Empowering of novel anti-tumor formulations with quinone-based active natural products

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ABSTRACT

Cancer remains one of the leading causes of death worldwide, representing a significant threat to human health. Consequently, there is an urgent need to develop effective treatment strategies with low toxicity. Quinone-based natural products have garnered considerable attention in the field of anticancer research due to their distinctive chemical structures. These compounds play a crucial role in treating various cancers and in overcoming chemotherapy resistance through several mechanisms, including the inhibition of cell proliferation and migration, as well as the modulation of multiple signaling pathways. However, their clinical application is limited by severe side effects, which arise from certain physicochemical properties, such as poor water solubility and low biocompatibility. The advent of nanotechnology has led to the development of nanomedicine delivery systems, offering a groundbreaking approach to overcome these limitations. Nanocarriers, characterized by their excellent biocompatibility, favorable pharmacokinetics, and high drug-loading capacities, enhance the bioavailability and targeting of natural products while reducing adverse effects. Therefore, integrating quinone-based natural products with nanocarrier delivery systems has proven to be an effective anticancer strategy. This approach not only improves the absorption of drugs with poor bioavailability but also significantly reduces side effects. Various nanodelivery systems, including micelles, liposomes, inorganic nanoparticles, and biomimetic nanocarriers, are particularly effective in delivering quinone-based natural products due to their unique physical and chemical properties, thereby enhancing their solubility and stability. In addition, targeted modifications, intelligent controlled release, and combination therapy strategies have significantly improved their bioavailability and antitumor efficacy. This review systematically examines the antitumor potential of quinone-based natural products and provides a comprehensive overview of the current research and clinical application prospects of their nanodelivery systems in cancer treatment. It aims to summarize the current progress and clinical prospects of integrating these compounds with nanocarrier-based drug delivery systems in cancer treatment.

Keywords:
Drug delivery; Nanotechnology; Natural products; Quinones

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1. Introduction

Quinones are naturally occurring compounds found extensively in plants, fungi, bacteria, and animals.[1] These compounds either possess an intramolecular unsaturated cyclic diketone structure or can readily transform into such a structure.[2] Structurally, natural quinones are primarily classified into four categories: benzoquinone, naphthoquinone, phenanthrenequinone, and anthraquinone.[3] The presence of chromophores, such as –OH and $–OCH_3$, imparts vivid colors such as yellow, red, and purple to these molecules. Quinones and their derivatives are integral components of several widely used traditional Chinese medicines (TCMs), including *Rhei radix et rhizome*, *Polygoni cuspidati rhizoma et radix*, *Salviae miltiorrhizae radix et rhizoma*, and *Arnebiae radix*, among others.

Natural benzoquinones are categorized into two types: Ortho-benzoquinone and para-benzoquinone, as depicted in **Figure 1**. The

structure of ortho-benzoquinone tends to be unstable due to steric hindrance, making para-benzoquinone the more prevalent natural form. On the other hand, the majority of naturally occurring naphthoquinones are derivatives of alpha-naphthoquinone, exemplified by shikonin (SHK) and isoshikonin derivatives found primarily in the TCM *Arnebiae radix*. Meanwhile, phenanthrenequinone derivatives, such as tanshinone I, tanshinone IIA (TSIIA), dihydrotanshinone, and cryptotanshinone, are extractable from the roots of *S. miltiorrhiza* Bunge, a prominent TCM source of phenanthrenequinones.[4] Finally, anthraquinones are classified based on their nuclear structure into monoanthracene and bianthracene types, including substances such as rhein, emodin, alizarin, aloin, and hypericin.

Extensive research, both domestic and international, has highlighted the diverse biological activities of quinones,[5-11] including antitumor, anti-inflammatory, antibacterial, antiviral, antifungal, and antimalarial properties, as well as neuroprotective effects against Alzheimer's disease. These biological activities position quinones as significant agents in medicinal chemistry,[12] offering promising prospects for the development of medical applications.[13] Quinone-based natural products can function as anticancer agents through various mechanisms, such as inducing cancer cell death by inhibiting quinone oxidoreductase 1 (NQO1), leading to reactive oxygen species (ROS) generation, and inhibiting tumor growth through the suppression of signal transducer and activator of transcription 3 (STAT3).[12]

Despite the extensive documentation of their anticancer potential, the clinical application of these compounds is often hampered by challenges such as low solubility, poor absorption, rapid metabolism, and low bioavailability *in vivo*. To overcome these limitations, substantial research has been conducted on various nanomaterial drug delivery systems that are suitable for quinone-active compounds, aiming to enhance the targeting capability and bioavailability of these drugs.

Nanotechnology offers a promising alternative to traditional treatment methods by creating efficient and safe targeted delivery systems through the encapsulation of drugs within nanoparticles.[14, 15] This review provides a comprehensive overview of current methodologies and key reference points for optimizing the formulation of quinone-based natural products using various drug delivery systems to enhance efficacy (**Figure 2**). It compiles and summarizes both classical and recent studies, highlighting the biological activities and potential limitations of nanomaterials. The aim is to offer valuable insights into nanodelivery systems for quinone-based natural products, with a specific focus on enhancing their anticancer efficacy.

2. Research methodology

An extensive electronic search was conducted across prominent databases, including PubMed, ScienceDirect, CNKI, Web of Science, and Google Scholar. The search also extended to clinical trial studies listed on ClinicalTrials.gov. Strategies of the search involved identifying key terms, such as "Quinone," "benzoquinone," "naphthoquinone," "phenanthrenequinone," "anthraquinone," "structure," "bioactivity," "anti-tumor," "nanotechnology," "bioavailability," and "anti-cancer." These terms were specifically searched within the "Title/Abstract/Keywords" fields of the databases, with no restrictions on publication date. The primary aim of this comprehensive search was to identify and retrieve all relevant published studies encompassing extensive experimental designs, *in vitro* and *in vivo* analyses, clinical trials, and case–control studies. These studies primarily focused on investigating the role of nanotechnology in advancing the development, formulation, and therapeutic applications of quinone-based natural products for antitumor therapy. Special attention was given to factors such as improved bioavailability, targeted tumor delivery, enhanced cellular uptake, controlled drug release, and overall advancements in cancer treatment. In addition, information on the efficacy of preclinical models and results that have already been applied in clinical settings were also the focus. Duplicate publications were excluded from the review, and the findings regarding the antitumor activities of quinones were systematically organized within the relevant sections.

3. Antitumor activity and mechanisms of action of quinones

Quinone compounds are ubiquitously present in nature and can be synthesized by a variety of organisms.[16] This widespread availability provides a rich resource base for the exploration and application of quinones. The plethora of natural products not only facilitates the identification and development of quinone compounds with potential antitumor properties but also supports their large-scale production and clinical utilization. Quinone compounds exhibit diverse antitumor mechanisms, targeting multiple cellular components and signaling pathways, thus offering broad therapeutic possibilities. Extensive research has investigated the use of quinones and their analogs in treating various cancers, including those of the lung, liver, breast, colon, cervix, prostate, and leukemia.[17-19] At the molecular level, the anticancer efficacy of quinones is attributed to several mechanisms, such as the inhibition of cell proliferation and migration, the induction of apoptosis, and the modulation of autophagy and other cellular pathways.[20, 21] Some quinones disrupt cell cycle progression, thereby inhibiting cell proliferation. For instance, thymoquinone (TQ) impedes the activity of cyclin-dependent kinases, arresting human breast and colon cancer cells in the G1 phase.[22] In addition, emodin targets the HER-2/neu tyrosine kinase activity, consequently inhibiting the proliferation of breast cancer cells.[23]

Tumor growth and metastasis depend on neovascularization, which provides nutrients and pathways for invasion. Quinone

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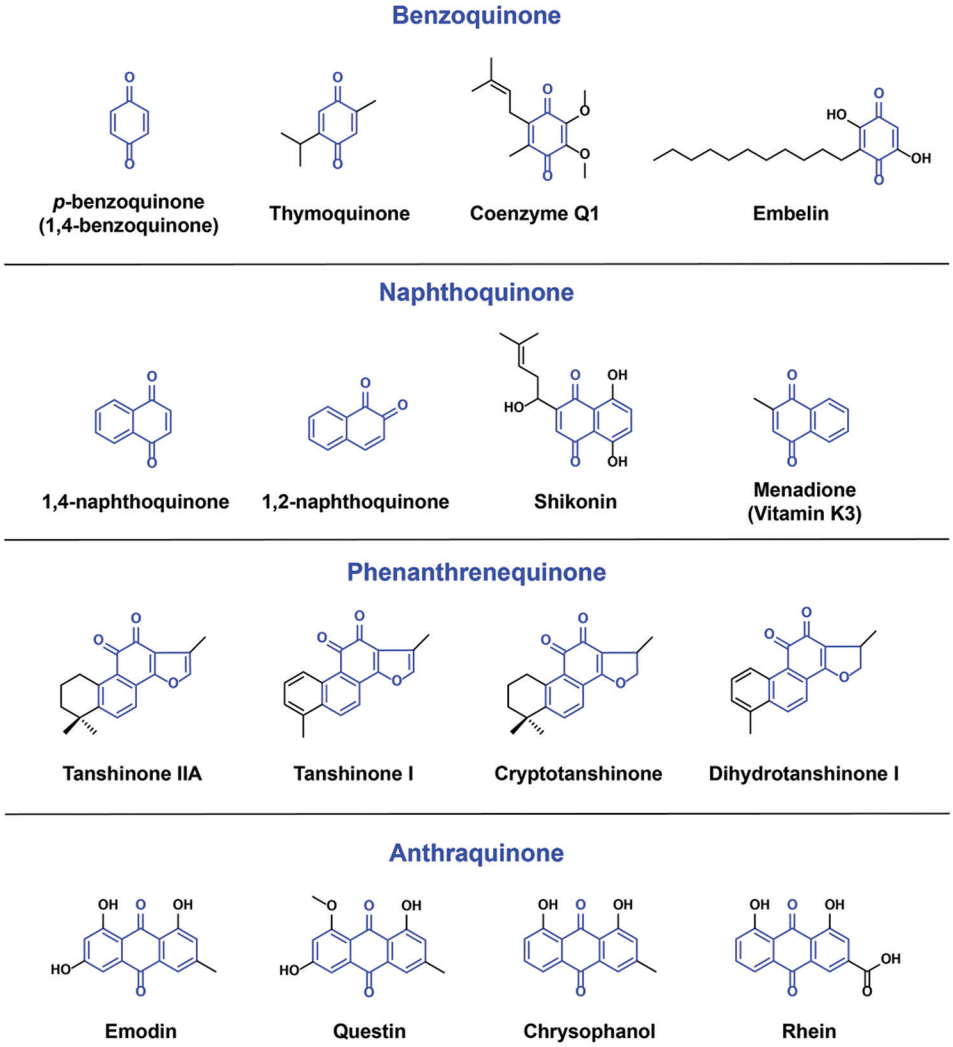

