

# Sonodynamic and Acoustically Responsive Nanodrug Delivery System: Cancer Application

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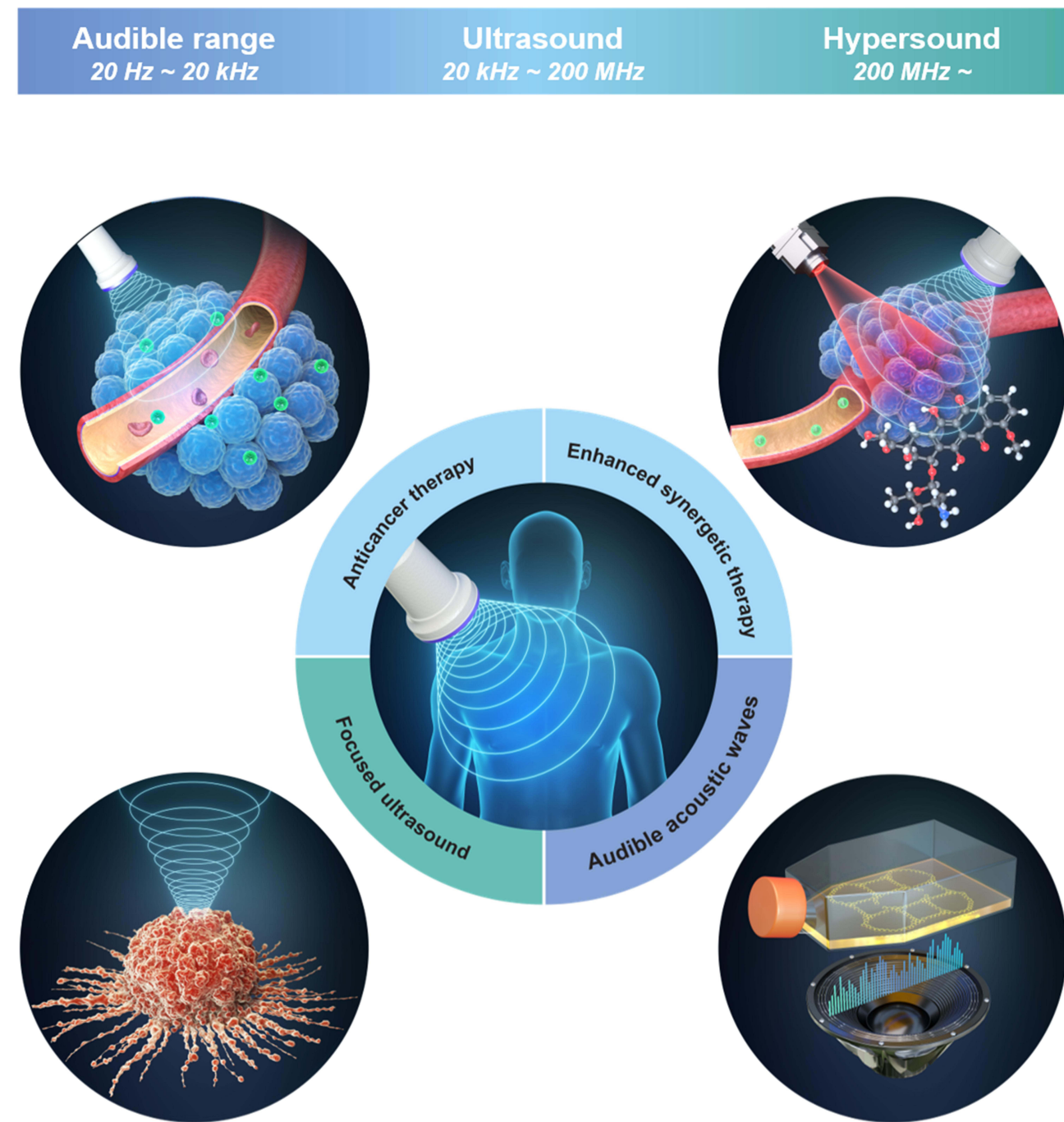
**Abstract:** The advent of acoustically responsive nanodrugs that are specifically optimized for sonodynamic therapy (SDT) is a novel approach for clinical applications. Examining the therapeutic applications of sono-responsive drug delivery systems, understanding their dynamic response to acoustic stimuli, and their crucial role in enhancing targeted drug delivery are intriguing issues for current cancer treatment. Specifically, the suggested review covers SDT, a modality that enhances the cytotoxic activity of specific compounds (sonosensitizers) using ultrasound (US). Notably, SDT offers significant advantages in cancer treatment by utilizing US energy to precisely target and activate sonosensitizers toward deep-seated malignant sites. The potential mechanisms underlying SDT involve the generation of radicals from sonosensitizers, physical disruption of cell membranes, and enhanced drug transport into cells via US-assisted sonoporation. In particular, SDT is emerging as a promising modality for noninvasive, site-directed elimination of solid tumors. Given the complexity and diversity of tumors, many studies have explored the integration of SDT with other treatments to enhance the overall efficacy. This trend has paved the way for SDT-based multimodal synergistic cancer therapies, including sonophototherapy, sonoimmunotherapy, and sonochemotherapy. Representative studies of these multimodal approaches are comprehensively presented, with a detailed discussion of their underlying mechanisms. Additionally, the application of audible sound waves in biological systems is explored, highlighting their potential to influence cellular processes and enhance therapeutic outcomes. Audible sound waves can modulate enzyme activities and affect cell behavior, providing novel avenues for the use of sound-based techniques in medical applications. This review highlights the current challenges and prospects in the development of SDT-based nanomedicines in this rapidly evolving research field. The anticipated growth of this SDT-based therapeutic approach promises to significantly improve the precision of cancer treatment.

**Keywords:** sonodynamic therapy, ultrasound, synergistic therapy, sonosensitizer, nanomedicine, cancer treatment, acoustic audible wave

## Introduction

Cancer continues to pose a significant threat to human health and longevity, driving the ongoing search for more effective and less harmful treatments. Traditional cancer therapies, such as surgical tumor resection, chemotherapy, radiotherapy, and immunotherapy, remain essential pillars of oncological care.<sup>1,2</sup> Although these treatments can be effective, they are often accompanied by substantial side effects that negatively impact a patient's quality of life. For instance, surgery may lead to complications and disrupt the functioning of healthy organs, particularly in cases involving deep-seated or inoperable tumors.<sup>3</sup> Moreover, the inability of surgery to eliminate microscopic residual tumor cells necessitates the adjunctive use of chemotherapy and radiotherapy. While these therapies target cancer cells, they also harm healthy tissues and may promote resistance in cancer cells.<sup>4</sup> This resistance often leads to the survival and proliferation of cancer cells with mutations, making subsequent therapies less effective and contributing to disease recurrence or progression.<sup>5-9</sup>

## Graphical Abstract



Non-targeted agents used alongside chemotherapy and radiotherapy can also cause various adverse effects, which may range from acute symptoms such as nausea and hair loss to long-term consequences like organ damage and secondary cancer. Likewise, immunotherapies that aim to engage the immune system of the body in fighting cancer may trigger dysregulated immune responses, potentially resulting in autoimmune disorders or cytokine release syndrome.<sup>10–14</sup>

Given these challenges, there is growing interest in developing alternative therapeutic strategies that selectively target tumor cells while sparing healthy tissues. Among these approaches, photodynamic therapy (PDT), photothermal therapy

(PTT), hyperthermia and radiotherapy have emerged as promising techniques. PDT uses photosensitizers and PTT employs photothermal agents, both of which are activated by specific wavelengths of light to induce localized tumor cell death through the production of reactive oxygen species (ROS) or heat.<sup>15–17</sup> While PDT and PTT offer advantages such as reduced systemic toxicity and the ability to target specific tumor sites, their clinical applicability is limited by the shallow tissue penetration of light, restricting their use to superficial or endoscopically accessible tumors.<sup>18,19</sup> Hyperthermia, which relies on localized heating to kill cancer cells, can be challenging to control, potentially damaging healthy tissues surrounding the tumor.<sup>20</sup> Similarly, radiotherapy, though effective in inducing DNA damage to cancer cells, involves ionizing radiation that carries risks such as secondary cancers and long-term tissue damage.<sup>21</sup> In contrast, SDT combines the production of ROS with acoustic cavitation, enabling more precise tumor targeting with deeper tissue penetration and fewer side effects. Moreover, SDT utilizes ultrasound waves, eliminating the radiation-related risks associated with radiotherapy. These unique attributes position SDT as a promising alternative to existing non-invasive cancer therapies, offering more versatility and safety in clinical applications.

