International Journal of Public Health and Medical Research
ISSN: 3006-7707 (Print), ISSN: 3006-3752 (Online)
Volume 6, Number 8, Year 2026
DOI: https://doi.org/10.62051/ijphmr.v6n8.01

Multifunctional Acoustic Nanoplatforms based on Sonodynamic Therapy for Solid Tumor: A review

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ABSTRACT

The main clinical treatment options for solid tumor include surgery, radiotherapy, chemotherapy, targeted therapy, and immunotherapy. However, these treatments all have limitations. Surgery is generally not feasible for the majority of patients with advanced or metastatic disease, whereas chemotherapy, owing to its limited targeting specificity, is frequently accompanied by severe systemic toxicity. In addition, targeted therapy and immunotherapy are only beneficial for selected subsets of patients. Therefore, there is a compelling need for combination strategies to overcome these challenges. As an emerging non-invasive modality for cancer treatment, sonodynamic therapy (SDT) mainly exploits sonosensitizer-nanoparticle conjugates (SNCs) to generate abundant reactive oxygen species (ROS) under ultrasound (US) irradiation, thereby inducing apoptosis of malignant tumor cells. SDT has the advantages of noninvasiveness, geographic targeting, deep penetration, and minimal side effects. The SNCs in this review refer to multifunctional nanoplatforms loaded with sonosensitizers and therapeutic antitumor agents, combining SDT with other modalities. This review focuses on the critical components of SNCs and recent developments in SNCs-assisted SDT in anticancer therapy, elaborates on the potential mechanisms of SDT, as well as the related outcomes. Moreover, this review highlights the promising benefits of synergistic treatment achieved by combining SDT with other therapeutic strategies. Despite the promising potential of SDT in cancer medicine, this review acknowledges the challenges of this strategy and proposes a positive direction for SNC-assisted SDT in anticancer medicine.

KEYWORDS

Sonosensitizer; Sonodynamic therapy; Low-intensity focused ultrasound; Cavitation; Reactive oxygen species

1. INTRODUCTION

Solid tumor remains a major global medical challenge and is one of the leading causes of disease-related mortality worldwide [1]. Current standard clinical management strategies primarily include surgical resection, radiotherapy, and systemic therapeutic approaches, such as chemotherapy, targeted therapy, and immunotherapy. However, all of these antitumor modalities have inherent limitations. Surgical intervention places high demands on the patient's physiological condition, and only those who are able to tolerate surgery can benefit from this approach. In addition, surgery may not only cause substantial physical trauma but also impose considerable psychological stress on patients. More importantly, for most patients with advanced or metastatic disease, the optimal window for surgical intervention has often already passed. Radiotherapy primarily exerts its antitumor effects through

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localized tumor cell killing; nevertheless, due to the limited precision in controlling deep tissue irradiation, unintended damage to the surrounding normal tissues is often unavoidable [2]. Chemotherapeutic agents are always hindered by inadequate drug delivery, insufficient tumor-specific targeting, severe systemic toxicity and chemoresistance. The clinical benefits of targeted therapy and immunotherapy are profoundly influenced by tumor heterogeneity and the tumor microenvironment (TME), and these approaches are also prone to therapeutic resistance, thereby benefiting only a subset of patients. Therefore, the development of more effective and precise therapeutic strategies is of critical importance for overcoming these limitations and improving antitumor efficacy.

Nanomedicine has shown extensive potential in the treatment of solid tumor. Conventional nano-systems mainly depend on the enhanced permeability and retention effect (EPR) for passive tumor accumulation. Nevertheless, it is often insufficient in most solid tumors due to the dense extracellular matrix and poor drug penetration. Besides, hypoxia and immunosuppression in the tumor microenvironment (TME) limit the therapeutic efficacy. The concept of sonodynamic therapy (SDT) was first proposed by Umemura in 1992 [3]. Noninvasive SDT aims to achieve geographic tumor-targeting, deep penetration, controllable drug release and enhanced anticancer efficiency through activation upon low-intensity focused ultrasound (LIFU). Through delicate design, acoustic nano-systems can serve as carriers of sonosensitizers and therapeutic agents, improving drug stability and solubility, prolong systemic circulation, overcome physiological barriers, and enhance endocytosis, thereby increasing drug accumulation at tumor sites [4]. Meanwhile, LIFU plays a trigger role in SDT, achieving precise spatial control of focused energy and responsive release of payloads [5]. Such acoustic responsiveness of these nano-systems endows the outstanding biosafety of SDT under physiological conditions. Additionally, sonosensitizers induce large amounts of cytotoxic reactive oxygen species (ROS) through electron or energy conversion during the acoustic cavitation process, thereby inducing tumor cell apoptosis [6]. As an emerging treatment method, SDT has demonstrated promising therapeutic efficacy across a variety of preclinical tumor models. Moreover, its synergistic integration with conventional treatment modalities—such as chemotherapy, targeted therapy, and immunotherapy—has exhibited substantial potential for enhanced anticancer outcomes. Nevertheless, SDT still faces multiple challenges that hinder its broader clinical translation and practical application. For example, the hypoxia in tumor microenvironment (TME) of most solid tumors markedly limits the efficacy of oxygen-dependent SDT [7]. Therefore, it is necessary to conduct a comprehensive review of SDT in order to provide a reference for the future design of acoustic nanoplatforms and to provide a more comprehensive analysis for the clinical translation of SDT.

This review aims to establish a clinically oriented framework for the rational design, mechanistic understanding, preclinical evaluation and translational development of multifunctional acoustic nanoplatforms in cancer medicine. It focuses on the critical components of sonosensitizer, elucidates the mechanical and sonochemical effects of SNCs-assisted SDT, and provides a comprehensive overview of recent developments and applications of SDT. Owing to the limitations of a single treatment strategy, the combination of SDT with other therapeutic modalities is also discussed, including chemotherapy, targeted therapy, immune checkpoint inhibitor (ICIs) therapy, chemodynamic therapy (CDT), photothermal therapy (PTT), and gas therapy. Despite the proven advantages of SDT, this review acknowledges the challenges in SNCs design and clinical translation, and further proposes a positive envision of SNC-assisted SDT in cancer medicine.

2. MECHANISMS OF SDT

Despite the exact mechanism underlying SDT-mediated antitumor effectiveness remains unclear, the most probable and plausible mechanism of SDT is related to mechanical effect of ultrasonic cavitation and sonochemical effect of cytotoxic ROS [8]. Notably, the SDT-induced immune response and immunogenic cell death (ICD) has attracted increasing attention in recent years [9].