Figure 1. Representative structures of quinones from different categories, including natural products derived from quinones and synthetic quinones used as drugs

compounds counteract tumor angiogenesis by inhibiting vascular endothelial growth factor (VEGF) and its signaling pathways. For example, research by Xie *et al.*[24] demonstrated that TSIIA inhibits angiogenesis in the A549 human non-small cell lung cancer cell line by targeting the protein kinase domain of VEGF/VEGFR2, thereby impeding tumor growth and metastasis. Quinones also promote tumor cell apoptosis through various mechanisms.[25-27] A significant pathway involves the regulation of cellular redox homeostasis and the mediation of ROS production. Lu *et al.*[28] discovered that SHK enhances the expression of receptor-interacting protein kinase 1 (RIPK1) and RIPK3, leading to the excessive accumulation of intracellular ROS and mitochondrial superoxide in a concentration-dependent manner. This accumulation forms a positive feedback loop with RIP1 and RIP3, triggering necroptosis in glioma cells, with ROS playing a central role in the expression of RIPK1 and RIPK3 and the assembly of necrotic bodies. Similarly, research by Liu *et al.*[29] suggests that ROS acts as an upstream signal for RIPK1 and RIPK3, mediating not only SHK-induced necrotic apoptosis in nasopharyngeal carcinoma cells but also regulating the expression of the RIPK1/RIPK3/MLKL complex, thereby highlighting the pivotal role of ROS in quinone-induced necrotic apoptosis. In addition, quinones can mitigate tumor chemotherapy resistance by inhibiting the overexpression of ATP-binding cassette transporters and modulating multiple signaling pathways.[30, 31] This inhibition enhances the efficacy of chemotherapy drugs and synergistically combats tumors in conjunction with other chemotherapeutic agents.

Quinone compounds, encompassing various types such as benzoquinone, naphthoquinone, phenanthrenequinone, and anthraquinone, feature a core structure with conjugated double bonds and active functional groups, including carbonyl groups. This distinct structural configuration confers substantial chemical reactivity upon them. In the context of structure-activity relationships, quinones such as SHK, tanshinones, and emodin are increasingly recognized as potential candidates for anticancer drug development. Despite the absence of quinone-based natural products being independently utilized as anticancer agents in current clinical practice, ongoing clinical registration studies are likely to expedite their translation into clinical applications. For instance, an early clinical trial demonstrated that an SHK derivative could inhibit lung cancer growth and was both safe and effective.[32, 33] In addition,

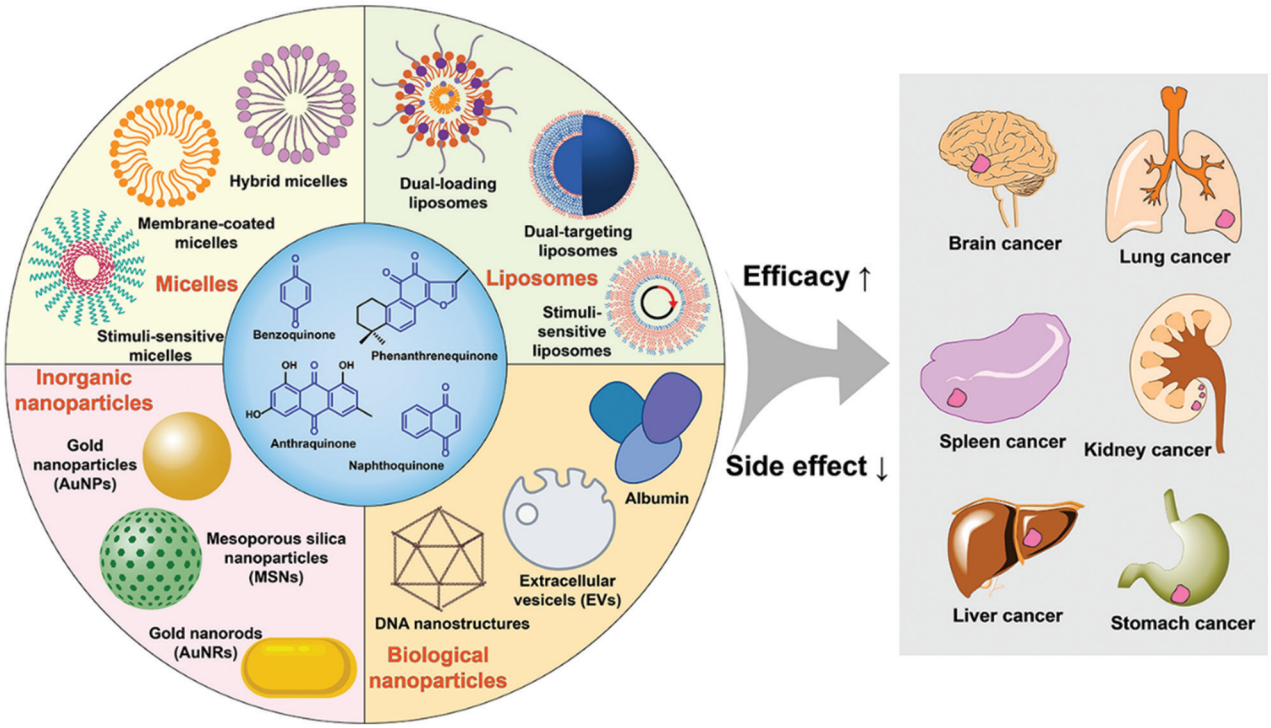

Figure 2. A series of nanomaterials that could be used in quinone formulations for precise delivery and treatment of various types of cancer

SHK has also been registered for clinical trial studies on the treatment of bladder urothelial carcinoma and breast cancer.[34]

Benzoquinone, a class of quinones featuring a single six-membered ring,[35] exists primarily in two isomeric forms: 1,4-benzoquinone and 1,2-benzoquinone.[36] The more prevalent 1,4-benzoquinone, with the chemical formula $C_6H_4O_2$, is an oxidized derivative of 1,4-hydroquinone and is commonly referred to as para-benzoquinone (or *p*-benzoquinone).[35] It forms the basic unit of ubiquinone (coenzyme Q),[37] playing a crucial role as an electron carrier in various bioenergetic processes, including phosphorylation and electron transport within mitochondria.[38] Furthermore, it has demonstrated significant anticancer potential. For instance, TQ, an active constituent extracted from the black seed (*Nigella sativa* L.), has been extensively investigated as an anticancer agent.[39] It exerts its effects by arresting proliferation and mitosis through the stabilization of microtubules, inducing G2/M cell cycle arrest, inhibiting histone deacetylase and human telomerase reverse transcriptase activity, promoting histone acetylation and autophagy, and reducing the phosphorylation of protein kinase B (AKT) and S6 kinase beta-1. Moreover, the combined use of TQ with paclitaxel (PTX) or doxorubicin (Dox) has shown enhanced antitumor activity compared to the use of each agent individually.[40] Notably, pre-treatment with TQ has been found to sensitize 4T1 cells to PTX, resulting in increased cytotoxicity.[41]

Naphthoquinones, naturally occurring as 1,4-naphthoquinone (para-isomer) and 1,2-naphthoquinone (ortho-isomer), are characterized by a C6 – C4 skeleton.[42] These compounds are categorized based on their nuclear structures into three types: "1,4-naphthoquinones," "1,2-naphthoquinones," and "2,6-naphthoquinones", with 1,4-naphthoquinones being the most prevalent. The 1,4-naphthoquinones are noted for their ability to alkylate tumor cells through the electrophilic arylation of their core structure and the potent reducibility of hydroxyl groups. As electrophilic agents, naphthoquinones interact with electronegative substances within cells, thereby manifesting pharmacological activities.[43] Among these, SHKs are particularly noteworthy. Extracted from the Boraginaceae family, an important group in TCM, SHKs possess a 5,8-dihydroxy-1,4-naphthoquinone structure with an isohexenyl side chain.[44] Research has consistently shown that SHKs exert robust anticancer properties across various cancer types by inhibiting cell proliferation and migration, as well as inducing apoptosis, autophagy, and necroptosis. In addition, SHKs promote ROS generation, suppress exosome release, and enhance antitumor immunity through modulation of the phosphoinositide 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) and mitogen-activated protein kinase signaling pathways. They also inhibit the activity of proteins such as thioredoxin reductase 1, pyruvate kinase muscle isozyme, PIP1/3, proto-oncogene tyrosine-protein kinase Src, and focal adhesion kinase, and regulate the expression of endoplasmic reticulum protein 57, matrix metalloproteinases, activating transcription factor 2, C-Myc proto-oncogene, miR-128, and glucose-regulated protein 78 (binding immunoglobulin protein).[45] SHKs can overcome drug resistance mechanisms in tumor cells, induce programmed cell death (necroptosis), and demonstrate efficacy against both drug-sensitive and drug-resistant tumor cells. These cells often exhibit high expression of proteins such as P-glycoprotein, B-cell lymphoma 2, and B-cell lymphoma-extra large, and SHKs show significant antitumor activity both *in vitro* and *in vivo*. Yang *et al.*[46] identified that the interaction of carbonyl

carbons C1 and C4 of SHK with the tumor proteasome contributes to the suppression of proteasomal activity and the induction of cell death *in vivo*. Furthermore, menadione (vitamin K3), another naturally occurring 1,4-naphthoquinone lacking 5,8-hydroxy groups, induces classical oxidative stress-induced necrosis but not necroptosis.[47] Xuan *et al.*[48] noted that the presence of 5,8-hydroxy groups in the 1,4-naphthoquinone nucleus is crucial for inducing necroptosis when comparing naphthoquinone derivatives of SHK with vitamin K3.

