Review Article

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Hepatotoxicity of nanomaterials: From mechanism to therapeutic strategy

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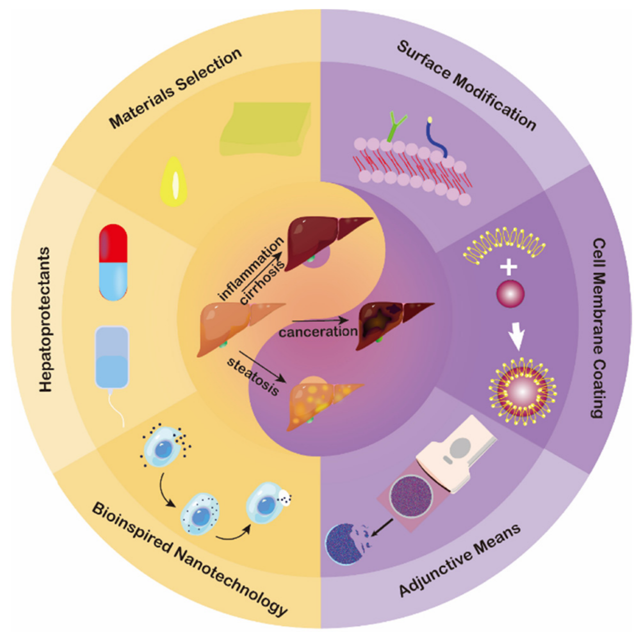
Abstract: Most nanoparticles are metabolized and accumulated in the liver; therefore, this review, based on most data collected from PubMed.gov between 2012 and 2023 with the keywords "nanomaterials induced hepatotoxicity," aims to elucidate the mechanism of nanoparticles leading to liver injury and propose relevant strategies. We discuss the biomedical approaches and strategies for mitigating liver injury, including 1) principle and recommendation of material selection; 2) nanoparticle surface modulation; 3) strategies inspired by virus and other biological phenomenon; and 4) drug and other possible adjunctive strategies. The optimal design of nanomaterials and therapeutic strategies to attenuate hepatotoxicity is critical for the development of nanomedicine.



Graphical abstract

Keywords: nanomaterial, hepatotoxicity, liver injury

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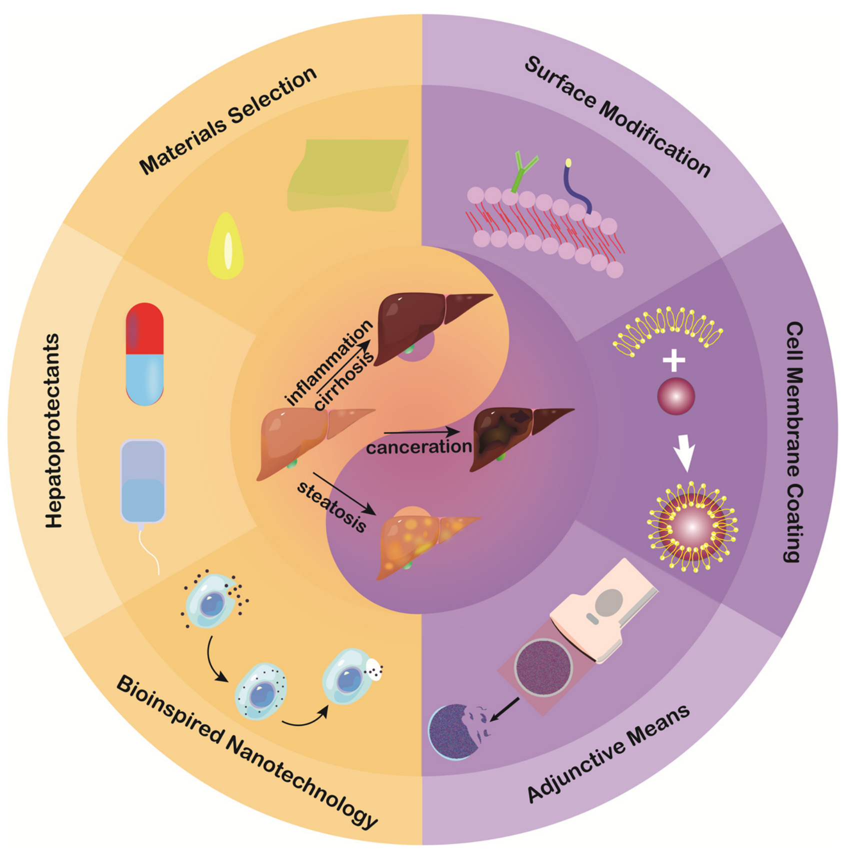
1 Introduction

Nanomaterials have been widely used in the medical field to deliver drugs and improve therapeutic efficacy due to their unique nanoscale size [1]. Nanoparticles can improve vascular permeability and favor the enhanced permeability and retention (EPR) effect, which is very advantageous in the treatment of inflammation or cancer with non-targeted drugs. In addition, bio-inspired nanotechnology, including vesicles, exosomes, or engineered cell membranes, endows the active-targeting capability to the specific lesion [2]. The incorporation of molecular imaging probes could also monitor the delivery and release behavior of nanomaterials using computed tomography (CT), magnetic resonance imaging (MRI), ultrasound (US), fluorescence imaging (FL), photoacoustic imaging (PAI), and some emerging imaging methods. Importantly, some nanomaterials can act as sensitizers to improve efficacy and increase bioavailability, thereby reducing tumor drug resistance. The development of multifunctional nanomaterials also endows nanocarriers with other biological effects, such as light response (photothermal therapy or photodynamic therapy), ultrasonic response (sonodynamic therapy or high-intensity focused ultrasound), magnetic response (magnetic hyperthermia), and other synergistic therapeutic effects.

However, there are still safety concerns, among which are the reactive oxygen species (ROS). Besides the immediate cytotoxicity to damage cell components, ROS also triggers signal pathways to cause necrosis, necroptosis, or apoptosis [3]. Nanomaterial-induced inflammation, both acute and chronic, increases the risk of liver fibrosis and pathological changes [4]. Genotoxicity, including damage to DNA structure, revealed potential carcinogenicity. Some evidence indicates that nanomaterial-induced epigenetic effects include abnormal DNA methylation and histone modifications, which could act as potential biomarkers for predicting the adverse effects of nanomaterials [5].