2.1. Mechanical Effect of SDT

The mechanical effect of SDT is determined by the intensity of the acoustic radiation force, which is the force exerted on suspended micro-objects arising from spatial gradients of ultrasound (US) pressure [10]. High-intensity focused ultrasound (HIFU), characterized by high energy density and a specific focus area, can produce local high temperatures and cause irreversible tissue damage, and is generally utilized for local hemostasis and tumor ablation [11]. Compared to HIFU, LIFU distributes acoustic energy evenly to regulate membrane permeability and facilitates enhanced drug delivery without causing permanent tissue damage [12]. Specifically, cavitation is initiated when the negative pressure of US is low enough to overcome intermolecular cohesion in the liquid, thereby promoting the nucleation and expand of gas bubbles from the liquid. Under low acoustic pressure, the suspended gaseous core undergoes small-amplitude expansion and oscillates around its equilibrium radius, leading to stable cavitation [13]. During stable cavitation, acoustic streaming and mild shear stress contribute to structural rearrangements of the phospholipid membrane, thereby enhancing cell permeability [13]. When the acoustic pressure exceeded a critical threshold, the gaseous core rapidly expanded and subsequently collapsed, ultimately resulting in inertial cavitation [14]. During inertial cavitation, mechanical damage is induced by the formation of powerful liquid microjets, shock waves, shear forces, and acoustic pressure, thus forming instantaneous micropores on the membrane structure, which is called sonoporation [15]. After the US stimulation was stopped, the micropores were automatically repaired [16]. These reversible micropores allow more SNCs to pass through the cell membrane and promote cellular internalization. Generally, SNCs accumulate around tumor blood vessels through an enhanced permeability and retention (EPR) effect at the tumor site [17]. However, the passive EPR effect was insufficient to achieve adequate accumulation of SNCs for effective tumor eradication. Therefore, LIFU can be applied for SDT to increase cell membrane permeability and intratumoral accumulation of SNCs without local irreversible damage to normal tissues.

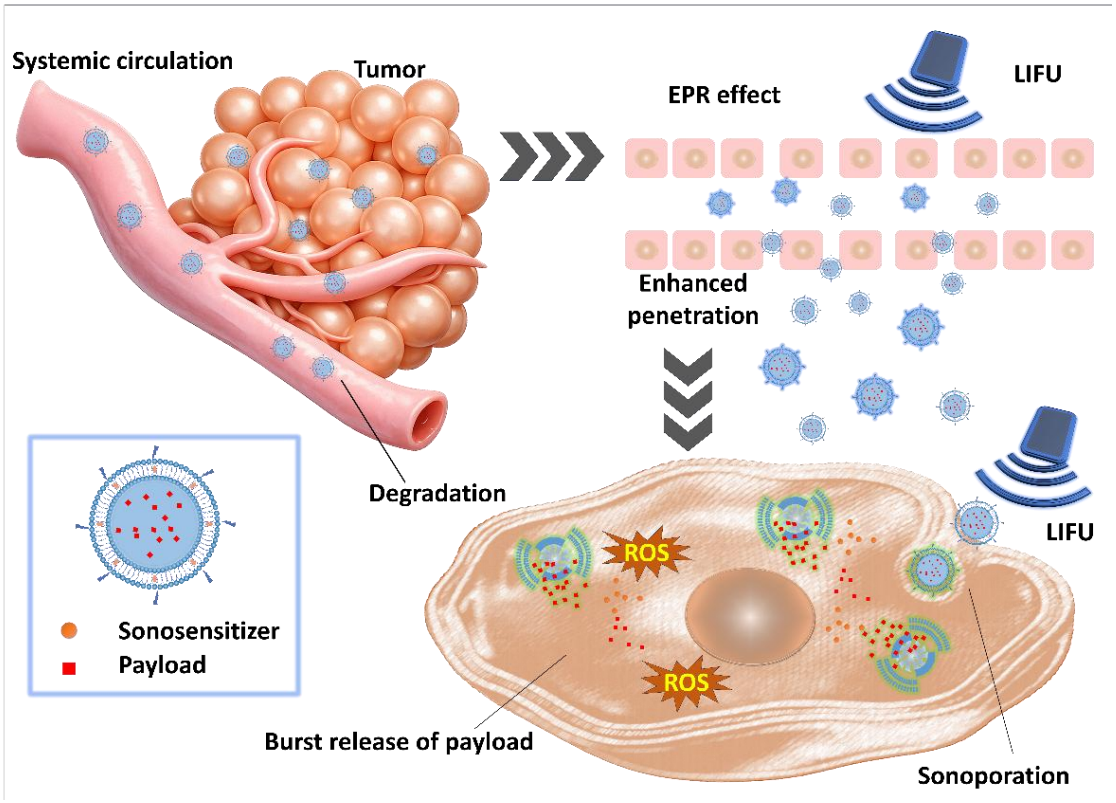


Figure 1. Mechanical effect of SDT. Acoustic cavitation enhances membrane permeability and promotes intratumoral accumulation of SNCs, whereas the subsequent collapse of SNCs triggers the release of the encapsulated therapeutic payloads.

Beyond membrane permeability enhancement, the rupture of nanobubbles further facilitates the release of encapsulated therapeutic payloads (Figure 1). Recently, Huang et al. developed a liposome-based nanoplatform loaded with a chemotherapeutic agent and PFP for the treatment of pancreatic ductal adenocarcinoma [18]. Under US irradiation, PFP inside the liposomes changed from nanodroplets to microbubbles and then reassembled into smaller nanobubbles, disrupting the surface protein corona of liposomal nanocarriers. Chemotherapeutic agents were then released at the tumor site following the destruction of nanobubbles, demonstrating the feasibility and effectiveness of US targeted drug delivery. This strategy can effectively reduce the required dosage of conventional therapeutic agents and minimize associated adverse effects. In another study conducted by Thomas McKaig et al., docetaxel-loaded SNCs have been constructed to evaluate the synergistic effects of SNCs-mediated SDT combined with acoustic cavitation-enhanced chemotherapy for prostate cancer [19]. Unexpectedly, the dosage of DTX required for SDT was 91% lower than that required for standard DTX monotherapy, significantly reducing the acute toxic effects.