Phenanthrenequinones, another quinonoid compound, bind to DNA molecules to exert cytotoxic effects.[49] Tanshinones, a prominent class of phenanthrenequinones, are the principal compounds extracted from the dried roots and rhizomes of *S. miltiorrhiza* Bge.[50] The structure of tanshinones underlies their cytotoxic capabilities.[51, 52] Their molecular configuration, which includes furan rings and quinone structures, generates free radicals and induces DNA damage, thereby inhibiting DNA synthesis in tumor cells. This leads to alterations in the expression of numerous genes associated with tumor cell proliferation, differentiation, apoptosis, and invasion. It also affects the expression of cell surface antigens and reverses multidrug resistance.[53] TSIIA, the most studied lipophilic component of *S. miltiorrhiza*, significantly inhibits tumor proliferation, disrupts the cell cycle, and induces apoptosis through the PI3K/AKT/mTOR and the c-Jun N-terminal kinase signaling pathways. In addition, it promotes autophagic death and inhibits cell migration and invasion.[54]

The core structure of anthraquinones consists of a rigid, planar three-ring aromatic anthracene system, featuring two keto groups at the 9- and 10-positions. The planar anthraquinone core can integrate into the DNA double helix of cancer cells, where it participates in a specific redox cycle. This cycle generates the superoxide radical anion (O^{2-}) *in vivo*, leading to the interruption of DNA replication and the induction of DNA coding errors.[55] Anthraquinones disrupt the proliferation and differentiation of tumor cells, promote apoptosis, obstruct the cell cycle, modulate immune signaling, alter cell migration, and counteract multidrug resistance in the progression of malignant tumors.[56] For instance, emodin, a natural derivative of anthraquinone found in widely used TCMs such as *Rheum palmatum*, *Polygonum cuspidatum*, and *Polygonum multiflorum*,[57] has demonstrated significant therapeutic efficacy against various tumors.[58] Researchers have designed and synthesized numerous anthraquinone derivatives targeting diverse cancer types, with several drugs, including mitoxantrone,[59] Dox,[60] and epirubicin,[61] already approved for clinical use.

In summary, distinct quinone compounds exhibit unique antitumor mechanisms and hold potential for drug development.[35] Benzoquinones, with their relatively simple structures, are readily amenable to chemical modification. By introducing various substituent groups, their antitumor activity and pharmacokinetic properties can be effectively enhanced. Despite their high chemical reactivity, which may contribute to pronounced cytotoxicity and adverse reactions, these compounds remain of interest. On the other hand, naphthoquinones primarily induce cell apoptosis or necrosis through the promotion of ROS accumulation[62] and ferroptosis.[63] Their high redox activity, however, may result in significant cytotoxicity and oxidative stress damage. Phenanthrenequinones, noted for their unique DNA embedding abilities, also exhibit anti-inflammatory properties,[64] which are beneficial for improving the tumor microenvironment. Nonetheless, their pharmacokinetic attributes require further optimization. Anthraquinones, recognized for their substantial antitumor efficacy, are among the most extensively studied quinone compounds. Despite their widespread clinical use, issues such as cardiotoxicity and drug resistance persist. Moreover, the generally poor water solubility of quinone compounds limits their stability and bioavailability *in vivo*. Thus, strategic approaches involving structural optimization, targeted modification, and nanodelivery systems can significantly enhance the antitumor efficacy of various quinone compounds, reduce their toxicity, and augment their clinical value, thereby fostering their advanced development in clinical applications.

4. Development of nanotechnology-based quinone delivery systems

Quinone-based compounds have demonstrated substantial antitumor efficacy *in vitro*, yet their clinical application is hindered by several challenges, including low stability, poor water solubility, erratic pharmacokinetics, and a lack of targeting specificity. For instance, SHK and its derivatives, despite their significant therapeutic potential, are plagued by issues related to pharmacokinetics, toxicity, and stability, such as poor bioavailability, nephrotoxicity, and susceptibility to photodegradation.[65, 66] Similarly, the natural hydrophobic compound TSIIA, exhibits a brief half-life ($t_{1/2}$) of only 44 min[67] and a low oral bioavailability of approximately 2.9 – 3.4% in rats.[68] Furthermore, the water solubility of emodin is limited to a mere 70 mg/L,[69] while plumbagin is constrained by a median elimination half-life and a mean residence time of 9.6 and 5.0 h, respectively.[70]

Nanotechnology has emerged as a novel cancer treatment strategy, particularly as an efficient delivery system with significant therapeutic potential. Nanocarriers, characterized by their excellent biocompatibility, favorable pharmacokinetics, and high drug-loading capacity, enhance the bioavailability and targeting precision of natural products while diminishing side effects.[71-73] Nanomaterials typically range in size from 1 to 100 nm and exhibit unique optical, magnetic, and electrical properties, rendering them optimal for biomedical applications.[74] Over the past two decades, nanomaterials have garnered significant interest in the biomedical domain, prompting the development of various nanodelivery systems designed to amplify the anticancer efficacy of quinone-based natural products (**Figure 3**). **Table 1** provides a compilation of anticancer quinone-based drugs utilizing a diverse array of nanomaterials, including micelles, lipid-based systems, dendrimers, and inorganic and biological nanomaterials.

4.1. Micelles

Polymeric micelles consist of amphiphilic polymers that form structures with an internal hydrophobic core, which entraps

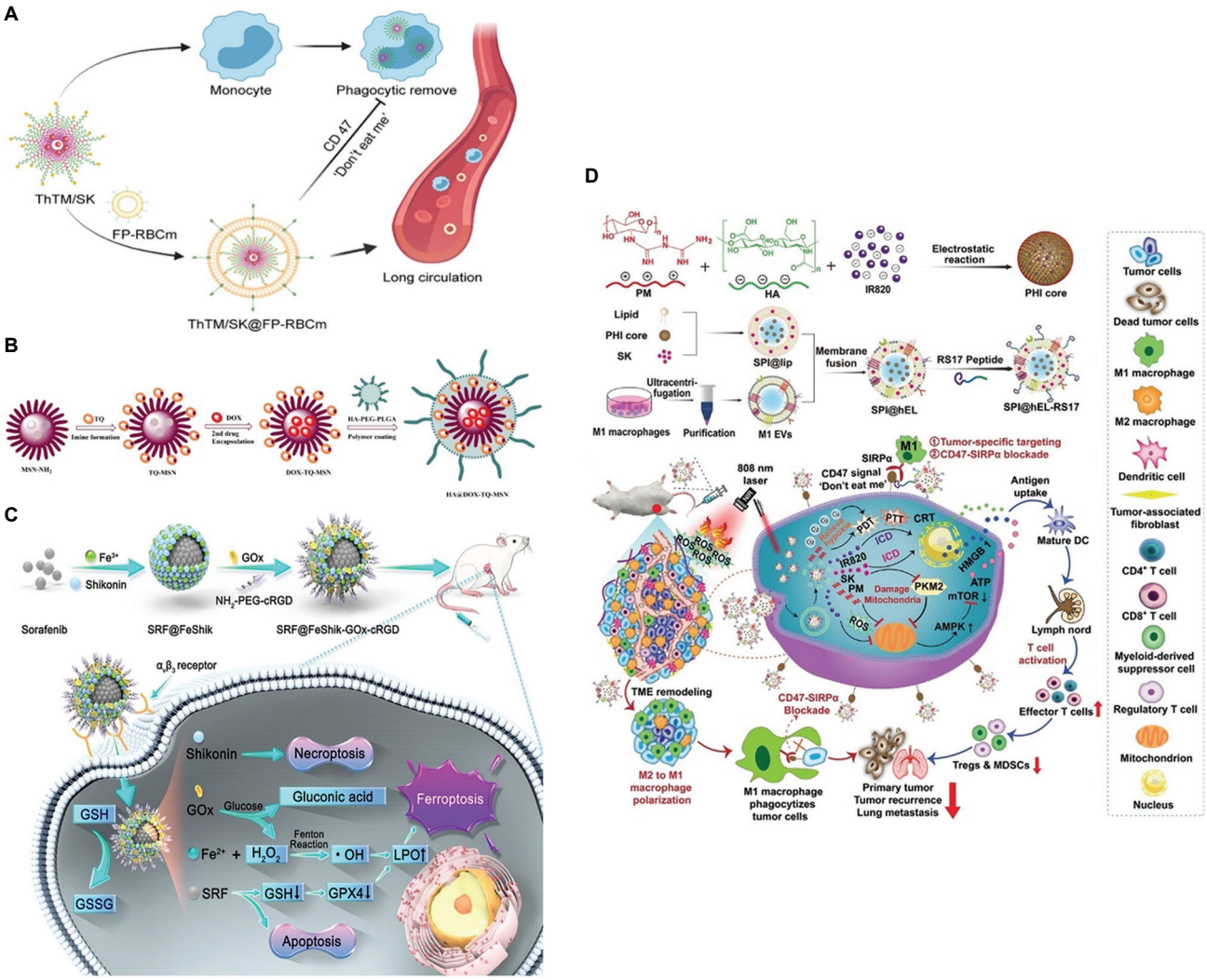

Figure 3. Schematic illustrating several nanomaterials-based intracellular delivery systems for the accurate delivery of quinones and quinone derivatives. (A) The effect of micelles *in vivo*, including two scenarios: with and without RBCm camouflage. Micelles with RBCm camouflage (ThTM/SK@FP-RBCm) can evade phagocytic cells and exhibit prolonged circulation compared to those without RBCm camouflage. Reprinted from Peng *et al.*[76] Image used with permission from Wiley-VCH GmbH, Copyright © 2022, Wiley-VCH GmbH. (B) The amine functional groups on the side-chains of MSNs react with the carbonyl groups of TQ to form TQ-MSN. Subsequently, DOX is added to generate DOX-TQ-MSN. Finally, hyaluronic acid-polyethylene glycol-poly(lactic-co-glycolic acid) (HA-PEG-PLGA) is used for encapsulation, resulting in a simple, effective, and pH-responsive drug delivery system (HA@DOX-TQ-MSN). Reprinted from Bhattacharjee *et al.*[117] Image used with permission from American Chemical Society, Copyright © 2024, American Chemical Society. (C) Fe(III)-Shikonin (FeShik) is used as a carrier to internally load sorafenib (SRF) and externally attach GOx and amine-polyethylene glycol-cyclo(Arg-Gly-Asp-*d*-Phe-Lys) (NH2-PEG-cRGD). FeShik releases Fe^{2+} and consumes GSH in tumor cells overexpressing GSH, thereby inducing tumor cell death through iron deposition. GOx promotes the production of •OH by providing an acidic environment and a high concentration of H_2O_2. Following the decomposition of SNs, the released SRF inhibits GSH biosynthesis, leading to the inactivation of GPX4 and enhancing the iron deposition effect for tumor treatment. Reprinted from Feng *et al.*[123] Image used with permission from American Chemical Society, Copyright © 2022, American Chemical Society (D) PM interacts with polyanions, multivalent charged HA, and the photosensitizer IR820 via electrostatic reactions to form a kernel formed by PM, HA, and IR820 together (PHI) core. This water-soluble PHI core is loaded into the hydrophilic cavity of liposomes, while the hydrophobic drug shikonin (SK) is accommodated in its phospholipid bilayer, resulting in the formation of SPI@lip. SPI@lip then fuses with M1 macrophage extracellular vesicles (M1 EV) to form hybrid nanovesicles, SPI@hEL. The RS17 peptide is subsequently incorporated into SPI@hEL using post-insertion technology, resulting in SPI@hEL-RS17 nanoparticles (NPs). Reprinted from Tang *et al.*[77] Image used with permission from Wiley-VCH GmbH, Copyright © 2023, Wiley-VCH GmbH.

