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Ultrasound-Based Nanocarriers: Advances and Applications in Tumor Therapy

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ABSTRACT

Ultrasound (US), known for its non-invasive nature and high tissue penetration, has demonstrated remarkable potential in medical diagnostic imaging and tumor therapy. Nanocarriers, through the use of nanomaterials, has exhibited significant advantages in targeted drug delivery, improving bioavailability and reducing side effects. The integration of these two technologies enables sensitive diagnose, precise drug release under ultrasound activation, enhancing comprehensive therapeutic efficacy, which make ultrasound-driven nanocarriers a hotspot in the field of tumor diagnosis and treatment. Therefore, this review provides a comprehensive overview of the biophysical effects of ultrasound and the advantages of ultrasound-driven nanocarriers. Subsequently, it systematically summarizes the classification of ultrasound-based nanocarriers, including both organic and inorganic carriers. Furthermore, the article elaborates in detail on the applications of ultrasound-mediated nanocarriers systems in oncology, including ultrasound-enhanced nanocarriers systems for imaging applications, sonodynamic therapy (SDT), and high-intensity focused ultrasound (HIFU). Finally, the work conducts an in-depth analysis of the challenges hindering clinical translation and offers perspectives on future research directions.

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Introduction

Cancer remains one of the most significant threats to human health worldwide. According to the International Agency for Research on Cancer (IARC), there were approximately 20 million new cancer cases and 9.7 million cancer-related deaths globally in 2022.[1] Conventional therapeutic strategies, including surgery, chemotherapy, radiotherapy, targeted therapy, and immunotherapy, have significantly improved patient outcomes. However, their clinical efficacy is still limited by several challenges. These include systemic toxicity, poor tumor selectivity, multidrug resistance, and insufficient penetration into deep-seated tumors.[2] Therefore, developing more precise, controllable, and minimally invasive therapeutic strategies remains urgently needed.

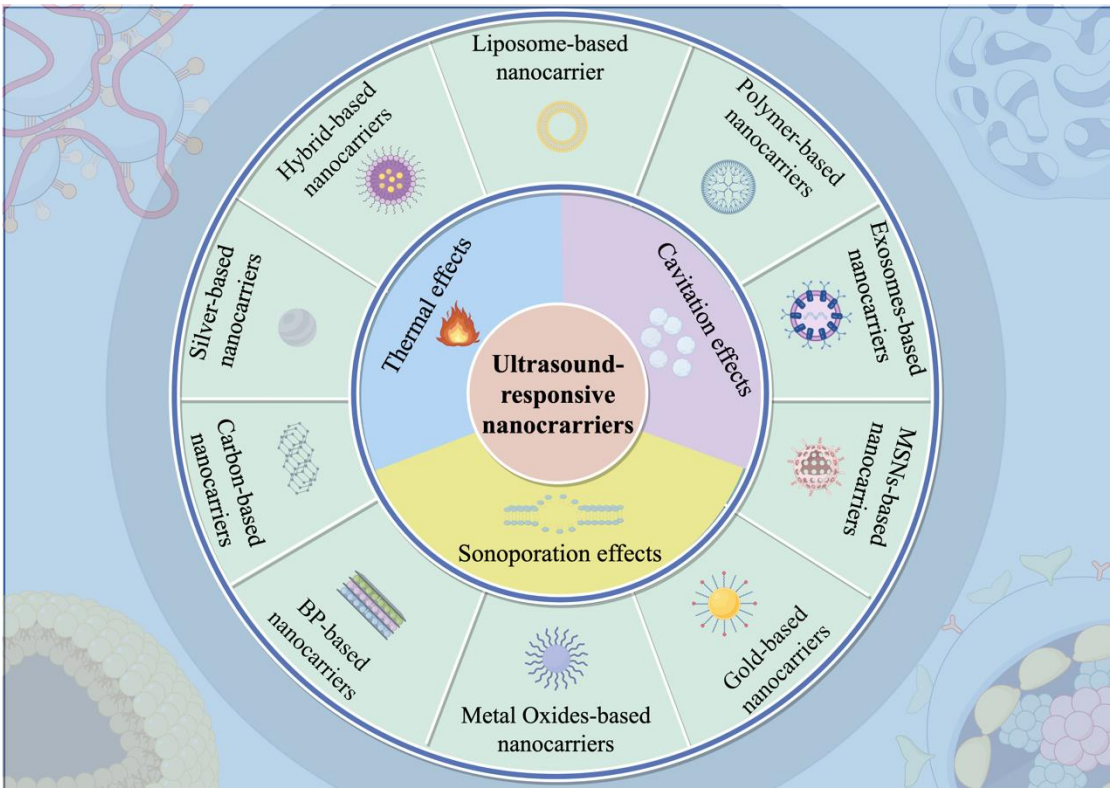
Ultrasound (US) has attracted increasing attention in tumor diagnosis and therapy due to its unique advantages. These include non-invasiveness, deep tissue penetration, real-time imaging capability, absence of ionizing radiation, and flexible spatiotemporal control.[3] Beyond its well-established role in diagnostic imaging, ultrasound can also exert therapeutic effects through thermal effects, cavitation, and sonoporation. These mechanisms enable enhanced tumor permeability, localized ablation, and stimulus-triggered drug release.[4] These characteristics make ultrasound an ideal external trigger for precision oncologic intervention.

Meanwhile, rapid advances in nanotechnology have enabled the development of multifunctional nanocarriers. These nanocarriers possess high drug-loading capacity, prolonged circulation time, tumor-targeting capability, and stimulus-responsive release behavior.[5] The integration of ultrasound with nanocarrier systems has given rise to ultrasound-responsive nanocarriers. These systems combine the advantages of both modalities. Under ultrasound stimulation, these nanocarriers can achieve on-demand and site-specific drug release. They also enable enhanced intratumoral penetration and real-time monitoring of biodistribution and therapeutic response. This significantly improves therapeutic precision while minimizing off-target toxicity.[6]

Importantly, ultrasound-based nanocarrier systems have shown broad potential in cancer theranostics.[7] These applications include contrast-enhanced imaging, sonodynamic therapy (SDT), high-intensity focused ultrasound (HIFU)-assisted therapy, and chemotherapy sensitization.[8] Compared with other externally triggered systems such as light-responsive platforms, ultrasound has deeper tissue penetration and better suitability for treating deep-seated tumors, which supports its potential for clinical translation.[9]

In recent years, several reviews have discussed ultrasound-mediated cancer therapy and nanocarrier-based drug delivery systems. However, most existing reviews focus on a single therapeutic modality, such as SDT or HIFU or concentrate on either organic or inorganic nanocarriers without systematic integration. For example, some studies describe SDT mechanisms and sonosensitizers, but provide limited discussion on nanocarrier design, imaging functions, or differences among carrier types. In contrast, nanocarrier-focused reviews often overlook the biophysical effects of ultrasound parameters and their key role in therapeutic performance. In addition, only a few reports have connected ultrasound-triggered drug delivery, multimodal imaging, and combination therapies. Importantly, key translational issues are still not fully addressed, including parameter standardization across models, long-term biosafety differences between organic and inorganic carriers, limitations of preclinical models, and cost-related challenges.

Therefore, this review differs from previous studies in several aspects: (1) it provides an integrated overview of both organic and inorganic nanocarriers with a comparative analysis from a translational perspective. (2) it links ultrasound biophysical mechanisms with specific applications, including SDT, HIFU, and immunotherapy combinations. (3) it summarizes emerging imaging strategies such as gas vesicle-based imaging and acoustic reporter gene imaging. In addition, it highlights current knowledge gaps and translational barriers and discusses future research directions. Overall, this review aims to serve as a useful reference for the development of ultrasound-responsive nanomedicines with improved clinical potential (Scheme 1).



