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REVIEW

# Hepatotoxicity of Nanoparticle-Based Anti-Cancer Drugs: Insights into Toxicity and Mitigation Strategies

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**Abstract:** Despite significant progress in developing novel, efficient nanoparticle-based anticancer drugs, hepatotoxicity remains a major challenge. The liver, as the primary organ responsible for detoxification, is particularly susceptible to nanoparticle accumulation, particularly through the action of Browicz-Kupffer cells (B-KCs) and liver sinusoidal endothelial cells (LSECs). These phagocytic cells accumulate nanoparticles, leading to the production of reactive oxygen species (ROS), interleukin 1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α), which ultimately cause hepatocyte damage. In recent years, various nanoparticle modification strategies have been investigated to reduce hepatotoxicity. One of the most common and effective approaches is the PEGylation of liposomes and graphene nanoparticles, which decreases their uptake by the liver via the reticuloendothelial system (RES). Other strategies to mitigate hepatotoxicity are also being explored, including the incorporation of negatively charged lipids into liposomes, charge manipulation of inorganic-organic nanoparticles, the use of specific protein-based nanoparticles that selectively bind to cancer cells (thereby reducing hepatic uptake), the use of appropriate viral capsids in the production of virus-like protein-based drugs, and the manipulation of the size of protein, metal and graphene nanoparticles. Moreover, modifications aimed at pH-responsive drug release are employed in liposomes, self-assembled and graphene nanoparticles. This article discusses several types of nanoparticles used as carriers in currently approved therapies and explores potential strategies to minimize their hepatotoxicity.

**Keywords:** hepatotoxicity, nanoparticles, cancer treatment, Browicz-Kupffer cells, endothelial cells

## Introduction

Significant progress has been made in cancer treatment in recent years. Due to its systemic approach, chemotherapy remains a cornerstone of oncology, as it can target cancer cells throughout the body, including those that have metastasized. However, its effectiveness is limited to only a subset of patients. Chemotherapy has been shown to be effective against various cancers, including leukemia, lymphoma, breast cancer, lung cancer, colorectal cancer, and ovarian cancer.

Ongoing chemotherapy research aims to improve efficacy while minimizing adverse effects. These effects can range from mild symptoms, such as nausea and hair loss, to severe complications, including cardiac dysfunction and cognitive impairment. Certain chemotherapy drugs are notably associated with organ-specific toxicities. For instance, doxorubicin has been linked to the development of cardiomyopathy, and bleomycin has been associated with pulmonary fibrosis. Furthermore, many chemotherapy drugs can induce liver damage, including anti-tumor antibiotics (eg, mitomycin and dactinomycin) and platinum-based agents (eg, oxaliplatin and cisplatin). One promising strategy for mitigating these adverse effects is the precise delivery of chemotherapeutic agents via nanoparticles.[1–3]

Nanotechnology has emerged as a pivotal element in advancing drug delivery systems. Nanoparticles, such as liposomes and polymeric nanoparticles, are engineered to deliver drugs directly to target cells. This enhances therapeutic efficacy and minimizes the side effects commonly associated with traditional delivery methods. These nanoscale systems can traverse biological barriers, release drugs in a controlled manner, and respond to specific internal stimuli, such as changes in pH or temperature.[4,5]

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One of the key advantages of nanoparticle-based drug delivery systems is their ability to target tumor cells. This targeting is largely driven by the enhanced permeability and retention (EPR) effect, which causes nanoparticles to accumulate in tumor tissues because of their leaky vasculature.[6,7] This mechanism has been shown to increase the concentration of therapeutic agents at the tumor site. This reduces systemic toxicity by limiting exposure to healthy tissues.[8] The EPR effect is a tumor-specific phenomenon influenced by vascular permeability factor production and defective blood vessels. These vessels supply tumor tissues with essential nutrients and oxygen, supporting rapid growth. This distinctive vascular structure promotes the transport of macromolecules, facilitating passive targeting.[9] Delivery efficiency is determined by a variety of factors, including the size, shape, and surface charge of the nanoparticles. These factors interact with the tumor microvasculature and microenvironment and play a crucial role in delivery efficiency.[10] Therapeutic macromolecules typically require a circulation time of at least six hours and an apparent molecular weight exceeding 40–50kDa to achieve sufficient accumulation in neoplastic tissue.[11,12] Additionally, the pore size cutoffs of tumor vasculature range from 400 to 600 nm in diameter,[13] with optimal tissue absorption occurring for supramolecular assemblies around 100 nm in diameter.[14,15]

Moreover, nanoparticles can be engineered to carry multiple therapeutic agents simultaneously, enabling combination therapies that can target different pathways involved in cancer progression.[6] This capability is particularly valuable for overcoming drug resistance, a common challenge in cancer treatment. Delivering multiple agents in a single nanoparticle system has been shown to improve treatment efficiency and reduce the likelihood that cancer cells will develop resistance.[16,17]

Nanoparticle-based drug delivery systems have emerged as a promising strategy, particularly for treating solid tumors. Improving therapeutic efficacy and minimizing systemic toxicity are of paramount importance in these cases. These systems use the unique physicochemical properties of nanoparticles to enhance drug solubility and stability and to deliver drugs more precisely to tumor sites. Currently, many types of nanoparticles are undergoing clinical trials, and several have received regulatory approval for use in cancer therapy (Table 1).

Despite the wide use of nanoparticle-based anticancer drugs, their toxicity, particularly hepatotoxicity, remains a substantial concern.

As the primary organ involved in drug metabolism and detoxification, the liver is susceptible to drug-induced toxicity.[23] When drugs are administered to the bloodstream, they undergo metabolic processes in the liver. The resulting metabolites or parent compounds can directly or indirectly damage this vital organ.

In recent years, the hepatotoxicity of nanoparticles, particularly in drug delivery systems for anticancer therapies, has received significant attention. Research has demonstrated that the interaction of nanoparticles with liver cells can trigger adverse effects such as oxidative stress, inflammation, and apoptosis.

A major cause of hepatotoxicity is the accumulation of nanoparticles in Browicz-Kupffer cells (B-KCs). These cells can contribute to hepatotoxicity by producing inflammatory mediators such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1b),[24] and reactive oxygen species (ROS). These mediators can lead to hepatocyte dysfunction, necrosis, and apoptosis. Furthermore, the activation of B-KCs has been associated with the secondary activation of hepatic stellate cells (HSCs). This further exacerbates tissue fibrosis and injury by enhancing extracellular matrix deposition and altered tissue remodelling.[24] In the context of nanoparticle-based drug delivery, B-KCs present a substantial challenge because nanoparticles are often sequestered by the mononuclear phagocyte system, which includes B-KCs in the liver. This sequestration can limit nanoparticle delivery to the target site, increasing hepatotoxicity.[25–27] This phenomenon, referred to as the "Browicz-Kupffer cell barrier", can significantly diminish the therapeutic efficacy of nanoparticle-based drugs.[25]

Liver sinusoidal endothelial cells (LSECs) have been shown to play a role in nanoparticle-induced hepatotoxicity. LSECs serve as a selective barrier within the hepatic sinusoid and possess specialized properties that facilitate the exchange of materials between the blood and liver parenchymal cells.[28] LSECs can efficiently take up nanoparticles and other macromolecules, primarily through clathrin-mediated endocytosis. Studies have shown that long-term exposure to certain nanoparticles can lead to the activation of genes and markers linked to fibrosis. This suggests that LSECs may play a role in the development of liver fibrosis.[29] During periods of liver stress or injury, LSECs can undergo capillarization, losing their fenestrated morphology, which is essential for their filtering function[30] (Figure 1).