2.2. Sonochemical Effect of SDT

The sonochemical effect of SDT involves a process in which sonosensitizers are activated from the ground state to an excited state upon LIFU irradiation and, during returning to the ground state, induce abundant ROS production through energy-transfer and electron-transfer reactions with surrounding oxygen molecules [20]. ROS are a group of reactive oxygen-derived chemical species, including singlet oxygen (1O2), superoxide anions (O2-), hydroxyl radicals (•OH), and hydrogen peroxide (H_2O_2) [21]. Among them, 1O2 has been reported as the main product of SNCs-mediated SDT [22]. As a double-edged sword, ROS play critical roles in various physiological and pathological processes, such as the cell cycle, programmed cell death, autophagy, and immunity [23]. At physiological levels, ROS act as secondary messengers in cellular signaling pathways, contributing to activation of critical physiological processes, maintenance of intracellular homeostasis, and modulation of diverse biological functions [24]. When the rate of ROS generation exceeds the clearance capacity of the endogenous antioxidant system, ROS-induced oxidative stress disrupts redox homeostasis, ultimately leading to cellular damage and functional dysfunction [25]. In brief, cytotoxic ROS can initiate lipid peroxidation chain reactions, inactivate endogenous antioxidant systems, and thereby compromise cellular redox balance. These processes ultimately lead to oxidative damage to lipids, proteins, and nucleic acids, resulting in cellular dysfunction and induction of multiple forms of apoptotic cell death [26].

Based on the rudimentary theory of the cavitation effect, sonoluminescence and pyrolysis have been proposed to explain ROS generation. During cavitation, the expansion and subsequent collapse of nanobubbles generates instantaneous transfer of heat and pressure, contributing to sonoluminescence [27]. Sonosensitizers can be activated by sonoluminescence to generate electron–hole (e^-–h^+) pairs and simultaneously react with O2 or H2O, thus achieving excessive generation of ROS [24]. Pyrolysis has also been proposed as an additional trigger for ROS generation in SDT. Local instantaneous energy hotspots with heat (up to 50,000 K) during cavitation lead to the generation of hydrothermal decomposition and free radicals (such as O2- and •OH), which react with other endogenous substrates to generate ROS [22]. Cytotoxic ROS that stem from sonoluminescence and pyrolysis can lead to DNA breakage, protein denaturation, mitochondrial stress, and widespread oxidative damage to cellular structures [24]. These processes disrupt tumor cell homeostasis and induce apoptosis, contributing to effective therapeutic outcomes (Figure 2A).

2.3. SDT-induced Acoustic Immune Response

SDT has been proven to facilitate the active emission of antigens and damage-associated molecular patterns (DAMPs) from dying tumor cells, such as adenosine triphosphate, calreticulin, high-mobility group box 1, and heat shock proteins [28]. These DAMPs ignite the “immune spark” in TME to awaken the antitumor immune response, inducing immunogenic cell death (ICD) [29]. Dendritic cells

(DCs) present these antigens and DAMPs to CD4 + and CD8 + T cells via major histocompatibility complex molecules [30]. This process initiates a potent systemic antitumor immune response mediated by cytotoxic T lymphocytes (CTLs), ultimately resulting in tumor cell clearance and formation of durable immunological memory (Figure 2B). For instance, Cheng et al. successfully developed an engineered liposomal nanoplatform capable of robust ROS generation under US irradiation, thereby inducing tumor cell apoptosis [31]. This nanoplatform simultaneously exerted potent immunomodulatory effects, promoting DCs maturation and enhancing CTLs infiltration into tumor tissues, which collectively amplified the antitumor immune responses in a synergistic manner. By simultaneously inducing direct tumor cell apoptosis and stimulating antitumor immune responses, SNC-mediated SDT can effectively reprogram the TME, transforming it from an immunologically "cold" state into a "hot" one.

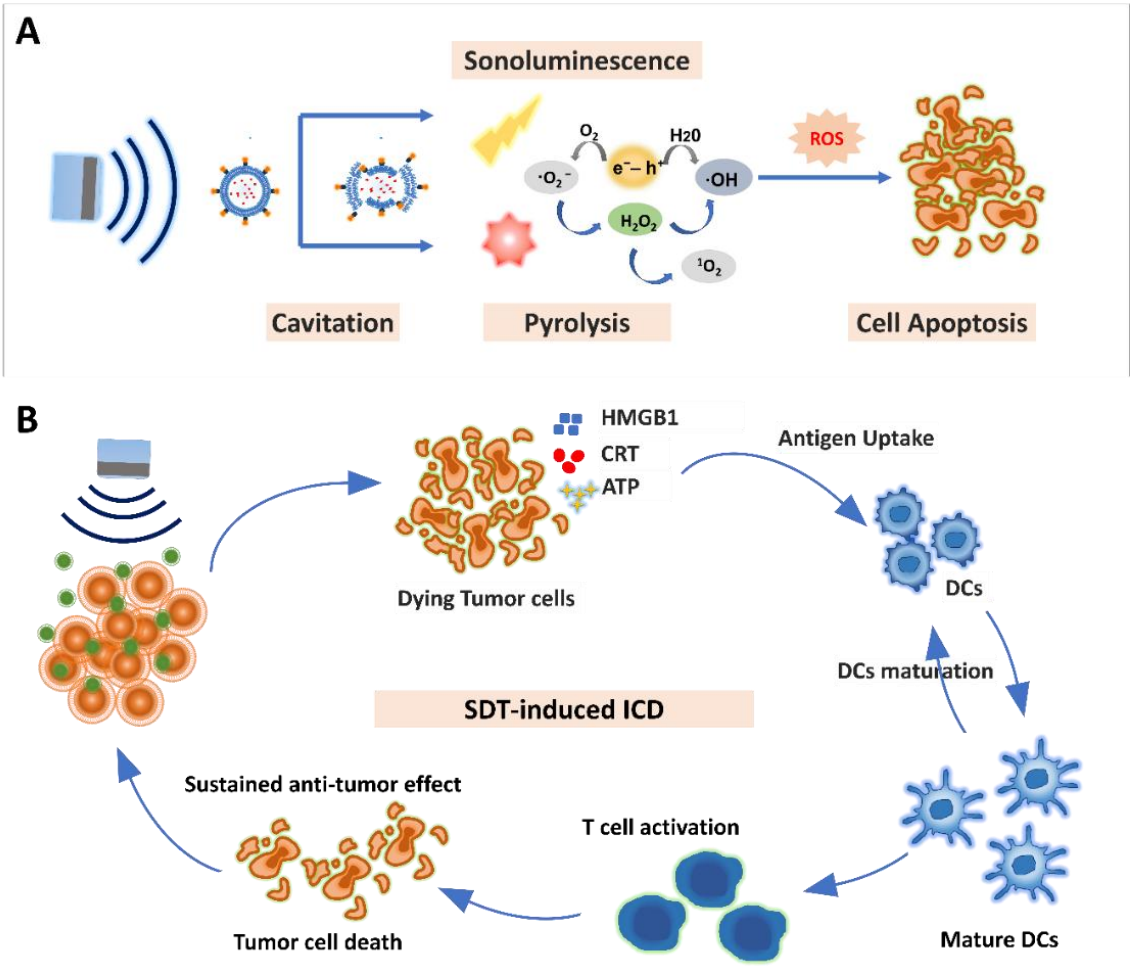


Figure 2. A. Sonochemical effect of SDT: sonoluminescence and pyrolysis lead to the production of ROS, leading to tumor cell homeostasis and apoptosis; B. SDT-induced acoustic immune response: SDT facilitates the emission of antigens and DAMPs from dying tumor cells and activates the antitumor immune response. ATP: adenosine triphosphate; CRT: calreticulin; HMGB1: high-mobility group box 1.