The unique properties of ultrasound (US), a well-established tool in medical imaging and therapy, present a promising alternative for cancer treatment. Unlike light, US can penetrate deeper into tissues, potentially overcoming the limitations of phototherapy. Sonodynamic therapy (SDT) is an emerging technique that combines US with acoustically sensitive drugs to induce cytotoxic effects at tumor sites. By harnessing the cavitation effect of US, SDT can increase the permeability of cancer cell membranes, facilitating the targeted delivery and activation of therapeutic agents. Additionally, incorporating acoustically responsive nanomaterials into SDT enables precise control of drug release and activation, further minimizing collateral damage to healthy tissues.<sup>22,23</sup>

The synergistic combination of US and sonosensitizers in SDT not only enhances tumor treatment efficacy but also opens new possibilities for combination therapies. Integrating SDT with conventional therapies such as chemotherapy, photothermal therapy, and immunotherapy could overcome treatment resistance and lead to more comprehensive tumor eradication. Furthermore, the exploration of acoustically responsive nanomaterials within SDT presents a frontier for innovation, with the development of multifunctional nanoparticles capable of responding to US stimuli for targeted drug delivery and therapy activation.<sup>24–26</sup>

Despite the potential of SDT, several challenges remain unresolved. These include optimizing the design and synthesis of sonosensitizers for maximum efficacy, understanding the complex interactions between US, sonosensitizers, and biological tissues, and developing protocols for safe and effective clinical application of SDT. Addressing these challenges is essential for fully realizing the potential of SDT as a precise, targeted, and minimally invasive cancer treatment strategy.<sup>26–30</sup>

## Therapeutic Mechanisms of SDT

SDT is a therapeutic approach that utilizes US and its interactions with chemical compounds known as sonosensitizers. The potential mechanisms of SDT include four primary concepts: direct US irradiation, cavitation, ROS generation, and thermal effects.<sup>31–34</sup> Direct US irradiation damages or denatures the targeted cancer tissue through high-intensity US beams.<sup>31,32</sup> Additionally, combining US with various sonosensitizers has been proposed as a strategy to inhibit tumor growth by inducing cell death via cavitation, ROS generation, and thermal effects. High-intensity focused US (HIFU) primarily operates within the frequency range of 0.8 to 3.3 MHz, using high-energy US to precisely target and treat tumor tissues with minimal collateral damage. Furthermore, SDT employing sonosensitizers typically operates within the frequency range of 0.5 to 3.0 MHz,<sup>33,34</sup> which is effective for deep tissue penetration and the generation of ROS and heat, leading to efficient tumor treatment. Acoustically responsive nanoparticles can be engineered to undergo structural transformations or release their payload upon exposure to specific US frequencies and intensities, providing a highly targeted approach to cancer therapy. The release of drugs from acoustically responsive nanoparticles is primarily governed by cavitation and sonoporation. Stable cavitation involves the gentle oscillation of microbubbles at low frequencies, which enhances drug penetration through the tumor vasculature. In contrast, inertial cavitation results from the violent collapse of bubbles, generating mechanical forces that break apart the nanoparticle shell, releasing the encapsulated drug. Additionally, sonoporation temporarily increases the permeability of tumor cell membranes, allowing drugs to infiltrate the tumor tissue more effectively.

## US-Direct Irradiation

HIFU therapy transmits energy in the form of US waves through intervening tissues to specific target points within body organs, thereby raising temperature or inducing other biological effects in a completely non-invasive manner. Therapeutic US uses higher energy and intensity compared to diagnostic US, although the fundamental principles of HIFU remain the same as those of conventional US.

The primary mechanisms of HIFU ablation are thermal and mechanical effects. HIFU generates heat by focusing US waves on a precise point within the tissue where the energy is concentrated. This focused energy leads to rapid molecular vibrations, producing frictional heat. The generated heat increases the tissue temperature to over 60 °C, causing coagulation necrosis, effectively destroying tumor cells. The Pennes bioheat transfer equation models the heat generation and transfer process in tissues subjected to HIFU. The equation is as follows:

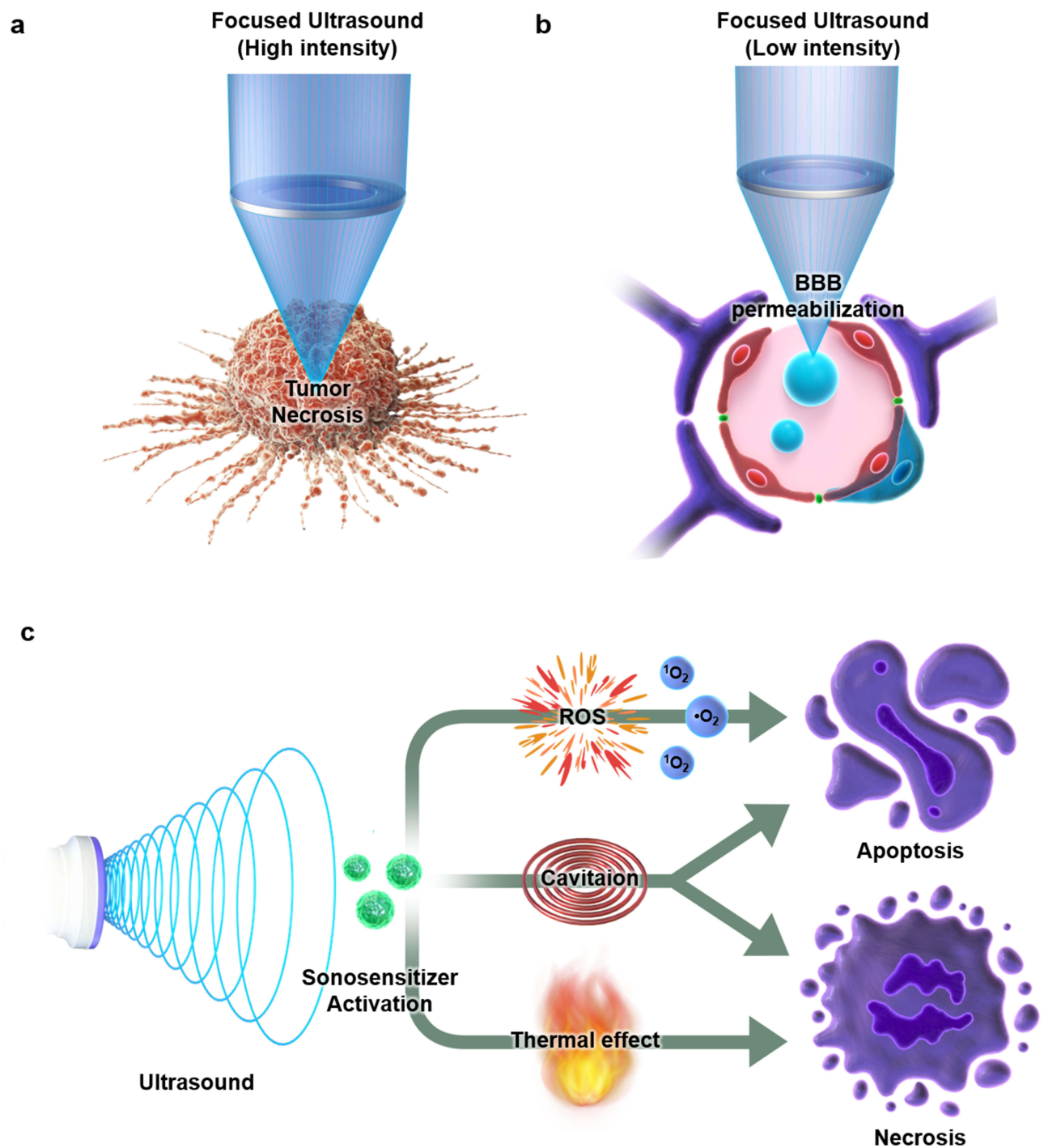
$$\rho_t C_t \frac{\partial T}{\partial t} = \nabla \cdot (k_t \nabla T) - \omega_b C_b (T - T_\infty) + Q$$

where the subscripts t and b relate to the tissue and blood phases, respectively. Additionally,  $\rho$ ,  $C$ ,  $k$ , and  $T$  represent the tissue density, specific heat, thermal conductivity, and temperature, respectively.  $\omega$  denotes the capillary bed perfusion rate, and  $T_\infty$  is the temperature at a distant location from the transducer focal region (typically 37°C).<sup>35,36</sup>

The mechanical effects of HIFU include microstreaming and cavitation.<sup>32,37</sup> Microstreaming refers to the small-scale fluid flow induced by US waves as they travel through tissues, generating shear forces that damage cell structures and promote cell death. Cavitation involves the rapid formation and collapse of bubbles caused by US waves.<sup>38</sup> The violent collapse of these bubbles generates high temperatures and pressures, producing strong mechanical shock waves that destroy cells and tissues.<sup>39</sup> When the ultrasonic energy is precisely focused on the target area, minimal adverse biological effects are observed in the surrounding tissues. Specific ultrasonic energy levels vary depending on the application, typically determined by the frequency and intensity settings of the US equipment, ensuring energy is concentrated in the intended area to minimize collateral damage. Due to its non-invasive nature, this technology has gained widespread attention from clinicians, researchers, and companies worldwide as a promising, minimally invasive therapeutic tool (Figure 1a).

A promising variation of focused US is low-intensity focused US (LIFU). LIFU is an innovative, non-invasive technique used to temporarily and reversibly open the blood-brain barrier (BBB).<sup>40–42</sup> This magnetic resonance imaging-guided focused US (MRIgFUS) technique uses low-frequency US combined with gas-filled microbubbles (MBs) to specifically disrupt the BBB.<sup>43</sup> MBs, typically composed of lipid-encapsulated carbon fluoride gas, range from 1 to 5  $\mu\text{m}$  in diameter and are inherently echogenic.<sup>44,45</sup> They are widely used as contrast agents in US imaging and help target and disrupt the BBB for therapeutic purposes.<sup>46</sup> The pressure amplitude for opening the BBB with FUS is kept below 1.5–2 MPa, comparable to diagnostic US, ensuring its safety for use in humans.<sup>47</sup> While US is believed to interact with brain tissue to open the BBB through stable and inertial cavitation, the exact mechanisms underlying LIFU-induced BBB opening remain unclear. Stable cavitation occurs when MBs rhythmically expand and contract in low-pressure environments, generating microflows in the surrounding fluid that apply mechanical forces on endothelial cells, temporarily disrupting tight junction proteins. In contrast, inertial cavitation occurs under high-pressure conditions, causing MBs to collapse violently, generating mechanical forces such as shock waves and microjets that perforate cell membranes and increase blood vessel permeability (Figure 1b).<sup>40</sup>

In summary, HIFU and LIFU are non-invasive therapeutic technologies that leverage US for various medical applications, utilizing high and low intensities, respectively.<sup>48</sup> HIFU is primarily used in tumor treatments, involving high-intensity US energy, typically exceeding 1000 W/cm<sup>2</sup>, directed at tumor tissue to increase its temperature and destroy it through a combination of thermal and mechanical effects. This method has demonstrated efficacy in treating several cancers, including prostate and liver cancers.<sup>31</sup> In contrast, LIFU is used in neuroscience research and neuro-modulation, applying lower intensities, generally below 3 W/cm<sup>2</sup>. Additionally, LIFU facilitates drug delivery by temporarily opening the BBB, making it valuable for studying brain functions and treating neurological disorders.<sup>49</sup> Ongoing research suggests that these technologies have broad potential for medical applications, promising significant advancements in non-invasive therapeutic methods.