In the following sections, we will review the primary types of nanoparticle-based anticancer drugs and explore of methodologies for mitigating their hepatotoxicity.

**Table 1** Approved Nanoparticle-Based Anticancer Drugs

| Nanostructure | Product | Drug | Indication | Company | Approval (Year) |
|---|---|---|---|---|---|
| Liposome-based nanoparticles | Doxil | Doxorubicin | Kaposi's sarcoma, ovarian Ca, multiple myeloma. | Ortho Biotech | FDA (1995) |
| | Caelyx | Doxorubicin | Metastatic breast, Ca., ovarian Ca., Kaposi's sarcoma, and multiple myeloma | Schering-Plough | EMA (1996) |
| | DaunoXome | Daunorubicin | Kaposi's sarcoma | Galen | FDA (1996) |
| | DepoCyt | Cytarabine | Neoplastic meningitis | Pacira Pharmaceuticals | FDA (1999) |
| | Myoce | Doxorubicin | Metastatic breast Ca. | Teva UK | EMA (2000) |
| | Lipusu | Paclitaxel | Breast, lung and ovarian cancer | Luye Pharma | NMPA (2006) |
| | Mepact | Mifamurtide | Osteosarcoma | Millenium | EMA (2009) |
| | Marqibo | Vincristine | Acute lymphoid, leukaemia | Spectrum | FDA (2012) |
| | Onivyde | Irinotecan | Pancreatic Ca., Colorectal Ca. | Merrimack | FDA (2015) |
| | Vyxeos | Daunorubicin Cytarabine | Acute myeloid, leukaemia | Jazz Pharmaceuticals | EMA (2018) |
| Protein-based nanoparticles | Oncaspar | Pegaspargase | Acute lymphoblastic leukaemia | Les Laboratoires Servier | FDA (1994) |
| | Ontak | Denileukin Diftitox | Cutaneous T-cell lymphoma | Les Laboratoires Servier | FDA (1999) |
| | Eligard | Leuprorelin acetate | Prostate cancer | Recordati Industria Chimica e Farmaceutica | FDA (2002) |
| | Abraxane | Paclitaxel | Breast Ca. Non-small lung Ca., Pancreatic Ca. | American Biosciencem, Inc. | FDA (2005) |
| | Kadcyla | DM1 (or Emtansine) | HER2+ breast Ca. | Roche Genentech | EMA (2013) FDA (2013) |
| | Pazenir | Paclitaxel | Metastatic breast Ca., metastatic adenocarcinoma of the pancreas, non-small cell lung Ca. | Ratiopharm GmbH | EMA (2019) |
| Metallic nanoparticles | NanoTherm | Fe2O3 | Glioblastoma, prostate, and pancreatic Ca. | Magforce | EMA (2013) |
| | Hensify | HfO2 | Locally advanced soft tissue sarcoma (STS) | Nanobiotix | EMA (2019) |
| Self-assembled nanoparticles | Genexol-PM | Paclitaxel | Head and neck, breast cancer | Samyang Biopharmaceuticals Corporation | Korea (2006) |
| | Nanoxel | Docetaxel | Metastatic breast cancer, ovarian cancer, non-small -cell lung cancer, prostate, gastric, esophageal, squamous cell carcinoma in the head and neck | Fresenius Kabi | DCGI (2007) |

**Notes**: Graphene and inorganic-organic nanoparticles are not yet approved for cancer therapy in humans. While these nanoparticles, have shown promising results in preclinical studies for cancer treatment, they are still under development and have not progressed to clinical trials or regulatory approval. Data from these studies.[18–22]

# Nanoparticles-Based Anticancer Drugs (Figure 2)

## Liposome-Based Nanoparticles

Liposomes are among the most widely studied and clinically utilized nanoparticle systems. These spherical vesicles are generally categorized as either multilamellar or unilamellar vesicles and play a fundamental role in drug delivery by

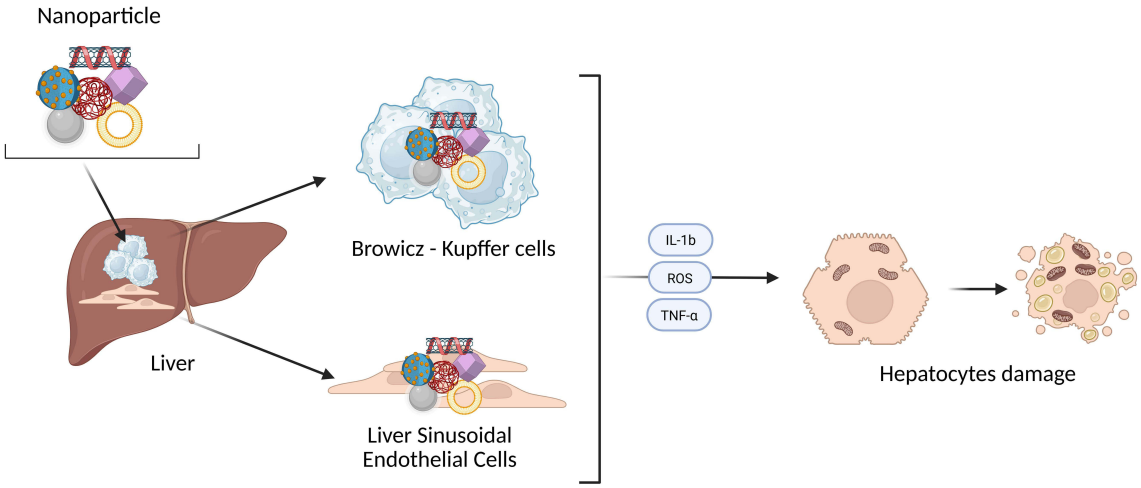


**Figure 1** Mechanism of nanoparticle-induced hepatotoxicity. Liver macrophages, known as Browicz-Kupffer cells (B-KCs) and liver sinusoidal endothelial cells (LSECs), internalize nanoparticles by phagocytosis. Upon nanoparticle uptake, these cells generate reactive oxygen species (ROS) and secrete tumor necrosis factor-alpha (TNF-α). The increased production of ROS and TNF-α leads to oxidative stress and inflammatory responses, which collectively contribute to hepatocyte damage. Created in BioRender. Taciak, B. (2025) https://BioRender.com/ucmzgur.