3. SONOSENSITIZERS

Sonosensitizers are the most critical components of SNCs that significantly influence their antitumor efficacy. Ideal sonosensitizers exhibit high acoustic responsiveness and remain nontoxic in the absence of US. SNCs act as "biochemical engines" to produce excessive ROS, achieving competence for anticancer therapy. Over the past few decades, various sonosensitizers have been extensively developed and investigated (Table 1), including organic and inorganic sonosensitizers.

Table 1. Some sonosensitizers used for SDT in recent years

Sonosensitizer	sonosensitizer-nanocomposite	Cancer	US Intensity	Reference
PpIX	DMSNs-PpIX-aPD-L1	Breast cancer	1 W/cm2, 5 min	[32]
	PpIX@ES-Cu	HCC	1 W/cm2, 5 min	[33]
	HA/GOx-MPDA@PpIX	Colonic cancer	3 W/cm2, 10 min	[34]
	PMPS NDs	Pancreatic cancer	1 W/cm2, 2 min	[23]
DVDMS	GDMCN2	Pancreatic cancer	1 W/cm2, 2 min	[35]
	DVDMS@MBs	HCC	3 W/cm2, 5 min	[36]
	Cu/DVDMS NPs	Breast cancer	1 W/cm2, 2 min	[37]
HMME	HMME@Lip	SCC	0.8 W/cm2, 3 min	[38]
	CAT@HA-HMME NPs	COAD	2.5 W/cm2, 3 min	[39]
	PHD@MnO_2	Breast cancer	0.75 W/cm2, 3 min	[40]
	HMME@Lip-Cas9	HCC	1 W/cm2, 3 min	[41]
Ce6	Fe3O4@SiO2-Ce6	Ovarian cancer	1 W/cm2, 5 min	[42]
	sPD-1/Ce6-NBs	HCC	1.8 W/cm2, 2 min	[43]
	CPDP NPs	Breast cancer	2 W/cm2, 2 min	[44]
	ZIF-8@TPZ/Ce6	Gastric Cancer	1.5 W/cm2, 3 min	[45]
	Ce6-PFP@PLGA	Melanoma	1.4 W/cm2, 5 min	[46]
	APm/Ce6/HIF	RCC	1 W/cm2, 2 min	[47]
RB	DTX-MB-RB	Prostate cancer	3 W/cm2, 3.5 min	[19]
TAPP	CuS@TAPP-CaCO3/HA	Cervical cancer	0.8 W/cm2, 5 min	[48]
Curcumin	Mesoporous CaCO3 NPs	Colon cancer	1 W/cm2, 3 min	[49]
ICG	ICG-NBs	HCC	3 W/cm2, 60 s	[50]
	ICG@O2 NBs	Esophageal cancer	1 W/cm2, 5 min	[51]
	ICG/RRx-001@CPGel	Breast Cancer	1 W/cm2, 1 min	[52]
	Lip-ICG-PFP-cRGD	Cervical-cancer	2 W/cm2, 200 s	[53]
Pp18	Pp18-lipos@SRA737&DOX	Breast Cancer	2 W/cm2, 30 s	[54]
MoS2	MoS2NF	Breast cancer	1.5 W/cm2, 3 min	[55]
SnS	SnSNPs@PEG	Breast cancer	1 W/cm2, 5 min	[56]
IR780	IRO@FA NPs	Ovarian cancer	2 W/cm2, 30 s	[57]
	IR780/PLGA@MnO_2 NPs	Breast cancer	1 W/cm2, 2 min	[58]
	IR780@FOM-cRGD	HCC	1 W/cm2, 3min	[59]
IR783	Cu-IR783 NPs	Glioblastoma	1 W/cm2, 5 min	[60]
TiO2	Fe3O4@TiO2@VISTAmAb	Pancreatic cancer	1.5 W/cm2, 3 min	[61]
	TiO2-x@GL NPs	Breast cancer	1 W/cm2, 4min	[62]
	HSIPT-NPs	SCC	5 W/cm2, 100 s	[63]
MnO_2	MO@FHO	Breast cancer	1.5 W/cm2, 2 min	[64]
Graphene	GQD/Cu_2O	Breast cancer	1 W/cm2, 10 min	[65]
CDs	Cu-CDs	Glioblastoma	1 W/cm2, 5 min	[66]
	C-dots MBs	Prostate cancer	1 W/cm2, 3 min	[67]
BP	BP-$FeSe_2$	Bladder cancer	1.5 W/cm2, 3 min	[68]
	BPNSs	Breast cancer	1 W/cm2, 5 min	[69]

DVDMS: porphyrin sodium; HP: hematoporphyrin; HMME: hematoporphyrin monomethyl ether; Ce6: chlorin e6; PpIX: Protoporphyrin IX; RB: Rose Bengal; ICG: Indocyanine green; P18: Purpurin 18; MoS2: molybdenum disulfides; SnS: Tin monosulfide; BP: Black phosphorus; CDs: Carbon dots; HCC: Hepatocellular carcinoma; RCC: Renal cell carcinoma; COAD: Colon adenocarcinoma; SCC: squamous cell carcinoma.

3.1. Organic Sonosensitizers

Porphyrins and their derivatives are a prominent class of organic sonosensitizers, mainly including protoporphyrin IX (PpIX) [70], chlorin e6 (Ce6) [46], porphyrin sodium (DVDMS) [37], and hematoporphyrin monomethyl ether (HMME) [38]. Some organic dyes known for remarkable

acoustic sensitivity have been widely applied in SNCs-mediated SDT, such as rose Bengal (RB) [19] and indocyanine green (ICG) [71]. Additionally, some natural products with aromatic structures exhibit excellent acoustic dynamic properties, such as curcumin [49] and hypericin [72].

