Review Article

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Sinoporphyrin sodium, a novel sensitizer for photodynamic and sonodynamic therapy

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Abstract: Sinoporphyrin sodium (DVDMS) is a novel sensitizer discovered by Professor Fang Qi-Cheng and widely used in photodynamic (PDT) and sonodynamic therapy (SDT). We searched databases including PubMed, Web of Science, CNKI, etc. for system review of its progress. We found that, both DVDMS-PDT and -SDT had been proven effective for inhibiting tumor growth and mechanisms involved reactive oxygen species, autophagy, and mitochondrial apoptosis pathways. Material advances enhanced antitumor effects and expanded its application. The safety of DVDMS in animals was evaluated, and metabolic parameters were uncovered. Additionally, DVDMS-PDT also exhibited therapeutic effects on non-neoplastic diseases like psoriasis and bacterial infections. Two phase I clinical trials of DVDMS have been documented, but recruitments had still not been completed. In conclusion, DVDMS is a promising sensitizer for both PDT and SDT; however, there are some shortcomings in previous studies like inconsistent treatment parameters, which need systematic assessments in future. Moreover, more mechanisms such as the role of autophagy need to be discovered. Further evidence of the safety and effectiveness of new materials are needed, and the application in non-neoplastic diseases like actinic keratosis and fungal infection deserves further development. Above all, promoting its clinical applications is the most important goal.

Keywords: material advances, photodynamic therapy, safety and metabolism, sinoporphyrin sodium, sonodynamic therapy

1 Introduction

What is the future of photodynamic therapy (PDT)? The answer may be finding of novel photosensitizers. Photofrin is a typical example of the first-generation photosensitizer, and it was synthesized 40 years ago based on the studies of the natural photosensitizer hematoporphyrin derivatives (HpD) [1,2]. HpD are endogenous porphyrins produced by the hydrolysis of hemoglobin acid. There are remarkable advantages of Photofrin like higher safety and pharmacological effects compared with HpD [3–5]. However, there are still many shortcomings mainly because it is a polymer, and some of its components are ineffective and toxic [2,6]. Fang and his team [7] established a HPLC method for analyzing porphyrin photosensitizers and systematically analyzed Photofrin. More than 20 derivatives were discovered from Photofrin, and three sodium salts of the porphyrin dimer with ether bonds were proven to be the strongest photosensors [8]. Among the three isomer dimers, the second one was chosen as the target compound on account of its high yield and purity, and better solubility. This compound was named sinoporphyrin sodium (DVDMS, Figure 1), and subsequently the synthesis route was redesigned [8]. By contrast to Photofrin, DVDMS is characterized in defined structure with more effectivity and safety [9,10]. Therefore, the discovery process from HpD to Photofrin and then to DVDMS is a milestone in PDT.

The company Qinglong Hi-Tech Co., Ltd. (Yichun, Jiangxi, China) quickly showed interest in DVDMS. After working with this company, Fang achieved the mass production of DVDMS. Soon after, the antitumor effects of DVDMS-PDT and safety evaluations were completed, the efficacy of monomeric DVDMS was 10-fold stronger compared with Photofrin, and the toxicity was only increased by 2-fold, so the therapeutic window was greatly