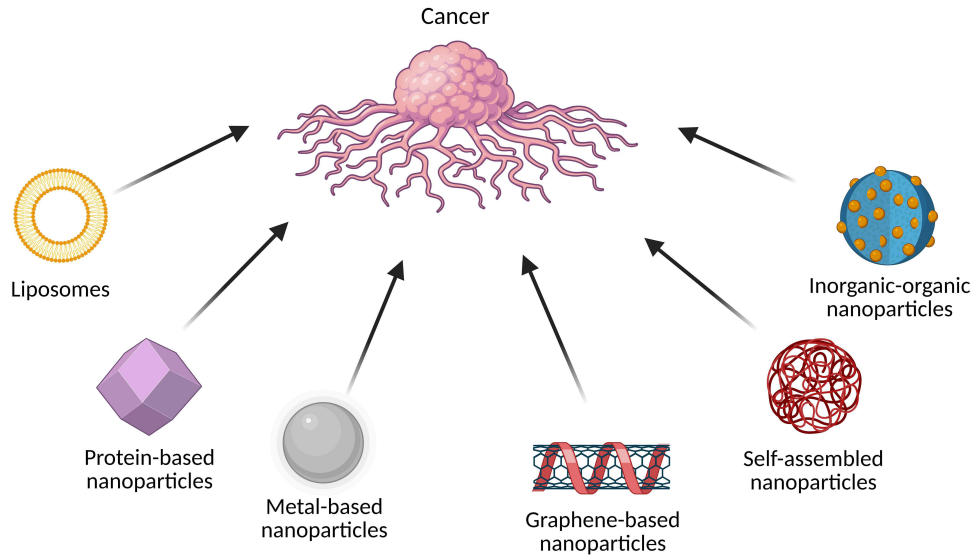


**Figure 2** Selected nanoparticles used in anticancer therapy. The application of nanoparticles in modern anticancer therapies enables improved biodistribution of drugs to tumor tissues, which may reduce off-target toxicity. However, their use remains associated with hepatotoxicity. Created in BioRender. Taciak, B. (2025) https://BioRender.com/j3mhlsa.

encapsulating both hydrophilic and hydrophobic agents within their aqueous core and lipid bilayer, respectively.[31,32] For instance, encapsulating cisplatin in sterol-modified phospholipid liposomes has been shown to improve antitumor efficacy compared to traditional formulations. This highlights the potential of liposomal modifications to enhance therapeutic outcomes.[33] Similarly, liposomal formulations have been shown to significantly increase drug uptake in cancer cells. For example, liposomal doxorubicin enhances the cytotoxic effects against tumor cells.[34] Cationic liposomes have also gained attention for their role in co-delivering small interfering RNA (siRNA) with chemotherapeutic agents, which enables a synergistic effect against resistant cancer cells.[34,35] The co-encapsulation of multiple drugs within liposomes has also been explored as a strategy to overcome multidrug resistance (MDR) in cancer therapy. For example, liposomal formulations containing both disulfiram and doxorubicin have been shown to reverse MDR in breast cancer cells by inhibiting P-glycoprotein, which is a key efflux pump responsible for drug resistance.[36] This co-delivery approach enhances treatment efficacy and reduces the required drug dose, thereby minimizing side effects.[37]

Liposomes are versatile and can be used to treat several types of cancer, including breast, lung, and ovarian. Liposomal doxorubicin (Doxil®), in particular, has received clinical approval for the treating of multiple myeloma and AIDS-related Kaposi's sarcoma, which demonstrates its efficacy in real-world oncology applications.[38]

In recent years, a specific type of liposome called a cubosome has been developed. Cubosomes are lipid-based nanocarriers with a bicontinuous cubic internal structure. Due to their high drug encapsulation efficiency, controlled release properties, and versatility in functionalization, they have emerged as promising platforms in cancer treatment.[39,40] Their unique architecture, consisting of an interconnected network of aqueous channels separated by lipid bilayers, enables the simultaneous incorporation of both hydrophilic and hydrophobic therapeutic agents. This is essential for effectively delivering chemotherapeutics to tumor.[39,40]

## Protein-Based Nanoparticles

Due to their biocompatibility, ability to target specific tissues, and controlled drug release properties, protein-based nanoparticles (PNPs) offer significant advantages in cancer therapy. They enhance drug accumulation in tumor tissues via the enhanced permeability and retention (EPR) effect, which is especially useful for treating solid tumors.[41]

PNPs can consist of multiple asymmetric subunits that self-assemble into highly symmetric three-dimensional hollow structures, typically ranging from 10 to 100 nm in diameter. Common structural symmetries used in biomedical applications include icosahedral, octahedral, and tetrahedral arrangements.[42,43] The hollow interior of such PNPs allows for the encapsulation of a wide range of therapeutic agents, which increases their potential applications in drug delivery.[44]

In addition to drug delivery, protein-based nanoparticles can exhibit immunogenic properties that enhance the antitumor immune response. They efficiently target antigen-presenting cells (APCs), significantly boosting antigen uptake by dendritic cells (DCs), key players in the initiation of adaptive immunity. Studies suggest that encapsulating soluble protein or peptide antigens within 20–50 nm nanoparticles can improve lymphatic drainage, enhance antigen presentation, and strengthen immune responses against tumors.[45]

One key example of a protein-based anticancer therapy is an antibody-drug conjugate (ADC). ADCs consist of monoclonal antibodies that are linked to cytotoxic drugs. This enables the drugs to be delivered directly to cancer cells that express specific antigens. This targeted approach improves the therapeutic index by concentrating the cytotoxic effects at the tumor site while reducing systemic toxicity.[46] Advances in ADC design have focused on optimizing linker chemistry and drug payloads to improve stability and efficacy.[47] For example, cleavable linkers that release the drug once inside cancer cells have shown promise in enhancing treatment efficacy.[46]

Virus-like particles (VLPs) are a prominent class of protein-based nanoparticles. Due to their unique structural properties and ability to induce immune responses, VLPs have gained significant interest in drug delivery and cancer immunotherapy. These non-infectious, self-assembled structures mimic viral morphology while lacking genetic material, making them safe for therapeutic use. VLPs can encapsulate various therapeutic agents, including chemotherapeutics and immunomodulatory compounds. This positions them as a versatile platform for targeted drug delivery in cancer treatment.[48,49] Encapsulating chemotherapeutic agents within VLPs enhances drug stability and bioavailability, thereby improving therapeutic efficacy.[50,51] For instance, Zhao et al showed that self-assembled VLPs made from rotavirus proteins could effectively deliver doxorubicin, thereby increasing its anticancer efficacy.[52]

## Metal-Based Nanoparticles

Metal-based nanoparticles have emerged as a promising drug delivery platform for cancer treatment. They offer unique advantages, such as enhanced stability and targeted delivery. They also have the ability to combine therapeutic and diagnostic functions.

One of the key advantages of metal-based nanoparticles, such as gold and silver, is that they can easily be functionalized with targeting ligands. This feature enables the selective delivery of anticancer drugs to tumor cells while minimizing exposure to healthy tissues. For instance, bombesin-functionalized gold nanoparticles have demonstrated receptor specificity for cancer cells, thereby enhancing their therapeutic efficacy in vitro and in vivo.[53]

In addition to their targeting capabilities, metal nanoparticles can also enhance the therapeutic effects of conventional chemotherapeutics through mechanisms such as photothermal therapy. For example, liquid-metal core-shell particles

have been developed to deliver doxorubicin and provide photothermal treatment when exposed to light, leading to increased cancer cell death.[54] This multifunctional approach is a significant advance in developing more effective cancer therapies.