To address these hidden hazards, sufficient efforts are being made to focus on physical and chemical strategies. Rod-shaped nanoparticles seemed to reduce the uptake by the liver compared to spherical nanoparticles [6]. Various aspect ratios of different shapes have an influence on the retention time in organs [7]. Enhanced elasticity and deformability also help nanoparticles avoid recognition and sequestration by the MPS (mononuclear phagocyte system) [8]. Even the same element, with a different valence, displayed a disparity in hepatotoxicity. Under the same injected dose, 70% MnO nanoparticles can be metabolized by the liver within 48 h [9], while only approximately 50% Mn_3O_4 is eliminated in 1.5 weeks [10], indicating the metabolic process of nanoparticles *in vivo* is complex, and its safety requires a comprehensive evaluation.

Given that most nanomaterials are sequestered by the liver, we mainly review how to mitigate the damages of nanomaterials to the liver on a biological basis, including materials selection, surface modification of nanomaterials, bio-inspired construction, and some adjunctive or strategies, to provide ideas for the clinical translation of nanomedicine (Scheme 1).



Scheme 1: Illustration of strategies for nanomaterial-induced hepatotoxicity.

2 Mechanism of nanomaterial-induced hepatotoxicity

Conventional drug-induced hepatotoxicity is mainly based on metabolism or accumulation of the drug in hepatocytes, with activation of CD4 or cytotoxic CD8+ T-cells [11] leading to antigenic binding, which triggers an immune response, whereas nanomedicine-induced hepatotoxicity is characterized by free radical generation and oxidative stress [12,13]. Therefore, we focus here on ROS and inflammation, with a broader discussion of other related issues.

2.1 ROS and inflammation

Hepatotoxicity is often the most significant safety concern associated with nanomaterial toxicity. The main cause of hepatotoxicity is the production of ROS, such as monolinear oxygen species, superoxide anion radicals, oxygen radicals, peroxide ions, hydrogen peroxide, and hydroxyl radicals, which enter cells *via* endocytosis and trigger a series of oxidative stress-related events [14]. In liver LO2 cells, mitochondria-derived ROS were found to activate the NOD-like receptor protein 3 (NLRP3) inflammasome, which promotes caspase-1-dependent thermal apoptosis [15]. ROS-induced mitochondrial swelling, loss of inner membrane and cristae, and increased mRNA levels of caspase-12, a marker of mitochondrial-caspase pathway activation, were found in the livers of normal mice exposed to SiNPs, confirming mitochondrial damage and apoptotic signaling. Upregulation of p53, Bax, and cleaved caspase-3 expression, as well as down-regulation of Bcl-2 and caspase-3 levels, was also detected when human and rat hepatocytes were exposed to SiO_2 nanoparticles [16].

The vast majority of nanodrugs are exogenous chemicals that inevitably cause immune recognition and inflammatory response. In HepG2 cells, nanoparticles activate cellular stress response signaling pathways, including mitogen-activated protein kinase (MAPK) and NF-κB (nuclear factor-κ-gene binding) signaling pathways, with significant changes in the phosphorylation levels of stress-activated protein kinase such as ERK1/2, p38, and JNK. The levels of TNF, a pro-inflammatory factor that promotes lymphocyte infiltration and necrosis, and IL-8, a chemokine that recruits and activates neutrophils, were also significantly increased, whereas the expression of A20, an anti-inflammatory gene, was suppressed [17]. Similarly, mice exposed to multi-walled carbon nanotubes exhibited severe inflammatory cell infiltration in the portal vein region, cellular necrosis and localized necrosis, mitochondrial damage, and lysis.

Changes in gene expression involving the antigen processing and presentation pathways, cholesterol biosynthesis, the IL-6 signaling pathway, the cell cycle, and the metabolism of cytochrome P450 to xenobiotics were detected across genomes, with TNF-α and NF-κB signaling pathways showing the most significant changes [18]. Exposure of C57BL/6 mice to peptide-functionalized gold nanorods resulted in a decrease in the activity of the anti-inflammatory genes Arg-1 and IL-4, while at the same time, the levels of TNF-α, a marker of M1 macrophages, were very high, suggesting activation of this cell, and Arg-1 is a marker of M2 macrophages. The time course of the nanoparticle-induced inflammatory response was also investigated. Injected silica nanoparticles activate a variety of inflammatory signaling pathways at different time points, including the G1-S cell cycle, IL-10, IL-6 pathways, phagocytosis-related inflammatory pathways, and Th-17-derived pathways [19]. These results indicate that there are different time windows for specific blocking strategies. However, two questions need to be answered:

1) Does human nanomaterial-induced hepatotoxicity also share similar physiological courses?
2) Do different materials or the same material in different doses and states also trigger similar changes *in vivo*?

Inflammation caused by ROS is difficult to distinguish from other types of inflammation. However, persistent reports of the NF-κB pathway and TNF-α factor may highlight key locations for blocking the inflammatory cascade. NF-κB nuclear factor and erythroid 2-related factor (NRF2) may be crucial to indicate whether the level of ROS is out of control [20]. In addition, inhibition of M1 macrophage activity may be another strategy to reduce nanoparticle-induced hepatotoxicity (Figure 1). Mitochondrial protectants can also be considered in the future design of biomedical nanoparticles.