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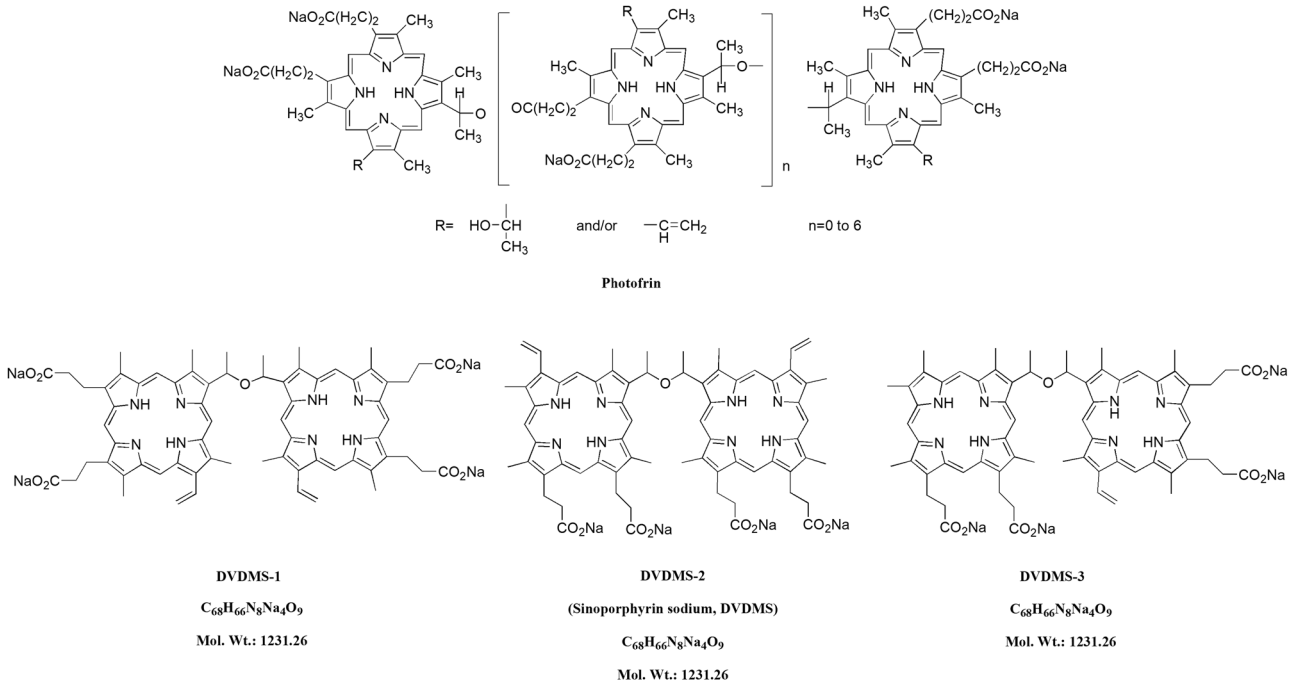

Figure 1: Structures of DVDMS and its isomer dimers. The three isomer dimers are derivates of photofrin.

increased [9–12]. Interestingly, DVDMS was subsequently found to be activated by ultrasound and its antitumor effects via sonodynamic therapy (SDT) were demonstrated [13–15]. On October 31, 2013, Qinglong Hi-Tech Co., Ltd. submitted applications to the China Food and Drug Administration (CFDA) to register DVDMS as a photosensitizer, sonosensitizer, and radiotherapy sensitizer (Nos. CXHL1300953; CXHL1300954), which were granted on April 8, 2015. Currently, DVDMS-mediated PDT and SDT have been proven effective on dozens of tumors in more than 40 preclinical studies, and two clinical trials have been registered (Nos. CTR20150690; CTR20150725). The details of these works are summarized below.

2 Antitumor effects of DVDMS-mediated PDT

To date, 21 human cancer cell lines from 12 types of human malignancies have been proven to be inhibited by DVDMS-PDT *in vitro* (Figure 2a); additionally, several mouse xenograft models have been used to confirm the antitumor effects of DVDMS-PDT *in vivo* (Figure 2b) [9,11,16–27]. The first report was published by Jiang et al. [11] in 2013, in which they proved that DVDMS-PDT significantly inhibited tumor proliferation both *in vitro* and *in vivo* using four cell lines and two xenograft models. One of the important contributions of this study was that they determined the optimal dose of DVDMS (0.5–2.0 mg/kg, i.v.) and PDT parameters (38–152 J/cm^2 at 24 h after administration) *in vivo*. Subsequent studies have followed these experimental conditions. Another study from this team [9] was similar but involved more tumor types.

Hu et al. revealed that the maximal uptake of DVDMS occurred within 3 h and that DVDMS had a mitochondrial subcellular localization [16]. Xiong et al. [17] found that the strategy of one administration combined with repeated exposure to light was more effective than three administrations combined with one irradiation after each injection. DVDMS-PDT induced DNA damage, loss of mitochondrial membrane potential (MMP), and triggered collapse of F-actin filaments, suggesting the induction of apoptosis by reactive oxygen species (ROS) [16,18]. Wang et al. [19] observed the effects of DVDMS-PDT in breast cancer both *in vitro* and *in vivo* and found that oxidative damage of proteins by DVDMS was the main reason for cell death [20]; they also proved that liposome-based DVDMS enhanced the therapeutic effect of Paclitaxel (PTX) through photochemical stimulation [21]. Shi et al. [22] found that DVDMS-PDT induced apoptosis and autophagy in esophageal cancer Eca-109 cells via ROS generation, while inhibiting autophagy reduced DVDMS-PDT-triggered apoptosis.