Metal nanoparticles can improve the solubility and stability of poorly soluble drugs. Gold nanoparticles (AuNPs), in particular, have been extensively studied for their ability to encapsulate various chemotherapeutic agents, thereby improving their bioavailability.[55]

Moreover, some metal nanoparticles act as therapeutic agents. Silver nanoparticles (AgNPs), for example, exhibit intrinsic cytotoxic properties against cancer cells.[56] They generate reactive oxygen species (ROS), which induce apoptosis in cancer cells. This enhances the overall therapeutic effect when AgNPs are used in combination with other drugs.[57] Furthermore, the photothermal properties of certain metal nanoparticles, such as gold, enable localized heating when exposed to light. This results in the selective destruction of tumor cells while sparing healthy tissue.[58]

## Self-Assembled Nanoparticles

Recent studies highlight self-assembled nanoparticles as a dynamic and versatile approach in cancer therapy. They offer significant advantages over conventional drug delivery systems, including improved targeting, controlled drug release, and minimized systemic toxicity. These nanoparticles form through noncovalent interactions, including hydrogen bonding and π-π stacking, which are noncovalent interactions between the pi bonds of aromatic rings, as well as hydrophobic effects. These interactions allow for the spontaneous organization of building blocks, such as peptides, small organic molecules, and polymers, into well-defined nanostructures.[59] Such self-assembly processes enable the incorporation of both hydrophilic and hydrophobic therapeutic agents, maximizing payload diversity while facilitating enhanced penetration and retention in tumor tissues. Self-assembled nanoparticles present a multifaceted platform capable of targeted drug delivery, controlled release, and synergistic combination therapy. These properties are critical for overcoming the limitations of traditional chemotherapeutics and immunotherapies.

## Graphene-Based Nanoparticle

Polymeric nanoparticles represent a promising class of nanocarriers for cancer therapy due to their inherent advantages, including high biocompatibility, controlled drug release, and the ability to be surface-functionalized for active targeting. Engineered from natural or synthetic polymers, these nanoparticles are characterized by tunable physicochemical properties that allow for the encapsulation of various chemotherapeutic agents. This improves therapeutic indices while minimizing systemic toxicity.[60] One promising nanopolymer is graphene. Due to their unique physicochemical properties, including a large specific surface area, excellent electrical conductivity, and remarkable optical characteristics, graphene nanoparticles have garnered significant attention in cancer therapy for both therapeutic and diagnostic applications.[61,62] Graphene oxide (GO), reduced graphene oxide (rGO), and graphene quantum dots (GQDs) are examples of these nanomaterials. They offer versatile platforms for photothermal and photodynamic therapies, targeted drug delivery, and imaging. This enables multimodal approaches to cancer treatment.[61,62]

The large surface area and ease of functionalization of graphene make it an excellent carrier for drug molecules. This allows for the co-delivery of chemotherapeutic agents and photosensitizers, facilitating combination therapy with synergistic effects.[63] Gold nanoparticle-graphene hybrid systems have been engineered to respond to visible and near-infrared light. This improves imaging contrast and ensures deep tissue penetration for effective photothermal and photodynamic treatment.[64]

## Inorganic-Organic Hybrid Nanoparticles

In recent years, inorganic-organic nanoparticles are increasingly recognized as a highly promising class of theragnostic agents in cancer treatment. These nanoparticles combine the robust, often unique physical properties of inorganic materials with the versatile, biocompatible functions of organic molecules. This hybridization enables for the simultaneous integration of diagnostic imaging, controlled drug release, and targeted therapeutic action into a single nanosystem.[65] The inorganic component, typically metals such as gold or silver and metal oxides, provides essential features like enhanced optical

absorption, magnetic properties, and high payload retention. Meanwhile, the organic moieties (eg, antibodies, polymers, and small molecules) improve biocompatibility, dictate biodistribution, and facilitate conjugation of targeting ligands.[65,66]

Hybrid inorganic-organic nanoparticles are particularly relevant in photothermal therapy and chemotherapy. For instance, antibody-conjugated gold nanorods have been used for the selective photothermal ablation of cancer cells. In this process, the gold core absorbs near-infrared light and generates localized heat, which induces tumor cell death without damaging the surrounding tissues.[67] Similarly, micellar hybrid nanoparticles, which often include inorganic cores encapsulated within organic shells, have been designed to improve circulation time and stability in vivo while addressing issues of targeted drug delivery.[68] These multifunctional platforms demonstrate how inorganic elements can efficiently mediate light-to-heat conversion or serve as contrast agents while the organic fraction ensures effective drug loading and selective tumor targeting.[67,68]

## Nanoparticles' Hepatotoxicity and Methods of Mitigation

The following sections describe mechanism of hepatotoxicity and discuss strategies to improve the effectiveness of nanoparticle-based anticancer drugs while reducing their toxicity, particularly hepatotoxicity (Figure 3).

### Hepatotoxicity of Liposome-Based Nanoparticles and Methods of Mitigation

The mechanisms underlying hepatotoxicity induced by lipid-based nanoparticles primarily involve oxidative stress, lipid peroxidation, and mitochondrial dysfunction.[69–71] Accumulation of lipid droplets in hepatocytes, impaired lipid metabolism, and increased oxidative stress contribute to steatosis and cellular apoptosis.[69] Mitochondrial dysfunction further exacerbates these effects by impairing energy metabolism and promoting apoptosis in liver cells.[72,73]

Furthermore, the size and surface properties of nanoparticles influence hepatotoxicity. Smaller nanoparticles tend to accumulate more readily in the liver, thereby exacerbating toxic effects.[74] Surface modifications, such as the incorporation of targeting ligands or protective coatings, affect nanoparticle-liver interactions and subsequent toxicity.

One strategy for prolonging the circulation of drug-loaded liposomes and reducing hepatotoxicity is to conjugate them with polyethylene glycol (PEG).[75] PEGylated liposomes exhibit reduced hepatotoxicity by altering biodistribution, decreasing reticuloendothelial system (RES) uptake, and enhancing biocompatibility. PEGylation shifts drug accumulation from the liver to other organs, such as the spleen. Studies have shown that extensive PEGylation reduces liver uptake by providing a shielding effect that decreases RES recognition and prolongs circulation time. This improves drug accumulation.[76,77]

Cationic lipids in liposomal formulations contribute to hepatotoxicity by inducing ROS generation and disrupting intracellular calcium homeostasis.[78] DOTAP (1,2-dioleoyl-3-trimethylammonium propane)-based particles, a subclass of cationic lipids, accumulate in the liver and spleen, thereby limiting their systemic and antitumor efficacy.[79]

Negatively charged liposomes have been shown to be less toxic and less hepatotoxic than their cationic counterparts, especially in drug delivery applications. This can be attributed to their interaction with biological membranes, biodistribution, and the stability of the formulations.[80] Studies have shown that the incorporating negatively charged gold nanoparticles into liposomes results in a stable formulation with a negative zeta potential, which is associated with reduced cytotoxicity.[81] Similarly, negatively charged liposomes tend to distribute differently than cationic liposomes, resulting in lower liver accumulation. For example, Vhora et al demonstrated that negatively charged liposomes exhibit reduced serum binding, which minimizes hepatic uptake and toxicity.[82] Alhariri et al showed that increasing the ratio of negatively charged phospholipids in liposomal formulations improved the gentamicin encapsulation efficiency.[83] This increased efficiency enables the use of lower drug doses, which reduces the risk of toxicity. The stability of negatively charged liposomes contributes to their reduced toxicity by preventing premature drug release and minimizing systemic exposure. This is crucial for maintaining the therapeutic efficacy of the encapsulated drug while minimizing adverse effects.[82,84]