**Figure 1** Therapeutic strategies using ultrasound (US) in cancer treatment include the application of US alone (a and b) or in combination with sonosensitizers (c). The potential mechanisms of sonodynamic therapy (SDT) involve focused US, the production of reactive oxygen species (ROS), hyperthermic damage, and the cavitation effect.

## SDT Induced by Sonosensitizers

Sonosensitizers optimize the therapeutic impact of US irradiation, playing a crucial role in SDT. These compounds absorb energy from US waves, converting it into localized ROS, which are vital in triggering apoptosis in cancer cells.<sup>29</sup> ROS can disrupt cellular structures, damage DNA, and initiate biochemical cascades that lead to programmed cell death.<sup>50,51</sup> In recent decades, sonosensitizers have been rapidly developed based on their role in SDT-induced cell apoptosis.

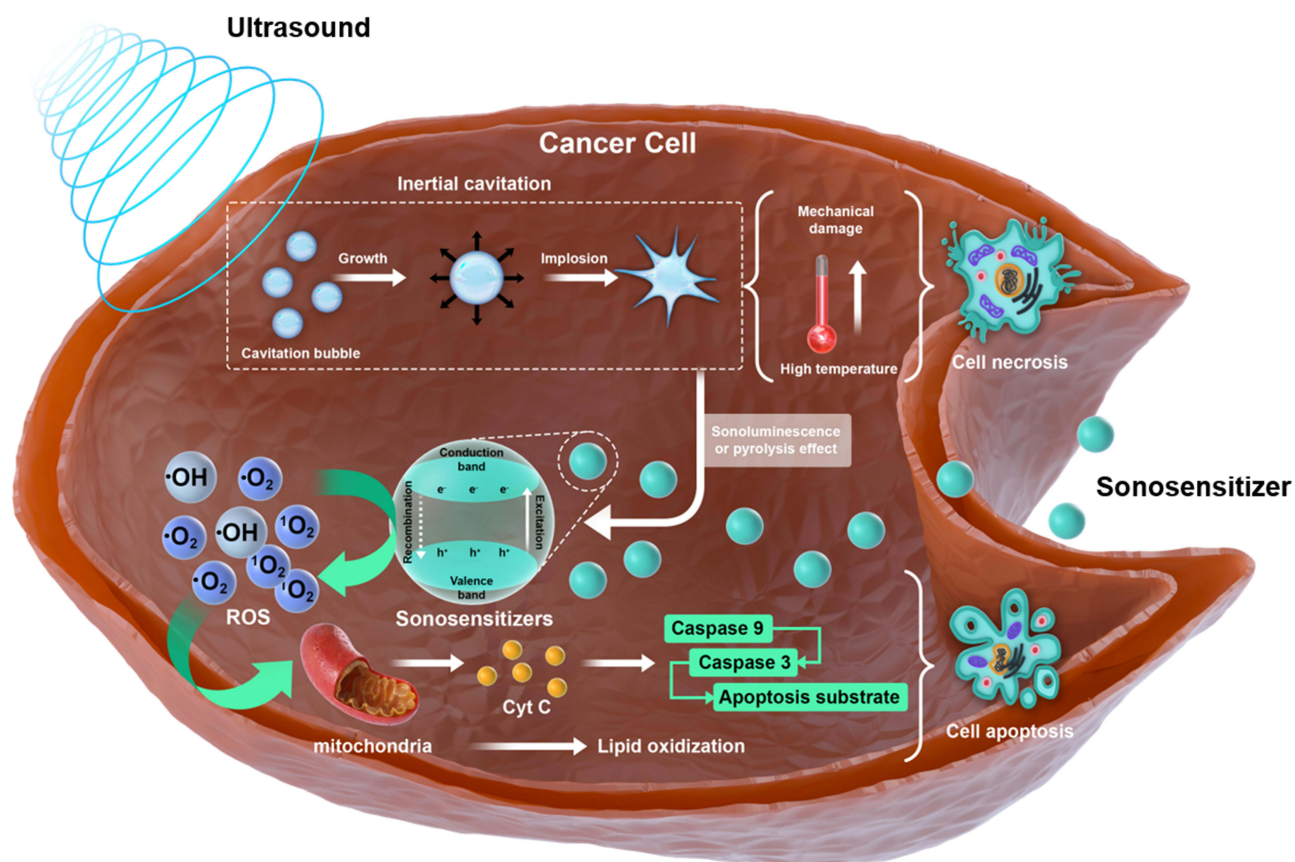
The development of effective sonosensitizers is essential for enhancing the therapeutic efficacy of SDT. Current research focuses on two main types of sonosensitizers: organic and inorganic. Organic sonosensitizers, often derived from natural compounds or synthetic analogs, are noted for their biocompatibility and efficient ROS generation.<sup>52,53</sup> Conversely, inorganic sonosensitizers, such as metal-based nanoparticles, offer advantages including high stability, functionalization ease, and robust ROS production.<sup>54,55</sup> Each type has distinct strengths and limitations, making the selection of the appropriate sonosensitizer crucial in optimizing SDT for cancer treatment.

Furthermore, choosing the appropriate sonosensitizer for SDT in cancer therapy is a major focus of current research. Comparing SDT with other treatment modalities, such as photodynamic therapy (PDT), underscores the importance of this selection. Unlike PDT, which relies on light-sensitive compounds and is limited by light penetration depth, SDT utilizes ultrasound waves that can penetrate deeper into tissues and are less dependent on oxygen levels. This characteristic makes SDT particularly effective in treating deep-seated and hypoxic tumors.<sup>56</sup>

The integration of these insights into the development and application of sonosensitizers in SDT highlights their potential for significant advancements in cancer therapy. This comprehensive approach enhances our understanding of the underlying mechanisms of SDT and paves the way for more effective and targeted cancer treatments (Figure 1c).

### Fundamental Mechanisms of SDT

SDT employs a multifaceted approach that involves both biochemical and biophysical interactions to effectively treat cancer (Figure 2). One of the key theories is the oxygen radical theory, which suggests that the primary mechanism of SDT is the generation of ROS through cavitation or US activation of sonosensitizers. ROS, mainly produced by the collapse of US-induced cavitation bubbles, play a critical role in damaging cellular components such as DNA, proteins, and lipids, thereby inducing apoptosis in cancer cells.<sup>56</sup> Furthermore, processes such as pyrolysis and sonoluminescence



**Figure 2** Mechanisms underlying sonodynamic therapy (SDT) include: 1) cavitation effects induced by ultrasound (US) and 2) the generation of reactive oxygen species (ROS), as depicted in this figure. The predominant and widely accepted mechanism is ROS production, triggered by either pyrolysis or sonoluminescence.

significantly enhance ROS production, further inhibiting tumor growth by promoting cellular oxidative stress. Pyrolysis involves the decomposition of materials due to localized heating generated by US waves, leading to the breakdown of chemical bonds and the formation of reactive radicals, which subsequently interact with oxygen to produce ROS.<sup>57</sup> In contrast, sonoluminescence occurs during the collapse of microscopic gas bubbles formed by cavitation. The extreme conditions within these collapsing bubbles lead to the emission of light and the dissociation of molecules, generating additional ROS that contribute to oxidative damage in tumor cells.<sup>30</sup> Simultaneously, the cavitation effect theory explains the physical phenomena triggered by US, emphasizing the dynamic process of cavitation, which involves the formation, growth, and implosion of bubbles within the liquid medium.<sup>23</sup> This process includes two main types of gas oscillation: stable (non-inertial) cavitation and inertial (transient) cavitation. In stable cavitation, bubbles oscillate in size around an equilibrium radius over many cycles of US waves without collapsing, typically occurring at US frequencies ranging from 20 to several hundred kHz. In contrast, inertial cavitation involves bubbles growing significantly during the negative pressure phase and then collapsing violently during the positive pressure phase, usually at frequencies ranging from 20 kHz to several MHz. This activity not only supports ROS generation by creating the physical conditions necessary for cavitation but also directly disrupts cellular structures. The mechanical forces generated by rapid bubble collapse produce high temperatures and pressures, leading to mechanical damage to cell membranes and subsequent cell necrosis. Additionally, US-induced cavitation enhances drug penetration and distribution by disrupting adjacent cell membranes, thereby facilitating the therapeutic effects of co-administered drugs.<sup>58–60</sup> Post-SDT morphological changes in cancer cells include the disappearance of microvilli, vacuolation of cell membranes, cell shrinkage, and cytoskeletal alterations. These changes align with the observed increase in apoptotic/necrotic ratios and significant post-treatment mitochondrial dysfunction, indicating the involvement of both ROS-mediated and mechanical damage pathways. ROS-induced damage leads to mitochondrial dysfunction, including the opening of the mitochondrial permeability transition pore (MPTP), which results in the release of cytochrome c into the cytosol. Cytochrome c binds to Apaf-1 and adenosine triphosphate (ATP), forming an apoptosome complex that activates pro-caspase-9. Activated caspase-9 then cleaves and activates caspase-3, a key executioner caspase responsible for the cleavage of various cellular substrates, leading to programmed cell death. Additionally, lipid peroxidation and the downregulation of antioxidant enzymes have been observed, illustrating the extensive impact of SDT on cellular functions.<sup>54,61–63</sup>