Scheme1： Summary of ultrasound-based nanocarrier systems and their biophysical mechanisms

2.Ultrasound Biophysical Effects

Ultrasound waves can penetrate human tissues and generate echo signals, which are then converted into ultrasound images.[10] Compared to X-ray, computed tomography (CT), and positron emission tomography (PET) scans, ultrasound has several advantages. These include absence of ionizing radiation, real-time imaging, lower cost, portability, high safety, non-invasiveness, and operational flexibility.[11] In addition to diagnostic imaging, ultrasound exhibits antitumor effects through the following primary mechanisms[12]: (1) Thermal effects occur when ultrasound energy is converted into heat within biological tissues, causing a local temperature increase. This allows for the selective destruction of tumor cells.[13] (2) Cavitation effects can be divided into two types: stable cavitation and inertial cavitation. Stable cavitation involves the oscillation of microbubbles, which generates shear forces that can disrupt cellular structures. Inertial cavitation occurs when bubbles collapse rapidly, causing extreme spikes in local temperature and pressure, as well as bursts of reactive oxygen species(ROS).[14] (3) Sonoporation effects occur when ultrasound-induced mechanical stress creates reversible pores in cell membranes. This process greatly improves the efficiency of transmembrane transport of nanocarriers and increases intracellular drug accumulation.[15] For example, focused ultrasound can temporarily disrupt the blood-brain barrier, allowing nanocarriers to penetrate glioblastomas more effectively and improve antitumor efficacy.[16]

Ultrasound parameters are key physical quantities.[17] They include frequency, intensity, mechanical index(MI), pulse width, pulse repetition frequency, duty cycle, and total ultrasound exposure time.[18] Precise adjustment of these parameters is essential to ensure therapeutic efficacy and safety. Studies show that ultrasound settings with a mechanical index of 0.28 and duty cycle of 0.20%, together with lower pulse width (3.0) and higher pulse repetition frequency (2000 Hz), have greater advantages in enhancing tumor blood flow and chemotherapy drug release than those with higher pulse width (34.5) and lower pulse repetition frequency (200 Hz).[19] Ultrasound-based nanocarriers involve different parameters in different tumors. For example, for breast cancer, ultrasound frequencies ranging from 1.0 Hz to 2.25 MHz have been applied.[20] For cervical cancer, parameters of 20 kHz and 45 W for 3 minutes were used.[21] In colon cancer, an intensity of 2.0 W/cm² with 50% duty cycle for 1 minute was reported.[22] For hepatocellular carcinoma, cervical carcinoma, and lung adenocarcinoma, a frequency of 12 MHz was employed.[23] These examples show that ultrasound parameters vary significantly with tumor type and treatment strategy.

3.The advantages of Ultrasound-Based Nanocarriers

3.1 Nanocarriers Empowering Ultrasound: Precise and Sensitive Diagnostic Tools

Nanocarriers improve the effectiveness of ultrasound-based diagnostics and therapeutics. Nanocarriers function as ultrasound contrast agents. Their excellent acoustic properties, prolonged circulation time, and targeting abilities offer better imaging sensitivity.[24] This is helpful for detecting diseases early. By functionalizing their surface with ligands, these nanocarriers can specifically accumulate at diseased sites. This boosts diagnostic accuracy and reduces nonspecific distribution in the body.[25] Chen et al. created a targeted ultrasound contrast agent using multi-walled carbon nanotubes. In prostate cancer cells, it showed nearly full specificity (about 100%). In vivo studies set the detection threshold at 10 μg/mL. Within 8 hours of administration, tumor - specific ultrasound signals got stronger in neoplastic and renal areas. But non-target organs like heart tissue had no contrast agent build-up.[26]

3.2 Ultrasound-Based Nanocarriers: Precise Triggering and Dynamic Monitoring

Ultrasound improves the targeted release of nanocarriers. It enables real-time tracking and dynamic monitoring of nanocarrier biodistribution and drug release. This makes therapeutic interventions more controllable and visible.[27] Ultrasound-induced cavitation also increases tumor tissue permeability. This enhances nanocarrier penetration and promotes their accumulation at the target site, improving treatment effectiveness.[28] Jing et al. developed ultrasound-responsive nanocarriers. Ultrasound increased the drug release efficiency compared to non-ultrasound controls ($P < 0.001$). The release rates for two therapeutic agents were 87.4 ± 3.8% and 61.7 ± 1.3% under ultrasound.[29]

3.3. Integration of Ultrasound and Nanocarriers: Comprehensive Therapy and Theranostic Integration

Combining ultrasound with nanocarriers creates a multifunctional platform for precision medicine. It can be integrated with chemotherapy, immunotherapy, and gene therapy. This combination maximizes therapeutic benefits. Dong et al. developed a drug delivery system using nano-ultrasound contrast agents. The system combines ultrasound imaging with treatment. By integrating ferroptosis and photothermal therapy (PTT) with

ultrasound imaging and immune stimulation, it achieves both diagnosis and therapy. Experimental results showed an 82.5% tumor suppression rate and significant inhibition of pulmonary metastasis. This strategy not only enhances therapeutic efficacy but also prevents tumor progression and metastasis by activating systemic immune responses.[15]

4. Ultrasound-Based Nanocarrier Systems

Ultrasound-Based nanocarrier systems are therapeutic platforms. These systems use the physical effects of ultrasound to trigger the release of the drug from nanocarriers in tumors, improving therapeutic efficacy.[30]

4.1 Organic Nanocarriers

4.1.1 Liposomes

Liposomes have some advantages such as biocompatibility, biodegradability, and low immunogenicity. Liposomes can carry both hydrophilic and lipophilic drugs. Surface modification with targeting ligands, like antibodies or peptides, greatly enhances their tumor-specific recognition.[31] In ultrasound imaging, first-generation contrast agents such as Levovist (now largely discontinued) had limitations in clinical. This limitation is mainly due to rapid gas diffusion and a short circulation time.[32] Lipid-shelled microbubbles represent a key improvement. The lipid bilayer reduces gas leakage and improves microbubble stability. It also lowers surface tension. In addition, the hydrophilic shell promotes systemic circulation.[33] Second-generation contrast agents, such as Sonovue (clinically approved and widely used), further improve stability through lipid shell design. Bauer et al. demonstrated that low MI enables effective contrast enhancement in cardiac and hepatic tissues. These microbubbles remain stable at MI < 0.4. In clinical practice, the MI is typically around 0.2. Low-MI operation reduces tissue damage and prolongs the imaging window. It also improves the signal-to-noise ratio.[34]

Ultrasound enhances drug delivery from liposomal carriers. Zhang et al. reported ultrasound-triggered cellular uptake of fluorescein at acoustic pressures of 0.19–0.3 MPa. A 40 s exposure at 0.24 MPa reduced the median nanoparticle size from 751 nm to 695 nm, indicating ultrasound-induced structural disruption of the nanocarriers. This process generates smaller and more stable particles and improves membrane penetration.[35] Yan et al. created paclitaxel-loaded microbubbles. These microbubbles achieved 74.39% drug release under ultrasound stimulation. In vitro studies showed significant inhibition of tumor cell growth.[20]

4.1.2 Polymers

Compared to conventional liposomes, polymer-based carriers have several advantages. First, the drug-loading capacity and stability are enhanced by the thicker shell structure. Roman et al. found that polymer shell thickness positively correlates with drug - loading performance.[36] Second, the shell structures can be engineered to respond to ultrasound. By encapsulating gas cores or constructing multi-layered interfaces, polymer nanocarriers can significantly enhance ultrasound contrast. Studies have shown that increasing the number of shell layers from 4 to 8 improves imaging contrast by 36%.[37] Third, ultrasound enhances the efficiency of therapy. Wei et al. showed that ultrasound-activated polymer nanocarriers not only boost cellular uptake but also facilitate endosomal escape, enabling direct drug delivery to the nucleus[21]. Additionally, the hydrogels are characterized by the ability to retain

drugs for extended periods. The drugs can also be rapidly released from hydrogels by external stimuli.[38] Zhou et al. developed ultrasound-responsive hydrogels. Under ultrasound, these hydrogels transition from a gel to a sol state, triggering drug release. After release, the hydrogels self-recover to their gel state. This dual-phase behavior ensures sustained drug retention and controlled release.[39]