Additionally, neutral-charge liposomes, such as 1,2-dioleoyl-sn-glycero-3-phosphatidylcholine (DOPC), demonstrate reduced toxicity compared to cationic liposomes. DOPC nanoliposomes have demonstrated effective systemic siRNA delivery and antitumor efficacy in preclinical models of various cancers, including ovarian,[79,85–87] colon,[88] breast,[89] prostate cancer,[90] and melanoma.[91] These formulations have a favorable safety profile, exhibiting minimal toxicity, no cytokine

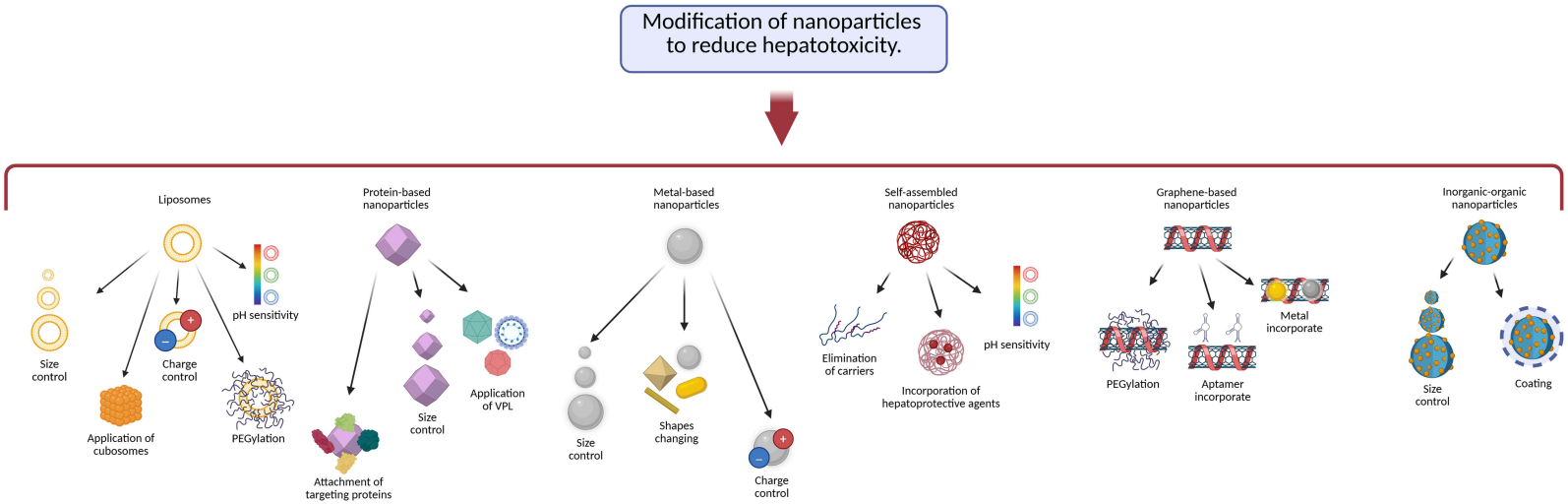


**Figure 3** Strategies for modifying various nanoparticle types to reduce hepatotoxicity. Approaches include size, charge, and shape manipulation; PEGylation; coating; pH-sensitivity; and incorporation of targeting or hepatoprotective agents. These alterations aim to improve biocompatibility, reduce liver accumulation, and enhance targeted delivery. Created in BioRender. Taciak, B. (2025) https://BioRender.com/kkllu37.

induction, and reduced ROS generation. Furthermore, DOPC nanoliposomes accumulate significantly more in tumor tissue than cationic liposomes, thereby enhancing therapeutic efficacy and minimizing hepatotoxicity.

Another promising strategy for enhancing liposomal specificity and reducing toxicity is development of pH-sensitive liposomes. These liposomes release their payload in response to the acidic tumor microenvironment, thereby improving drug delivery efficiency.[92] Incorporating specific lipids that undergo conformational changes at lower pH enhances tumor-targeted drug release while maintaining stability under physiological conditions. This approach minimizes systemic toxicity, including hepatotoxicity, and improves the therapeutic index of liposomal drug formulations.[93]

### Cubosomes

Cubosomes are an interesting example of liposomes with an unusual shape and structure. As previously mentioned, cubosomes are lipid-based nanocarriers with a bicontinuous cubic internal structure. Recent studies have highlighted their potential to enhance the therapeutic index of anticancer drugs. Xie et al demonstrated that when doxorubicin (DOX) is incorporated into pH-sensitive cubosomes, it exhibits minimal release under near-neutral conditions while showing enhanced release in the acidic tumor microenvironment. This reduces cytotoxicity in normal cells, including hepatocytes. These findings underscore how cubosomes can be engineered to exploit tumor-specific physiological conditions for improved drug delivery.[94]

Targeted delivery strategies further expand the therapeutic potential of cubosomes in oncology. The functionalization of cubosome surfaces with anti-CEA Affimer tags has been shown to actively target colorectal cancer cells.[95] Similarly, angiopep-2-functionalized cubosomes have been formulated to effectively cross the blood–brain barrier, facilitating the targeted delivery of cisplatin and temozolomide for glioblastoma treatment. Angiopep-2 is a 19-amino acid-long oligopeptide, derived from the Kunitz protease inhibitor domain, that effectively targets LRP1.[96] Further research on cubosome systems has demonstrated their potential to repurpose drugs, such as nitrofurantoin, for breast cancer treatment, highlighting their broad applicability to various cancer types.[97] Furthermore, the development of chitosan-coated cubosomes for colorectal cancer treatment has shown enhanced cellular internalization, suggesting that surface modifications can significantly optimize therapeutic outcomes.[98]

## Hepatotoxicity of Protein-Based Nanoparticles and Methods of Mitigation

The primary pathway underlying the liver toxicity associated with protein-based nanoparticles is the activation of B-KCs, the liver's resident macrophages, that play a critical role in the immune response and the clearance of foreign particles.[99] When these nanoparticles enter the bloodstream, B-KCs rapidly recognize and engulf them, leading to inflammation and potential liver injury. Other cells involved in nanoparticle-induced hepatotoxicity, such as LSECs, may contribute to liver fibrosis following exposure to nanoparticles.[100]

One approach to minimizing hepatotoxicity is using proteins that have a high affinity for cancer cells. Using transferrin as a protein-based nanoparticle enables the effective delivery of conjugated drugs to cancer cells. Transferrin is an iron-binding transport protein that specifically interacts with transferrin receptors, which is commonly overexpressed on cancer cells due to the increased iron demand. This makes transferrin a promising candidate for targeted drug delivery systems. This selective affinity significantly reduces the likelihood of nanoparticle-drug uptake by healthy liver cells.[101]

Another protein that uses the transferrin receptor for internalization is ferritin, which can also carry drugs. Due to their nanocage architecture, ferritins have been extensively studied for targeted drug delivery. Ferritin-based nanocarriers exhibit high drug loading efficiency and controlled release properties. They have been used to encapsulate chemotherapeutic agents, such as doxorubicin and cisplatin, thereby improving biocompatibility, circulation half-life, and target selectivity while reducing systemic toxicity. Additionally, ferritins have been used to encapsulate photosensitizers for photodynamic cancer therapy, improving targeting and safety.[102]