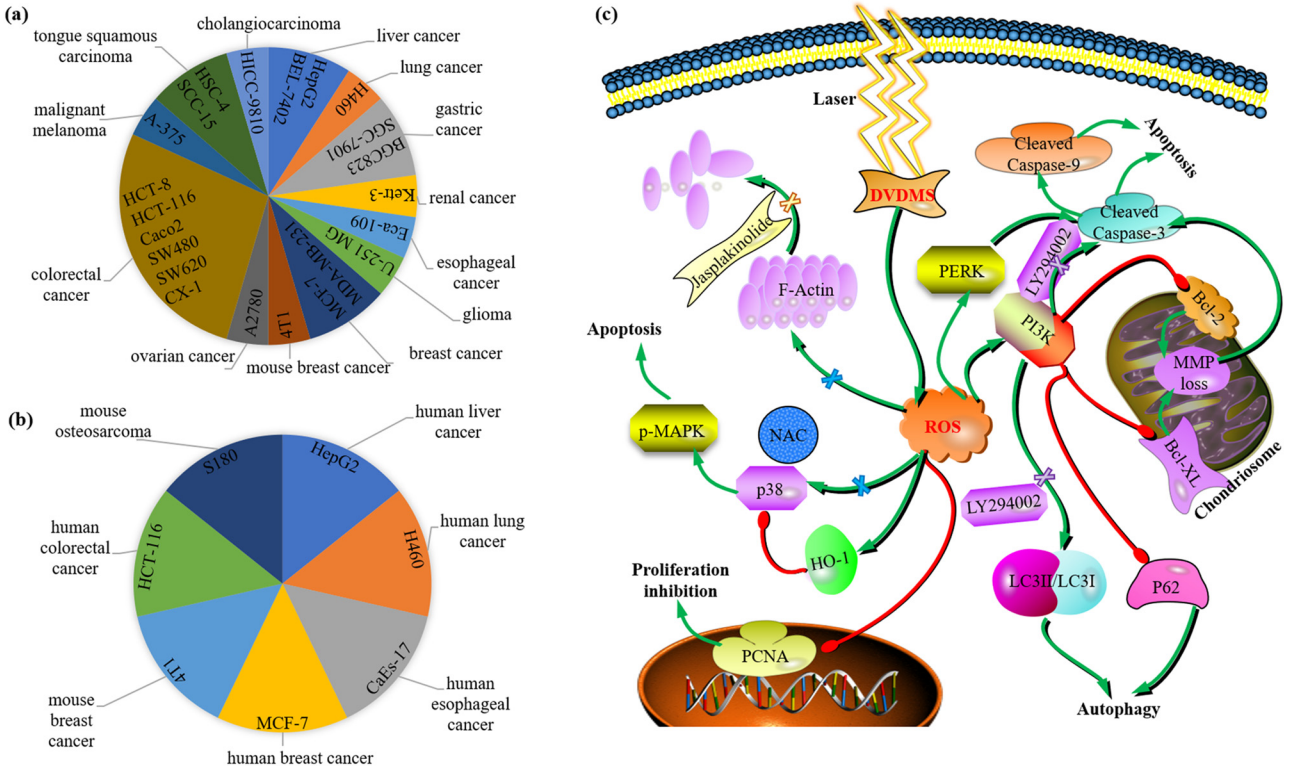

Figure 2: Antitumor effects and mechanism of DVDMS-PDT. (a) Cell lines used *in vitro*. (b) Xenograft tumor models. (c) Mechanisms of DVDMS-PDT.

Huang et al. [23] and Ma et al. [24] observed the effects of DVDMS-PDT on the proliferation and migration of tongue squamous carcinoma HSC-4 and SCC-15 cells. Zhu et al. [25] found that inhibiting autophagy with Chloroquine enhanced DVDMS-PDT-induced apoptosis in colorectal cancer cells, which might contradict previous work by Shi et al. [22]. Finally, Xiang et al. [26] investigated whether liposomal DVDMS-mediated PDT could decrease the viability of HICC-9810 cells.