Overall, SDT efficacy arises from a dual mechanism: the chemical effects mediated by ROS and the physical effects resulting from the mechanical forces of cavitation. Together, these effects lead to the comprehensive disruption of cancer cells through oxidative stress and direct physical damage, culminating in tumor regression and cell death. This integrated approach demonstrates that SDT is a potent therapeutic modality that leverages the synergistic effects of both biochemical and biophysical processes.<sup>64</sup>

### Organic Sonosensitizer-Based SDT

Sonosensitizers can be classified as either inorganic or organic. Both types share the ability to be activated by US irradiation to generate ROS, a critical factor in the efficacy of SDT. However, they differ significantly in their properties and applications. Organic sonosensitizers, like their photosensitizer counterparts, are activated by US irradiation to generate ROS through sonoluminescence or sono-chemical pyrolysis.<sup>65,66</sup> Generally, photosensitizers can also function as sonosensitizers, with the molecular design of the latter derived from the former.<sup>67</sup> Compared to inorganic sonosensitizers, organic ones typically exhibit a higher capability to generate ROS when activated from the ground state to the excited state under US. This characteristic has made organic sonosensitizers widely utilized in SDT research.<sup>68</sup> However, conventional organic sonosensitizers face limitations, such as poor water solubility, low chemical stability, and inadequate tumor targeting, which reduce their therapeutic efficacy and hinder SDT development.<sup>69</sup> Conversely, while inorganic sonosensitizers often demonstrate better chemical stability and water solubility, they may have different activation mechanisms and generally produce lower levels of ROS compared to their organic counterparts. Inorganic sonosensitizers may include materials like metal oxides, which can also be activated by US to generate ROS, albeit through different pathways, such as electron-hole pair generation.<sup>54,55,70</sup>

Organic sonosensitizers can be categorized into four types: porphyrin derivatives, cyanine derivatives, nanoliposomal sonosensitizers, and semiconducting polymer sonosensitizers. These compounds offer several advantages, including high

biocompatibility, excellent biodegradability, strong tumor-targeting potential, and ease of metabolism by the liver or kidneys in living organisms, making them highly promising for biomedical applications.<sup>53,71</sup>

Porphyrin derivatives have been extensively used in SDT due to their strong activity under ultrasonic stimulation. Hematoporphyrin (HP), the first sonosensitizer identified among porphyrins, was found to synergistically inhibit tumor growth through the production of singlet oxygen ( $^1\text{O}_2$ ) when ultrasonically activated. Since then, various porphyrins and their analogs, including hematoporphyrin monomethyl ether (HMME), protoporphyrin IX (PpIX), chlorin e6 (Ce6), sinoporphyrin sodium (DVDMS), tetra- $\alpha$ -(3-carboxyphenoxy) zinc(II) phthalocyanine (ZnPcC4), and di-sulfo-di-phthalimidomethyl phthalocyanine zinc (ZnPcS2P2), have been utilized in SDT.<sup>72–75</sup> Porphyrin-derived sonosensitizers possess an 18- $\pi$  aromatic macrocycle carbon core structure and are highly effective at generating ROS under US irradiation. Nevertheless, their application in SDT is significantly limited by their poor water solubility, biosafety concerns, and low tumor-targeting efficiency, necessitating the development of porphyrin-based nanomedicines with enhanced circulation and targeting capabilities.<sup>67,76</sup>

Recently, cyanine-based organic sonosensitizers, including indocyanine green (ICG), IR780, trifluoromethyl-heptamethine cyanine, and platinum(II)-cyanine complexes, have been applied in cancer sono-immunotherapy.<sup>77–79</sup> Heptamethine cyanine dyes are small organic molecules characterized by heterocyclic nitrogen atoms at both ends and a long conjugated methine chain, with strong absorption bands in the 700–900 nm range.<sup>68</sup> Indocyanine green (ICG), the first heptamethine cyanine dye approved by the US Food and Drug Administration (FDA) for use in angiography, offers significant benefits for clinical diagnostics and scientific research.<sup>80</sup> Moreover, newly developed heptamethine cyanine dyes, such as IR780, IR783, IR808, and MHI-148, exhibit a high molar absorption coefficient, strong fluorescence quantum yield, and excellent sonodynamic properties,<sup>81</sup> making them highly promising in the development of sonosensitizers and photothermal agents (PTAs).<sup>82</sup> However, due to poor biocompatibility, introducing trifluoromethyl groups, which enhance membrane permeability, metabolic stability, and bioavailability, may be necessary.<sup>83</sup>

Semiconducting polymer nanoparticles (SPNCs), a novel class of organic sonosensitizers derived from highly  $\pi$ -electron delocalized semiconducting polymers, exhibit high biocompatibility, significant chemical flexibility, and adjustable sizes.<sup>84</sup> SPNCs have been studied for various biomedical applications, such as optical imaging,<sup>85</sup> phototherapy, and biological regulation.<sup>86</sup> An SPNC that synergistically enhances tumor penetration and alleviates tumor hypoxia has been reported for SDT in large solid tumors. This SPNC consists of a semiconducting polymer nanoparticle core coated with polyethylene glycol as a sonodynamic converter. Catalase, an oxygen-modulating enzyme, is efficiently conjugated to the nanoparticle surface via a coupling reaction. The smallest SPNC (SPNC1) efficiently penetrates tumor tissue, alleviates hypoxia, and generates sufficient singlet oxygen to eradicate tumor cells at deep tissue levels upon US irradiation, significantly improving antitumor efficacy.<sup>53,65,87,88</sup>

Nanoliposomes, often selected as carriers, are essential for improving the bioaccumulation and stability of sonosensitizers at target sites. Composed primarily of phospholipids with bilayer structures, nanoliposomes are efficient drug carriers. For instance, liposome-encapsulated artemether (LEA) has shown notable sonodynamic anticancer activity.<sup>89,90</sup> Compared to artemether alone, SDT mediated by LEA demonstrated a stronger antiproliferative effect on HepG2 cells. In another innovative study, Li et al designed a liposome-microbubble complex loaded with the sonosensitizer DVDMS (DLMBs) to target breast cancer. Under US-induced cavitation, DLMBs released their payload, enhancing DVDMS cellular uptake and tumor penetration, thereby improving SDT efficacy.<sup>67,91</sup> Table 1 outlines the various categories of organic sonosensitizers.

### Inorganic Sonosensitizer-Based SDT

Inorganic materials demonstrate rapid metabolism, low toxicity, and high stability compared to organic materials. Their unique structures, compositions, and multifunctionality make inorganic micro- and nanomaterials a promising platform for SDT. Sonosensitizers are classified into two categories based on their primary components: metal-based and non-metallic.

TiO<sub>2</sub> nanoparticles are widely used in food, cosmetic, energy, and environmental protection industries because of their semiconductor properties. Their narrow bandgap (3.2 eV) and excellent biocompatibility make them suitable for a variety of applications. When exposed to UV irradiation, electrons in the valence band of TiO<sub>2</sub> nanoparticles are excited



**Table I** Categories of Organic Sonosensitizers

Category	Sonosensitizer	Key Features	Limitations
<b>Porphyrin Derivatives</b>	Hematoporphyrin, HMME, PpIX, Ce6, DVDMS, ZnPcC4, ZnPcS2P2	High ROS generation capability under ultrasound (US), 18- $\pi$ aromatic macrocycles, excellent sonodynamic activity	Poor water solubility, high biosafety concerns, low tumor-targeted accumulation
<b>Cyanine Derivatives</b>	ICG, IR780, trifluoromethyl-heptamethine cyanine, platinum(II)-cyanine complex	Intense absorption bands in 700–900 nm, approved for clinical use, high molar absorption coefficient, good sonodynamic activity	Poor biocompatibility, need for modifications to improve membrane permeability and metabolic stability
<b>Semiconducting Polymeric nanoparticles</b>	SPNCs	High biocompatibility, high chemical flexibility, tunable sizes, efficient tumor penetration, alleviates tumor hypoxia	Complex synthesis process, need for optimization in clinical applications
<b>Nanoliposome Sonosensitizers</b>	LEA, DLMBs	Enhances bioaccumulation and stability of sonosensitive molecules, effective drug carriers, improved antiproliferative effect	Potential for immune response, stability of encapsulated drugs, scalability of production

**Abbreviations:** HMME, hematoporphyrin monomethyl ether; PpIX, protoporphyrin IX; Ce6, Chlorin e6; DVDMS, sinoporphyrin sodium; ZnPcC4, tetra- $\alpha$ -(3-carboxyphenoxy) zinc(II) phthalocyanine; ZnPcS2P2, di-sulfo-di-phthalimidomethyl phthalocyanine zinc; ICG, indocyanine green; IR780, trifluoromethyl-heptamethine cyanine; SPNCs, Semiconducting polymer nanoparticles; LEA, Liposome-encapsulated artemether; DLMBs, DVDMS-loaded microbubbles.