4.1.3 Exosomes

Exosomes are naturally derived nanovesicles with a bilayer lipid membrane structure. They are characterized by low immunogenicity.[40] Jang et al. found that combining exosomes with lipid microbubbles to form exosome-microbubble (Exo-MBs), this overcomes the limitations of conventional microbubbles (MBs), such as poor stability and low drug delivery efficiency. About 70% of Exo-MBs remained intact after 40 hours, while traditional MBs broke down completely within the same period. When continuously exposed to ultrasound, conventional MBs lost their contrast-enhancing ability within 15 minutes, whereas Exo-MBs maintained this function for over 30 minutes. These results demonstrate that Exo-MBs are more stable and offer better imaging performance. In drug delivery experiments, 31.8% of cells in the MBs group were fluorescence-positive, compared to 78.6% in the Exo-MBs group, confirming the superior drug delivery efficiency of the hybrid system.[41]

4.2 Inorganic Nanocarriers

4.2.1 Mesoporous Silica

Mesoporous silica nanoparticles (MSNs) have a porous structure that allows for high drug loading. This makes them more favorable than organic nanocarriers. However, uncontrolled drug leakage remains a challenge. Current research focuses on improving the performance of MSNs by adjusting pore sizes and modifying their surfaces.[42] Ultrasound-responsive MSNs delivery systems have been developed to improve drug delivery. These systems can retain drugs during systemic circulation. Under ultrasound stimulation, they enable on-demand, spatially controlled drug release. This approach enhances therapeutic efficacy and minimizes off-target toxicity. Takashi Nozoe et al. developed PEI-coated MSNs. The PEI layer seals the drug payloads and enables ultrasound-triggered release.[23] Similarly, Andres Gantous et al. used polydimethylsiloxane as a gatekeeper on MSNs surfaces, enabling ultrasound-responsive drug release.[43] These innovations not only improve controlled release but also expand the clinical potential of MSN-based drug delivery systems.

4.2.2 Gold Nanocarriers

Gold nanocarriers is widely used in nanomaterial applications. Their photophysical properties provide dual advantages for tumor precision diagnostics.[44] Through a photocatalytic gas generation mechanism, gold nanocarriers produce nitrogen microbubbles under near-infrared (NIR) light excitation. These nanocarriers absorb NIR light, generating hot electrons that catalyze the decomposition of nitrogen-containing precursors (such as ammonium salts or amines) to form nitrogen microbubbles. These microbubbles enhance ultrasound imaging contrast.[45] Cheol et al. found that injecting synthesized gold nanocarriers and applying NIR light significantly enhanced ultrasound signals in tumor areas. Photoacoustic imaging revealed the strongest signals at 815 nm.[46] Using these properties, gold nanocarriers have been integrated into multifunctional theragnostic systems. For

example, gold nanoshell-embedded polylactic acid nanocarriers facilitate real-time ultrasound-guided photothermal therapy. Moreover, combining gold with Poly (lactic-co-glycolic acid) nanocarriers loaded with perfluorohexane (PFH) improves ultrasound responsiveness through liquid-gas phase changes. These advancements show the combination of imaging with therapy in oncology.[47]

4.2.3 Metal Oxides

Metal oxides, including titanium dioxide (TiO_2), zinc oxide (ZnO), iron oxide (Fe_3O_4), and copper oxide (CuO), have high stability and excellent biocompatibility. Therefore, they are considered promising ultrasound-responsive nanocarriers.[48] TiO_2 and ZnO are widely studied in SDT. They can generate reactive oxygen species (ROS) under ultrasound. TiO_2 nanocarriers show higher chemical stability and better resistance to photobleaching compared with organic sonosensitizers. However, their ROS generation efficiency is relatively low.[49] Surface modification or doping is often required to improve performance. Liu et al. developed nano-sized titanium hydride. This material produces ROS under ultrasound. It also improves tumor oxygenation and blood flow, which enhances SDT efficacy.[50] Sun et al. designed Fe-doped manganese oxide nanosonosensitizers using a vacancy engineering strategy. This system enables hypoxia irrelevant SDT. It overcomes the oxygen dependence of conventional SDT and improves therapeutic efficiency.[51]

4.2.4 Black Phosphorus (BP)

BP nanocarriers have gained increasing attention for ultrasound-based cancer therapy. BP is a two-dimensional material with good biodegradability and biocompatibility. It also shows high ROS generation under ultrasound.[52] Compared with traditional sonosensitizers, BP degrades into phosphate and phosphonate ions in physiological environments. These products are non-toxic and can be cleared from the body. This property reduces long-term retention risk.[53] In addition, BP has unique electronic and optical properties. These properties enable combined photothermal and SDT under NIR laser. BP-based nanocarriers have also been applied in multimodal imaging-guided therapy. They show improved antitumor efficacy with reduced systemic toxicity.[54]

4.2.5 Carbon-Based Nanocarriers

Carbon-based nanocarriers, such as carbon nanotubes (CNTs), graphene oxide (GO), carbon dots, and carbon nitride, have been studied for ultrasound-mediated tumor theranostics. They have high surface area, tunable surface chemistry, and intrinsic photoacoustic properties.[55] Multi-walled carbon nanotubes (MWCNTs) modified with targeting ligands have been developed as targeted ultrasound contrast agents. Chen et al. reported an MWCNT-based contrast agent for prostate cancer detection, demonstrating nearly 100% specificity in vitro and significantly enhancing tumor-specific ultrasound signals after intravenous administration.[26] Additionally, GO and carbon nitride nanocarriers have been used to develop multifunctional theranostic platforms. Carbon dots and graphene quantum dots have also been explored as sonosensitizers for SDT, with their small size, excellent biocompatibility, and efficient ROS generation.[56] Overall, carbon-based nanocarriers show strong potential for theranostic applications by integrating both imaging and therapeutic functions.

4.2.6 Silver Nanocarriers

Silver nanocarriers are widely studied in ultrasound-based cancer therapy. This is due to their strong antimicrobial properties and ability to enhance cavitation effects.[57] Silver nanocarriers enhance ultrasound-induced cavitation by acting as nucleation sites for bubble formation. This process improves drug delivery efficiency and sonoporation.[58] Furthermore, silver nanocarriers have intrinsic antitumor activity by inducing oxidative stress and apoptosis. When combined with ultrasound, they synergistically increase ROS production and enhance tumor cell killing.[59] Concerns about silver's cytotoxicity and long-term tissue accumulation still exist. However, surface passivation and encapsulation in biocompatible shells have been developed to improve the safety of silver nanocarriers.[60]

4.3 Hybrid Nanocarriers

Hybrid nanocarriers combine multiple components within a single platform. This combination enables synergistic therapy and imaging, overcoming the limitations of individual systems. Therefore, drug loading, ultrasound responsiveness, imaging contrast, and therapeutic efficacy can all be improved. For example, gold coated MSNs nanocarriers combine the high loading capacity of MSNs with the photothermal and photoacoustic properties of gold. This enables ultrasound and photoacoustic dual-modal imaging-guided therapy.[28] Similarly, iron oxide–gold hybrid nanocarriers provide MRI contrast enhancement and gold-mediated photothermal effects. This makes them theranostic agents.[61] In addition, hybrid platforms that incorporate phase-change materials can undergo ultrasound-triggered liquid-to-gas transitions. This enhances contrast imaging and facilitates HIFU-assisted therapy. Metal-organic frameworks have also emerged as promising hybrid carriers owing to their high porosity, tunable composition, and ultrasound-responsive controlled-release properties.[62] Overall, hybrid nanocarriers offer a promising direction for next-generation ultrasound-responsive nanomedicine. However, challenges related to synthetic complexity and large-scale production still remain.