In conclusion, DVDMS-PDT significantly inhibits tumor cell proliferation both *in vitro* and *in vivo* and induces apoptosis and autophagy. The most commonly used DVDMS doses *in vivo* were 0.5–2 mg/kg (i.v.); the absorption spectra of DVDMS were detected, and there were five absorption peaks at 359, 514, 548, 580, and 631 nm, respectively, and the maximum absorption peak was at 359 nm [28]. However, most laboratories have chosen 630 nm or 635 nm lasers as a light source for PDT, as infrared rays induce fewer side effects than ultraviolet light. Most *in vitro* experiments have used energy densities <10 J/cm^2, whereas in animal models the optical density tends to be 10-fold higher (Table 1). Unfortunately, most articles did not disclose the output power or the spot diameter of the laser, which is also very important for PDT treatment. As higher output power and smaller spot diameter usually led to greater thermal effect, and the thermal effect is beneficial for killing tumor cells in appropriate doses; conversely, it might lead to burns or local tissue necrosis, confounding the effects of heat itself from the biological effects of PDT. We think that systematic studies of laser conditions that include output power, spot size, and exposure time should be performed to assess the balance between efficacy and safety to provide more references for clinical treatments.

The molecular mechanisms of DVDMS-PDT mainly involve the generation of ROS. As shown in Figure 2c, DVDMS-PDT reduced proliferating cell nuclear antigen (PCNA) levels and ultimately inhibited cell proliferation [17,19]. Mitochondria are the major organelles of DVDMS localization, and PDT-induced ROS can cause mitochondrial-dependent apoptosis, including the downregulation of Bcl-2 and Bcl-xL, MMP loss, and the upregulation of PERK, cleaved-capsase-3 and -9. ROS can also induce autophagy, which is characterized by an increase in the LC3II/LC3I ratio and p62 inhibition. The PI3K inhibitor LY294002 can reverse both apoptosis and autophagy induced by DVDMS-PDT [16,21,22,25]. ROS induced by DVDMS leads to collapse of F-actin filaments, which can be reversed by the ROS scavenger *N*-acetylcysteine (NAC) and the F-actin stabilizer Jasplakinolide [18,19]. Additionally, ROS can also

Table 1: Experiment parameters of PDT mediated by DVDMS for treating cancers *in vitro* and *in vivo*

Ref.	Laser wavelength (nm)	*In vitro*			*In vivo*			
		Optical density (mW/cm^2)	Exposure time (s)	Energy density (J/cm^2)	Drug dosage (mg/kg)	Optical density (mW/cm^2)	Exposure time (s)	Energy density (J/cm^2)
Jiang et al. [11]	630	30	180	5.4	0.5–2	63.3–253.3	600	38–152
Shi et al. [9]	630	30	180	5.4	0.5–2	127.7	600	76.6
Hu et al. [16]	630	43.0	120–360	5.2–15.6	—	—	—	—
Xiong et al. [17]	635	—	—	—	2	—	—	50
Wu et al. [18]	635	23.85	60–240	1.43–5.72	—	—	—	—
Wang et al. [19]	635	23.85	60–300	1.43–7.15	0.5–2	416.7	120–360	50–150
Li et al. [20]	635	23.85	109–436	2.6–10.4	—	—	—	—
Wang et al. [21]	635	30.25	132	4	1	—	—	100
Shi et al. [22]	650	—	—	2–4	—	—	—	—
Huang et al. [23]	635	10	75–600	0.75–6	—	—	—	—
Ma et al. [24]	635	15	60–360	0.9–5.4	—	—	—	—
Zhu et al. [25]	630	19.1	265–530	5–10	2	318.5	314	100
Liu et al. [26]	630	—	—	10	—	—	—	—
Kong et al. [27]	635	—	—	10	—	—	—	—

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lead to oxidative stress, p38MAPK phosphorylation, and induce the short-term upregulation of Heme oxygenase-1 (HO-1), which can also be reversed by NAC [22].