2.2 Lipoapoptosis

Liposomes, the most common organic materials used in biological applications, are well-documented to be hepatotoxic upon systemic administration of cationic liposomes, exhibiting significant liver biochemical function abnormalities and histological damage [21]. In Gregory's report, inflammatory extracellular vesicles (EVs) containing expression of tumor necrosis factor-associated apoptosis-inducing ligand (TRAIL) can be induced by lipid in death receptor 5 (DR5)-dependent manner [22]. DR5 is a promoter that regulates hepatocyte lipoapoptosis and inflammatory signaling [23], and the knockdown of DR5 *in vivo* could significantly reduce hepatocyte lipotoxicity. Blocking Rho-associated-

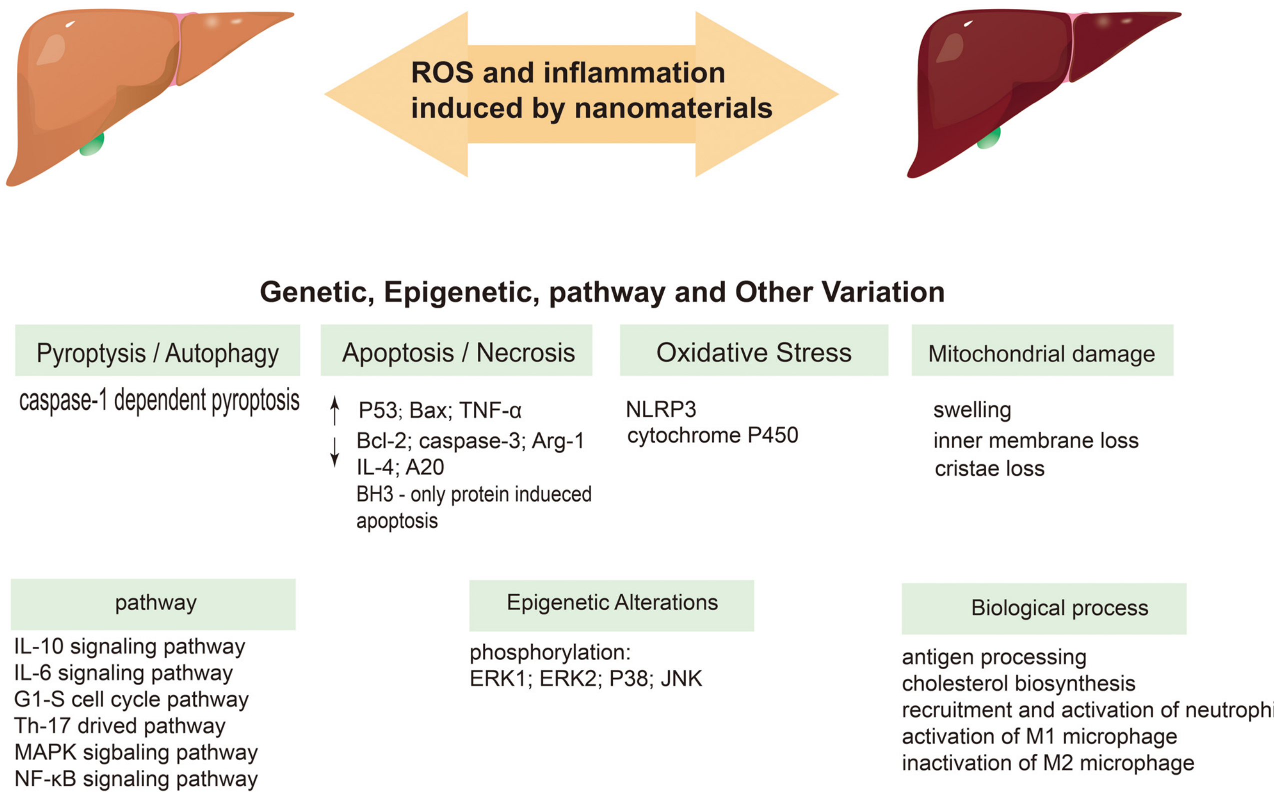


Figure 1: The genetic and epigenetic pathways and other variations in nanomaterial- induced hepatotoxicity.

coiled-containing protein kinase-1 (ROCK1), which promoted the release of EVs, could reduce lipid-induced liver damage [24]. Receptor-interacting protein kinase 1 (RIP1) also plays an important role in the expression of pro-inflammatory factors, such as the typical M1 macrophage markers IL-1β or IL-6, which act as pro-inflammatory factors and contribute to the inflammatory response in hepatocytes. From this perspective, the hepatotoxicity of EV applications deserves more attention. As emerging bio-inspired materials, EVs function as a drug delivery system that can deliver therapeutic drugs or imaging probes to designated disease sites through active targeting. Besides, the nanoscale size of EVs facilitates their passive targeting ability, which improves the potency of drug delivery and promotes diagnostic and therapeutic efficacy. Considering the potential role of lipid-induced EVs in the activation of pro-inflammatory macrophage, an in-depth assessment of the role of EVs in hepatotoxicity, particularly in the regulation of hepatic biochemical factors, is essential for biological applications.

However, though anti-DR5 chimeric antibodies work for tumor suppression [25], there are no reports on blocking DR5 to mitigate nanoparticle lipotoxicity. It remains to be further explored whether any small molecule or monoclonal antibody to DR5 can effectively inhibit hepatocyte lipoapoptosis *in vivo* (Figure 2).

2.3 Genotoxicity

The genotoxicity of nanoparticles has also caused great concerns. Researchers have found that titanium oxide nanoparticles deposited in liver DNA not only insert DNA base pairs but also bind to DNA nucleotides and alter the secondary structure of DNA. Furthermore, high doses of nano-anatase TiO_2 cause DNA breakage in hepatocytes [26]. Morphological scans show markedly reduced nuclei, nuclear vacuolization, and chromatin margination [27]. In HepG2 cells exposed to TiO_2 nanoparticles, DNA repair-related genes (including p53, MDM2, GADD 45α, and p21) were dramatically upregulated, and oxidative damage led to DNA strand breaks [28]. In another example, CuO nanoparticles induced the expression of 8-hydroxy-2′-deoxyguanosine(8-OH-dG), an indicator of oxidative DNA damage in the liver [29]. Nanoparticle-induced genotoxicity has also been reported in silica and gold nanoparticles, where significant DNA damage was detected after intravenous injection, especially in the smaller nanoparticles