The size of protein-based nanoparticles can be manipulated to significantly enhance their accumulation within the tumor microenvironment. This benefit is largely attributed to the enhanced permeability and retention (EPR) effect, which reduces damage and toxicity to normal cells by facilitating targeted delivery.[11] One way to improve EPR effect in protein-based nanoparticles is to design a system in which larger particles (~50 nm) are assembled from smaller particles

(<6 nm) using degradable linkers. This approach improves targeting efficiency through the EPR effect while enabling disassembly into smaller particles within the tumor microenvironment. This innovative method improves targeting capabilities and ensures deeper penetration into tumor tissue.[103]

### Virus-Like Particles

Using specific VLPs can significantly reduce hepatotoxicity. Clinical studies have provided insight into the safety profile of these VLPs. For example, Nakao et al conducted a Phase I trial of the oncolytic virus HF10, which demonstrated a broad spectrum of anticancer activity with minimal toxicity in humans. This study emphasized that the clinical effects of oncolytic virus therapy are closely related to the host immune response. This indicates that, although VLPs may be effective, their safety must be continuously monitored, especially when combined with other immune stimuli.[104]

Regarding specific VLP applications, Franke et al examined the use of the tobacco mosaic virus (TMV) as a nanocarrier for delivering cisplatin to platinum-resistant ovarian cancer cells. They found that TMV-based delivery systems could restore drug efficacy while minimizing the cytotoxicity associated with higher cisplatin doses.[105]

However, some studies have reported cytotoxic effects associated with certain VLP formulations. For instance, Shao et al developed polyethyleneimine-coated adeno-associated virus-like particles for siRNA delivery in breast cancer therapy. While the study found a mild immune response, it also raised concerns about the potential toxicity of the delivery system itself.[106] These findings highlight the importance of carefully considering the materials and methods used in VLP design to minimize adverse effects.

## Hepatotoxicity of Metal-Based Nanoparticle (MNP) and Methods of Mitigation

One of the primary mechanisms of MNP-induced hepatotoxicity is the production of reactive oxygen species (ROS). ROS can cause oxidative stress, which damages cellular components, including lipids, proteins, and DNA. Ying et al demonstrated that MNPs induce oxidative stress in hepatocytes, resulting in apoptosis and other forms of cell death.[107] This oxidative damage is exacerbated by the accumulation of MNPs in the liver, which is a primary site of xenobiotic metabolism and detoxification.[108] Khalaf et al further demonstrated that copper nanoparticles induce oxidative stress and lipid peroxidation in liver tissue, leading to hepatotoxicity.[109] Another critical aspect of MNP toxicity is their ability to disrupt cellular homeostasis. Elbadry et al reported that silver nanoparticles (AgNPs) alter biochemical markers indicative of liver function. These markers include elevated levels of creatinine and urea levels, which suggest hepatocellular injury and inflammation.[110] Hepatic dysfunction may result from direct cellular damage or an inflammatory response triggered by foreign nanoparticles. Furthermore, MNPs may exacerbate the toxicity of other substances. Isoda et al demonstrated that co-administration of gold nanoparticles with hepatotoxic drugs increased liver and kidney damage, indicating that MNPs may potentiate the toxicity of other compounds.[111]

Metallic nanoparticles (MNPs) can disrupt mitochondrial function. This leads to the release of cytochrome c and the activation of caspases, which play a key role in the apoptotic pathway. The generation of reactive oxygen species (ROS) exacerbates this process, causing lipid peroxidation and damage to subcellular organelles within hepatocytes. The accumulation of MNPs in the liver, primarily by B-KCs and LSECs, triggers inflammatory responses involving increased levels of proinflammatory cytokines, including IL-1β and IL-8. This inflammatory environment can further increase oxidative stress, creating a vicious cycle of cellular damage and apoptosis.[107]

The physicochemical properties of MNPs, such as size, shape, and surface charge, significantly influence their toxicity. Therefore, modifying these properties can mitigate the associated risk. Silver and gold nanoparticles have been studied for their ability to induce apoptosis in cancer cells by generating reactive oxygen species (ROS). While these nanoparticles exhibit cytotoxic effects on cancer cells, their design can be optimized to minimize hepatotoxicity by controlling their size and surface properties, which affect their interaction with liver cells.[112] Functionalizing metal nanoparticles with ligands such as folate or antibodies can significantly improve their specificity for tumor cells. This reduces off-target effects and improves therapeutic outcomes.[54]

Wang et al discovered that the transformation of copper-based nanomaterials under physiological conditions impacts their stability and toxicity. Typically, smaller particles exhibit higher reactivity and a greater potential to induce cellular damage.[113]

Several studies have documented the toxicological effects of iron oxide nanoparticles.[114–117] In particular, the size and morphology of these nanoparticles significantly impact their toxicity. For example, rod-shaped iron oxide nanoparticles are more toxic than spherical ones.[118,119] Further studies are needed to elucidate the toxic effects of iron oxide nanoparticles on different tissues. These studies should consider factors such as concentration, particle size, and routes of administration. However, Kiyani et al's findings suggest that spherical iron oxide nanoparticles with an average diameter of 50 nm are relatively nontoxic when administered orally in mouse models.[120]

## Hepatotoxicity of Self-assembled Nanoparticles and Methods of Mitigation

Similar to other nanoparticles, the hepatotoxicity of self-assembled nanoparticles arises due to multiple factors, such as their high surface reactivity, potential to generate reactive oxygen species (ROS), and subsequent inflammatory responses upon uptake and accumulation in hepatocytes.[24] Underlying mechanisms include oxidative stress through lipid peroxidation, protein oxidation, and DNA damage, as well as inflammatory cascades. These mechanisms may collectively impair hepatocellular function and contribute to liver injury over time.[24]

Many self-assembled nanoparticles are designed to maximize therapeutic efficacy while minimizing side effects, including hepatotoxicity. For example, the self-assembly of cisplatin (CDDP) and olaparib (OLA) through hydrogen bonding creates uniform nanoparticles that release their payloads preferentially within the acidic tumor microenvironment. This enhances chemotherapeutic sensitivity while mitigating systemic side effects.[121] This synergy is further enhanced when nanoparticles are engineered to respond to tumor-specific stimuli, such as pH levels or enzymatic activity. This ensures that the active agents are released directly at the tumor site.