Abbreviations: AMPK: Adenosine 5′-monophosphate-activated protein kinase; CD4/8/47: Cluster of differentiation 4/8/47; CRT: Calreticulin; DC: Dendritic cell; GSSG: Glutathione disulfide; HMGB1: High mobility group protein 1; ICD: Immunogenic cell death; LPO: Lipid peroxides; MDSC: Myeloid-derived suppressor cell; mTOR: Mammalian target of rapamycin; PKM2: Pyruvate kinase M2; ROS: Reactive oxygen species; SIRPα: Signal-regulatory protein alpha; TME: Tumor microenvironment; Tregs: Regulatory T cells; RBCm: Red blood cell membrane; MSNs: Mesoporous silica nanoparticle; TQ: Thymoquinone; DOX: Doxorubicin; GOx: Glucose oxidase; SNs: Supramolecular nanomedicines; GPX4: Glutathione peroxidase 4; PM: Polymetformin; HA: Hyaluronic acid.

Table 1. Examples of anti-cancer quinone drugs based on a variety of nanomaterials

Natural product	Formulation	Materials for delivery platform	Cancer type	Characteristics	References
Shikonin	STP-NG/SHK	*L*-phenylalanine N-carboxyanhydride, *L*-cystine N-carboxyanhydride, amino-terminated mPEG, trifluoroacetic acid, and tert-butoxycarbonyl-amino-modified PEG-NH2	Osteosarcoma	Mean particle size: 85.90±5.50 nm, Zeta potential: −2.21 mV	75
	ThTM/SK@FP-RBCm	NH_2-PEG_{2k}-$PCL_{6.6k}$, NH_2-$PEG_{3.4k}$-Hyd-$PCL_{6.6k}$, $mPEG_{2k}$-$PCL_{6.6k}$, and FA-PEG-FA (PEG_{1k}, PEG_{2k}, and $PEG_{3.4k}$)	Triple-negative breast cancer	Mean particle size: 140.00 nm	76
	SPI@hEL-RS17	Polymetformin, new indocyanine green, hyaluronic acid, M1 macrophages	4T1 breast tumor, B16F10 melanoma	Mean particle size: 131.90±4.00 nm, Zeta potential: −21.68±0.96 mV	77
Emodin	SNM|EO;	Mesoporous propylamine;	Colon cancer	Mean particle size: 250.00±80.00 nm;	78
	SNM~M | EO;	Mesoporous propylamine and N-methyl isatoic anhydride;		230.00±90.00 nm;	
	SNM~L | EO	Mesoporous propylamine and lissamine rhodamine B sulfonyl chloride		260.00±80.00 nm	
	MLE	1,2-dioleoylsn-glycero-3-phosphoethanolamine-n- [poly (ethyleneglycol)]; ferromagnetic iron oxide nanocubes	Breast cancer	Mean particle size: 136.30 nm, Zeta potential: −18.10 mV	79
	E-SLNs	Glycerol monostearate, stearic acid, Tween 80, Poloxamer 188	Breast cancer	Mean particle size: 28.60±3.10 nm, Zeta potential: −17.00 – −24.00 mV	80
Tanshinone IIA	MSN-FA-TAN-MB	Mesoporous silica nanoparticle, microbubbles	Hepatocellular carcinoma, cervical carcinoma, lung cancer	-	81
	Gal-pH-TanIIA-NSVs	Non-ionic surfactant vesicles, galactosylated stearate	Liver cancer	Mean particle size: 53.72±0.91 nm, Zeta potential: −28.31±1.44 mV	82
	MSN-TanIIA-PEG	Polyethyleneimine-polyethylene glycol, mesoporous silica	Liver cancer	Mean particle size: 117.00 nm, Zeta potential: 43.20 mV	83

Abbreviations: FA: Folic acid; mPEG: Methoxypolyethylene glycols; PCL: Polycaprolactone; PEG: Polyethylene glycol; STP-NG: Sarcoma-targeting peptide-decorated disulfide-crosslinked polypeptide nanogel.

poorly water-soluble drugs, and an external hydrophilic shell that insulates the encapsulated drugs.[84] Recent advancements in micelle-based drug delivery systems have markedly enhanced the therapeutic efficacy, specificity, and safety of quinone-based bioactive natural products in cancer treatment. These systems utilize innovative strategies, including targeted delivery, reactive drug release, and combination therapy, to optimize the anticancer potential of quinone compounds. Functionalized micelles, such as those incorporating glycyrrhetinic acid (GA) and triphenylphosphine, facilitate tumor-specific and mitochondria-targeted delivery. Chen *et al.*[85] reported the development of a novel redox-responsive micellar system (GA-PEG-SS-PLGA) with GA-mediated hepatoma-targeting capabilities. This system has been shown to effectively deliver TSIIA for hepatocellular carcinoma (HCC) therapy, resulting in elevated liver TSIIA accumulation, targeted delivery, enhanced bioavailability, increased pro-apoptotic effects, and robust antitumor efficacy both *in vitro* and *in vivo*. Furthermore, Peng *et al.*[76] developed an innovative "right-side-out" red blood cell (RBC) membrane-coated cationic micelle system (ThTM/SK@FP-RBCm) specifically for the treatment of triple-negative breast cancer (TNBC). This system enhances the mitochondria-targeted delivery of SHK facilitated by triphenylphosphine while also reducing non-specific serum binding, immune recognition, and rapid cationic nanoparticle elimination in circulation. The strategy demonstrated enhanced tumor accumulation of the drugs, effective mitochondrial biogenesis inhibition through DNA polymerase subunit gamma downregulation, and significant antitumor and antimetastatic effects, with high safety and potential applicability for other mitochondria-dependent cancers (**Figure 3A**).

Stimuli-responsive micelles, encompassing pH-, ROS-, and temperature-sensitive systems, significantly enhance drug delivery by improving solubility, stability, and controlled release. Su *et al.*[86] developed thermosensitive nanomicelles (STNs) through reversible deactivation radical polymerization to enhance the solubility, tumor targeting, and therapeutic

efficacy of SHK in breast cancer treatment. This was achieved by leveraging temperature-regulated drug release and passive targeting mechanisms, resulting in enhanced cellular uptake, cytotoxicity, and *in vivo* tumor accumulation. It was observed that STNs at 40°C facilitated rapid internalization and release of SHK into the cytoplasm of breast cancer cells, yielding a heightened cytotoxic effect compared to STNs at 37°C and free SHK (**Figure 4A**). Cheng *et al.*[87] engineered a pH-responsive and cluster of differentiation 44 (CD44)-targeting polymer micelle (Emo@CD44p-PM), self-assembled from a CD44 peptide-conjugated polyethylene glycol-block-hydroxyethyl starch-block-poly(*L*-lactic acid) (CD44p-conjugated PEG-b-HES-b-PLA). This formulation enhances the stability, cellular uptake, and antitumor efficacy of emodin by utilizing an acid-labile acetal bond. Under acidic tumor environments (pH 6.5), this bond triggers the detachment of the PEG layer and the exposure of the CD44-targeting peptide, facilitating targeted breast cancer therapy (**Figure 4B**). Furthermore, Hu *et al.*[88] developed ROS-responsive micelles (SHK@HA-PBAP) for targeted ovarian cancer therapy. These micelles, loaded with SHK through hyaluronic acid-phenylboronic acid pinacol ester conjugation (HA-PBAP), degrade in high ROS environments to release SHK and quinone methide, simultaneously inducing ROS production, depleting intracellular glutathione (GSH), and disrupting redox homeostasis to effectively eradicate tumor cells. Liang *et al.*[89] designed and synthesized ROS/pH dual-sensitive dendrimer polymer micelles (p[mPEG-co-HPBE-co-EMD]@CLB) for the co-delivery of emodin and chlorambucil. These micelles were prepared with methoxypolyethylene glycols (mPEG) as the hydrophilic end and p-(hydroxymethyl) phenylboronic acid pinacol ester (HBPE) and emodin as the hydrophobic end, enabling tumor-targeted drug release through mechanisms of oxidative stress induction, GSH depletion, and sustained drug release through ROS generation and pH-triggered structural disruption at tumor sites. In addition, a GSH-responsive, lipoic acid-inulin-based delivery system was developed for TSIIA targeting colorectal cancer cells.[90] This system not only enhances drug release in tumor environments but also exhibits potent anticancer effects and supports *Bifidobacterium longum* growth, thereby merging

