration of PD-MC as a ROS and pH dual-responsive nanodrug to regulate multiple cell types for the treatment of liver fibrosis. Adapted with permission [15]. Copyright 2020, Wiley-VCH. (b) Formation and intracellular kinetics of M/Se-PEI/siTNF- α polyplexes and ROS-triggered siRNA release. Adapted with permission [193]. Copyright 2018, The Royal Society of Chemistry. (c) Schematic illustration of POC as an ultrasound imaging and therapeutic agent for acute liver failure. Adapted with permission [194]. Copyright 2019, Elsevier. (d) Schematic illustration of H₂O₂-activatable hybrid prodrug nanoassemblies as a pure nanodrug for hepatic ischemia/reperfusion injury. Adapted with permission [195]. Copyright 2022, Elsevier.



Fig. 15. (a) Schematic illustration of a self-activated cascade-responsive co-delivery system (Gal-SLP) for synergetic cancer therapy. Adapted with permission [196]. Copyright 2021, Wiley-VCH. (b) Schematic illustration of integrated micellar nanoparticles with tumor-specific H₂O₂ generation to elevate the oxidative stress in tumor tissue and simultaneous GSH depletion to suppress the antioxidant capability of cancer cells for amplified oxidation therapy. Adapted with permission [197]. Copyright 2017, American Chemical Society.

Wang revised the manuscript carefully.

Ethics approval and consent to participate

Live animals or human subjects is not involved in the review. Therefore, there is no ethical statements that are provided by authors.

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Declaration of competing interest

The authors declare no competing interests.

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