to the conduction band, where they interact with surrounding oxidizing agents ( $O_2$  and  $H_2O$ ) to generate reactive oxygen species (ROS), such as  $\bullet OH$ ,  $O_2^-$ ,  $H_2O_2$ , or other active substances. This property has led to their use in tumor photodynamic therapy. However,  $TiO_2$  nanoparticles activated by UV irradiation have limited tissue penetration, restricting their photodynamic therapy applications. Recent studies have shown that  $TiO_2$  nanoparticles activated by US effectively kill tumor cells, resulting in extensive research into their use as key sonosensitizers.<sup>92</sup> GNR-PEG, a commonly used photosensitizer, underscores the potential of  $TiO_2$  nanoparticles as sonosensitizers, as they are generally non-toxic to experimental cells or animals.<sup>93</sup> However, bare  $TiO_2$  nanoparticles are unstable and tend to be cleared rapidly by the reticuloendothelial system, which limits their accumulation in tumor areas and reduces their therapeutic efficacy. To address this issue, surface modifications using high-polymer materials such as proteins, glucans, and polyionic complexes have been implemented to enhance their stability. Moreover, biomimetic cell membrane-based nanocomposite structures have been developed to improve both stability and tumor-targeting ability. By coating nanoparticles with cancer cell membranes (CM), a C- $TiO_2$ /TPZ@CM composite sonosensitizer was created, enabling tumor targeting through homologous binding via CM components.<sup>94</sup>

In addition to  $TiO_2$  nanoparticles, transition metal oxide nanomaterials can also serve as sonosensitizers when activated by US irradiation. Nanoparticles of transition metal oxides, such as  $Fe_3O_4$  (magnetite) and  $Fe_2O_3$  (maghemite), have garnered significant attention due to their superparamagnetic properties and role in Fenton reactions.<sup>95</sup> To improve therapeutic outcomes, Shen et al developed a core-shell sonosensitizer comprising an  $Fe_3O_4$  nanoparticle core and a  $TiO_2$  shell loaded with doxorubicin (DOX). The  $Fe_3O_4@TiO_2$ -DOX nanoparticles generated substantial amounts of ROS for SDT.<sup>96</sup> Under US irradiation, the nanostructure released DOX, which synergistically worked with SDT to destroy cancer cells. A recent study reported a sonosensitizer (MnWOx-PEG) that demonstrated highly efficient US-triggered production of  $^1O_2$  and  $\bullet OH$ .<sup>97</sup>

Noble metal nanoparticles, such as Au, Ag, and Pt, have also gained attention as effective sonosensitizers due to their stability, water solubility, lack of skin photosensitivity, and inherent acoustic cavitation properties. Incorporating noble metals such as Au, Ag, and Cu into nanomaterials enhances SDT efficacy by reducing electron-hole recombination and increasing ROS production.<sup>98</sup> Among these, Au nanoparticles are notable for their remarkable sonodynamic activity, biocompatibility, adjustable surface properties, and efficient photothermal conversion, making them a focus of sonosensitizer research.<sup>57,99</sup> These metals naturally promote cavitation under US irradiation, with Au nanoparticles being particularly advantageous for cancer therapy due to their ease of synthesis and surface modifiability. Recent studies have highlighted the acoustic cavitation effects of Au nanoparticles on colon cancer, showing that the uneven surfaces of these nanoparticles act as nucleation sites for

cavitation, reducing the cavitation threshold.<sup>100</sup> Modifications of Au nanoparticles, such as functionalization with  $\delta$ -aminolevulinic acid (ALA) or PPIX, have been shown to significantly boost therapeutic efficacy by increasing singlet oxygen production and enhancing the SDT effect through plasmon resonance and cavitation.<sup>101,102</sup> The various categories of inorganic sonosensitizers are summarized in Table 2. Compared to organic sonosensitizers, inorganic alternatives offer enhanced biocompatibility, stability, and multifunctionality, with their distinct chemical and physical properties enabling synergistic combinations that significantly improve SDT effectiveness.

Therefore, developing biocompatible sonosensitizers with robust ROS generation capabilities remains essential. Innovations in sonosensitizer design aim to overcome current limitations by combining the strengths of both inorganic and organic materials, enhancing ROS production while improving stability, solubility, and tumor-targeting efficiency.

### Organic-Inorganic Hybrid Sonosensitizer-Based SDT

The utilization of organic-inorganic hybrid sonosensitizers in SDT confers distinctive advantages, primarily due to their capacity to augment ROS generation, enhance biocompatibility, and maintain stability under physiological conditions. These hybrid materials are composed of both organic and inorganic components, offering a unique combination of properties. Organic sonosensitizers are typically renowned for their high biocompatibility and reduced systemic toxicity. However, they may exhibit limitations in ROS generation and stability. Inorganic components, such as metal-based nanoparticles, address these limitations by enhancing ROS production and improving the overall stability of the system. This combination enables a more controlled and efficient therapeutic response in cancer treatment. One experimental example of this approach is the use of metal-organic frameworks (MOFs), which have demonstrated promising results in enhancing the therapeutic efficacy of SDT. MOF-based hybrid sonosensitizers exploit the structural characteristics of inorganic metals to generate a substantial ROS response under US activation, while simultaneously benefiting from the biocompatibility of organic ligands. A study utilizing MOF sonosensitizers demonstrated enhanced ROS generation and prolonged retention in tumor tissues, resulting in improved tumor suppression in vivo models.<sup>103,104</sup> Similarly, hollow mesoporous organosilica nanoparticles (HMONs) have also shown significant potential as organic-inorganic hybrid sonosensitizers. In one study, HMONs were loaded with protoporphyrin IX (PpIX) as the organic sonosensitizer and doxorubicin (DOX) as the chemotherapeutic agent. The hybrid system took advantage of the high surface area and mesoporous structure of HMONs, leading to enhanced ROS production under US irradiation. Furthermore, the organic components improved biocompatibility and responsiveness to the tumor microenvironment, while the inorganic silica matrix provided structural stability and controlled drug release. This combined approach resulted in synergistic effects in both in vitro and in vivo models, significantly improving tumor suppression through the dual action of SDT and chemotherapy.<sup>105</sup> This demonstrates how hybrid materials not only bridge the gap between organic and inorganic sonosensitizers but also significantly enhance therapeutic outcomes in SDT applications. Table 3 outlines the comparing organic, inorganic, and organic-inorganic hybrid sonosensitizers with detailed focus on ROS generation capacity, biocompatibility, flexibility and toxicity.

**Table 2** Categories of Inorganic Sonosensitizers

Category	Sonosensitizer	Key Features	Limitations
<b>Metal-based Sonosensitizers</b>	TiO <sub>2</sub> nanoparticles	High ROS generation under US, good biocompatibility, used in tumor photodynamic therapy	Limited tissue penetration under UV activation, easy electron-hole recombination, poor stability without surface modification
<b>Transition metal oxides</b>	Fe <sub>3</sub> O <sub>4</sub> , Fe <sub>2</sub> O <sub>3</sub> , MnWO <sub>x</sub>	Superparamagnetic properties, Fenton reaction, can be combined with other materials to enhance ROS production	Complex synthesis and stability issues, potential toxicity
<b>Noble metal nanoparticles</b>	Au, Ag, Pt, Cu-based nanoparticles	Exceptional stability, water solubility, intrinsic acoustic cavitation properties, high biocompatibility, efficient photothermal conversion	High cost, the potential for aggregation, requires surface modifications for optimal use

**Abbreviations:** TiO<sub>2</sub>, titanium dioxide; Fe<sub>3</sub>O<sub>4</sub>, magnetite; Fe<sub>2</sub>O<sub>3</sub>, maghemite; MnWO<sub>x</sub>, Manganese oxide catalyst.

**Table 3** Comparison of Organic, Inorganic, and Organic-Inorganic Hybrid Sonosensitizers

Category	Organic Sonosensitizers	Inorganic Sonosensitizers	Organic-Inorganic Hybrid Sonosensitizers
<b>ROS Generation Capacity</b>	Moderate (limited ROS generation)	High (strong ROS generation from metal nanoparticles)	High (enhanced ROS from combined organic-inorganic components)
<b>Biocompatibility</b>	High (derived from natural molecules, low toxicity)	Moderate (metal-based nanoparticles, potential toxicity)	High (improved biocompatibility due to organic component)
<b>Stability</b>	Low (rapid degradation, poor stability in vivo)	High (chemically stable, slow degradation in the body)	High (enhanced stability from inorganic components)
<b>System Design Flexibility</b>	Limited (difficult to modify structure)	High (wide range of inorganic nanoparticle designs)	High (flexible design, enhanced functionality through combination)
<b>Toxicity</b>	Low (derived from natural materials, low systemic toxicity)	Moderate (potential toxic by some metal nanoparticles)	Moderate (toxicity from inorganic part, mitigated by organic component)

## Comparison Between SDT and PDT

SDT and PDT are innovative cancer treatments that differ significantly in their mechanisms and applications. PDT relies on light activation to generate ROS, requiring direct light exposure and being heavily dependent on tissue oxygen levels.<sup>15,17,19,106</sup> This dependence limits the effectiveness of PDT in treating deep-seated tumors and hypoxic tumor environments, where light penetration and oxygen are insufficient. In contrast, SDT uses US waves, which can penetrate deeper into tissues and are less reliant on oxygen, making it particularly effective in treating deep-seated and hypoxic tumors (Figure 3).<sup>107,108</sup>