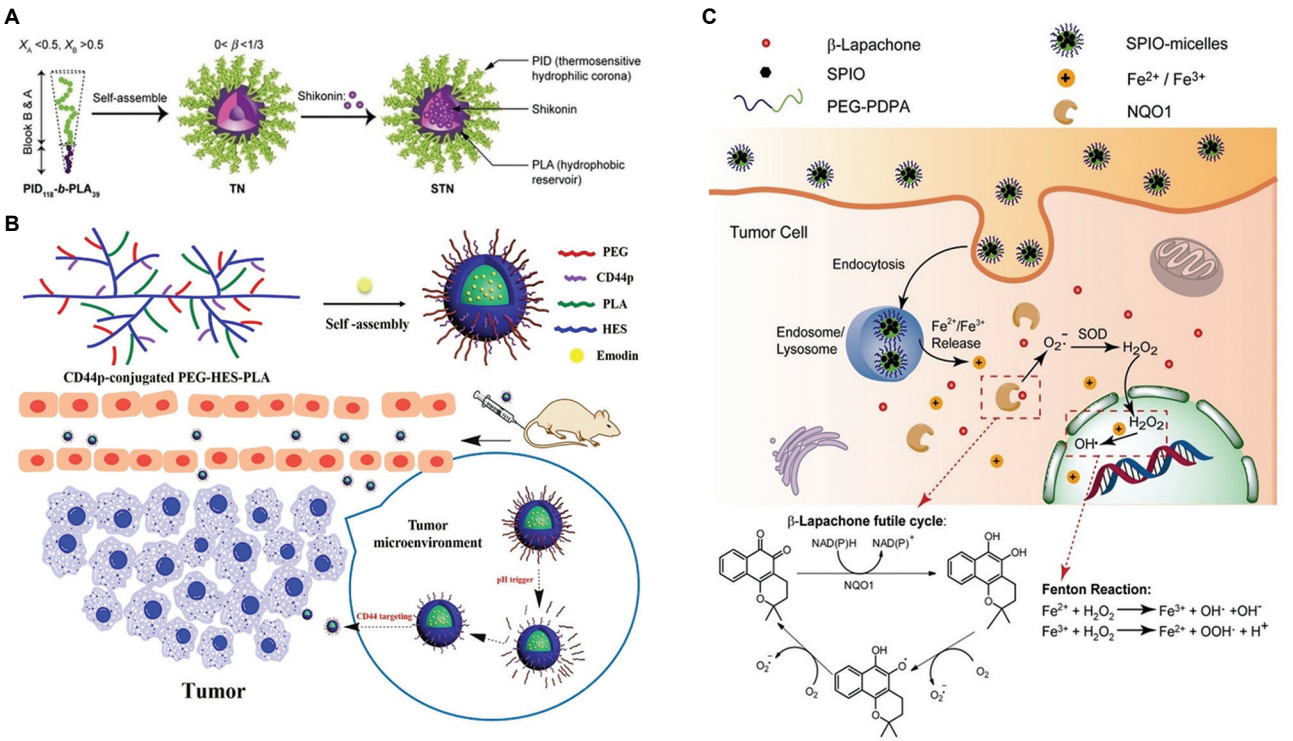

Figure 4. Micellar systems enhance the anticancer activity of quinone-based natural products. (A) The self-assembly of shikonin (SHK)-loaded thermosensitive nanomicelles (STN) in water. Reprinted from Su *et al.*[86] Image used with permission from Dove Medical Press, Copyright © 2017, Dove Medical Press. (B) Polymer micelles (Emo@CD44p-PM) are formed by the self-assembly of amphiphilic block copolymers (PEG-b-HES-b-PLA), which consist of the cluster of differentiation 44 (CD44)-targeting peptide CD44p, the hydrophobic chain polylactic acid (PLA), the hydrophilic chain polyethylene glycol (PEG), and hydroxyethyl starch (HES). When exposed to a physiological environment (pH ≈ 7.4), these micelles passively accumulate in tumor tissue through the enhanced permeability and retention effect and enter the acidic tumor microenvironment (pH<6.8), causing the separation of the PEG layer and the protein crown, increasing the accumulation of micelles and enhancing the antitumor effect. Reprinted from Cheng *et al.*[87] Image used with permission from IOP Publishing, Copyright © 2022, IOP Publishing. (C) The pH-sensitive superparamagnetic iron oxide nanoparticles (SPION) micelles act as intracellular iron donors in cancer cells, degrading and releasing iron ions in acidic organelles. Subsequently, they react with hydrogen peroxide generated by the ineffective redox cycle of β-lapachone to form highly active hydroxyl radicals, increasing reactive oxygen species (ROS) stress in cancer cells. Reprinted from Huang *et al.*[91] Image used with permission from Ivyspring International Publisher, Copyright © 2013, Ivyspring International Publisher.
Abbreviations: CD44p: CD44 peptide; NAD(P)H: Quinone oxidoreductase 1; PEG-PDPA: PEG-poly(2-[diisopropylamino] ethyl methacrylate); PID: PNIPAM-c-DMAAm random copolymer; SOD: Superoxide dismutase; TN: Thermosensitive nanomicelle.

cancer therapy with microbiota benefits in an innovative therapeutic approach.

In another study, Huang *et al.*[91] explored the synergistic effects of pH-responsive superparamagnetic iron oxide nanoparticle micelles with β-lapachone (β-lap) to increase therapeutic efficacy in NQO1-overexpressing cancer cells. These micelles release iron ions within acidic organelles, where they react with β-lap-generated hydrogen peroxide to amplify ROS stress, inducing cancer-specific cytotoxicity. This mechanism presents a promising theranostics nanomedicine strategy (**Figure 4C**). The ferrimagnetic mPEG-b-PHEP copolymer micelle, loaded with iron oxide nanocubes and emodin, demonstrated high heating conversion efficiency and alternating magnetic field (AMF)-activated drug release. This combined approach of magnetic hyperthermia and chemotherapy achieved over 70% tumor cell death and complete tumor elimination in mice.[92]

Advanced systems have demonstrated the potential to enhance oral bioavailability. Hou *et al.*[93] developed a novel self-assembled micelle system (SHK/GFB@WGA-micelles) that effectively encapsulated SHK and gefitinib (GFB) using an innovative supercritical reverse phase evaporation method. This system was designed to improve the oral absorption of SHK and GFB by facilitating mucus penetration and enterocyte uptake, thereby significantly enhancing their bioavailability and antitumor efficacy against drug-resistant lung cancer, both *in vitro* and *in vivo*.

Hybrid micelles have broadened the scope of cancer therapy by addressing significant challenges such as drug resistance and immunosuppression. Notably, the development of valid hybrid micelles (such as SHK/siIDO1-HMs) enabled the co-delivery of SHK and indoleamine 2,3-dioxygenase 1 (IDO-1) knockdown siRNA (siIDO1), showing considerable potential for colon cancer treatment.[94] These micelles induce immunogenic cell death (ICD) and modulate IDO-1-mediated immunosuppression, suggesting a potent therapeutic approach. In addition, the pH/ROS-responsive micellar nanosystem (PPDC@β-Lap), loaded with β-lap and camptothecin, demonstrates enhanced tumor cell uptake through charge reversal, self-amplifying drug release through ROS generation, effective multidrug resistance circumvention, and potent synergistic antitumor efficacy with low systemic toxicity *in vivo*.[95] Furthermore, a compound formulation comprising epidermal growth factor (EGF)-modified PTX micelles and EGF-modified emodin micelles has been developed for ovarian cancer.[96] This formulation demonstrates specific targeting of SKOV3 ovarian cancer cells, effectively inhibiting proliferation, invasion, and metastasis. The system exhibits significant *in vivo* pharmacodynamic results, highlighting its potential as a promising strategy for ovarian cancer treatment.

Moreover, clinically viable platforms, such as β-lap-loaded micelles, address challenges like hemolytic anemia and short circulation times, achieving effective targeting of NQO1-overexpressing tumors with reduced toxicity. Blanco *et al.*[97] established a clinically viable β-lap nanomedicine platform using polymeric micelles. This system demonstrates enhanced tumor targeting, improved drug stability, and superior therapeutic efficacy against NQO1-overexpressing non-small cell lung cancer. The platform exhibits increased tumor accumulation, prolonged circulation, reduced hemolytic toxicity, and potent antitumor effects in both subcutaneous and orthotopic lung cancer models.

In summary, micelle-based drug delivery systems represent a promising strategy in cancer therapeutics, offering enhanced tumor targeting, controlled release, and synergistic therapeutic mechanisms. These versatile platforms significantly enhance the clinical potential of quinone-based natural products by enhancing the pharmacokinetics of hydrophobic drugs while reducing systemic toxicity. However, the effectiveness of these systems depends on critical factors, including the biological characteristics of the tumor, the specificity of the targeted ligand, and the stability of the formulation. Future research should focus on optimizing micelle-based delivery systems, expanding their clinical applications, minimizing potential side effects, and addressing challenges related to tumor heterogeneity and non-specific organ accumulation.

4.2. Lipid-based nanoparticles

Liposomes closed spherical vesicles comprising lipid bilayers, possess several appealing properties, such as superior biocompatibility, excellent biodegradability, low clearance, and minimal toxicity.[98] Recent efforts have led to the development of various delivery systems based on liposomes or lipid nanoparticles, aimed at augmenting the anticancer efficacy of quinones. For instance, Meng *et al.*[99] engineered hyaluronic acid-coated SHK liposomes (HA-SHK-Lip) specifically for the treatment of TNBC. These liposomes demonstrated enhanced drug encapsulation, targeted uptake through the CD44 receptor, increased ROS production, reduced GSH level, and significantly improved antitumor effects compared to free SHK, as observed in both *in vitro* and *in vivo* studies. Besides, Luo *et al.*[100] described the development of a dual-targeting liposome (CS/LyP-1-PC Lip), co-loaded with PTX and cryptotanshinone, also for TNBC chemoimmunotherapy. This formulation enhances tumor targeting through dual-receptor-mediated endocytosis, induces ICD to stimulate immune responses, and counteracts the immunosuppressive tumor microenvironment by inhibiting STAT3 activation, thereby significantly suppressing tumor growth and reducing lung metastases in TNBC models (**Figure 5A**).