Study by Liu et al demonstrated that pH-responsive polymer–drug conjugate micelles could optimize drug release kinetics and significantly reduce hepatotoxicity associated with the free drug. Their system is designed so that the self-assembled micellar nanoparticles remain stable in neutral pH conditions and undergo rapid disassembly in the acidic environment of tumor cell endosomes.[122]

Recent developments have highlighted the role of self-assembled, peptide-based nanoparticles in modulating the immune response to cancer. A notable example is peptide-derived proteolysis-targeting chimera (PROTAC) nanoparticles, which have been shown to durably degrade PD-L1 on tumor cells, paving the way for more effective and sustained anticancer immunotherapy. The ability to fine-tune the self-assembly process enables the creation of nanostructures that mimic natural cellular components. This facilitates improved cellular uptake, which may help avoid liver damage.[123]

Another effective strategy is to incorporate hepatoprotective agents into the self-assembled structure. Huang et al reported on the development of self-assembled nanoparticles composed of chitosan and heparin that deliver fibroblast growth factor 21 (FGF21). In a murine model of acetaminophen-induced acute liver injury, these nanoparticles provided a sustained release of FGF21. This attenuated oxidative damage and suppressed inflammatory responses in the liver. The study highlighted the potential of such self-assembled delivery systems to effectively target therapeutic agents and actively counteract drug-induced hepatotoxicity by improving the in vivo distribution and release profile of FGF21.[124]

Advances in pure drug self-assembled nanosystems (PDANSs) have expanded the therapeutic possibilities for cancer treatment. These systems capitalize on the intrinsic self-assembly properties of therapeutic agents, providing a novel route for combination therapy that enhances safety and efficacy. By eliminating the need for additional carrier materials, PDANSs reduce potential toxicity, simplify regulatory approval, and maintain the drug concentration within the tumor at an optimal therapeutic level.[125] These systems are a significant breakthrough in nanomedicine design for cancer treatment, combining the benefits of self-assembly with the specificity and potency required for modern anticancer therapies.

## Hepatotoxicity of Graphene-Based Nanoparticles (GNPs) and Methods of Mitigation

Graphene-based nanoparticles (GNPs) have emerged as a promising material in various fields, including drug delivery. However, concerns have been raised about their potential hepatotoxicity, which calls into question their safety and biocompatibility. The toxicity mechanisms associated with GNPs, particularly in the liver, are attributed to several factors, including oxidative stress, cellular uptake, and inflammatory responses.

One of the primary mechanisms of hepatotoxicity associated with GNPs is the production of ROS. Studies have shown that exposure to GO and other graphene derivatives can increase ROS production. This, in turn, induces oxidative stress in liver cells. This oxidative stress can result in cellular damage, apoptosis, and necrosis. For example, GNPs have been reported to deplete mitochondrial membrane potential and elevate intracellular ROS levels, thereby triggering apoptotic pathways in various cell types, including hepatocytes.[112,126] Oxidative damage caused by ROS can lead to lipid peroxidation and protein oxidation, which can further exacerbate liver injury.

The size and surface properties of GNPs significantly influence their toxicity. Smaller nanoparticles tend to be more toxic due to their increased surface area and reactivity, which allows for higher cellular uptake. Additionally, surface functionalization can alter graphene's interaction with biological systems, affecting its biocompatibility. For instance, studies have demonstrated that functionalized graphene oxide exhibits dose- and size-dependent toxicity. This finding suggests that the concentration and physicochemical properties of GNPs play critical roles in their hepatotoxic effects.[127,128]

Another critical aspect of GNP-induced hepatotoxicity is inflammatory responses. The accumulation of GNPs in the liver activates immune cells, which leads to the release of pro-inflammatory cytokines and chemokines. This inflammatory response can contribute to liver damage and dysfunction. Furthermore, studies have shown that GNPs can affect the quantity and activity of B-KCs cells, which are the liver's resident macrophages and play a vital role in maintaining hepatic homeostasis and responding to injury.[129]

In vivo studies have demonstrated that GNPs can accumulate in the liver following intravenous administration, raising concerns about their long-term effects on liver function. The biodistribution of GNPs is influenced by their size, surface charge, and coating. These factors can affect clearance from the body and potential toxicity.[127,130]

Studies has shown that GO can be functionalized with PEG to form a stable, biocompatible nanocarrier for anticancer drugs, such as doxorubicin and cisplatin. This process, known as PEGylation, enhances the solubility and dispersibility of the nanoparticles in biological fluids, thereby improving their efficacy in targeting tumor cells.[131] Furthermore, incorporating aptamers (short, single-stranded DNA or RNA molecules that bind to specific targets) into graphene-based systems enhances the specificity of drug delivery to cancer cells.[132,133]

Furthermore, graphene-based nanoparticles can be engineered to respond to specific stimuli, such as changes in pH or temperature, that are characteristic of the tumor microenvironment. This behavior allows for the controlled release of encapsulated drugs, ensuring that therapeutic agents are released precisely where and when needed.[134]

Chen et al developed a nanographene oxide-based multifunctional nanosystem that has been constructed by a unique sequential double redox strategy to co-integrate superparamagnetic $Fe_3O_4$ and paramagnetic MnO x NPs on GO. DOX connected with FeMn-GO NPs is released at a low pH. This behavior is very suitable for tumor chemotherapy. These synthesized FeMn-GO NPs are highly biocompatible, as demonstrated by the low cytotoxicity and high histocompatibility.[135]

In addition to their role in drug delivery, graphene-based nanoparticles are being studied for their potential in immunotherapy. Their inherent properties can stimulate immune responses, making them suitable adjuvants for cancer vaccines. For example, combining graphene with gold nanoparticles has been shown to enhance photothermal therapy. In this therapy, localized heating induced by near-infrared light can selectively destroy cancer cells while sparing healthy tissue.[136] This dual functionality-acting as a drug carrier and an immunomodulator-positions graphene-based nanoparticles as versatile tools in the fight against cancer.

## Hepatotoxicity of Inorganic-Organic Hybrid Nanoparticles and Methods of Mitigation

Hybrid systems combine the unique optical, magnetic, and structural properties of inorganic materials with the biocompatibility, targeted binding, and drug loading capabilities of organic molecules. This produces multifunctional platforms suitable for diagnosis, therapy, and theranostics.[137,138] Integrating these materials allows for the fine-tuning of physicochemical properties, such as size, charge, and surface architecture, which directly influence the cellular uptake, biodistribution, and release kinetics of chemotherapeutic agents.[139] These properties may contribute to the enhanced accumulation of nanoparticles within the tumors, thereby minimizing their impact on the liver.

Inorganic-organic hybrid systems developed for breast cancer and other tumors have been engineered to carry large amounts of chemotherapeutic drugs. For example, high-load nanoparticles have been developed to encapsulate SN-38

and FdUMP.[137] These hybrid nanoparticles exploit strong ionic or coordination interactions between inorganic cations and drug anions, achieving high loading and controlled release of the drugs. This design enhances the therapeutic index and reduces off-target toxicity.

Furthermore, advanced synthesis strategies such as anionic emulsion polymerization have made it possible to encapsulate inorganic cores with tailored organic polymers. This technique improves nanoparticle stability and allows for the incorporation of multiple functional groups, which is essential for targeted delivery and efficient drug release under physiological conditions.[139]

## Conclusion

Nanoparticle-based drug delivery systems have revolutionized cancer therapeutics. These systems enable the targeted delivery of chemotherapeutic agents, reduce off-target toxicity, and improve pharmacokinetics. These systems use materials like lipids, proteins, metals, polymers, graphene, and hybrid structures. They are designed to take advantage of the EPR effect. This effect allows nanoparticles to accumulate in tumor tissues because of their abnormal vasculature and impaired lymphatic drainage.[6,9,12] Despite these therapeutic advances, however, hepatotoxicity remains a significant concern due to the liver's central role in nanoparticle clearance. Hepatic cells, particularly B-KCs and LSECs, are primarily responsible for nanoparticle uptake. However, this process can result in oxidative stress, inflammatory responses, and apoptosis, collectively compromising liver function.[24,27] One of the main challenges in the clinical application of nanomedicines is addressing liver toxicity without compromising therapeutic efficacy (Table 2).