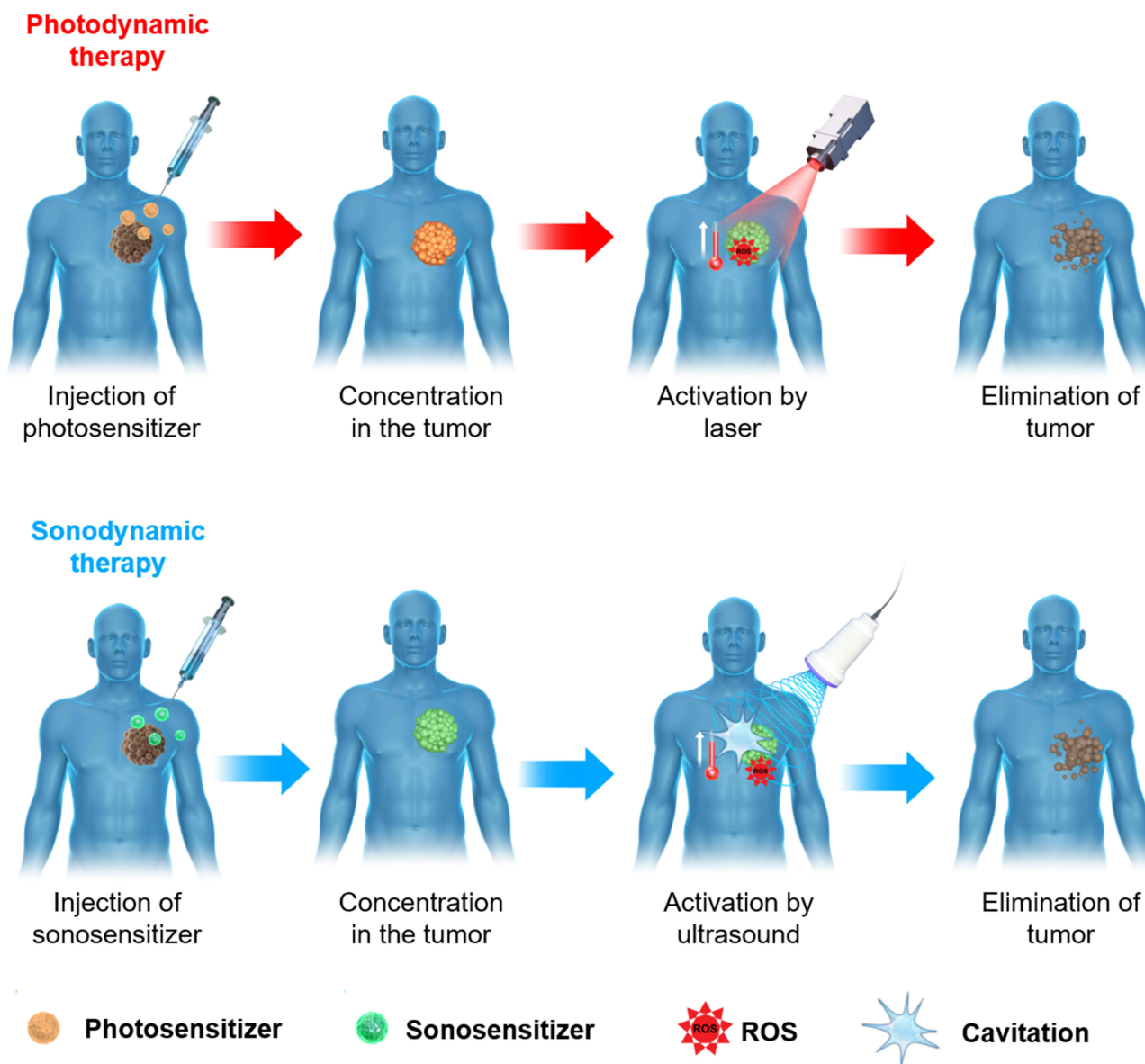
In SDT, US waves induce thermal effects through a process known as cavitation, where the rapid collapse of bubbles results in localized high temperatures and pressures, leading to cellular damage and necrosis. Similarly, PDT can also produce thermal effects; light-activated photosensitizers generate localized heat, along with ROS, both contributing to tumor cell destruction.<sup>109,110</sup>

Both PDT and SDT effectively destroy tumor cells through their distinct mechanisms.<sup>111</sup> However, the ability of SDT to produce ROS with minimal oxygen dependence gives it a clear advantage in hypoxic tumor environments where PDT may be less effective. The combination of chemical damage (via ROS generation) and physical damage (through thermal and mechanical effects) makes SDT a highly adaptable and potent therapeutic option.<sup>112,113</sup> Furthermore, SDT can be enhanced using targeted delivery systems to increase specificity and minimize side effects. Significant advancements have been made in developing sonosensitizers activated specifically by US.<sup>26</sup> These sensitizers can be tailored to target tumor cells more accurately, optimizing therapeutic outcomes while reducing damage to healthy tissues. Although PDT also uses photosensitizers to target tumor cells, its efficacy is limited by the need for light exposure and adequate oxygen levels.<sup>114</sup>

In summary, while PDT is well-suited for treating superficial tumors via light activation, SDT offers a more versatile treatment approach that can penetrate deeper into tissues and function effectively in hypoxic conditions. Ongoing research and technological advancements are expected to refine SDT further, leading to improved patient outcomes and expanding the potential of this promising cancer therapy. The following sections explore combination therapy strategies and their potential to enhance cancer treatment by integrating the mechanisms of SDT and PDT. Leveraging their complementary strengths may yield a more comprehensive and effective cancer treatment approach, offering new hope for managing challenging tumor types.

## SDT-Derived Synergistic Therapy

Cancer is a heterogeneous disease characterized by rapid and uncontrolled progression, making it difficult for SDT alone to effectively suppress tumors. Consequently, the approach to SDT-based cancer therapy has shifted from monotherapy to multimodal therapy to enhance treatment effectiveness.<sup>115</sup> Comprehensive treatment strategies are being developed by combining SDT with chemotherapy, PTT, and immunotherapy, aiming to overcome the limitations of monotherapy and offer more effective, long-lasting cancer treatments (Table 4). The synergistic potential of these multimodal therapies



**Figure 3** A general outline of photodynamic therapy (PDT) and sonodynamic therapy (SDT) in cancer treatment involves the administration of photo- and sonosensitizers, which can be delivered throughout the body or directly into the tumor. Activation occurs via laser for PDT and ultrasound for SDT, leading to the reduction or, ideally, complete elimination of cancerous tissue.

shows great promise for improving clinical outcomes and enhancing the quality of life for cancer patients. Clinical trials have investigated the combination of SDT with these treatment modalities, yielding promising results in improving therapeutic efficacy and minimizing side effects. For example, the integration of SDT with chemotherapy has led to

**Table 4** Synergistic Effects of SDT-Derived Therapies with Chemotherapy, Photothermal Therapy, and Immunotherapy

Synergistic Treatment	Mechanism of Action	Key Advantages	Unique Feature
<b>Chemotherapy</b>	Enhances drug delivery via sonoporation	Lowers drug dose and side effects	Overcomes drug resistance
<b>Photothermal Therapy</b>	Heat combined with SDT-induced ROS	Improves tumor destruction	Dual effect: Heat and ROS
<b>Immunotherapy</b>	Stimulates immune response with ROS	Boosts immune system activation	Supports long-term immune memory

increased drug uptake and improved tumor reduction in preclinical models.<sup>116</sup> Similarly, combining SDT with PTT has demonstrated synergistic effects in tumor ablation, while adding immunotherapy has been found to enhance the anti-tumor immune response, potentially leading to more sustained cancer control.<sup>117,118</sup>

## SDT Combination with Chemotherapy

Despite the significant benefits that many chemotherapeutic regimens have provided to patients in recent years, the increasingly recognized adverse effects resulting from the off-target actions of conventional chemotherapy have spurred the search for more effective treatment options. Even highly targeted molecular therapies have exhibited off-target effects that contribute to the development of drug resistance.<sup>119,120</sup> SDT can enhance the uptake of chemotherapeutic drugs into cancer cells and promote their distribution throughout poorly vascularized solid tumors due to its sonoporation effect. As a result, SDT plays a crucial role in sensitizing tumors to chemotherapy, allowing for a reduced dose of the chemotherapeutic drug to achieve a cytotoxic effect.<sup>121</sup>

Liu et al designed multifunctional nanoparticles (HPDF) with a core-shell structure incorporating hematoporphyrin (HP, a sonosensitizer), doxorubicin (DOX), and pluronic F68 as the encapsulation agent.<sup>122</sup> The hydrophobic components, HP and DOX, formed the core of the nanoparticles through  $\pi$ - $\pi$  stacking, while the hydrophilic pluronic F68 created the shell. The average diameter of the HPDF nanoparticles was approximately 87.9 nm, enabling them to accumulate in tumors via enhanced permeability and retention (EPR) effects. Pluronic F68 inhibits the efflux activity of adenosine triphosphate (ATP)-binding cassette transporters by depleting ATP,<sup>123</sup> which increases the sensitivity of multidrug-resistant HepG2 cells to DOX. Additionally, when combined with SDT, the resulting ROS damage the mitochondria, further reversing multidrug resistance by downregulating ATP levels.<sup>124</sup> The viability of HepG2 cells was almost eliminated by the combined effects of DOX-induced DNA damage and ROS production from HP-mediated SDT. Consequently, the growth of HepG2-derived tumors in mice was significantly inhibited following intravenous injection of HPDF nanoparticles and subsequent US irradiation.<sup>52</sup>

O<sub>2</sub>-loaded microbubbles (O<sub>2</sub>MB) can act as carriers for delivering sonosensitizers (RB) and antimetabolic drugs (5-fluorouracil, 5-FU). Callan et al developed O<sub>2</sub>MB-RB and O<sub>2</sub>MB-5-FU using avidin-biotin binding interactions.<sup>125</sup> The combined SDT and antimetabolite treatment produced significant cytotoxic effects in three different pancreatic cancer cell lines, with similar results observed in a xenograft mouse model. Therefore, O<sub>2</sub>MB-based therapy, when combined with antimetabolite drugs, may enhance the efficiency of SDT and reduce the side effects associated with systemic antimetabolite administration.