For example, a novel cascaded nanosystem loaded with PpIX was designed to confirm the ROS storm capability of PpIX-mediated SDT for cancer treatment [34]. In this study, the PpIX encapsulation efficiency was 63.32%. Approximately 78.3% of the encapsulated PpIX was successfully released under acidic conditions, thereby enabling abundant $^1O_2$ generation upon US irradiation. Notably, the imaging capability of SNCs has also been applied to visualize drug delivery at the tumor site. Meiting Li et al. successfully designed an organic polymer nanosonosensitizer (mHM@HMME) to induce SDT and promote mitochondrial-caspase apoptosis by generating ROS [73]. Under US stimulation, mHM@HMME demonstrated pronounced antitumor efficacy in both in vitro and in vivo. Furthermore, the synergistic effect of mHM@HMME-mediated SDT and glutathione-triggered drug release within tumor cells effectively induced ICD, thereby further amplifying the therapeutic outcomes of SDT. An US-responsive nanosystem (GC-NBs) loaded with Ce6 and PFP was synthesized through an acoustic-emulsification method for the visualized treatment of hepatocellular carcinoma [74]. The GC-NBs demonstrated excellent physicochemical stability and a high Ce6 encapsulation efficiency, reaching 71.5%. In addition, echo signals of the phase changes of PFP were detected to comply US imaging ability of GC-NBs, achieving visualized monitoring during treatment. Moreover, GC-NBs under US irradiation significantly induced 1O2 production and changes in mitochondrial membrane potential, successfully leading to ROS-mediated apoptosis of tumor cells. These results demonstrated that SNCs effectively prevented the premature deactivation of sonosensitizers in the systemic circulation, significantly improving ROS generation efficiency. In Huajing Yang et al.'s study, the antitumor efficacy of DVDMS-mediated SDT was further confirmed, as evidenced by a markedly increased apoptosis rate in vitro and pronounced tumor growth inhibition in vivo [36]. Importantly, the authors further showed that this therapeutic modality could induce immunogenic cell death (ICD) within the TME.

Nevertheless, the practical application of organic sonosensitizers is still constrained by several intrinsic drawbacks such as poor hydrophilicity and rigid molecular frameworks. Inspiringly, surface modification and structural regulation have proven to be well-suited and effective strategies for synthesizing hybrid sonosensitizers, including approaches such as metal ion coordination, conjugation extension, and solubility modification [75].

3.2. Inorganic Sonosensitizers

Compared to organic sonosensitizers, inorganic sonosensitizers have advantages such as low toxicity, mechanical and chemical stability, hydrophilicity, and minimal aggregation [76]. Inorganic sonosensitizers, such as TiO_2, MnO_2, graphene and black phosphorus (BP).

As a stable semiconductor material, TiO2 can absorb acoustic irradiation energy to induce ROS generation by producing electron-hole pairs. To enhance the separation of electrons (e-) and holes (h+), atoms or ions were deposited onto TiO2 to synthesize composite sonosensitizers, such as Au/TiO2, Pt/TiO2, Ru/TiO2, Nb/TiO2, and Cu/TiO_2. These atoms or ions can trap electrons via plasmon resonance and effectively compromise the recombination of electron-hole pairs. For instance, a nanohybrid of titanium dioxide-gold-polyethylene glycol-curcumin (TiO2-Au-PEG-Cur NH) was designed and applied to SDT [77]. The incorporation of Au into TiO_2 significantly facilitated charge separation and suppressed electron-hole recombination, thereby enhancing the acoustic sensitivity of TiO_2. Consequently, the heterostructure of TiO2-Au-PEG-Cur NH promoted the generation of abundant ROS, leading to remarkable effectiveness in the destruction of cancer cells. In addition, certain piezoelectric materials, such as black phosphorus, can be polarized under US irradiation and exhibit outstanding sonodynamic performance [78]. Au/BP@MS, which was constructed by coating MnO2 on Au-anchored BP followed by surface modification with soybean phospholipids, has been

explored to achieve an enhanced SDT [78]. BP excited the separation of electron-hole pairs under US irradiation, whereas Au restricted the recombination of electron-hole pairs. Thus, this system enhances ROS generation and induces intratumoral oxidative stress amplification, resulting in potent antitumor efficacy. Additionally, carbon-based nanomaterials, such as graphene, have been developed for SDT owing to their high stability, low cytotoxicity, and excellent sonodynamic activity [79].

However, inorganic sonosensitizers are still constrained by several inherent limitations, including relatively low ROS generation efficiency, poor aqueous solubility, and insufficient tumor-targeting capability, which collectively hinder their broader application in SDT [76]. To address these challenges, future development of inorganic sonosensitizers should focus on integrating advanced structural design strategies. For instance, the incorporation of specific targeting ligands can enable selective recognition of particular cancer cell types, thereby improving the targeting precision and ultimately enhancing their therapeutic efficacy in SDT.

4. SDT-BASED SYNERGISTIC CANCER TREATMENT

Owing to tumor heterogeneity and the complexity of the TME, single-mode SDT often has limitations in achieving satisfactory therapeutic effects. For example, the hypoxia in the TME significantly limits the efficacy of oxygen-dependent SDT [7]. Therefore, synergistic therapies have attracted widespread attention. Numerous SDT-based combination therapeutic strategies have been investigated including targeted therapy, chemotherapy, ICIs, CDT, PTT, and gas therapy. It is worth noting that multimodal nanoplatforms integrating more than two therapeutic modalities are gradually emerging and attracting increasing research attention.

4.1. SNCs-assisted SDT Combined With Targeted Therapy

Nanomedicine-based cancer-targeted therapy represents a precise therapeutic strategy that selectively modulates specific molecular targets within cancer cells, thereby improving treatment accuracy and therapeutic efficacy. In recent years, the combination of SNCs-assisted SDT and active targeted therapy has been widely recognized as an effective strategy for overcoming the limitations of passive drug delivery mediated by the EPR effect. Nanomaterials enable SNCs-based SDT to achieve multiple targeting modes.

For example, belzutifan, which is a HIF-2α inhibitor, was approved by the FDA in 2021 for the treatment of renal cell carcinoma [80]. A targeting nanosystem (APm/Ce6/HIF) loaded with belzutifan as a HIF-2α inhibitor and Ce6 as a sonosensitizer was designed by the group of Xiongjun Ye et al. to produce synergistic antitumor effects for renal cell carcinoma [47]. Upon US stimulation, APm/Ce6/HIF released abundant ROS and inhibited the expression of HIF-2α, effectively increasing the tumor inhibition rate. In addition, APm/Ce6/HIF-mediated SDT induced the maturation of DCs and infiltration of CD8+ T cells through ICD, subsequently reprograming the TME and enhancing antitumor immune responses.