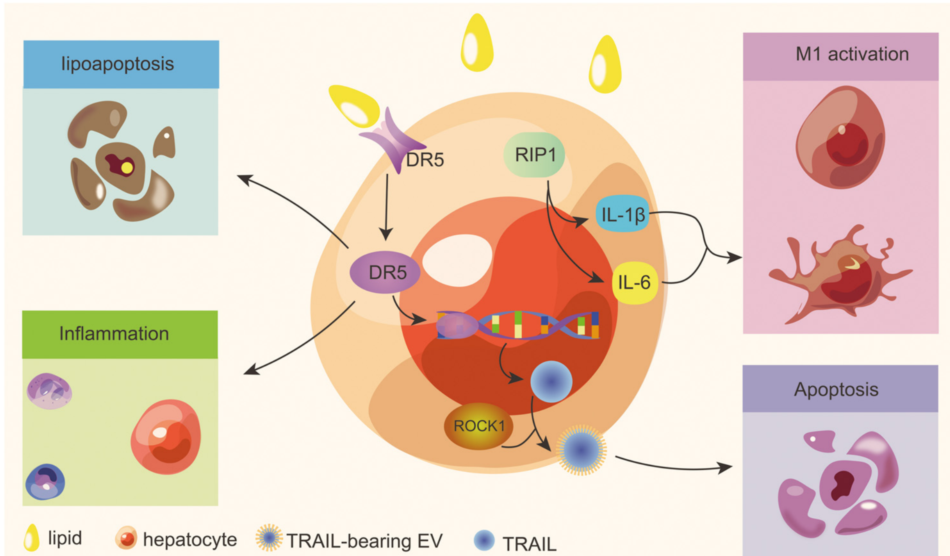


Figure 2: The mechanism of DR5-introduced lipoapoptosis. Lipid activates DR5, which regulates the expression of TRAIL and RIP1, causing inflammation and activating M1 macrophages. ROCK1 contributes to the release of TRAIL.

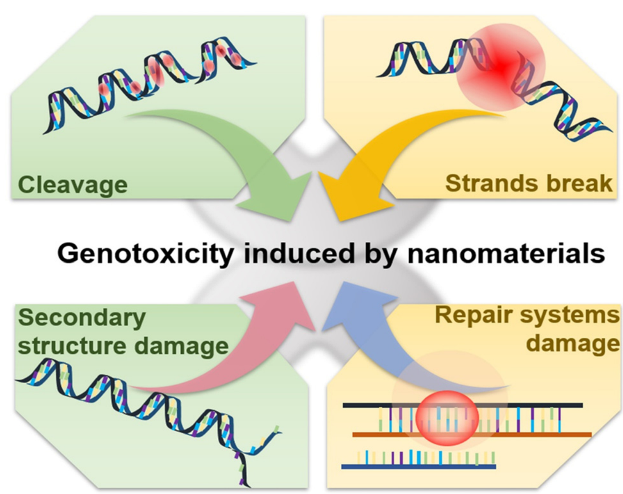


Figure 3: The genotoxicity induced by nanomaterials, including DNA cleavage, DNA strands break, DNA secondary structure damage, and DNA repair system damage.

[19,30]. All of these studies suggest that DNA damage caused by nanomaterials may lead to carcinogenicity and severe cellular degeneration (Figure 3).

3 Material selection for low hepatotoxicity in biological view

Material strategies to reduce hepatotoxicity are as follows: (1) selecting materials that can be degraded by more pathways in the body; (2) selecting materials that can be rapidly metabolized in liver; (3) targeting the site of the lesions, thus reducing the total amount of drugs; and (4) sustained and stable release of the drug, thus keeping the blood level low.

The longer metabolism time of iron nanoparticles compared to zinc or manganese is due to a later breakdown in the liver, particularly in Kupffer cells [31]. For organic materials, lipid H, lipid M, lipid P, lipid Q, lipid N, and lipid Y showed significantly less accumulation in the liver after intramuscular injection compared to lipid MC3. However, it must be recognized that these molecules, from the degradation of organic materials like hydrogel and lipids, would increase the liver burden [32,33] and aggravate hepatopathy [34].

Gelatin nanoparticles are good colloidal drug carriers for anticancer chemotherapy, which have, *e.g.*, an arginine–glycine–aspartic acid sequence identified by integrin αV (especially αVβ3). Integrin αV is highly expressed in tumor vasculature and endothelial cells lining tumor tissues but less so in normal organs [2]. From this, gelatin-based nanocarriers (GNPs) are also suited for the central nervous system as they may passively target the injured brain tissue or brain tumors upregulated by gelatinases A and B [35]. Organic nanomaterials have advantages such as high loading capacity and low hepatotoxicity, but they also have drawbacks like limited stability. In contrast, the opposite is metal-based nanomaterials. To mitigate hepatotoxicity, metal–organic frameworks (MOFs) have been designed. In 2006, it was discovered that MOFs can hold a high concentration of medication and release them steadily over time. Stability and stiffness from the metals

Table 1: Comparison of different hypotoxic materials for the nanocarriers and their mechanism to reduce hepatotoxicity

Nanocarrier	Categories	Mechanism	Subjects/cells	Ref.
Zinc oxide-engineered nanoparticles	Inorganic materials	Degraded by MPS in the endolysosomal compartments of phagocytic cells	BALB/c mice and Wistar–Han rats	[9,31,37]
MnO	Inorganic materials	Unknown hepatobiliary clearance pathway	Balb/c female mice	[9]
Lipid H	Organic material	Degraded by MPS or serum protein	Sprague–Dawley rats	[38]
cRGD–chitosan–gold nanoparticles	Organic materials (gelatin and hydrogel)	Targeting delivery	MCF-7 and HUVEC cells	[2]
5-FAM/FA/TP@Fe-MIL-101	Composite materials (MOF)	Targeting delivery	Balb/c nude mice	[39]
γ-CD-MOF	Composite materials	Sustained drug release	L929 cells	[40]
PCP-Mn-DTA@GOx@1-MT	Composite materials (MOF)	Targeting delivery	C57BL/6 mice and Balb/c mice	[41]

enable a high drug loading, while the safety and porosity of organic components ensure tunable release behaviors [36]. Works including stimuli-responsive MOF framework (*e.g.,* pH/ROS dual-sensitive) and tumor-designed MOFs with decoys have reported better therapeutic efficacy of MOFs with minimal damage to normal liver cells due to improved drug efficiency, controlled drug release, prolonged duration of action, and drug targeting [3,31,35–39] (Table 1).

4 Engineering strategies for modifying nanoparticles

Surface engineering can be achieved by targeting while preventing non-specific interactions. There are two common ways to alter the surface of nanomaterials: non-covalent conjugation and covalent conjugation, both of which can be used to target lesions and mitigate their hepatotoxicity.