4.4 Comparative Analysis and Critical Evaluation of Nanocarriers for Clinical Translation

From a translational perspective, ultrasound-based nanocarriers show quintons in biosafety, acoustic responsiveness, drug-loading capacity, manufacturing scalability, in vivo stability, biodegradability, and regulatory feasibility.[63] Liposomes have the highest near-term clinical potential. They have well-established biosafety and regulatory approval history. They also support the encapsulation of both hydrophilic and hydrophobic drugs. However, they still face limitations, including batch variability, drug leakage, and limited circulation stability.[64] Polymer-based nanocarriers provide strong structural tunability and mechanical stability. They allow precise control of ultrasound-triggered drug release and circulation behavior. However, complex compositions and potential toxicity of degradation products may hinder clinical translation.[65] Exosome-based nanocarriers show good biocompatibility and natural targeting ability. However, large-scale production, purification standardization, cargo heterogeneity, and storage instability remain major challenges.[66] Inorganic nanocarriers, including mesoporous silica, metal oxides, BP, and carbon-based materials, offer excellent imaging performance and strong therapeutic functions. However, their limited biodegradability, long-term tissue retention, and potential chronic toxicity remain major concerns.[67] Hybrid nanocarriers combine advantages from multiple material systems. They show great promise for multimodal theranostics. However, their complex synthesis, poor reproducibility, high cost, and manufacturing challenges limit clinical translation.[68] Overall, no single nanocarrier meets all clinical requirements. Future research should focus on biodegradability, scalable synthesis,

reproducibility, biosafety standardization, and mechanism-guided design rather than only improving therapeutic performance (Table 1).

Table 1. Comparison of ultrasound-responsive nanocarriers

Type	Advantages	Limitations
Liposomes	Biocompatibility; Clinical maturity;	Drug leakage; Limited stability;
Polymers	Tunable structure; High loading;	Complex synthesis; Potential toxicity of degradation products
Exosomes	Natural targeting; Low immunogenicity	Poor scalability; Heterogeneity;
Mesoporous silica (MSNs)	High loading; Structural robustness	Limited biodegradability; premature leakage
Gold nanocarriers	Excellent imaging contrast; Photothermal synergy	High cost; Long-term retention
Metal oxides	ROS generation; SDT applicability	Low efficiency; Potential long-term toxicity
Black phosphorus	Biodegradability;	Chemical instability; Oxidation sensitivity
Carbon-based materials	High surface area; Multimodal imaging	Biopersistence; Safety concerns
Silver nanoparticles	Cavitation enhancement; intrinsic cytotoxicity	Cytotoxicity; Accumulation risk
Hybrid systems	Multifunctionality; Synergistic effects	Complex synthesis; Poor reproducibility

5. Clinical Applications Based on Ultrasound-Based Nanocarrier Systems

Ultrasound-based nanocarrier systems enable precise diagnosis and therapy. They integrate imaging guidance, stimulus-responsive drug delivery, and multimodal treatment strategies. These systems can be applied in both imaging and therapeutic modalities. Common mechanisms include acoustic cavitation, thermal effects, sonoporation, and stimulus-triggered release. These mechanisms enhance spatially controlled therapy and enable real-time monitoring.[69]

5.1. Ultrasound-Enhanced Imaging Systems

Ultrasound-based nanocarrier imaging systems improve diagnostic performance by enhancing acoustic contrast, enabling multimodal imaging, and supporting real-time disease monitoring. Compared to conventional contrast agents, nanoscale systems offer better stability, longer circulation times, and enhanced tumor-targeting potential.[70]

5.1.1Ultrasound Imaging

Contrast-enhanced ultrasound has traditionally relied on exogenous microbubbles to enhance vascular and tumor imaging. However, conventional microbubbles suffer from limited circulation stability due to gas diffusion and Laplace pressure-induced collapse.[71] To overcome these limitations, perfluorocarbon-based phase-change nanocarriers have been developed as an alternative contrast platform. Upon ultrasound, these nanocarriers undergo acoustic droplet vaporization to generate microbubbles, thereby significantly enhancing imaging contrast.[72] In recent years, the development of targeted microbubbles has improved the specificity and sensitivity of ultrasound imaging, providing innovative strategies for precision medicine. For instance, a research team has developed B7-H3-targeted microbubbles to detect breast cancer metastasis. Nevertheless, challenges remain in optimizing circulation stability, targeting efficiency, and clinical translation.[73]

5.1.2 Photoacoustic Imaging (PAI)

PAI is a hybrid technique that converts pulsed laser energy into ultrasonic signals through thermoelastic expansion. It provides high-resolution imaging with deeper tissue penetration than optical methods alone.[74] To enhance signal sensitivity and molecular specificity, various exogenous contrast agents have been developed. Carbon-based nanomaterials are widely used due to their strong optical absorption and tunable physicochemical properties. Zhang et al. found that the carbon nanomaterial accumulates at tumor. This allows for multimodal imaging, combining fluorescence, infrared thermal imaging, and ultrasound. The ultrasound signal intensity changes over time.[75] Additionally, PAI plays a critical role in detecting metal ions, assessing pH levels, monitoring reactive oxygen species generation, enzyme activity, temperature changes, and measuring oxygen content.[76] However, clinical translation is still limited by optical penetration depth and reliance on external laser excitation systems.

5.1.3 Gas Vesicles (GVs) Imaging

GVs are gas-filled protein nanostructures derived from genetic engineering. They serve as nanoscale acoustic scatterers because of their strong acoustic impedance mismatch with biological tissues. Compared to conventional microbubbles, GVs provide better signal stability and contrast enhancement in tumor environments.[77] Wei et al. demonstrated that under ultrasound with a mechanical index of 0.149, GVs produced stronger echo signals in tumor regions with insufficient blood flow compared to conventional microbubbles.[78] Gong et al. revealed that GVs not only exhibit exceptional ultrasound imaging capabilities but also enable real-time tracking of the migration and homing of mesenchymal stem cells in the body.[79] In summary, GVs are promise ultrasound contrast agents. Currently, GVs are primarily used in preclinical research settings and have not entered routine clinical practice.

5.1.4 Acoustic Reporter Gene (ARG) Imaging

ARG imaging enables molecular-level ultrasound imaging by genetically engineering cells to express gas vesicle-forming genes. These intracellular gas vesicles generate ultrasound-detectable signals upon ultrasound excitation. This enables real-time monitoring of gene expression, tumor progression, and microbial dynamics in vivo. ARG systems provide long-term and highly specific imaging signals.[80] However, their clinical translation is still hindered by concerns regarding genetic modification safety and regulatory constraints.

5.1.5 Multimodal Imaging

To overcome the limitations of single-modality imaging, ultrasound is increasingly integrated with complementary techniques such as fluorescence imaging, magnetic resonance imaging (MRI), CT, and thermal imaging. These multimodal systems enable the simultaneous acquisition of structural, functional, and molecular information. As a result, they significantly improve diagnostic accuracy and disease characterization.[81]

Overall, ultrasound-based nanocarrier imaging systems have evolved from conventional contrast enhancement toward multifunctional and molecular imaging platforms (Table 2). Although their design strategies are diverse, they share a common principle of enhancing acoustic or opto-acoustic signal generation. This enables more precise diagnosis and image-guided therapy. However, clinical translation is still constrained by challenges related to stability, targeting specificity, scalable manufacturing, and regulatory approval.

Table 2. Comparison of ultrasound-based imaging nanocarriers

Platform	Imaging mechanism	Advantages	Limitations	Clinical barrier
Microbubbles	Acoustic scattering	High contrast	Poor stability	Rapid clearance
Phase-change droplets	Liquid-gas transition	Deep imaging	Activation threshold	Control difficulty
Carbon-based probes	Photoacoustic signal	Multimodal capability	Limited penetration	Biosafety concern
Gas vesicles	Protein scattering	Biocompatible	Early stage	No approval
Acoustic reporter genes	Gene-expressed vesicles	Long-term monitoring	Gene safety	Regulatory hurdle

5.2 Ultrasound-Mediated Therapeutic Systems

Ultrasound-based therapy relies on physical energy conversion and stimulus-responsive nanocarrier activation. The primary mechanisms include ROS generation, thermal ablation, mechanical disruption, and enhanced membrane permeability. These effects can be combined with chemotherapy, immunotherapy, and phototherapy to achieve synergistic therapeutic outcomes.[82]

5.2.1 SDT

SDT is based on ultrasound-activated sonosensitizers that generate ROS. This process induces oxidative stress, mitochondrial dysfunction, and ICD, leading to tumor suppression.[83] Additionally, SDT can suppress intratumoral angiogenesis. Gao et al. demonstrated that using the sonosensitizer ALA alone resulted in a 96.4% proliferation rate of endothelial cells. Ultrasound treatment alone reduced this rate to 81.6%, while the combined use of ALA and ultrasound further decreased it to 70.6%.[84] Furthermore, SDT is not restricted by light penetration depth and has stronger tissue penetration capabilities. This makes it promising for treating deep tumors.[85]