In addition to improving the precision of targeting, liposome-based nanodelivery systems have alleviated the limitations associated with quinone-based natural products as pharmaceutical agents and have made advancements in the field of cancer immunotherapy. Wang *et al.*[101] formulated a novel liposomal emodin by incorporating *D*-α-tocopheryl polyethyleneglycol 1000 succinate, achieving high encapsulation efficiency, enhanced stability, extended circulation time, improved biodistribution to the lung and kidney, and increased cytotoxicity against leukemia cells in comparison to mPEG2000–DSPE liposomal emodin. On the other hand, Chen *et al.*[102] developed aloe-emodin (AE)-loaded solid lipid nanoparticles (SLNs), which notably enhanced the anticancer

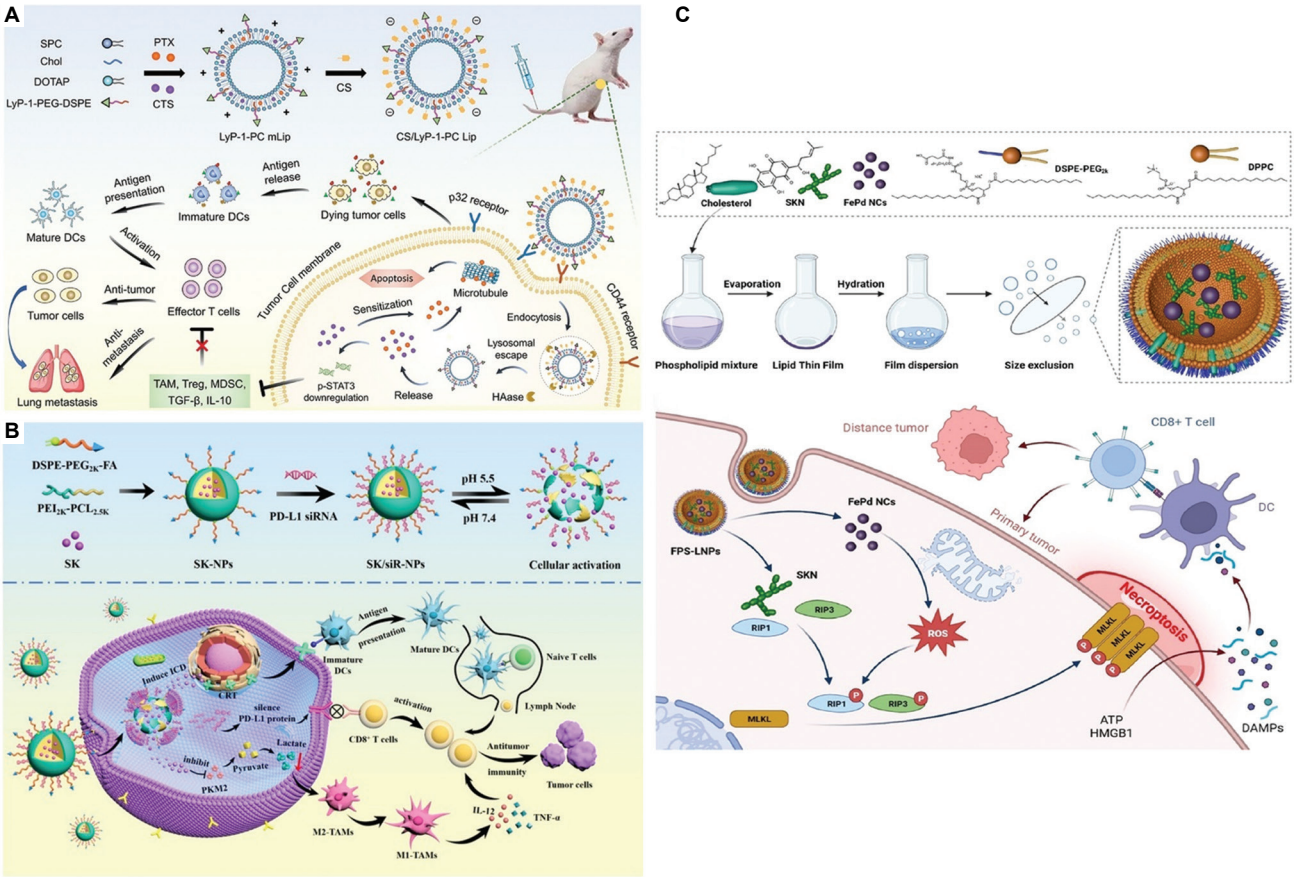

Figure 5. Lipid-based systems enhance the anticancer activity of quinone natural products. (A) Paclitaxel (PTX) and cryptotanshinone (CTS) were co-loaded into LyP-1 (CGNKRTRGC) (LyP-1) modified cationic liposomes, which were subsequently coated with anionic chondroitin sulfate (CS) via electrostatic interactions, resulting in the fabrication of negatively charged LyP-1/CS dual-modified liposome (CS/LyP1-PC Lip). This dual-targeted liposomal system mediates cellular uptake through dual-receptor binding of p32 and CD44. Degradation of the CS layer by hyaluronidase (HAase) triggers the release of cationic liposomes, enabling intracellular drug delivery. CTS potentiates the chemosensitivity of paclitaxel (PTX) against 4T1 tumor cells, while PTX inducesimmunogenic cell death (ICD). Concurrently, CTS inhibits signal transducer and activator of transcript-3 (STAT3) activation to reverse immunosuppressive tumor microenvironment (ITM), thereby achieving both primary tumor suppression and inhibition of lung metastasis. Reprinted from Luo *et al.*[100] Image used with permission from Wiley-VCH GmbH, Copyright © 2023, Wiley-VCH GmbH. (B) Folic acid (FA)-conjugated 1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine-*N*-([polyethylene glycol]-2000) (DSPE-PEG_{2K}-FA) and polyethyleneimine–poly (epsilon-caprolactone) (PEI–PCL) are used to co-deliver programmed cell death ligand 1(PD-L1) small interfering RNA (siRNA) and SK, synergistically treating cancer by simultaneously inducing immunogenic cell death (ICD), repolarizing M2-tumor associated macrophages (M2-TAM), and alleviating immune tolerance regulated by the PD-L1 pathway. Reprinted from Li *et al.*[108] Image used with permission from American Chemical Society, Copyright © 2020, American Chemical Society. (C) Iron palladium nanoenzymes (FePd NZ) and shikonin (SKN) were co encapsulated using thin film hydration method to obtain lipid nanoparticles (FPS-LNPs). In cells, SKN can mediate necrotic apoptosis, while FePd NZs promote ROS overexpression, thereby enhancing necrotic apoptosis. FPS-LNPs induced necrotic apoptosis further triggers CD8+ T cell-mediated immune response, enhancing its anti-tumor efficacy. Reprinted from Xie *et al.*[111] Image used with permission from American Chemical Society, Copyright © 2024, American Chemical Society.
Abbreviations: DAMPs: Damage-associated molecular patterns; DCs: Dendritic cells; DPPC: 1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine; IL-12: Interleukin-12; IT: Immunotherapy; Met: Metformin; MTPTT: Mild-temperature photothermal therapy; NPs: Nanoparticles; PKM2: Pyruvate kinase-M2; TAA: Tumor-associated antigen; TME: Tumor microenvironment; TNF-α: Tumor necrosis factor-alpha; Treg: Tumor infiltration of regulatory T cell.

effectiveness of AE by improving its solubility, bioavailability, and cellular uptake. These nanoparticles demonstrated heightened cytotoxicity and induced apoptosis in cancer cells more effectively than the AE solution, although additional molecular and *in vivo* studies are required to fully elucidate their mechanisms. Feng *et al.*[103] described the preparation of rhein-loaded SLNs through hot homogenization and ultrasonication, showing improved stability, sustained drug release, increased cellular cytotoxicity, and enhanced oral bioavailability compared to rhein suspensions. Sunil Kumar *et al.*[104] generated PEGylated liposomal formulations of plumbagin (PLB) using the thin-film hydration method, achieving optimal entrapment efficiency, biphasic release, prolonged plasma half-life, and enhanced antitumor efficacy against B16F1 melanoma, along with minimal toxicity to normal tissues. These findings underscore their potential as an effective parenteral delivery platform for PLB. Meanwhile, Rachamalla *et al.*[105] crafted a cationic liposomal formulation of TQ (D1T) to improve its bioavailability and tumor-specific anticancer efficacy. The formulation exhibited improved pharmacokinetics, increased

tumor suppression, elevated cellular uptake, and reduced toxicity compared to pristine TQ in an orthotopic xenograft pancreatic tumor model. Similarly, Kontogiannopoulos *et al.*[106] successfully developed and characterized novel SHK-loaded liposomes using 1,2-dipalmitoylphosphatidylcholine (DPPC) and egg phosphatidylcholine lipids, enhancing the therapeutic index, aqueous solubility, and stability of SHK while mitigating adverse effects. They demonstrated favorable physicochemical properties, controlled-release profiles, and moderate cytotoxicity against human cancer cell lines, with DPPC liposomes showing superior drug-loading capacity and release characteristics. In their study, Eskandani and Nazemiyeh[107] successfully developed and characterized SHK-Act-loaded SLNs using a hot homogenization method, producing stable, spherical nanoparticles (70 – 120 nm) with high entrapment efficiency, sustained release, and enhanced fluorescent imaging properties. These nanoparticles exhibited superior *in vitro* cytotoxicity, DNA damage, and prolonged antitumor effects compared to intact SHK-Act, highlighting their potential for improved therapeutic efficacy and biodistribution studies in drug delivery research. Li *et al.*[108] engineered a versatile nanoparticle (SHK/siR-NPs) for co-delivering SHK and programmed death-ligand 1 (PD-L1)-knockdown siRNA, which demonstrated prolonged blood circulation and increased tumor aggregation, thereby enhancing cancer immunotherapy (**Figure 5B**). Wu *et al.*[109] constructed a laser-triggered thermosensitive metabolic nanomodulator (denoted as ISM liposome) co-encapsulating IR825-NH2, SHK, and metformin. This approach synergized phototherapy, chemotherapy, and immunotherapy, achieving robust tumor elimination after a single injection and irradiation by amplifying oxidative stress, alleviating hypoxia, inducing ICD, and sensitizing immunosuppressive tumors to immune therapy, with minimized systemic toxicity and no observed adverse effects *in vivo* in mice.