Epidermal growth factor receptor (EGFR) is a transmembrane tyrosine kinase receptor that is frequently overexpressed or mutated in various cancers, including HER1, HER2, HER3, and HER4 [81]. Cetuximab (CTX), a macromolecular monoclonal antibody, competitively binds to EGFR on tumor cell membranes and abrogates the activation of downstream signaling pathways, thereby inhibiting tumor cell proliferation, migration and invasion [81]. Liu et al. constructed a nanoplatform loaded with CTX and sonosensitizer IR780 to overcome drug resistance in non-small-cell lung cancer [82]. The synergistic effect of targeted therapy with CTX and IR780-mediated SDT induced extensive tumor cell necrosis and demonstrated a robust inhibitory efficacy against tumor growth. Another study engineered targeted nanoparticles (TPPO NPs) loaded with perfluorooctyl bromide as the oxygen carrier, pyropheophorbide lipid as a sonosensitizer, and trastuzumab as the targeted drug for

the treatment of HER-2 positive gastric cancer [83]. Notably, US-triggered topical delivery of oxygen from perfluorooctyl bromide significantly alleviated hypoxia in the TME and further improved the efficacy of oxygen-dependent SDT, in cooperation with toxic trastuzumab released at the tumor site.

4.2. SNCs-assisted SDT Combined With Chemotherapy

Chemotherapy serves as the first-line treatment for most malignant tumors and plays an indispensable role in inhibiting tumor progression. However, the clinical efficacy of chemotherapy is severely hampered by inherent limitations such as poor bioavailability and severe systemic side effects. By leveraging advances in nanotechnology, SNCs can transport both hydrophobic and hydrophilic agents to optimize the biocompatibility of these chemotherapeutic agents, achieving synergistic sono-chemotherapy and reducing side effects.

For example, doxorubicin (DOX) is a genotoxic agent that is widely used in anticancer treatment. Wang et al. recently synthesized an acoustic-responsive liposome conjugate to boost sono-chemotherapy, in which lipid-purpurin 18 conjugates (Pp18-lipids) induced ROS generation under US irradiation, DOX caused DNA damage, and SRA737 acted as a CHK1 inhibitor [54]. These SNCs, termed Pp18-lipos@SRA737&DOX (PSDL), achieved an efficient release of DOX of as high as 70% at the targeted tumor site by overcoming physiological barriers, thereby improving the bioavailability of DOX. Unexpectedly, PSDL-mediated SDT increased the tumor volume inhibition ratio by up to 92.21% compared with SRA737/DOX alone (53.59%) and Pp18-liposome plus US (25.19%). In another study, Poly (2,2'-thiodiethylene 3,3'dithiodipropionate) polymers loaded with DOX and Ce6, termed DOX/Ce6-LiPTD NPs, were engineered to cross the blood-brain barrier and address the drug resistance of glioblastoma to conventional chemotherapy [84]. DOX/Ce6-LiPTD NPs exhibited outstanding serum stability and long circulation lifespan after intravenous administration. The cumulative release of DOX was increased up to 97.3% owing to the expansion and rupture of DOX/Ce6-LiPTD upon US irradiation. Abundant 1O2 generated via Ce6-mediated SDT synergized with the enhanced chemotherapeutic effects of DOX (Figure 3A). This combination significantly increased the tumor volume inhibition rate and enhanced the survival of the tumor-bearing mice.

Gemcitabine (GEM) is currently the most commonly used chemotherapeutic agent for pancreatic cancer and has proven to be more effective in combination with SDT. A novel drug delivery system (GDMCN2) was designed by the group of Fanghong Luo et al., integrating GEM-mediated chemotherapy, DVDMS-assisted SDT, and targeted therapy to overcome the drug resistance of pancreatic cancer with less cytotoxicity to normal tissues [35]. In this study, stable release of GEM and ROS triggered by US irradiation was achieved, decreasing cell viability to only 1.33% compared to free GEM alone (95.7%) and single DVDMS-mediated SDT (70%).

4.3. SNCs-assisted SDT Combined with CDT

It is well known that TME of most solid tumour was characterized by hypoxia, lower pH, overexpression of H_2O_2 and glutathione (GSH), and enhanced metabolism [85]. CDT based on Fenton/Fenton-like reactions can catalyze the conversion of endogenous H_2O_2 into the highly toxic •OH, thereby inducing irreversible oxidative damage to cancer cells [86]. Several metals have been proposed for CDT, such as Fe, Cu, Ag, and Mn. Based on both sonosensitizer-mediated ROS generation and Fenton/Fenton-like reaction-driven •OH production, synergistic SDT-CDT is considered a promising strategy to achieve oxidative stress cascades and enhance antitumor efficacy.

An acidic TME and abundant H_2O_2 create proper conditions for the Fenton/Fenton-like reaction. Zhu et al. constructed a TME-activated Cu-crosslinked sonosensitizer (Cu-IR783 NPs) to achieve an enhanced synergistic SDT-CDT [60]. By utilizing the coordination bond between IR783 and Cu ions, the sonodynamic activity of IR783 was completely passivated within Cu-IR783 NPs under normal physiological conditions. Cu ions released from Cu-IR783 NPs in an acidic TME induce toxic •OH generation through a Cu+-mediated Fenton-like reaction, leading to cuproptosis via Cu+-induced

mitochondrial dysfunction. After the disassembly of Cu-IR783 NPs, selective activation of IR783 occurred under US irradiation to achieve in situ cascade amplification of ROS generation at the tumor site. This study demonstrated the passivation and selective activation of Cu-IR783 NPs, achieving enhanced synergistic SDT-CDT. Similarly, a pH-sensitive system, CTFAP, which was composed of Fe3+ based metal-organic framework, calcium peroxide (CaO2) and tetracarboxylic porphyrin, was developed for cancer-immunogenic ferroptosis and SDT [87]. CaO2 was utilized to supply both O2 and H_2O_2 as substrates for the SDT and Fenton-like reactions, respectively. The TCPP-mediated SDT and Fe-mediated Fenton-like reactions were verified to induce the robust generation of 1O2 and •OH. Thus, abundant ROS production directly induces lipid peroxidation and tumor cell apoptosis. Simultaneously, DCs present DAMPs to T-cells, triggering an effective systemic immune response.

GSH serves as an essential cofactor for the lipid repair system mediated by glutathione peroxidase 4 (GPX4). The depletion of intracellular GSH impairs GPX4 expression, promoting lipid peroxidation [87]. Wang et al. constructed iron oxyhydroxide (FeOOH)-coated MnO2 NPs (MO@FHO) as bifunctional SNCs to promote the synergistic antitumor efficacy of SDT and CDT [64]. Based on the catalase-like properties of MnO2, endogenous H_2O_2 decomposes into O2 to relieve hypoxia in the TME, providing assistance for oxygen-dependent SDT. Simultaneously, GSH depletion was achieved by GSH peroxidase-like characteristics of intrinsic Mn and Fe elements. The FeOOH coverage acted as a hole conductor and reduced the recombination of electron–hole pairs, enhancing the US-triggered ROS production rate as well as the Fenton-like reaction for CDT. These integrated advantages synergistically converged to elicit a robust and highly efficient tumor suppressive outcome (Figure 3B).