4.1 PEGylation and conditional release modulation

When the nanomedicines enter the body, the surface coating of its nanoparticles with polyethylene glycol (PEG: PEGylation) prevents the nanoparticles from aggregating in the blood circulation and has a phagocytic effect. The MPS in the body has many opsonin-recognizing receptors on the cell surface, which can form a hydration cloud that sterically prevents nanomaterials from binding or interacting with the PEG chains immobilized on the surface of the nanomaterials, preventing the nanomaterials from combining or interacting with other nanomaterials or blood components from a three-dimensional structure [42,43]. The molecular weight (MW) and surface density of PEG are the main parameters affecting interactions and nanodrug metabolism; an MW greater than 2–10 kDa is essential for a low recognition level of MPS, partly due to less protein absorption [44,45].

PEG with MW less than 20 kDa are primarily metabolized in the renal system, whereas those more than 30 kDa are metabolized in the liver [46,47]. When PEGylated gold NPs are administered systemically, the circulation half-life is prolonged with MW increase between 2 and 10 kDa MW [48]. Also, it was shown that liver uptake of 5 kDa PEG was higher compared to 20 kDa PEG-coated NPs. In a subsequent study, NPs coated with 20 kDa PEG decreased hepatic uptake *in vivo* compared to NPs coated with 5 kDa PEG, resulting in prolonged circulation time [49]. Increased surface PEG density leads to PEG chain overlap and constitutes a maskant, which decreases the uptake of MPS cells by the liver [50,51]. Alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase level, and histopathological evaluation are the main indicators that support the hepatoprotective effect of PEG-coated gold nanomaterials [52]. However, besides the high cost, the shortcomings of conventional PEGylation involve obvious loss of efficacy, as the PEG chains may occupy the active sites of drugs [53,54], and most polyacids are difficult to degrade enzymatically [55].

High lactic acid level leads to paradoxically acidic extracellular and intracellular tumor microenvironments in almost all tumors. In order to coat nanomaterials with pH-responsive layers used to regulate the release of cancer chemotherapeutic drugs, researchers have coated the nanomaterials with poly(β-amino ester)(PBAE), whose tertiary amine residues may be ionized in an acidic environment. In BALB/c nude mice injected with A549 cells, doxorubicin (DOX)-coated PBAE nanomaterials were more efficiently absorbed by cancer tissues despite causing modest levels of hepatic function indicators (ALT and AST) [56].

In addition, the surface of nanomaterials can be modified with ligands (*e.g.*, peptides, nucleic aptamers, polysaccharides, or antibodies) that recognize antigens expressed on the surface of diseased cells to improve the specificity of nanodrug delivery. In SCID Beige mice, gelatin nanoparticle surface-modified with an epidermal growth factor receptor (EGFR)-targeting peptide were almost double as effective as PEG-modified or untreated nanoparticles for tumor targeting without adding any additional hepatotoxicity [57]. High levels of programmed death ligand protein-1(PD-L1) expressed in cancer cells are associated with immune evasion and a dismal prognosis. Hyperbranched, multivalent poly(amidoamine) dendrimers can be used to bind the PD-1/PD-L1 antibody. Nanoparticle–antibody conjugates promoted T-cell antitumor immunity while reducing tumor chemoresistance to DOX compared to PD-L1 human antibody and showed no additional hepatotoxicity [58].

4.2 Bioinspired cell membrane coating nanotechnology

Cell membrane coating nanotechnology further advances surface modification [59,60]. The particle cores of cell membrane-coated nanoparticles are covered by natural

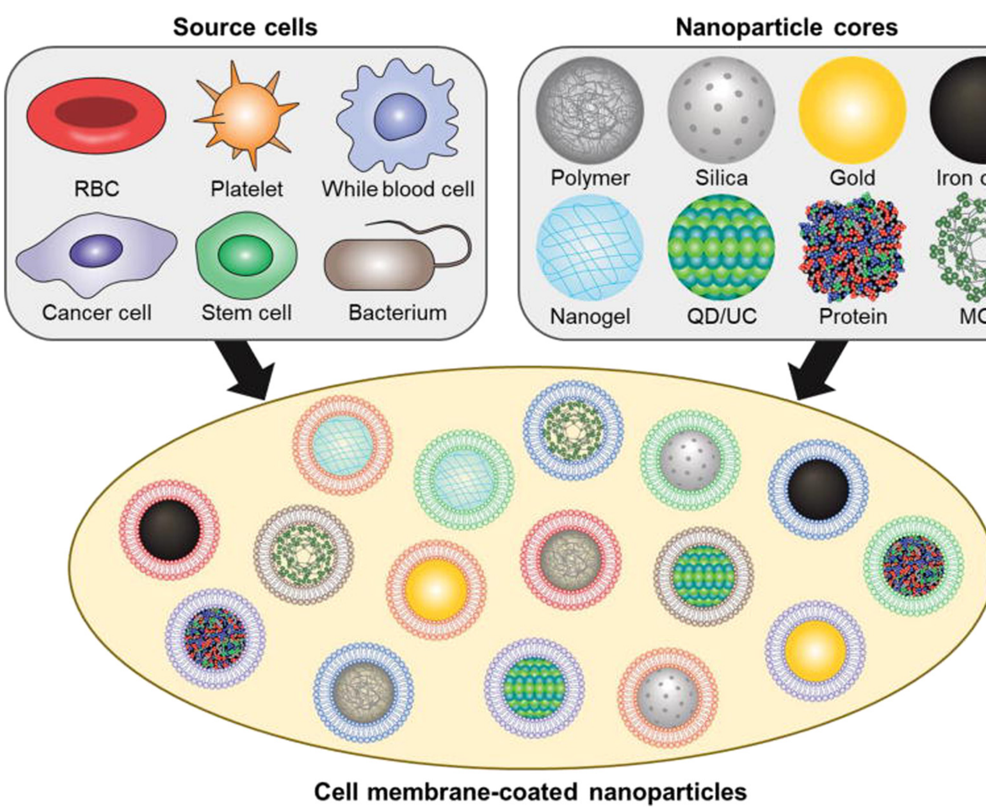


Figure 4: A drawing of nanoparticles with cell membrane coatings. Membrane sources for coating nanoparticles. Each cell membrane type may use different features to offer functionality to nanoparticulate cores, the substance of which can vary depending on the application [53]. Reproduced with permission from the study of Fang *et al.* [61]. Copyright 2018, WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

or artificial cell membranes and have some of the intrinsic features of source cells (Figure 4) [61].