In addition to single-drug loading, dual or multi-drug loading systems have been developed to address multidrug resistance and facilitate the concurrent administration of multiple therapies, thereby enhancing the efficacy of quinone-based treatments for cancer. For instance, a nanostructured lipid carrier that co-delivers β-lap and Dox has been demonstrated to effectively circumvent multidrug resistance in breast cancer therapy.[110] This system increases the retention of Dox and exhibits superior anticancer activity both *in vitro* and *in vivo* compared to single-drug delivery systems. Similarly, Xie *et al.*[111] designed iron–palladium nanozyme (FePd NZ)- and SHK-encapsulated functional lipid nanoparticles (FPS-LNPs) that significantly improve cancer therapy by inducing necroptosis through ROS overexpression, overcoming resistance to apoptosis, inhibiting tumor growth, and stimulating the cytotoxic T cell immune response (**Figure 5C**). Meanwhile, Sakpakdeejaroen *et al.*[112] have reported that transferrin-conjugated lipid–polymer hybrid nanoparticles loaded with PLB effectively target tumors, achieving significant regression and elimination of B16-F10 melanoma in mice. The findings demonstrate their potential as a promising anticancer nanomedicine. Furthermore, N'Diaye *et al.*[113] developed biodegradable lipid nanoparticles that co-encapsulate β-lap in the polymeric core and the photosensitizer m-THPC in the lipid shell for combined chemo- and photodynamic therapy (PDT) of retinoblastoma. This combination shows additive cytotoxic effects and enhanced efficacy at lower doses compared to single therapies. In the research conducted by Yang *et al.*,[114] a dual-responsive lipid nanoparticle co-delivering nitric oxide and β-lap was crafted using zinc-coordinated lipids (DSNO[Zn]) alongside helper lipids (DOPE and DSPE-PEG2000). This formulation demonstrated synergistic antitumor effects by inducing oxidative stress, disrupting redox homeostasis, damaging nuclear DNA and mitochondria, and activating caspase-3, underscoring its potential as a multifunctional tumor therapy platform. A magnetic liposomal emodin nanocomposite was developed to enhance the anticancer efficacy and targeting of emodin, achieving improved tumor cell elimination, magnetic guidance for targeted drug accumulation, and significant *in vivo* tumor suppression, highlighting its potential as a magnetically guided theranostic nanoagent.[79]

In summary, liposomes represent a highly efficient delivery system for quinone-based natural products, offering advantages such as greater stability, prolonged circulation time, controlled release, and enhanced anticancer efficacy. These liposome-based delivery systems provide effective approaches to overcome challenges associated with traditional anticancer strategies, ranging from improving drug delivery to enhancing therapeutic effectiveness. These benefits contribute to the enhanced anticancer activity of quinone-based natural products by improving their pharmacokinetics and enabling targeted delivery. However, the application of these systems is currently limited by factors such as system instability, the complexity of preparation processes, and the inefficiency in targeting. Future studies are required that involve the integration of novel materials, multimodal targeting strategies, and optimization of production processes to overcome these limitations and facilitate clinical translation.

4.3. Inorganic nanoparticles

The development of inorganic nanodelivery systems for quinone-based natural products in cancer treatment has progressed through various innovative approaches. These delivery systems, which utilize inorganic nanomaterials, substantially enhance drug targeting, improve treatment efficacy, and optimize therapeutic outcomes through a range of novel methods. Concurrently, these systems aim to reduce side effects and offer a safer, more effective strategy for managing cancer. One notable study by Saeed *et al.*[115] reported on a hybrid drug, THQG, created by chemically linking the hydrophilic compound gallic acid with the hydrophobic compound TQ. This compound was subsequently loaded onto polyethyleneimine functionalized antimonene quantum dots. The resulting drug carrier system exhibited several advantageous features, including pH-sensitive drug release, low cytotoxicity, enhanced capacity to withstand oxidative stress, capabilities for radiolabeling to analyze organ deposition, and increased efficacy compared to the individual drugs. These characteristics suggest that this nanodrug could serve as a multimodal theranostic agent in the treatment of breast and oral cancer cell lines. Similarly, gold nanoparticles conjugated with anti-EGFR antibodies and loaded with the

radiosensitizer β-lap have shown enhanced tumor targeting, pH-sensitive drug release, and improved radiotherapeutic efficacy both *in vitro* and *in vivo*.[116] This approach presents a promising strategy for selective cancer therapy with minimal off-target effects. In a related study, a hyaluronic acid-coated mesoporous silica nanoparticle system (HA@TQ-DOX-MSN) co-delivering TQ and Dox specifically targets Dox-resistant breast cancer cells.[117] This system reduces multidrug resistance 1 expression, enhances miR-298 levels, and overcomes drug resistance while supporting sustained pH-sensitive drug release and specific targeting of cancer cells (**Figure 3B**).

Inorganic nanocarrier drug delivery systems can significantly enhance the efficacy of quinones in cancer treatment through functional modifications or integration with various therapeutic strategies. Zhang *et al.*[118] employed molecular docking to select TSIIA from a group of phytoestrogens as a target ligand for nanodelivery systems, incorporating modifications. Their research indicates that TSIIA-modified mesoporous silica nanoparticles offer enhanced targeted delivery to estrogen receptors, effective antitumor and antimetastatic effects, high drug-loading capacity, and reduced toxicity, presenting a promising phytoestrogen-based nanoplatform for breast cancer therapy. Similarly, Zhu *et al.*[83] discovered that polyethyleneimine-polyethylene glycol-coated mesoporous silica nanoparticles enhance HCC treatment by delivering TSIIA in a sustained manner combined with efficient glypican-3-shRNA gene therapy. This approach improves antitumor efficacy, reduces glypican-3 expression, and provides a potential synergistic therapeutic platform. Meanwhile, Lv *et al.*[81] developed a multifunctional drug delivery vehicle by combining folate-modified mesoporous silica nanoparticles with microbubbles to load TSIIA. This system integrates multiple benefits, such as high drug-loading capacity, enhanced cell membrane translocation, low cytotoxicity, ultrasound-triggered release, and tumor-imaging capabilities. It demonstrates improved cellular uptake through folate receptor-mediated endocytosis *in vitro* and significant tumor suppression *in vivo* with external ultrasound irradiation. This innovation offers a novel strategy for tumor theranostic applications. Furthermore, Ren *et al.*[119] created the multifunctional theranostic nanoplatform Fe_3O_4-PEG-Cy7-EMO, combining emodin and magnetic nanoparticles for both fluorescence and magnetic resonance imaging (MRI) and targeted therapy. The system demonstrates effective pancreatic cancer diagnosis, tumor suppression, and minimal side effects through passive targeting and synergistic therapeutic properties. Liang *et al.*[120] developed MUC1-aptamer-targeted nanoparticles (MUC1@ACS) co-delivering SHK and chitosan silver nanoparticles to induce necroptotic ICD, enhance immune cell infiltration, and suppress the growth and metastasis of TNBC through tumor-specific targeting and immune activation. In addition, Zhao *et al.*[121] designed a GSH-sensitive Fe-based coordination polymer-based nanosystem functionalized with calcium peroxide (CaO_2) and β-lap as donors of O_2 and H_2O_2 for dual cascade-amplified tumor chemodynamic therapy (CDT). This system can internalize in cancer cells, release cargoes in response to cytoplasmic GSH, self-produce H_2O_2 through cyclic reactions, activate ferroptosis and Ca^{2+} overload pathways, exacerbate tumor damage, enhance CDT efficiency, relieve hypoxic restriction, and display effective MRI capabilities. Thus, the system provides a novel tumor-initiated nano-bomb platform for dual-enhanced tumor CDT efficiency.

Supramolecular nanomedicine based on Fe-SHK has been shown to enhance therapeutic efficacy. Feng *et al.*[122] demonstrated that Fe(III)-SHK supramolecular nanomedicine, when modified with NH_2-PEG-cRGD, improves antitumor therapy by inducing ferroptosis and necroptosis, enhancing SHK's bioavailability, reducing its toxicity, and overcoming apoptosis-induced chemoresistance. In addition, a triple ferroptosis amplification strategy incorporating Fe(III)-SHK metal-polyphenol networks, sorafenib, and glucose oxidase markedly increases oxidative stress and enhances tumor therapy through GSH-responsive effects, thereby improving antitumor efficacy through mechanisms including ferroptosis, apoptosis, and necroptosis.[123] It offers superior therapeutic effects for 4T1 tumors (**Figure 3C**). Likewise, a 177Lu-MFeCu@Tan nanotheranostic platform was developed, combining the chemotherapy agent Tan with the radionuclide 177Lu within a dual-metal nanozyme carrier MFeCu.[124] This platform enables single-photon emission computed tomography and employs a quadruple-synergistic tumor therapy approach that encompasses internal radioisotope therapy, catalysis therapy, chemotherapy, and MFeCu-mediated ferroptosis and cuproptosis therapy. Both *in vitro* and *in vivo* studies of this platform have shown significant efficacy in tumor elimination and recurrence reduction. The platform's specific response to the tumor microenvironment and high retention effect further enhance its safety, providing an effective and secure quadruple synergistic antitumor therapy, particularly beneficial for TNBC. Meanwhile, Song *et al.*[92] developed ferrimagnetic micelles containing iron oxide nanocubes and emodin, which achieve superior magnetic hyperthermia performance, enhanced MRI contrast, and AMF-activated drug release. This system enables tumor-targeted chemotherapy and complete cancer cell elimination at low dosages, with potential applications for other hydrophobic natural products in cancer therapy. Moreover, Shi *et al.*[125] designed cytosine-guanine dinucleotide (CpG) oligodeoxynucleotide-loaded aluminum hydroxyphosphate nanoparticles coated with Fe-SHK metal-phenolic networks (Alum-CpG@Fe-SHK NPs). These personalized *in situ* nanovaccines exhibit potent antitumor effects, including the elimination of primary tumors, inhibition of distant tumors, and prevention of metastasis and recurrence. They present a viable strategy to advance personalized antitumor immunotherapy by utilizing autologous tumor cell lysates *in situ* without complex *ex vivo* processes. These diverse delivery systems offer multiple strategies, including drug combination, targeted delivery, gene therapy integration, enhanced therapeutic modalities, immunotherapy, and theranostic applications for improved cancer treatment.

Inorganic nanoparticles provide unique advantages for the antitumor application of natural products, including high stability, multifunctional synergistic therapy, and precise

controlled-release capabilities. Their multifunctionality opens avenues for therapeutic and diagnostic applications, yet challenges concerning their biological safety, preparation cost, and targeting efficiency remain. Future research and optimization of these nanoparticles are essential to maximize their effectiveness and safety in cancer treatment.