The efficacy of SDT depends on the selection of sonosensitizers. Inorganic sonosensitizers such as TiO_2, ZnO, and BP show high stability and strong ROS generation capability.[86] However, oxygen dependence in hypoxic tumor environments remains a major limitation. To resove this, multiple strategies have been used to improve oxygen supply in tumor tissues and enhance SDT outcomes. For example, Yang et al. developed hypoxia-responsive nanocarriers that generate oxygen and deliver sonosensitizers within the tumor microenvironment, significantly improving therapeutic efficacy.[87] Moreover, recent studies found that glucose oxidase enhances SDT effects by inducing energy deprivation in tumor cells and generating oxygen. Wu et al. utilized catalase activity to cactivity to catalyze hydrogen peroxide into oxygen, alleviating hypoxic conditions in tumors.[88]

5.2.2 SDT-Based Combination Therapy

To improve therapeutic outcomes, SDT has been integrated with chemotherapy, photodynamic therapy (PDT), PTT, and immunotherapy. These combinations enhance ROS production, improve drug penetration, and modulate the tumor immune microenvironment.[89]

(1) Chemotherapy combinations

The synergistic effect between SDT and chemotherapy mainly results from ROS-mediated intracellular damage and enhanced drug sensitivity. SDT increases cell membrane permeability. This promotes intracellular drug uptake. An et al. developed platinum-hollow polydopamine nanocarriers co-loaded with doxorubicin and the sonosensitizer Ce6. This combination therapy showed superior breast cancer cell killing compared to doxorubicin alone. Additionally, SDT can enhance chemotherapy by reversing multidrug resistance. It can sensitize drug-resistant tumor cells to doxorubicin through ROS-mediated mitochondrial membrane depolarization.[90] Chen et al. further developed biomimetic nanoparticles (MDNPs) composed of a polyglutamic acid (pH-sensitive) core loaded with doxorubicin, coated with DSPE-PEG and tumor cell membrane fragments, enabling homologous targeting and improved tumor penetration (Figure 1A-B). When combined with SDT, these MDNPs suppress factors related to resistance, such as heat shock factor-1 and P-glycoprotein, in glioblastoma. As shown in the treatment timeline (Figure 1C), tumor-bearing mice received four intravenous injections combined with ultrasound on days 5, 7, 9, and 11 post-inoculations. MDNPs plus ultrasound treatment exhibited the strongest antitumor effect compared to MDNPs alone, free doxorubicin (DOX), or PBS control, with tumor growth suppression observed from day 6 to day 18 (Figure 1D). This dual-action strategy both adjusts drug resistance and causes apoptosis at the same time. However, this strategy is still limited by systemic toxicity and insufficient

tumor-specific accumulation. These issues remain major barriers to clinical translation.[91]

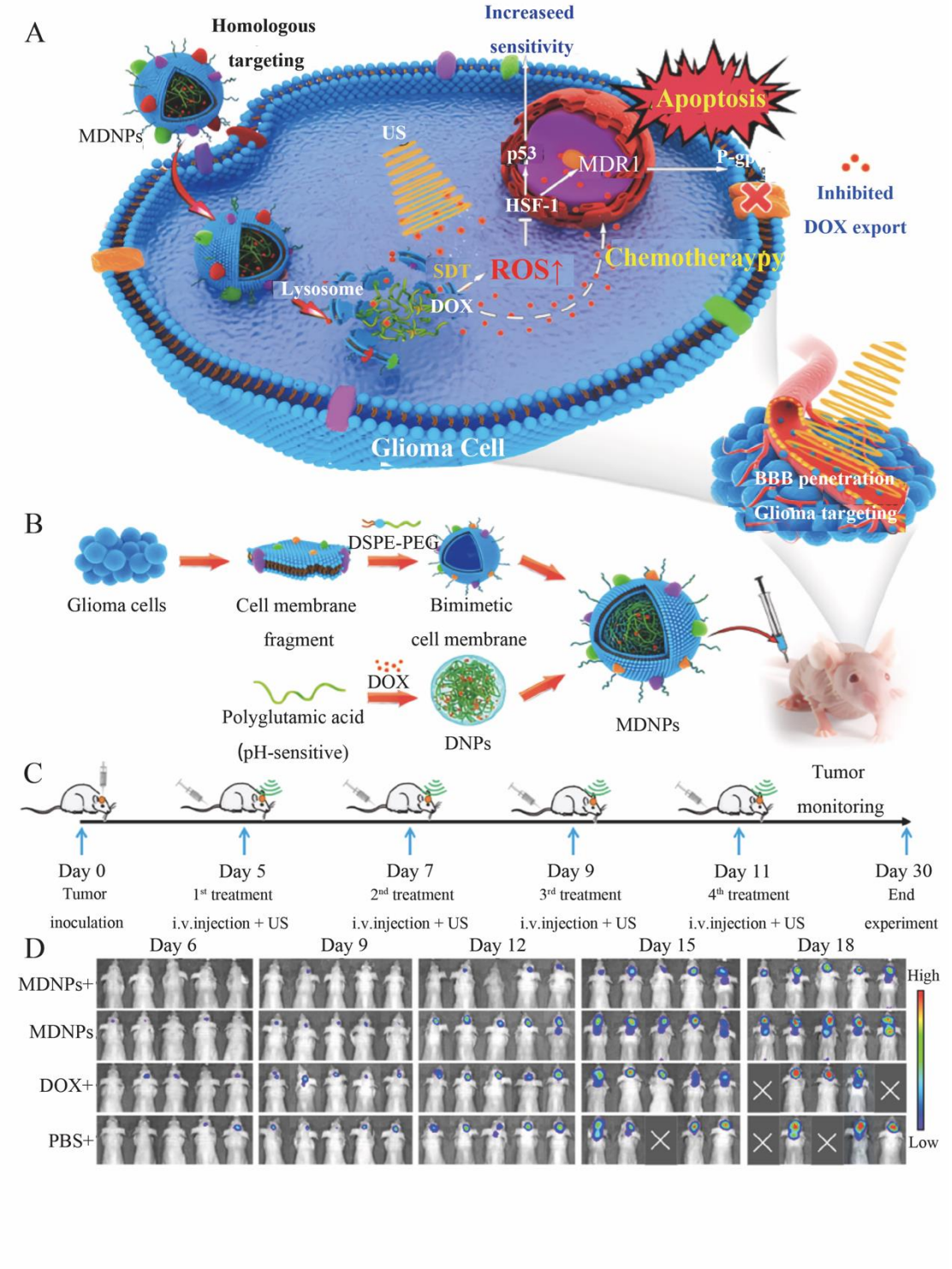


Figure1. Combination therapy using SDT and chemotherapy. (A) Schematic illustration of MDNPs crossing the BBB under ultrasound assistance, releasing DOX in acidic endo/lysosomes, and inducing ROS to downregulate resistance-related markers (HSF-1, mutant p53, MDR1, P-gp) for synergistic SDT and chemotherapy. (B) Preparation of MDNPs: PGA-DOX nanoparticles (DNPs) coated with tumor cell membrane fragments and DSPE-PEG. (C) In vivo treatment timeline. Tumor inoculation on day 0, followed by intravenous injections of MDNPs combined with ultrasound on days 5, 7, 9, and 11. The experiment was completed on day 30. (D) Tumor growth inhibition curves of different treatment groups (PBS^+, DOX^+, MDNPs, MDNPs+US) measured on days 6, 9, 12, 15, and 18. The MDNPs+US group showed the strongest antitumor effect. BBB: blood-brain barrier; DOX: doxorubicin; HSF-1: heat shock factor-1; MDR1: multidrug resistance 1; P-gp: P-glycoprotein; PGA: polyglutamic acid; DNPs, DOX-loaded PGA nanoparticles; DSPE-PEG: 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-polyethylene glycol; i.v.: intravenous; PBS^+: phosphate-buffered saline plus ultrasound; DOX^+: free doxorubicin plus ultrasound. Copyright 2022, American Chemical Society.