Erythrocytes were the first cells of origin to be utilized to encapsulate cell membranes with nanoparticles and are also the most intensively researched cells in this field [62,63]. Erythrocytes are the best source of nanocarriers due to (1) the lack of organelles in this cell, (2) circulation in the blood for up to 4 months, and (3) the detoxification activity of its surface proteins. The liver is the primary organ responsible for the detoxification of hemoglobin and the majority of chemotherapeutic drugs. The toxin affinity of the erythrocyte membrane may be used to prevent the hemolytic impact of hemolysin [64], though mechanisms are not clear. RBC-membrane-coated nanomaterials carrying doxorubicin significantly increased the survival rates of C57BL/6 mice carrying EL4 cells compared to free doxorubicin administration in the same dose, while no significant increase in ALT and AST was detected, and low IL-6 levels indicated no acute liver and systemic responses [65]. Similar findings revealed that RBC membranes could bind DOX, thereby reducing its harmful activity, and their complexes are stable in serum, most likely due to the surface charge of RBC surface proteins of membrane-coated nanoparticles. In contrast to the total retention of PEG-coated nanoparticles of 11% (24 h after injection) and 2% (48 h after injection), the retention of RBC membrane-coated nanoparticles exhibited 29 and 16%, showing that RBC membrane coating was efficient in evading the reticuloendothelial system (RES) [62].

Besides RBC membranes, other sources such as leukocyte membranes, stem cell membranes, endothelial cell

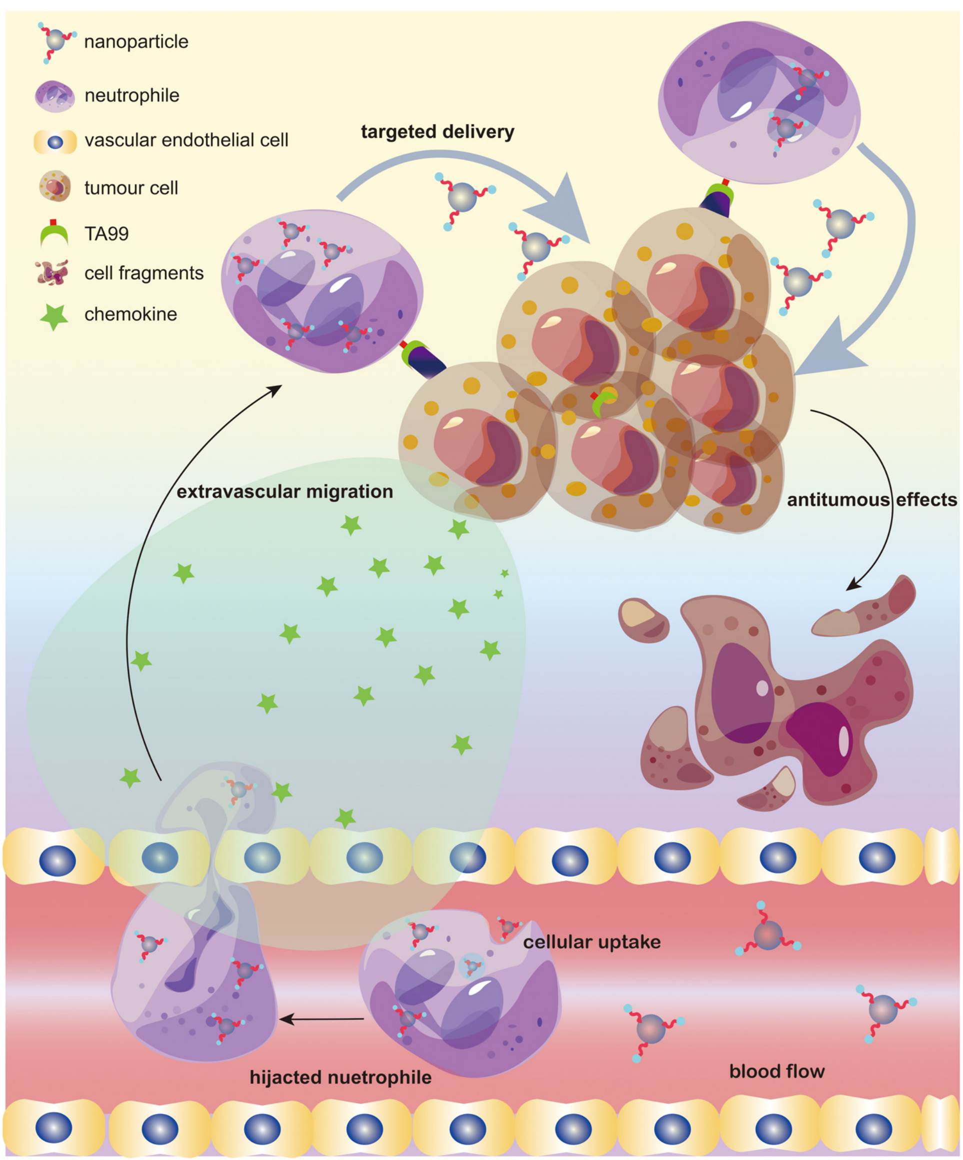


Figure 5: Diagram of hijacking cell strategy. Neutrophils hijacked by nanoparticles in the bloodstream are attracted by chemokines and then bind to tumor cells with TA99.

membranes, cancer cell membranes, and even hybrid cell membranes have shown promise for liver protection in the way of increasing the targeting of drug delivery; immune modulation or direct binding ability by surface proteins [58,66–68]. However, a certain amount of antigens or even autoantigens may be present in T/B cells and cause serious immune response [69–71].