4.4. SNCs-assisted SDT Combined with PTT

PTT harnesses designated photothermal agents to absorb light of a specific wavelength and convert light energy into heat, rapidly increasing the local temperature of target tumor lesions to realize ablation, demonstrating substantial anticancer potential [88]. One of the significant drawbacks of PTT is the low penetration of light. SDT based on LIFU was proposed to compensate for this inherent deficiency, achieving synergistic SDT-PTT.

For instance, Fei Yan et al. designed dual-functional liposomes (MC@Lip) by encapsulating biosynthetic melanin and Ce6 into liposomes to achieve synergistic SDT-PTT [89]. In vitro assessments demonstrated that MC@Lip, at a favorable concentration, could achieve a remarkable temperature increase after near-infrared (NIR) irradiation and simultaneously induce abundant ROS generation. Followed by US and NIR irradiation at the tumor site, the surface temperature of tumor lesions went up from 29.1 ± 0.5 °C to 52.7 ± 1.3 °C and the final tumor regression was carried out with no metastasis, accompanied by significant survival improvement (Figure 3C). This study concluded that MC@Lip-based SDT-PTT showed superior therapeutic efficacy compared with monotherapy with PTT or SDT.

For the rational design of multifunctional therapeutic SNCs, it is essential to ensure structural stability under complex physiological conditions and enable precise activation. Biocompatible smart polymers have been increasingly favored for photothermal and sonodynamic cancer therapy, as thermoresponsive polymers exhibit rapid and pronounced solubility changes upon minor temperature fluctuations [90]. Poly-N-isopropylacrylamide (PNIPAM) is one of the most widely used thermoresponsive polymers with a lower critical solution temperature [91]. Recently, HCuS@Cu2S@Au–P(NIPAM-co-AAm)-PpIX nanohybrids (HCAPPs) were designed to achieve synergistic therapeutic effects in breast cancer [92]. By copolymerizing with a hydrophilic monomer, the critical solution temperature of HCAPPs was increased from 32 °C to 44 °C, allowing HCAPPs to work at a physiological temperature of 37 °C. More importantly, HCAPPs successfully induced abundant ROS production via PpIX-mediated SDT and achieved sufficient heat anergy via an NIR laser, showing outstanding cell-killing capability.

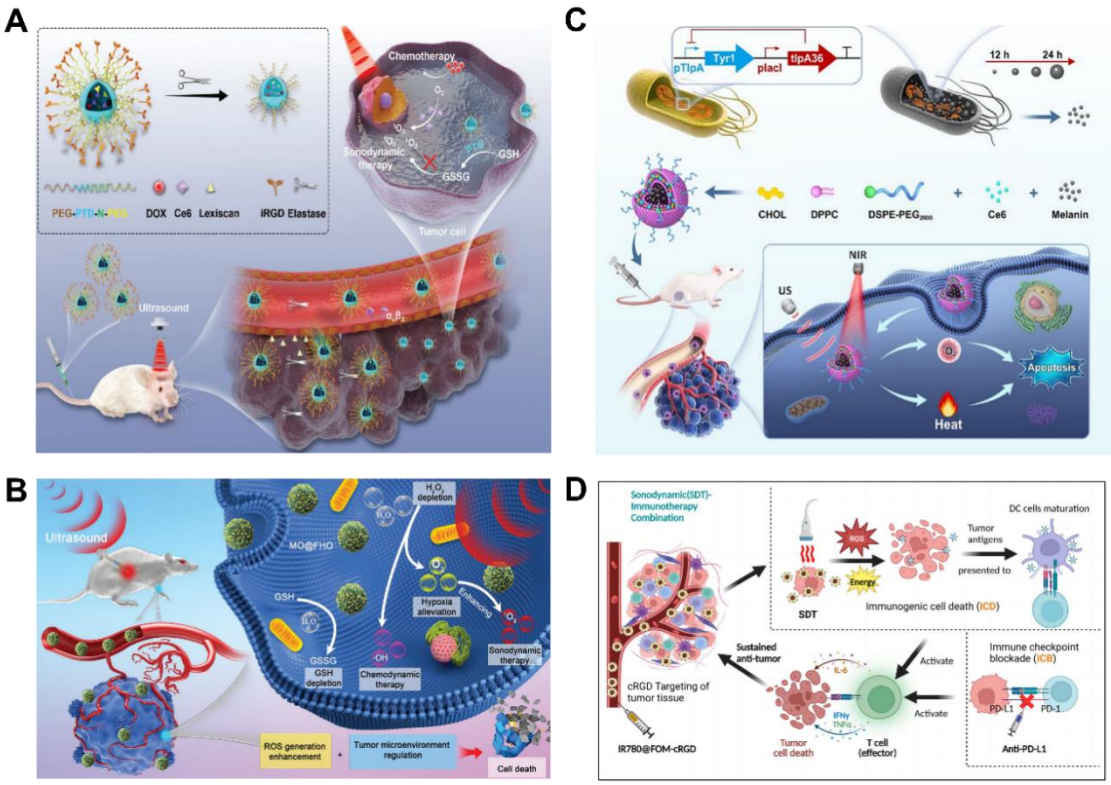


Figure 3. A. Schematic illustration of LiPID NPs-mediated sono-chemotherapy. Taking the advantage of the enhanced the penetration of LiPID NPs under US irradiation, DOX/Ce6-LiPID NPs improved the synergistic antitumor efficacy of DOX-mediated chemotherapy and Ce6-induced SDT for the treatment of GBM. Reproduced from 2022, Advanced Science [84]. B. Schematic diagram for MO@FHO-mediated SDT-CDT. The depletion of H_2O_2 and GSH achieved ROS generation enhancement and TME regulation, promoting the combination of CDT and oxygen-dependent SDT. Reproduced from 2022, Advanced Science [64]. C. Schematic illustration of synergistic MC@Lip-based SDT- PTT. Biosynthetic melanin and Ce6 were encapsulated into liposomes to obtain MC@Lip. Following NIR and US irradiation applied at the tumor site, MC@Lip produced abundant 1O2 though SDT and localized heat via PTT, improving the synergistic antitumor efficacy. Reproduced from 2023, Pharmaceutics [89]. D. Potential mechanisms of IR780@FOM-cRGD, combining IR780-mediated SDT and Anti-PD-L1 therapy. Reproduced from 2022, International Journal of Nanomedicine [59].