(2) PDT and PTT combinations

The combination of SDT and PDT not only increases the depth of treatment but also enhances cytotoxicity. Chen et al. developed nanocarriers loaded with indocyanine green and perfluoropentane for ovarian cancer treatment. Their study showed that using PDT and SDT worked better than PDT or SDT alone. Similar synergistic effects have been validated in liver cancer and melanoma. Additionally, the integration of SDT with PTT shows significant advantages.[92] Xu et al. created nanocarriers (SMAH). They used the photothermal and acoustic properties of nanocarriers, which exhibited efficient singlet oxygen production and photothermal conversion capabilities upon ultrasound and NIR laser irradiation. As shown (Figure 2A), the SMAH nanocarriers were synthesized by assembling a manganese-based sonosensitizer (MnTEPP) with gold nanostructures. In their in vivo experiment (Figure 2B), 4T1 tumor-bearing mice received intravenous injection of SMAH on day 0, followed by combined ultrasound and 1064 nm laser irradiation at 8 hours post-injection, with tumor growth monitored until day 14. The tumor growth curves (Figure 2C-D) demonstrated that this dual-modality treatment achieved superior antitumor efficacy compared to monotherapy or control groups. This dual-modality treatment significantly enhanced antitumor efficacy both in vitro and in vivo, achieving tumor regression in tumor-bearing mice, highlighting the advantages of combining SDT with PTT.[93]

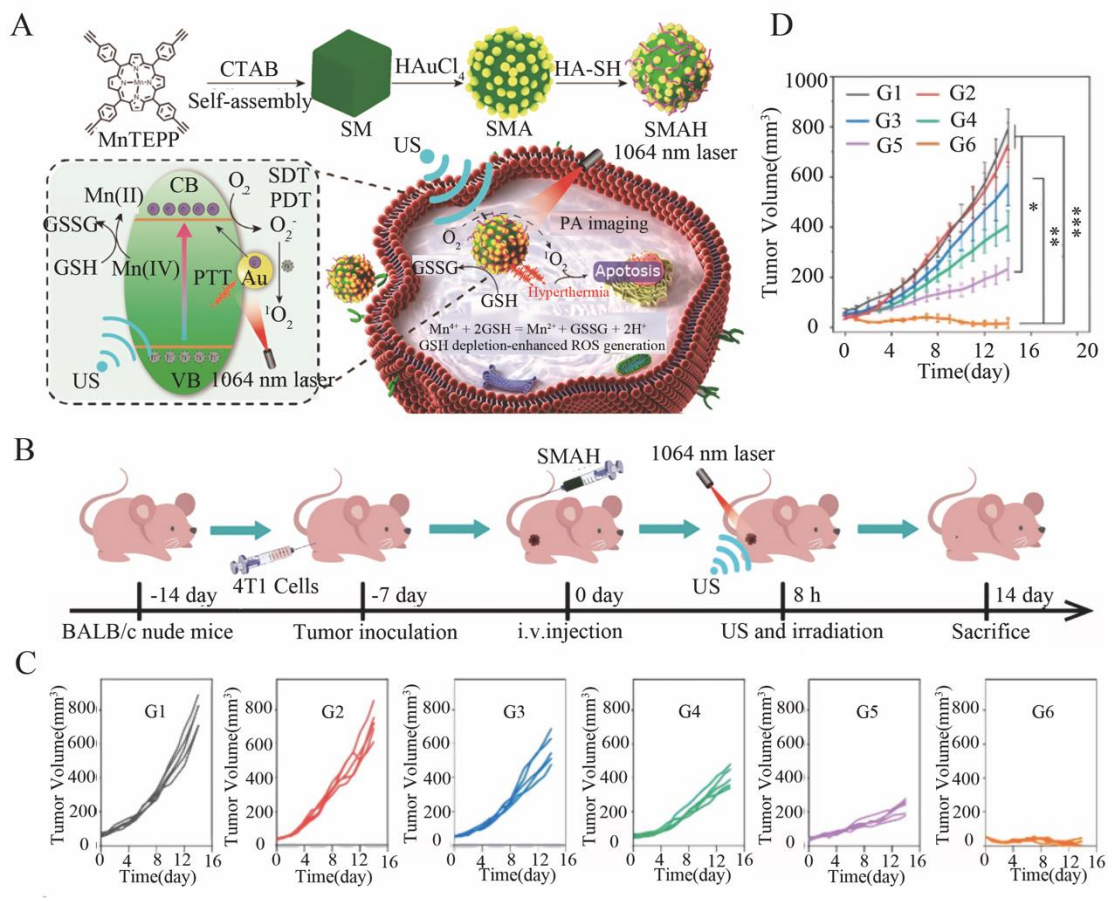


Figure2. Combination therapy using SDT and PTT. (A) Schematic illustration of SMAH synthesis. MnTEPP is assembled with CTAB and CB, followed by the incorporation of $HAuCl_4$ and HA-SH to form gold nanocarriers. The resulting SMAH nanocarriers generate ROS under US irradiation and produce photothermal effects under 1064 nm laser irradiation, while also enabling PA imaging and GSH depletion to enhance ROS generation. (B) In vivo treatment timeline: 4T1 cells were inoculated on day -14, followed by tumor inoculation on day -7, intravenous (i.v.) injection of nanocarriers on day 0, combined US and 1064 nm laser irradiation at 8 h post-injection, and sacrifice on day 14. (C) Tumor growth curves of different treatment groups (G1 to G6) measured over 16 days, showing the antitumor effect of each regimen. (D) Comparative tumor volume changes

among treatment groups, further demonstrating the enhanced efficacy of SDT and PTT combination. G1: saline; G2: saline+US+laser; G3: SMAH; G4: SMAH+US; G5: SMAH+laser; G6: SMAH+US+laser. CTAB: cetyltrimethylammonium bromide; CB: carbon black; $HAuCl_4$: chloroauric acid; HA-SH: hyaluronic acid-thiol; PA, photoacoustic imaging; GSH: glutathione. Copyright 2023, American Chemical Society.

(3) Immunotherapy combinations

SDT-based "physical killing–immune activation" is a synergistic strategy. It combines SDT-mediated tumor ablation with immunomodulatory approaches to enhance systemic antitumor immunity. However, SDT alone often induces limited immune responses. This is mainly due to the immunosuppressive tumor microenvironment.[94] To overcome this limitation, SDT has been combined with immune checkpoint blockade therapies, such as anti-PD-1/PD-L1. These therapies reinvigorate exhausted T cells and enhance antitumor immune responses. Yue et al. developed a liposomal nanocarrier (HMME/R837@Lip) co-encapsulating the sonosensitizer HMME and the immune adjuvant R837 (Figure 3A). In vivo experiment using a bilateral breast cancer model (Figure 3B), mice were inoculated with primary and distant tumors to model metastasis, followed by SDT combined with anti-PD-L1 therapy. The tumor growth curves showed that the combination of SDT and anti-PD-L1 significantly suppressed both primary tumors (Figure 3D) and distant tumors (Figure 3C), demonstrating a systemic abscopal effect. This combination therapy enhanced dendritic cell maturation, pro-inflammatory cytokine secretion, and promoted tumor infiltrating $CD8^+$ T cell expansion.[95] Similarly, studies on malignant melanoma and pancreatic cancer have shown that combining anti-PD-1 antibodies with SDT can block immune checkpoints and reshape the immunosuppressive microenvironment.[96]

In addition, metabolic immune suppression plays an important role in tumor immune evasion. Indoleamine 2,3-dioxygenase (IDO) is a key immunosuppressive enzyme. It catalyzes the degradation of tryptophan into kynurenine metabolites. This pathway suppresses effector T cell activity and promotes regulatory T cells (Tregs) expansion.[96] Studies show that SDT combined with the IDO inhibitor NLG919 improves the immunosuppressive microenvironment in pancreatic cancer. SDT kills tumor cells and releases antigens, while NLG919 inhibits IDO activity to reduce Tregs and promotes dendritic cell maturation.[97] The combination therapy reduced tumor volume, increased $CD4^+/CD8^+$ T cell ratio, and decreased Tregs levels.