4.4. Biological nanoparticles

Ideally, a drug delivery system should remain stable within the bloodstream while effectively releasing drugs at the target site. However, exogenous nanoparticles are readily identified and eliminated by the immune system. To circumvent this, leveraging endogenous components such as proteins and cell membranes for camouflage – to evade immune detection and enhance tumor-specific uptake – presents a highly promising approach.[126] The biomimetic nanodelivery system employing quinone-based natural products in cancer therapy primarily aims to address the multifaceted challenges of cancer treatment. It integrates various therapeutic modalities, including chemotherapy, phototherapy, immunotherapy, and treatment for iron deficiency, into highly targeted and efficient formulations. Tang *et al.*[77] designed bioinspired hybrid nanovesicles (SPI@hEL-RS17) by merging extracellular vesicles from M1 macrophages with liposomes and decorating them with the RS17 peptide to target tumors. This design blocks the CD47-SIRPα checkpoint and reprograms tumor-associated macrophages into tumor-inhibiting M1-like phenotypes, thereby enhancing phagocytosis and sustaining immune responses. The co-encapsulation of SHK, the photosensitizer IR820, and the immunomodulator polymetformin provides synergistic effects in chemotherapy, phototherapy, and immunotherapy that suppress tumor growth, inhibit metastasis, and prevent recurrence in highly invasive tumor models (**Figure 3D**).

Similarly, to address the challenges posed by the complex preparation and adverse tumor microenvironment effects on previously reported PDT and ferroptosis-combined nanocomposites, Wu *et al.*[127] discovered that AE can induce ferroptosis by inhibiting GSH S-transferase pi 1. They prepared a biomimetic nanoplatform, AE@RBC/Fe nanocrystals, integrating AE as both a photosensitizer and ferroptosis activator with ferritin and RBC membranes. This enhances antitumor effects through synergistic PDT and ferroptosis, with ferritin providing oxygen and Fe^{3+}, while the biomimetic modification aids in circulation and targeting. However, AE's blue light absorption limits its application in deep tumors, which suggests a future focus on both efficacy and application limitations. Zhang *et al.*[128] developed ERFe_3O_4 nanoparticles, a red-blood-cell-membrane-coated, emodin-loaded iron-based nanoplatform. This platform synergistically reprograms tumor-associated macrophages, reverses the tumor immune suppressive microenvironment, and enhances antitumor immunity and apoptosis by modulating lactate production and promoting M1 macrophage polarization.

In a distinct approach, Liu *et al.*[129] developed a biomimetic nanoreactor, SOD-Fe^0 @Lapa-ZRF, in which SOD-Fe^0 and Lapa cargo were encapsulated within zeolitic imidazolate framework 8 (ZIF-8) through self-assembly. This design facilitates tumor-targeted multi-enzyme cascade therapy, generating hydroxyl radicals (•OH) that selectively eradicate cancer cells while simultaneously bolstering the antioxidant capacity of normal cells and minimizing oxidative stress-related systemic toxicity. In the study by Wang *et al.*,[130] a mannosylated lactoferrin nanoparticulate system (Man-LF NPs) was crafted for the dual-targeted biomimetic delivery of SHK and JQ1. This system effectively remodels the tumor immune microenvironment by inducing immune cell death, repolarizing tumor-associated macrophages, inhibiting glucose metabolism, and obstructing the PD-L1 checkpoint, thereby augmenting antitumor immunity and representing a promising polypharmacological approach to cancer immunotherapy. Similarly, Cui *et al.*[131] developed a biomimetic nanodrug delivery system (CpG-EXO/TGM) based on endogenous exosomes for targeted brain delivery. This system co-delivers TSIIA and glycyrrhizic acid nanomicelles along with immune adjuvants, demonstrating enhanced therapeutic efficacy against glioblastoma by improving blood-brain barrier penetration, stimulating anti-glioblastoma immune responses, and preventing postoperative recurrence, thus offering a viable strategy for chemo-immunotherapy and personalized treatment. Besides, Han *et al.*[132] designed a biomimetic nanodrug formulation (Comb-NP) that co-encapsulates PLB and dihydrotanshinone I to induce ICD in HCC cells and to reverse the immunosuppressive tumor microenvironment. This formulation enhances tumor targeting and prolongs survival in HCC mice, presenting a promising approach for chemo-immunotherapy with the potential for broader application in solid tumors.

These studies underscore the multifunctionality and potential of biomimetic nanodelivery systems to enhance the efficacy of quinone-based cancer immunotherapy by targeting the tumor microenvironment, improving drug delivery, and inducing multimodal therapeutic responses. They significantly enhance the biocompatibility of quinone-based natural products, increase cellular uptake, and improve therapeutic efficacy by mimicking biological characteristics. However, their clinical applications remain constrained by challenges related to preparation complexity, stability, and potential immunogenicity. Further optimization of biomimetic designs and in-depth evaluation of long-term toxicological properties are essential through synthetic biology techniques to advance their translational application in tumor therapy.

4.5. Others

Beyond the primary categories previously discussed, numerous scholars have further augmented the anticancer properties of quinone-based natural products through various carrier systems. For instance, Soni *et al.*[133] synthesized poly (DL-lactide-co-glycolide) (PLGA) nanoparticles that encapsulated TQ and PTX using a single emulsion solvent evaporation technique. These nanoparticles not only enhanced the anticancer activity but also reduced the toxic effects of PTX by decreasing the required effective dose. Likewise, Li *et al.*[134] engineered lactoferrin-modified poly(ethylene glycol)-PLGA nanoparticles for the delivery of SHK, addressing its poor aqueous solubility

and non-selective biodistribution. Their system demonstrated high drug-loading capacity, sustained release, enhanced brain targeting, prolonged circulation, and superior antiglioma efficacy compared to free SHK, underscoring its potential as a targeted delivery mechanism for glioblastoma. Peng *et al.*[135] utilized polyamidoamine (PAMAM) dendrimers and PEGylated derivatives to create acetylshikonin nanoparticles, which effectively inhibited tumors despite a reduction in antitumor activity owing to strong intermolecular forces; polyethylene glycol (PEG); PEG-PAMAM (PPG) emerged as a more stable and less cytotoxic carrier. In addition, a novel galactose-modified, pH-sensitive niosome delivery system specifically targeted HCC cells, enhanced the release and bioavailability of TSIIA, and demonstrated superior antitumor efficacy and liver specificity both *in vitro* and *in vivo*.[82] Jiang *et al.*[136] developed emodin-loaded stearic acid-grafted chitosan oligosaccharide micelles (CSO-SA/EMO), which showed enhanced drug uptake, sustained release, and significant antitumor effects *in vitro* and *in vivo* against gastric cancer cells, presenting a promising delivery system for cancer therapy.

Furthermore, quinone-based natural products not only serve as active agents but also contribute to the structural framework of drug carriers for other therapeutics. For example, an amphiphilic carboxymethyl chitosan-rhein conjugate was designed to form micelles for the oral delivery of PTX, enhancing its bioavailability, ensuring sustained release, and demonstrating significant antitumor efficacy with low toxicity.[137] This approach suggests a potential for the oral delivery of water-insoluble drugs. Moreover, a novel PEG 3500-embelin (PEG3.5k-EB2) micelle system was developed to improve the solubility and bioavailability of embelin, facilitating its capacity to efficiently transport hydrophobic drugs like PTX and exhibiting potent antitumor activity and synergistic effects at lower doses.[138] This dual functionality highlights the significant potential of quinone-based natural products in drug therapy and opens new avenues for innovation and optimization in drug delivery systems.

5. Limitations of the study

Before concluding, it is crucial to recognize the limitations inherent in the review's design. First, the selection of specific keywords for the literature search may have excluded relevant studies that used different terminologies or presented their findings differently. Second, the focus primarily on common nanodelivery systems may have overlooked emerging or less-developed nanocarriers with unique benefits. Third, the studies included in this review varied in experimental design, as well as in the types of quinone-based natural products and nanodelivery systems investigated. Such diversity makes it difficult to directly compare results across studies and draw definitive and generalizable conclusions. Finally, although significant progress has been made in enhancing the antitumor efficacy of quinone-based natural products through nanodelivery systems, most research remains in the preclinical phase. The transition from preclinical findings to clinical applications is often complex and unpredictable, as factors such as pharmacokinetic and toxicity profiles may differ significantly between human subjects and animal models. Therefore, further validation through rigorous clinical trials is essential to establish the efficacy and safety of these nanodelivery systems.

6. Conclusions and future perspectives

Quinone-based natural products hold considerable potential for anticancer applications but also encounter numerous challenges. Active compounds such as SHK and its derivatives, TSIIA, emodin, and PLB demonstrate promising antitumor activity *in vitro.* However, their clinical application faces challenges such as low bioavailability, poor solubility, short *in vivo* release time, and potential side effects. Considerable efforts have been made to overcome these hurdles. Nanocarriers have gained significant attention for their ability to enhance the solubility of TCMs, provide excellent stability, improve absorption, and offer better sustained-release and targeting capabilities. This review has outlined the main types of nanocarriers used in this area, including micelles, liposomes, inorganic nanocarriers, and biomimetic nanocarriers. These nanocarriers demonstrate substantial promise in enhancing the efficacy of quinone-based natural products and addressing the challenges associated with their clinical application.

Although numerous reports have explored this topic, the development of nanomedicine for delivering quinone-based natural products remains in its early stages. The limited research on quinone nanoparticles in clinical trials has slowed their clinical application, which is the ultimate goal of drug research. However, translating nanomedicine into clinical practice is a complex and lengthy process, involving significant challenges related to safety, efficacy, and production costs. Nanocarriers can introduce increased toxicity, heightened immunogenicity, higher manufacturing costs, and unforeseen risks. Consequently, the development of quinone-based nanoformulations requires conclusive evidence to establish their clinical efficacy, stability, and cost-effectiveness. To advance this field, it is crucial to conduct thorough pharmacokinetic and pharmacodynamic studies on nanocarriers containing quinone-based natural products. A deeper understanding of the interactions between nanocarriers and quinone-based natural products, along with optimization of drug release modes and timing, is critical for achieving more precise treatments. Additionally, studying the metabolism and distribution of nanodelivery systems *in vivo* is essential to minimizing side effects on normal tissues. By addressing key questions related to drug delivery, pharmacokinetics, safety, and efficacy, we aim to facilitate their clinical translation.

Although clinical research remains limited, promising results from *in vitro* studies and animal models justify further investigation into quinone-based nanoparticles as a novel approach to cancer treatment. With continuous advancements in nanomaterials and their clinical applications, new formulations of quinone-based natural products are expected to drive breakthroughs and improve therapeutic outcomes in the future.

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The authors declare no conflicts of interest.

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