Gemcitabine, a widely used antineoplastic agent, is particularly effective in treating pancreatic cancer and is suitable for encapsulation within O<sub>2</sub>MB nanoparticles. Both *in vitro* and *in vivo* studies have demonstrated that chemo-SDT following the US-targeted microbubble destruction (UTMD) of O<sub>2</sub>MB-Gem and O<sub>2</sub>MB-RB serves as an effective and targeted approach for treating pancreatic cancer.<sup>126</sup> Moreover, the biosafety of O<sub>2</sub>MB-Gem was assessed in a healthy mouse model, with no significant renal or hepatic damage observed. The inclusion of superparamagnetic iron oxide nanoparticles (MAG-Lipid) in the preparation of O<sub>2</sub>MB resulted in the creation of magnetically responsive microbubbles (MagO<sub>2</sub>MBs), which were used to deliver RB and 5-FU to pancreatic tumors. The application of an external magnetic field to the tumor site enhanced the accumulation of MagO<sub>2</sub>MB-RB and MagO<sub>2</sub>MB-5-FU in the tumor regions, further improving the therapeutic effect of the combined chemotherapy and SDT regimen.<sup>127</sup>

## SDT Combination with PTT

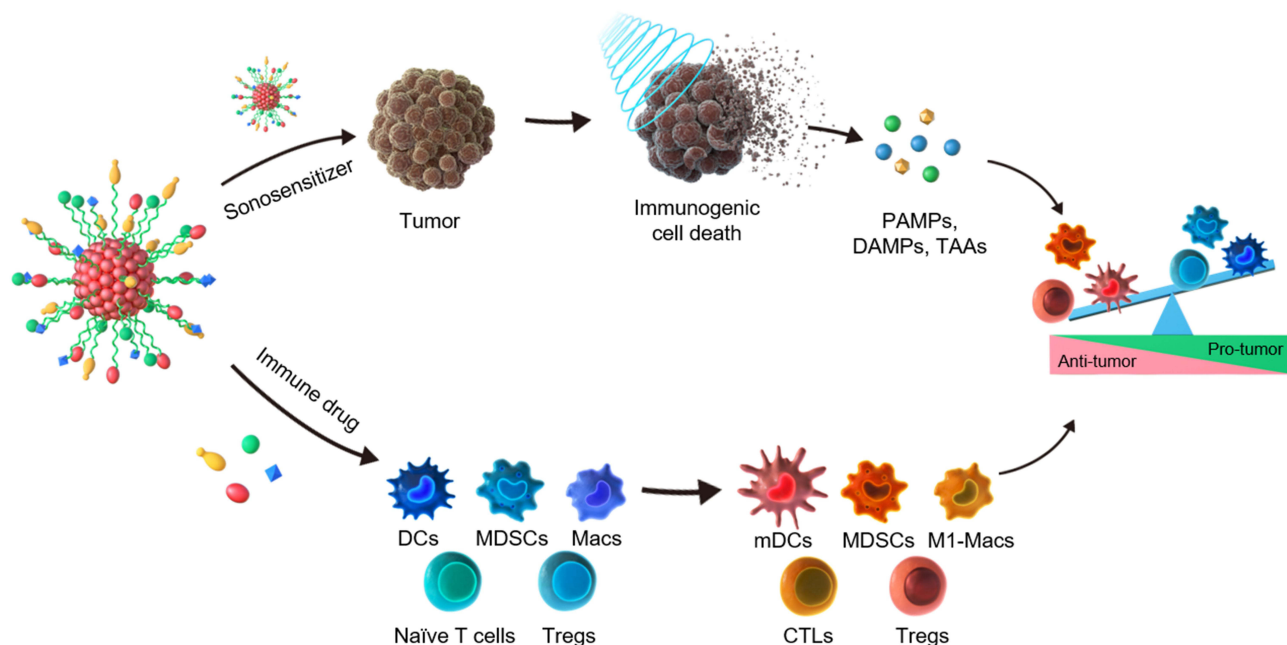
NIR-responsive photosensitizers have been widely applied in PDT to address penetration depth issues; however, the efficiency of PDT in deep-seated tumors still requires improvement.<sup>128</sup> For skin tumors, necrotic epidermis and deposited pigments can further reduce light penetration, diminishing the therapeutic efficacy of PDT.<sup>129</sup> The combination of SDT and PDT can overcome these challenges by utilizing the deep penetration of US. When SDT is enhanced by catalysis and combined with photothermal effects, it nearly achieves complete tumor inhibition while maintaining a favorable biosafety profile.<sup>130</sup> For example, combining SDT with PDT takes advantage of the deep tissue penetration of US and the surface-targeting abilities of light-based therapy, potentially addressing the limitations of each method when used alone.<sup>117</sup> Innovative approaches, such as mesoporous silica nanoparticles activated by HIFU, are being developed to

enhance US applications and generate substantial thermal effects for tumor ablation.<sup>131</sup> Furthermore, recent studies have utilized biodegradable PLGA as a carrier to encapsulate ICG and HP, forming NPs with an average diameter of 200–270 nm for SDT and PDT. Cytotoxic effects of these NPs were observed both in vitro and in vivo, with spectrophotometric analysis confirming efficient HP and ICG encapsulation.<sup>132</sup>

There is growing recognition that combining SDT with PTT or PDT, which generates both toxic ROS and heat, can effectively lower the required concentration of sensitizers while enhancing tumor cytotoxicity. Studies have reported the initial combination of SDT and PTT using AuNPs as sensitizers, with tumor-bearing mice showing significantly longer survival times when treated with NIR, US, and Au nanoparticles, compared to those receiving only monotherapy (NIR or US).<sup>133,134</sup> Encouraged by these promising results, numerous sonosensitizers with strong photothermal conversion capabilities have been developed over recent decades. Gao et al reported a TiO<sub>2</sub>-coated Au nanoplate (Au NPL@TiO<sub>2</sub>) for synergistic PTT/SDT therapy.<sup>135</sup> Modifying TiO<sub>2</sub> shells on the surface of 2D Au NPLs led to Au NPL@TiO<sub>2</sub> nanoagents displaying a red shift in the optical window from the NIR I to the NIR II region, achieving a remarkable photothermal conversion efficiency of 42.05% under 1064 nm laser irradiation. These metal-semiconductor nanoagents created a charge transfer channel at the Au NPL@TiO<sub>2</sub> interface, effectively suppressing the recombination of electrons (e<sup>-</sup>) and holes (h<sup>+</sup>) generated by TiO<sub>2</sub> under US, thus significantly enhancing ROS production (1.5 W cm<sup>-2</sup>, 3 MHz). This synergistic anticancer treatment reduced cell viability to 20.3% in vitro and eliminated tumors in vivo.<sup>135</sup> The combination of PTT and SDT has demonstrated superior anticancer efficacy under laser and US irradiation. Therefore, it is crucial to develop technologies that achieve the combined therapeutic effects of SDT and PTT while maintaining low toxicity, efficient targeting, and high photothermal-sonodynamic conversion.<sup>68</sup>

## SDT-Enhanced Immunotherapy

Emerging research has highlighted the immunomodulatory effects of SDT. By inducing localized tumor destruction and releasing tumor antigens, SDT has the potential to stimulate an immune response against the tumor, paving the way for its combination with immunotherapy to improve overall treatment outcomes (Figure 4).<sup>24</sup> In immunotherapy, SDT can be leveraged as immune cells, including T lymphocytes, dendritic cells, and macrophages, play crucial roles in anti-tumor



**Figure 4** The mechanism of cancer sono-immunotherapy involves two key processes: (i) sonosensitizer-mediated SDT, which induces immunogenic cell death (ICD) and the release of damage-associated molecular patterns (DAMPs), pathogen-associated molecular patterns (PAMPs), and tumor-associated antigens (TAAs); and (ii) immunology drug-mediated remodeling of the tumor immune environment (TIEM), including dendritic cell (DC) maturation, activation of cytotoxic T lymphocytes (CTLs), inhibition of myeloid-derived suppressor cells (MDSCs), polarization of M1 macrophages (M1-Macs), and suppression of regulatory T cells (Tregs).

immunity through cellular immune mechanisms.<sup>136</sup> Studies have demonstrated that SDT promotes the activation and proliferation of immune cells in three key ways. First, SDT enhances T cell activation and improves antigen presentation, leading to more effective recognition and elimination of cancer cells. Second, SDT induces dendritic cells (DCs) activation and strengthens the anti-tumor immune response. Finally, the tumor debris generated by SDT triggers immune and anti-inflammatory responses, promoting the transition of alternatively activated M2 macrophages to the pro-inflammatory M1 phenotype, thereby enhancing the immune response.<sup>137–139</sup> These mechanisms primarily boost the immune system of the patients, aiding in the fight against cancer cells.