5 Biological camouflage strategy

5.1 Hijacking cells

Besides MPS, the tumor vasculature and blood–brain barrier (BBB) remain barriers to nanodrug delivery [72]. A strategy to hijack cells *in vivo* across vessel barriers and to target the inflamed lesion can dramatically alleviate hepatotoxicity because of little liver uptake. Liberal amounts, excellent locomotion ability, and 8 h half-time make neutrophils the most popular platform for the strategy [73–75]. Among PEG, IgG, and anti CD11b antibody-modified nanoparticles, the CD11b Abs decorated nanomaterials have shown the highest uptake specificity of neutrophils. Under the conditions of acute inflammation induced by photodynamic therapy, the accumulation of CD11b nanoparticles was 35 times higher than PEG-modified nanoparticles in lesions [76]. TA99 administration further enhances the therapeutic effect due to antibody-dependent cellular cytotoxicity mechanisms [75], and the pretreatment of TA99 in a mice model of melanoma has the following three merits: (1) promoting neutrophils to infiltrate into tumors; (2) significantly increased uptake radio of the nanoparticles by neutrophil, and thus (3) improved the survival rate (Figure 5) [77].

5.2 Transient depletion of host Kupffer cells

Kupffer cells in hepatic sinusoids are resident macrophages that play a major role in phagocytosing nanoparticles in the bloodstream, consistent with the role of MPS [78]. A previous study has shown that transient depletion of host Kupffer could alleviate liver injury induced by alcohol in rats [79]. This strategy is equally effective for nanoparticle-induced hepatotoxicity. Substances including gadolinium chloride [80], methyl palmitate [81], dextran sulfate (500 kDa) [82], carrageenan [83], and clodronate liposomes [78] were used for transient depletion of Kupffer cells. In mice models bearing SUIT-2 cells (a human pancreatic adenocarcinoma cell line), injection of clodronate caused almost complete depletion of Kupffer cells on Days 2 and 3, and the amount of Kupffer cells started to recover on Day 5. Clodronate pretreatment reduced the accumulation of doxorubicin from 6.4 to 4.7 μg/g-tissue by Kupffer cell depletion [84]. However, recovery in cell mass does not mean recovery in cell quality. All these studies did not present convincing evidence that regenerated cells have no genetic damage and epigenetic changes to further induce cirrhosis or malignant transformation. Notably, depletion of Kupffer cells may lead to significant accumulation of drugs in other organs (*e.g.*, spleen, lung, heart, or kidney). Whether this strategy poses a risk by disrupting the immune system, especially for those with immunologic deficiency and serious infection, needs to be confirmed.

6 Drugs and other possible strategies

In addition to the development of nanoparticles, combination therapy with other drugs and methods (*e.g.*, ultrasound or photodynamic therapy) may be considered to alleviate hepatotoxicity. Standard methods of clinical treatment of drug-induced liver injury include *N*-acetylcysteine and corticosteroids [85,86]. However, there are no specific treatments for nanomaterial-induced toxicity.

6.1 Hepatoprotectors

There are a number of hepatoprotective species, including vitamin E (Vit E), α-lipoic acid (ALA), quercetin (Qur), and arginine (Arg), which act as antioxidants mainly by inhibiting the peroxidation of fatty acids and by increasing the levels of cysteine and glutathione in the liver [87–89]. In a study aimed at comparing the hepatoprotective effects of these four antioxidants with those of melanin, melanin was shown to be the most significant in ameliorating gold nanoparticle-induced hepatic dysfunction, as measured by a comprehensive evaluation of all indicators of liver functions in experimental male rats [90]. ALA also downregulated iNOS, which is responsible for nitrosative stress, and reduced the overexpression levels of apoptotic genes C-Jun and C-Myc in the liver [91]. Moreover, ALA reduces CNP accumulation in hepatic tissue by unknown mechanisms [91].

In terms of natural extracts, beetroot juice has also shown powerful liver protective effects and anti-inflammatory and anti-mutagenic properties [92]. The hepatoprotective effect of beetroot juice is supported by the fact that the effects of oxidative stress on silver nanoparticle-induced

Table 2: Comparison of different hepatoprotectors and their mechanism to reduce hepatotoxicity

Hepatoprotectors	Mechanism	Ref.
Melanin	Anti-inflammation and activating antioxidant system	[93]
α-Lipoic acid (ALA)	Relieving nitrosative and inhabiting apoptosis	[91]
Beetroot juice	Anti-inflammation and attenuate ROS, activating the antioxidant system	[92]

liver injury in rats can be attenuated by maintaining the activity of antioxidant systems (*e.g.*, SOD and CAT) and by increasing the amount of GSH in the liver, and by the improvement in the expression of p53 and anti-apoptotic Bcl-d2, with little DNA fragmentation [92] supported the hepatoprotective effects of beetroot juice. However, it is unclear what played a major role in this effect. Grape seed proanthocyanidin extract (GSE) also alleviated TiO_2 nanoparticle-induced liver injury and oxidative stress in rats. GSE treatment mediated the expressions of TLR-4, NF-κB, NIK, and TNF-α genes and maintained a high level of GSH in the liver.

Despite various advances, it is disputed whether the effects of hepatoprotectors could be repeated on animal models induced by different nanomaterials. Most studies focused on anti-inflammation strategy. Unfortunately, no reports have shown a critical factor in nanoparticle-induced inflammation, probably because there are too many imponderables, for example, sizes, doses, or subjects themselves, to distinguish one significant blocking target. Thus, it is practical to try compound hepatoprotection in clinical study and practice (Table 2).

6.2 Ultrasound-assisted strategy

The ultrasound cavitation effects create pores between cells, which means improved vascular permeability and, thus, effective nanodrug transportation and fewer side effects [94]. Ultrasound-induced transient opening of the BBB is of great significance for nanoparticles to reach the central nervous systems and target lesions. Temozolomide (TMZ), a clinical first-line