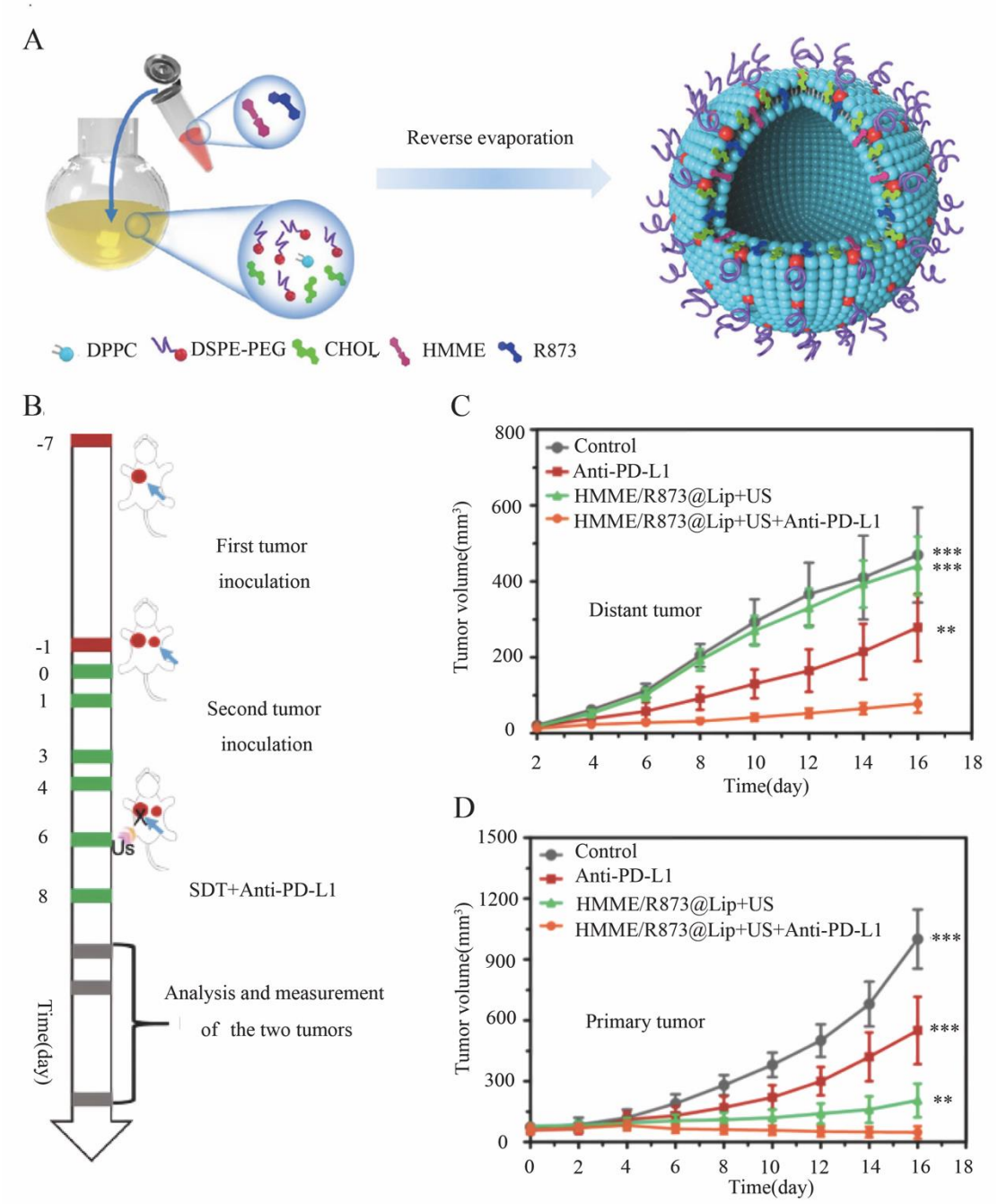


Figure 3. Ultrasound combined with immune checkpoint blockade therapy enhances the immune response to cancers. (A) Schematic illustration of the liposomal nanocarrier (HMME/R837@Lip) composed of DPPC, DSPE-PEG, CHOL, encapsulating the sonosensitizer HMME and the immune adjuvant R837. (B) In vivo treatment timeline: first and second tumor inoculations were performed, followed by SDT combined with anti-PD-L1 therapy, with analysis and measurement of both primary and distant tumors. (C) Tumor growth curves of distant tumors in different treatment groups (Control, Anti-PD-L1 alone, HMME/R837@Lip+US, HMME/R837@Lip+US+Anti-PD-L1), showing the abscopal effect of the combination therapy. (D) Tumor growth curves of primary tumors in different treatment groups, demonstrating the enhanced antitumor efficacy of SDT combined with immune checkpoint blockade. DPPC: dipalmitoylphosphatidylcholine; DSPE-PEG: 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-polyethylene glycol; CHOL: cholesterol; HMME, hematoporphyrin monomethyl ether; R837: imiquimod (immune adjuvant); US, ultrasound; Anti-PD-L1, anti-programmed death-ligand 1 antibody. Copyright 2019, Springer Nature.

5.2.3 HIFU

HIFU is a noninvasive therapy that precisely concentrates acoustic energy on tissues. This process induces rapid thermal accumulation and coagulative necrosis, leading to effective tumor ablation. Compared with conventional

invasive thermal ablation techniques, HIFU avoids probe insertion and reduces procedural risks.[98] However, HIFU monotherapy may show limited efficacy in large or deep-seated tumors. To overcome these limitations, HIFU is increasingly integrated with multifunctional nanocarriers. Zhang et al. developed a nanoplatform (HMPBs-DOX/PFH) that combines HIFU with chemotherapy (Figure 4A). This platform enables dual-modality photoacoustic/ultrasound imaging for guiding and monitoring therapy and enhances therapeutic efficacy through PFH phase transformation and HIFU-triggered drug release (Figure 4B). Ex vivo studies demonstrated that HMPBs-DOX/PFH significantly increased HIFU ablation volume at different powers (120W, 150W, and 180W) compared to controls (Figure 4C-D).[99] Tang et al. designed a multifunctional nanocarriers, which improves the hypoxic tumor microenvironment to boost HIFU efficacy. When combined with immune checkpoint inhibitors, it further enhances T-cell responses and suppresses distant tumor growth. Additionally, HIFU treatment triggers the release of tumor-associated antigens, activating specific antitumor immune responses. Mechanical HIFU (M-HIFU) promotes dendritic cell infiltration, T-cell aggregation, and macrophage polarization, thereby enhancing antitumor outcomes and reducing the risk of metastasis.[12] These studies confirm that multimodal strategies offer new approaches for cancer therapy. Overall, the integration of HIFU with nanocarriers represents a promising multimodal strategy for tumor treatment. Nevertheless, challenges remain in deep-tissue energy efficiency, safety, and clinical translation.

Overall, ultrasound-based therapeutic strategies have evolved from single SDT toward synergistic combinations and HIFU (Table 3). However, clinical translation remains constrained by challenges such as hypoxia dependence, off-target heating, depth mismatch, and treatment optimization.