Research has confirmed that during SDT treatment, high levels of ROS are produced, which disrupt the mitochondrial membrane and reduce the mitochondrial membrane potential. In addition, ROS mediates apoptosis through the mitochondrial caspase pathway, releasing tumor antigens and promoting cytotoxic T lymphocyte (CTL) infiltration.<sup>54,61–63</sup>

Studies have shown that SDT enhances the immune response against tumors by inducing immunogenic cell death (ICD) and releasing tumor-associated antigens.<sup>140–142</sup> ICD results from damage-associated molecular patterns (DAMPs), a group of highly immunostimulatory signals. These DAMPs interact with their respective receptors, leading to immune cell activation. For instance, extracellular ATP generates “find me” signals that promote the rapid recruitment of antigen-presenting cells (APCs) to apoptotic tumor cells. HMGB1 binds to Toll-like receptor 4, aiding APCs in presenting tumor antigens to T cells. Additionally, calreticulin (CRT) is transported to the surface of tumor cells, producing “eat me” phagocytic signals that prompt phagocytes, such as dendritic cells, to recognize and engulf cancer cells. ICD induced by SDT and the resulting tumor cell lysates can elicit a robust immune response.<sup>143–145</sup>

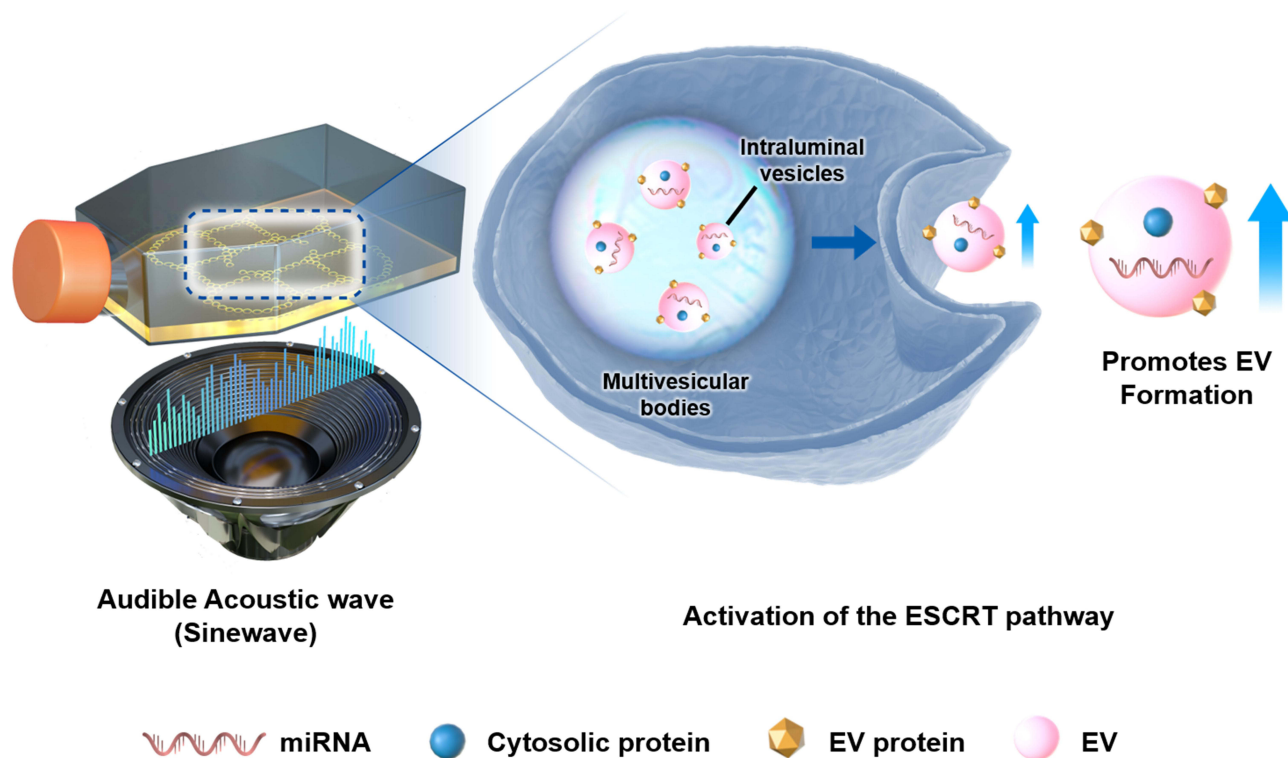
## Application of Audible Sound waves in Biological Systems

US for SDT has primarily been studied in the frequency range above 20 kHz. However, there are limited reports on the use of sound waves within the audible frequency range for SDT. Researchers are increasingly exploring the potential of audible sound waves for various biological and biomaterial applications.<sup>146,147</sup>

Recent studies have shown that sound waves in the audible range can create temporal patterns and gradients in the domains of glucose oxidase (GOx) and horseradish peroxidase (HRP) in solution, thereby regulating cascade reaction networks.<sup>148</sup> This approach can precisely position temporally formed supramolecular aggregates in solution, addressing a challenge that has largely remained elusive in out-of-equilibrium self-assembly and systems chemistry. Additionally, experimental results demonstrated that the formation and aggregation of gold nanoparticles (AuNPs) could be guided to desired locations within hydrogels using acoustic waves, promoting cell growth at specific sites. This suggests an innovative method for spatially and temporally controlling chemical reactions using acoustic waves.<sup>149</sup>

There have also been reports of audible sounds affecting cell-to-cell interactions. Surface acoustic waves (SAW) have been investigated for their ability to regulate intercellular interactions. In one study, HEK 293T cells were arranged in a linear array using the gap junctional coupling-forming calcein-AM dye. The findings revealed that the greater the number of cells, the longer it took for the dye to reach the terminal cells of the linearly arranged group, demonstrating that SAW can precisely control cell positioning to regulate intercellular distance and spatial arrangement.<sup>150,151</sup>

Research has shown that audible acoustic waves (AAWs) stimulate the formation and secretion of extracellular vesicles (EVs) in cancer cells. To verify the enhancement of EV formation under AAW conditions, we measured the relative expression of EV markers such as Calnexin, CD63, CD81, and TSG101. Our findings indicated that the size and distribution of EVs produced under AAW conditions were similar to those generated under static conditions. Additionally, AAWs increased EV production by promoting membrane fusion through the regulation of gene translation, particularly via the ESCRT (endosomal sorting complex required for transport) pathway and upregulation of membrane fusion-associated proteins. These EVs were found to contribute to cancer cell migration and invasion, providing new insights into cancer metastasis research.<sup>152</sup> Another study found that high-frequency acoustic stimulation of cells promotes exosome release in a calcium-dependent manner. These results suggest that acoustic waves enhance exosome production, which is crucial for intercellular communication. This process involves the regulation of intracellular calcium levels, indicating that acoustic stimulation may be an effective method for manipulating exosome generation and influencing cellular communication and signaling pathways. Furthermore, research has demonstrated that audible sound stimulation can selectively suppress mechanosensitive genes depending on the cell type. Various sound



**Figure 5** The schematic diagram illustrates the methodology using audible acoustic waves (AAWs) to enhance extracellular vesicle (EV) production. The speaker emits audible acoustic waves that induce mechanical stimulation of the cells. The process of EV formation and secretion within the cell is depicted, showing that mechanical stimulation generated by AAWs promotes this process.

parameters, including frequency, waveform, and sound pressure levels, were tested on different cell types. The study showed that ST2 stromal cells and C2C12 myoblasts exhibited strong responses to sound waves, while NIH3T3 fibroblasts and NB2a neuroblastoma cells showed partial or no responses. These findings suggest the potential of using audible sound as a non-invasive tool for the targeted modulation of gene expression and cellular functions (Figure 5).<sup>153,154</sup>

Integrating these findings illustrates that the application of sound waves in the audible range can significantly influence various biological processes, including EV formation, gene expression suppression, and exosome release. These insights offer promising avenues for further research and potential clinical applications in fields such as cancer treatment, gene therapy, and modulation of cellular communication.

## Conclusion and Future Perspective

In summary, the integration of nanotechnology with US-based therapy represents a significant advance in both basic research and clinical applications.<sup>155,156</sup> NP-associated sonosensitizers, particularly those incorporating valuable organic, inorganic and organic-inorganic hybrid sonosensitizers, have shown great promise in enhancing the efficacy of SDT due to their superior stability, solubility, and acoustic cavitation properties.<sup>66,67,157</sup> These US-activated sonosensitizers can work synergistically with US waves to achieve targeted therapeutic effects with fewer side effects than conventional therapies. Furthermore, they can be combined with established cancer therapies such as chemotherapy, photothermal therapy, and immunotherapy to achieve synergistic effects.<sup>158–160</sup> This review has highlighted the significant progress made in nanomedicine-enhanced US therapy, particularly the interplay between US applications and nanoscience, which has advanced our understanding of SDT mechanisms and its applications in disease treatment. Despite these advances, several issues still need to be addressed.<sup>67,161</sup> One primary concern is the toxicity of certain sonosensitizers, particularly inorganic and hybrid nanomaterials, which can exhibit long-term cytotoxicity. Further evaluation of the biocompatibility and clearance mechanisms of these agents is essential to mitigate potential side effects. Additionally, the long-term



stability of sonosensitizers in physiological conditions is crucial for ensuring sustained treatment efficacy, especially in chronic conditions. Another significant challenge lies in the translation from preclinical to clinical settings, as the success observed in animal models may not directly translate to human trials due to the complexity of the human tumor microenvironment. Optimizing treatment parameters such as ultrasound frequency, intensity, and exposure duration will be crucial for successful clinical translation. Moreover, developing more precise sonosensitizer delivery systems capable of deep tissue targeting remains a critical area of research.

To advance the clinical application of sonotherapy, the following points must be addressed. First, the long-term biological stability of SDT should be thoroughly evaluated.<sup>161</sup> The results so far are preliminary, based on short-term toxicity data from mice, which are insufficient to predict outcomes in humans.<sup>158</sup> A new standard evaluation protocol is needed to obtain comparable clinical data. Current US therapy equipment is complex, requiring hospital visits, and developing more user-friendly, precise systems remains a key challenge. Furthermore, a sonosensitizer that can be mass-produced while maintaining high quality is needed for realistic clinical applications.<sup>66</sup> Production quality and cost control are also essential considerations for achieving large-scale clinical application.<sup>110</sup> Moreover, the intrinsic mechanisms of US-responsive sonosensitizers in disease treatment remain poorly understood, complicating the regulation of SDT efficacy. Advances in biological, medical, and chemical research may optimize the performance of sonodynamic therapies and enhance their efficacy in treating diseases.<sup>162</sup> In particular, research on nanomaterials that respond to sound waves within the audible frequency range, which is currently underexplored, may open new areas of SDT research in the future.<sup>163</sup> Based on these considerations, efforts to complement and advance SDT for treating a wide range of intractable diseases, including cancer, will pave the way for breakthroughs that contribute to medical science and improve patient outcomes.

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## Disclosure

The authors report no conflicts of interest in this work.

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