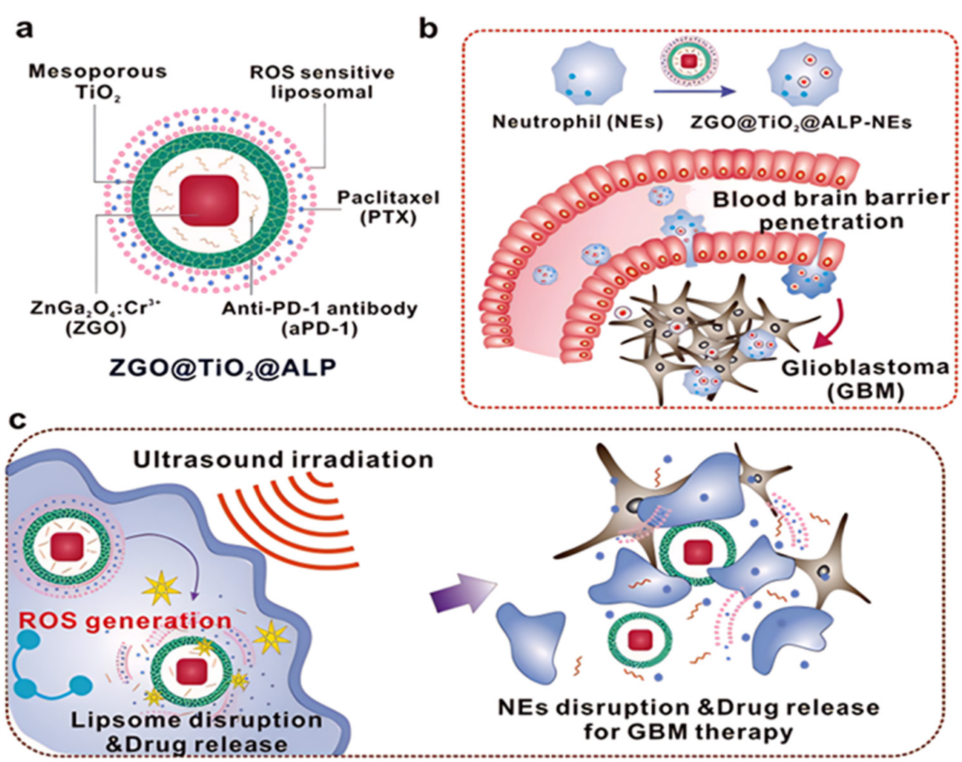


Figure 6: Schematic illustration of hollow TiO_2 covered persistent luminescent nanosensitizer for ultrasound amplified chemo/immuno GBM therapy. (a) Composition of ZGO@TiO_2@APL. "A" represents anti-PD-1 antibody, "L" represents liposome, and "P" represents PTX in the abbreviation "ALP". (b) BBB penetration process of ZGO@TiO_2@APL-NEs. ZGO@TiO_2@APL was loaded by neutrophils to form ZGO@TiO_2@APL-NEs in vitro. The injected ZGO@TiO_2@APL-NEs could be attracted by the inflammation in GBM to traverse the BBB. (c) Ultrasound-triggered drug release from ZGO@TiO_2@APL-NEs for GBM therapy. Activated by ultrasound, ROS was generated from ZGO@TiO_2@ALP to break up liposome coverage for PTX, and an anti-PD-1 antibody was released to kill the tumor and induce local inflammation, which in turn attracted more ZGO@TiO_2@ALP-NEs to GBM sites for sustained therapy [97]. Reproduced with permission from the study of Li *et al.* [97]. Copyright 2021, Advanced Science, published by Wiley-VCH GmbH.

glioma chemotherapy drug, can be loaded in a zirconium-based frame, which collapses under ultrasonic stimulation due to low-frequency oscillations and cavitation effect [95]. Ultrasound can be combined with other strategies to further improve efficacy and alleviate hepatotoxicity. Nanoparticles modified with angiopep-2 peptide, a ligand targeting LRP1 (low-density lipoprotein receptor-related protein 1), which is highly expressed in tumors, achieved glioma-specific delivery in mice, but nanoparticles remain in the liver [96]. Further attempts included a nanodrug for luminescence imaging. Its hollow acoustic-sensitive TiO_2 shell produced ROS for controlled drug release. It also encapsulates an immune checkpoint inhibitor (anti-PD-1 antibody) for glioma immunosuppression and paclitaxel. *In vivo,* liver luminescence images show fewer residues in the livers of C57 mice using ultrasound compared to those not using ultrasound [97]. Compared with photodynamic therapy and intervention techniques, ultrasound is non-invasive, focusable, and more penetrating, which also makes it difficult to handle ultrasound-induced bleeding. Whether ultrasound irradiation does not influence molecular structural stability of loading cannot be neglected (Figure 6) [98,99].

7 Conclusions and discussion

In this article, we discuss innovative ways to reduce liver damage caused by nanoparticles. Hydrogel and lipids are recommended for their high degree of biocompatibility. There are also more niche options, such as gelatin-based nanoparticles for brain medication delivery. Surface modification, bioinspired nanotechnology, and techniques like cell hijacking can be used to avoid liver uptake and achieve targeted medication distribution. Transient reduction of Kupffer cells reduces nanoparticle accumulation in the liver despite safety concerns. Hepatoprotective agents have unique pharmacological effects that help to reduce hepatotoxicity. Ultrasound, for example, can be used to aid nanoparticles in infiltrating lesions and to regulate the release of loads contained inside the nanoparticles.

Our knowledge about nanoparticle-induced damage is still limited, and few common features could cover most pathological processes. It seems that a special type of nanoparticle causes similar liver injury. Therefore, toxicological research focusing on FDA-approved carriers or nanoparticles of clinical translational value should be encouraged. Most studies have determined liver health only by testing for AST, ALA, and morphology. To thoroughly examine all potential alterations at the molecular level, it is advisable to provide evidence from protein mass spectrometry, RNA sequence, or gene sequencing. Second, studies on the long-term effects of nanoparticle-induced liver injury are lacking. However, cancer and AIDS treatment require long-term, often lifetime, care. Therefore, it is crucial to study the long-term effects of routinely used nanoparticles on the liver. In order to guide clinical therapy, we need more information to demonstrate a quantifiable link between targeted drug delivery and additional adjunctive techniques (*e.g.,* ultrasonography) and their indirect hepatoprotective effects.

There is a need to investigate some overarching therapy strategies for acute liver damage caused by nanoparticles for usage in clinical settings. The contradiction between the anti-tumor effect of ROS and its toxicity cannot be ignored. In order to maximize the protective effects on the liver, it may be necessary to combine several approaches.

In the future, 3D liver models may be a better option for *in vitro* assessment of hepatotoxicity [100–102]. In addition, it may be possible to develop small molecules or monoclonal antibodies against receptors such as DR5 or to inactivate Kupffer cells. Efforts to reduce the costs of cell membrane coating nanotechnology and materials are significant for clinical transformation. The development of wearable (ultrasound) devices could also assist in the long-term control of nanodrugs to a great extent [103].

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