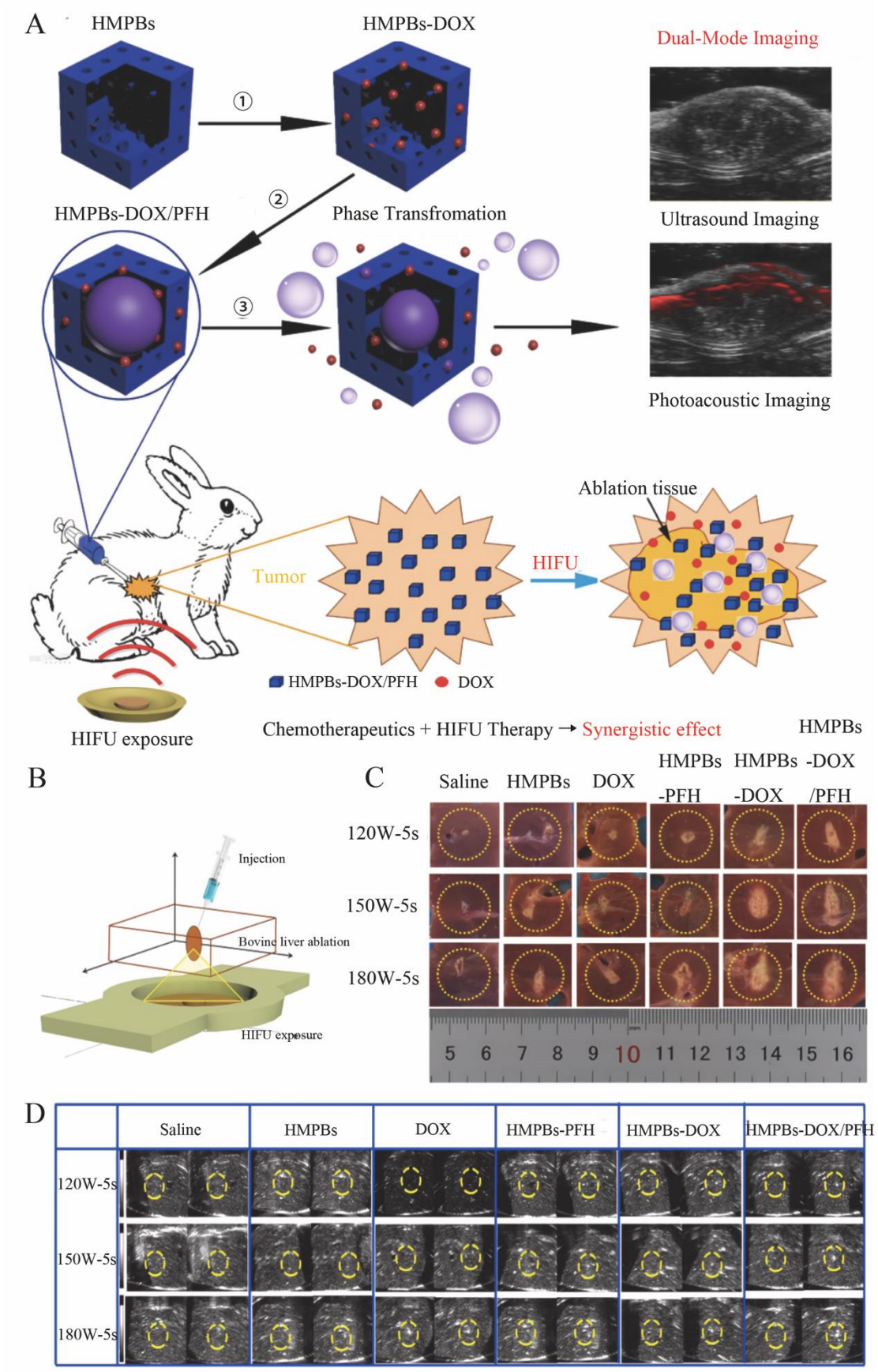


Figure 4. Combination therapy using HIFU and nanocarriers for enhanced tumor treatment. (A) Schematic illustration of HMPBs-DOX/PFH. Hollow mesoporous Prussian blue nanoparticles (HMPBs) encapsulate DOX and PFH. Upon HIFU exposure, PFH undergoes phase transformation, enabling dual-mode ultrasound (US) and photoacoustic (PA) imaging, as well as enhanced HIFU ablation and chemotherapy. (B) Synergistic therapeutic mechanism of HIFU

combined with HMPBs-DOX/PFH. (C) Ex vivo HIFU ablation at different powers (120W, 150W, and 180W for 5 seconds). (D) Comparison of necrotic volumes after HIFU exposure with different agents (Saline, HMPBs, DOX, HMPBs-DOX, HMPBs-PFH, and HMPBs-DOX/PFH). Copyright 2016, Theranostics.

Table 3. Comparison of ultrasound-based therapeutic strategies

Strategy	Mechanism	Advantage	Limitation	Clinical barrier
SDT	ROS	Deep penetration	Hypoxia dependence	Low efficiency
SDT+Chemotherapy	Synergistic cytotoxicity	Improved efficacy	Toxicity risk	Optimization needed
SDT+PDT	Dual ROS	Multimodal oxidation	Shallow light penetration	Depth mismatch
SDT+PTT	Thermal+ oxidative	Enhanced ablation	Off-target heating	Temp control
SDT+Immunotherapy	Immune activation	Systemic response	Immune suppression	Variability
HIFU	Thermal ablation	Precise targeting	Recurrence risk	Energy loss

6. Conclusion and Outlook

Ultrasound is a convenient, safe, and non-invasive way to deliver energy. It can penetrate deep tissues without inducing ionizing radiation. The combination of ultrasound and nanocarriers has led to the development of stimuli-responsive nanoplatforms. Their properties can be modulated in response to the tumor microenvironment. As a result, therapeutic efficacy is improved and damage to normal tissues is reduced. However, most ultrasound-responded nanocarriers are still at the preclinical stage, and clinical translation remains challenging.

(1) Optimization of Ultrasound Parameters

Ultrasound parameters are a critical and complex challenge. Therapeutic outcomes depend on the precise control of multiple parameters, and small variations can markedly affect efficacy. Differences in species further complicate parameter optimization. In addition, differences between animal models and humans make parameter optimization more difficult. Therefore, precise parameter control is required to achieve outcomes.

(2) Understanding Ultrasound Mechanisms

Ultrasound therapy involves multiple mechanisms. Their specific roles and interactions are not fully understood. The main mechanisms include thermal effects, mechanical effects, and sonoporation. However, their contributions vary under different tissue and treatment conditions. In addition, ultrasound propagation in tissues is affected by acoustic impedance differences, diffraction, scattering, attenuation, and reflection. These factors influence

therapeutic outcomes. Future studies should focus on clarifying these mechanisms and improving treatment precision through technological advances.

(3) Improving the Biosafety of Ultrasound-Based Nanocarrier Systems

The biosafety of ultrasound-based nanocarrier systems remains a key concern. Sonosensitizers are often derived from photosensitizers and may induce phototoxicity. Although nanocarriers show low short-term toxicity, their high stability may lead to long-term accumulation in the body. This accumulation can cause chronic toxicity in organs such as the lungs, liver, and kidneys. It may also trigger systemic inflammation and increase the risk of vascular embolism. In addition, long-term safety issues are more pronounced for inorganic and non-biodegradable polymer carriers than for liposomes or exosomes. Currently, standardized methods are lacking. Therefore, some protocols are needed to evaluate biocompatibility and toxicity. Long-term toxicity studies should be conducted.

(4) Limitations of Animal Models:

Animal models are widely used to evaluate the therapeutic efficacy. But they still have limitations. Differences between animal-derived and patient-derived tumor cells may reduce their ability to fully reflect the complexity of human tumors. Subcutaneous tumor models are commonly used for screening and evaluation of therapies. However, they do not fully reproduce the clinical tumor environment. In comparison, orthotopic tumor models better simulate clinical conditions and more accurately reflect tumor growth and treatment response. To improve the precision and relevance, more research using patient-derived tumor cells in orthotopic xenograft models is needed. These models better mimic the tumor microenvironment and growth behavior. They can also provide more reliable experimental data. This helps clarify both the potential and limitations of nanocarriers and supports their translation into clinical applications.

(5) Cost Challenges

Ultrasound-responded nanocarriers has shown potential in cancer treatment. But its high cost poses a significant challenge. As nanocarriers become more functional, their design and synthesis become more complex. This increases production costs. In addition, many nanocarriers require strict storage conditions, which further increases costs. The high cost of human clinical trials also adds to the financial burden and limits clinical translation. To overcome these problems, smart nanocarriers with simple synthesis methods and integrated functions should be developed. Simple synthesis can reduce production costs and improve efficiency. Integrated functions allow nanocarriers to perform multiple roles, including diagnosis, therapy, and monitoring.

The development of ultrasound and nanocarriers has improved the efficacy of tumor therapy. However, continuous innovation is still needed for clinical applications. By overcoming challenges, patients could benefit from this therapeutic strategy.

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Competing Interests

The authors have no conflict of interest to declare.

Ethical Approval

This study did not require ethical approval, as it is a review article based on existing literature.

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