4.5. SNCs-assisted SDT Combined with Immunotherapy

Compared with other antitumor strategies, immunotherapy not only inhibits tumor growth but also fosters a long immune memory against tumor recurrence and metastasis. Immune checkpoint inhibitors (ICIs), such as anti-CTLA-4 and anti-PD-1 agents, have been widely utilized for cancer medicine [93]. Activated CTLs are frequently inhibited by immune checkpoint molecules expressed by tumor cells, allowing them to evade immune surveillance. By selectively blocking immunosuppressive signaling pathways, ICIs effectively release the brakes of the immune response, restore suppressed CTLs, and enable sustained immune-mediated tumor cell elimination. SDT-induced ICD activates adaptive immune responses driven by CTLs, further enhancing the efficacy of ICIs . It has been confirmed that the combination of SDT and ICIs therapy can suppress tumor cell proliferation and migration, thus improving prognosis and prolonging survival effectively [94].

To overcome the insufficient antitumor immunity of SDT, Wu et al. developed a novel nanoplatform, IR780@FOM-cRGD, in which Fe_3O_4 served as the structural framework and cyclic arginine–glycine–aspartic acid (cRGD) was employed as the targeting ligand [59]. IR780-mediated SDT induces abundant ROS production, causing oxidative stress and lipid peroxidation, thereby

facilitating damage to cell membranes and organelles. The resultant cellular lysis released various tumor antigens and DAMPs, which were captured by antigen-presenting DCs to T cells and promoted DCs maturation and CTLs activation. Meanwhile, anti-PD-L1 could bind to PD-L1 expressed on tumor cells and block tumor immune escape (Figure 3D). In addition, the targeting capability of cRGD and the precise control of US irradiation significantly reduced immune-related adverse events. Thus, synergistic treatment involving anti-PD-L1-mediated immunotherapy and enhanced IR780@FOM-cRGD-mediated SDT significantly increased DNA damage and tumor cell eradication, leading to persistent and amplifying antitumor efficacy.

4.6. SNCs-assisted SDT Combined with Gas Therapy

Over the past few decades, several gases have been developed as supporting options for cancer therapy, such as hydrogen (H2), oxygen (O2), carbon monoxide (CO), carbon dioxide (CO2), nitric oxide (NO), hydrogen sulfide (H2S), and sulfur dioxide (SO2) [95]. Gas therapy has emerged as a potential therapeutic strategy for killing tumor cells and modulating the TME. This approach generally uses nanomaterials as delivery carriers for bioactive gaseous molecules, thereby inducing oxidative stress, metabolic perturbation, and immune activation in a precisely controlled manner [96]. As the delivery and release of gasotransmitters at deep tumor sites are difficult, SNCs can overcome this limitation of gas therapy. In return, gas therapy can amplify SNC-assisted SDT, enhancing subsequent antitumor immune responses.

For instance, iron carbonyl (Fe3CO12)-bridged mesoporous silica NPs loaded with Ce6, termed Fe3CO12-MSNs@Ce6@CM, were designed to prevent premature CO leakage during circulation and synergize with SDT to enhance the antitumor efficacy [97]. Sustainable CO release enhances mitochondrial respiration and increases the sensitivity of tumor cells to ROS. Under US irradiation, such a combined pattern at the tumor site resulted in a tumor inhibition rate of up to 69.2% because of burst Ce6-mediated ROS generation and US-controllable CO release. Similarly, Guo et al. developed a US-responsive nanosystem (PIH-NO) loaded with IR780 as a sonosensitizer to deliver NO, combining the SDT and gas efficacy [98]. Upon US irradiation, the energy activated by IR780 was transferred for burst generation of ROS. NO released from PIH-NO can react with ROS to increase the production of peroxynitrite anions, which can reprogram M2 macrophages to M1 macrophages to reverse immunosuppression in the TME. Upon such a combination of gas therapy and amplified SDT, PIH-NO inhibited tumor growth by up to 92% and significantly suppressed tumor metastasis.

5. CHALLENGES OF SNCS-ASSISTED SDT

Although SNCs-assisted SDT has shown considerable promise as an anticancer strategy, several challenges remain to be addressed before its clinical translation. Among these, the rigorous design of SNCs represents a fundamental prerequisite for the successful applications. The physicochemical properties, biological activity, and biosafety of SNCs critically determine the pharmacokinetic behavior, tumor accumulation, and therapeutic performance in vivo. Notably, different nanomaterials exhibit distinct biodistribution and clearance profiles, and even SNCs with similar compositions may display substantial differences in stability, biosafety, and efficacy when loaded with different therapeutic payloads. Therefore, achieving an optimal balance among structural stability, drug-loading capacity, biocompatibility, and therapeutic functionality to achieve optimal performance remains a major challenge in the design of SNCs.

Beyond SNCs design, the therapeutic outcomes are also highly dependent on LIFU exposure conditions, including frequency, intensity, pulse mode, mechanical index, and irradiation duration. Variations in these parameters can markedly influence cavitation behavior, ROS generation, drug release, and ultimately antitumor efficacy. However, standardized LIFU protocols for SDT are still lacking, which limits cross-study comparability and hampers clinical implementation. In addition, the

antitumor efficacy, mechanistic basis, and dose-response relationship of NP-mediated SDT must be rigorously validated in preclinical studies using appropriate animal models. Ultimately, novel SDT nanoplatforms will only possess meaningful clinical potential if they can demonstrate clear and reproducible advantages in efficacy, safety, reproducibility, and controllability over existing therapeutic strategies.

6. CONCLUSION AND PERSPECTIVES

Despite the lack of clinically approved SNCs-assisted SDT systems, rapid advances in this field have underscored its considerable potential as a versatile and programmable anticancer strategy. This review not only comprehensively summarizes the major sonosensitizers, mechanistic foundations, and representative therapeutic applications of SNCs-assisted SDT, but also reveals its therapeutic rationale, design principles, and translational barriers. More importantly, by highlighting the specific role of SNCs in improving sonosensitizer/drug delivery, enhancing ROS generation, inducing acoustic immune response and enabling synergistic therapeutic effects, this review provides a valuable theoretical framework for the rational design of next-generation SDT nanoplatforms. Collectively, future advances in material optimization, mechanistic understanding, and clinically relevant validation are expected to further accelerate the development of SNCs-assisted SDT toward effective cancer therapy.

DECLARATIONS

Conflicts of interest

All authors declared no potential conflicts of interest with respect to the research, authorship, and publication of this article.

Availability of Data and Materials

The data and materials used in this study are available from the corresponding authors upon request.

Author Contributions

Bo Ren: writing the original draft. CharngChoon Wong: Writing, review, and editing. This article was reviewed by all the authors.

Ethics statement

This study did not involve human or animal subjects.

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