Liposomes, a type of lipid-based nanoparticle, are widely used for encapsulating hydrophilic and hydrophobic drugs. Approved formulations like Doxil® have demonstrated clinical efficacy.[31,32] However, their tendency to accumulate in the liver depends heavily on particle size. Smaller particles (less than 100 nm) show higher hepatic uptake.[74] Surface charge also plays a crucial role. Cationic liposomes increase ROS generation and calcium imbalance, whereas neutral or negatively charged liposomes, such as those using DOPC, reduce inflammation and hepatic cell uptake.[80] The composition of liposomes influences toxicity. DOTAP-based formulations elevate hepatic retention, while PEGylation masks particles from the reticuloendothelial system, extends circulation time, and shifts biodistribution.[75,79] Cubosomes are a more recent type of lipid-based nanostructure with a cubic architecture that allows for controlled drug release and enhanced functionalization. Functionalization with ligands such as angiopep-2 facilitates crossing of the blood-brain barrier while minimizing hepatic impact,[96] and chitosan-coated cubosomes have demonstrated improved targeting in colorectal cancer models with lower liver accumulation.[97]

**Table 2** Strategies for Mitigating Hepatotoxicity of Various Types of Nanoparticles

| **Strategies for Mitigating Hepatotoxicity of Various Types of Nanoparticles** | | |
|---|---|---|
| **Nanoparticle Type** | **Mitigation Strategy** | **References** |
| **Liposomes** | PEGylation to reduce RES uptake, use of neutral/negatively charged lipids, pH-sensitive release, size control | [69–78,87,88] |
| **Cubosomes** | Surface ligand functionalization (eg, angiopep-2), pH-triggered release, chitosan coating | [91–93] |
| **Protein-Based NPs** | Use of cancer-specific ligands (transferrin, ferritin), size manipulation to exploit EPR, | [101–103] |
| **VLPs** | Careful material selection, monitor immune response, avoid immunogenic coatings | [104–106] |
| **Metal NPs** | Size, surface charge and shape control, functionalization (folate, antibodies) | [54,112,113,118–120] |
| **Self-Assembled NPs** | pH and enzyme sensitivity, eliminate carriers (PDANS), incorporate hepatoprotective agents | [121–125] |
| **Graphene NPs** | PEGylation, incorporate aptamer, metal particles addition (eg, gold) | [61,126–136] |
| **Hybrid Inorganic-Organic NPs** | Polymer coating for biocompatibility, optimize size and release kinetics | [66,137–139] |

Protein-based nanoparticles, including carriers such as albumin, transferrin, ferritin, and antibody-drug conjugates, offer biocompatibility and the ability to target specific areas. Ferritin and transferrin specifically bind to TfR1, which is overexpressed in many tumor types. This reduces hepatic uptake and enhances tumor specificity.[102] The EPR effect can also be optimized by modulating the size of the carriers. For example, assembling ~50 nm carriers from smaller units using degradable linkers enhances tumor penetration while limiting exposure to normal tissue.[103] VLPs, which are self-assembled protein shells lacking genetic material, have shown utility in drug delivery applications. When designed appropriately, VLPs can carry chemotherapeutic agents with minimal hepatotoxicity. However, caution is required, as some coatings, such as polyethyleneimine, may trigger immune activation.[46]

Metal-based nanoparticles, including silver and gold variants, have many uses in therapy and diagnostics. However, their use is limited by their ability to induce oxidative stress, mitochondrial dysfunction, and inflammation in hepatocytes.[108] Their toxicity is strongly linked to particle size and surface properties; smaller, more reactive particles pose a greater risk. Functionalizing them with ligands such as folate or tumor-targeting antibodies can reduce off-target liver uptake and enhance tumor specificity. Copper and iron oxide nanoparticles also exhibit size- and morphology-dependent toxicity. Spherical iron oxide particles measuring approximately 50 nm are relatively safer than rod-shaped or smaller analogues.[113]

Graphene-based nanoparticles, including GO, rGO, and GQDs are valued for their large surface area, drug-loading capacity, and potential applications in imaging and therapy. However, these nanoparticles present hepatotoxic risks, primarily through ROS generation, mitochondrial membrane disruption, and inflammatory responses involving hepatic immune cells, such as B-KCs.[126,127,129] These effects are often size- and dose-dependent, but can be mitigated by PEGylation and aptamer-based targeting strategies, which improve biocompatibility and selectivity.[134] Furthermore, GNPs can be engineered to release drugs in response to stimuli under tumor-specific conditions, thereby enhancing efficacy and minimizing liver toxicity.[61–63]

Self-assembled nanoparticles formed through non-covalent interactions, such as hydrogen bonding and hydrophobic effects, are a promising platform for pH-sensitive drug delivery. These structures can carry combinations of chemotherapeutics, such as cisplatin and olaparib, and release their payload in an acidic tumor microenvironment, sparing healthy liver tissue.[121] pH-responsive polymer-drug micelles further enhance tumor specificity and minimize systemic exposure.[122] Furthermore, PDANSs represent a strategy to eliminate the need for synthetic carriers altogether, thereby reducing the risk of off-target toxicity and simplifying formulation.[125]

Inorganic-organic hybrid nanoparticles combine the strength of inorganic components, such as gold nanorods or magnetic cores, with the flexibility and biocompatibility of organic polymers or antibodies. These systems can carry high drug payloads and enable controlled release and dual therapeutic and diagnostic functionality (theranostics).[66] Strategic surface modifications, polymer coatings, and optimization of physicochemical properties like particle size and charge minimize their hepatotoxic potential and reduce nonspecific uptake by the liver while enhancing tumor-targeted delivery.[18]

## Abbreviations

ADCs, antibody-drug conjugates; AgNPs, silver nanoparticles; APCs, antigen-presenting cells; AuNPs, gold nanoparticles; B-KCs, Browicz-Kupffer cells; CDDP, cisplatin; DOPC, 1,2-dioleoyl-sn-glycero-3-phosphatidylcholine; DCs, dendritic cells; DOTAP, 1,2-dioleoyl-3-trimethylammonium propane; DOX, doxorubicine; EPR, enhanced permeability and retention; FGF21, fibroblast growth factor 21; GNPs, Graphene-based nanoparticles; GO, graphene oxide; GQDs, graphene quantum dots; IL-1β, interleukin 1 beta; LSECs, liver sinusoidal endothelial cells; MDR, multidrug resistance; MNPs, metal-based nanoparticles; OLA, olaparib; PDANSs, pure drug self-assembled nanosystems; PEG, polyethylene glycol; PNPs, protein-based nanoparticles; PROTAC, peptide-derived proteolysis-targeting chimera; PTT, photothermal therapy; RES, reticuloendothelial system; rGO, reduced graphene oxide; ROS, reactive oxygen species; siRNA, small interfering RNA; TfR1, transferrin receptor 1; TMV, tobacco mosaic virus; TNF-α, tumor necrosis factor-alpha; VLPs, virus-like particles.

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