3 Antitumor effects of DVDMS-mediated SDT

Li et al. [13] and Hu et al. [28] first confirmed that DVDMS could be used as a sonosensitizer both *in vitro* and *in vivo*. Wang et al. [29] found that DVDMS-SDT triggered mitochondrial-dependent apoptosis in ECA-109 cells via the ROS pathway and microbubbles (MBs) enhanced the antitumor effects of DVDMS-SDT both *in vitro* and *in vivo* [30]. Xiong et al. [31] found that multiple focused ultrasounds combined with DVDMS are a promising strategy for treating tumors. Liu et al. [32] evaluated the combined effects of DVDMS-mediated SDT and PDT (Sono-photodynamic therapy; SPDT) for breast cancer treatment. DVDMS-SPDT-induced higher cytotoxicity *in vitro* compared with PDT or SDT alone, the cavitational effects and cell membrane permeability changes after ultrasound irradiation was the potential mechanism for the enhancement of combination therapy. DVDMS-SPDT elicits more antitumor effects such as inhibiting tumor weight growth, suppressing tumor proliferation and metastasis than either SDT or PDT *in vivo* but did not produce more side effects. Zhang et al. [33] evaluated the combination of SDT, chemotherapy and PDT, with the aid of ultrasound irradiation, the combined PDT and chemotherapy achieved effective tumor growth inhibition. Liu et al. [15] designed a functionalized smart nanosonosensitizer (EXO-DVDMS) that facilitates simultaneous imaging, inhibition of tumor metastasis, and enhanced homogenous tumor targeting and SDT toxicity. Li et al. [34] investigated the feasibility of using DVDMS loaded into liposome–microbubble complexes (DLMBs) with SDT against breast cancer. Xie et al. [14] found that 2-deoxyglucose (2DG), an antiglycolytic agent, enhanced the cytotoxicity and ROS generation of DVDMS-SDT. Sun et al. [35] reported that ultrasound-targeted microbubble destruction (UTMD) and internalizing RGD (iRGD)-modified DVDMS liposomes (iRGD-Lipo-DVDMS) augmented the efficacy of SDT.

Moreover, Zhou et al. [36] and Liu et al. [37] fabricated SDT agents using DVDMS chelation with manganese ions into nanoliposomes (DVDMS-Mn-LPs), which provided a potential strategy for an imaging-guided treatment modality for glioma. Pi et al. [38] used focused ultrasound (FUS) and MBs to open the blood–brain barrier (BBB) and enhance the delivery of DVDMS to brain tumors, which was then followed by the second-step SDT therapy. Li et al. [39] and Shen et al. [40] systematically studied the apoptotic mechanisms induced by DVDMS-SDT, especially the apoptosis-related signaling pathway.

The cancer cell lines and xenograft models that have been used to study DVDMS-SDT are summarized in Figure 3a and b; ultrasound parameters are shown in Table 2. For *in vivo* experiments, the common dose of DVDMS was 2 mg/kg (i.v.) except for Li et al. [34], who used 0.4 μg/injection (PEI). A focused ultrasound transducer was used as the energy source for SDT in almost all *in vivo* studies and in nearly half of the *in vitro* experiments. However, there were also many groups who used a planar transducer as the energy source. Ultrasonic parameters including frequency, load power, power density, and exposure time have been significantly different in different research groups and even in different studies by the same group. These studies suggest that DVDMS can be activated by both focused and planar ultrasound over a wide frequency range (0.5–1.9 MHz). There is little evidence for differences in the same model between focused and planar ultrasound, which may be a direction for future studies.

The potential molecular mechanisms of DVDMS-SDT are shown in Figure 3c. Similar to PDT, DVDMS-SDT significantly inhibited PCNA levels and induced MMP loss [14,15,31,32,34,40]. ROS-induced mitochondrial-dependent apoptosis was the primary mechanism of cell killing by DVDMS-mediated SDT [34,37–39], as evidenced by the upregulation of cleaved-caspase-3, -8, and -9, caspase-10, p-p38, p53, and Bax, the downregulation of Bcl-2 and RIPI3, and the release of cytochrome c (CytoC) [14,29,39,40]. DVDMS-SDT-induced ROS also led to a G2/M phase cell cycle arrest, decreased CDK1 and Cyclin B1 protein levels, and increased levels of the CDK inhibitors p21 and p27 [39]. These changes by DVDMS-SDT could all be reversed by the ROS scavenger NAC. Moreover, DVDMS-SDT could also inhibit the mRNA expression of TNF-α and VEGF. What was unlike PDT was that SDT resulted in ultrasound cavitation [32], which is a unique advantage of SDT over PDT.

4 Material advances of DVDMS based on PDT and SDT

Graphene oxide (GO) can effectively deliver photosensitizers (PSs) by pep stacking for PDT. Yan et al. [41,42] designed a novel phototheranostic agent based on DVDMS-loaded PEGylated GO (GO–PEG–DVDMS). This

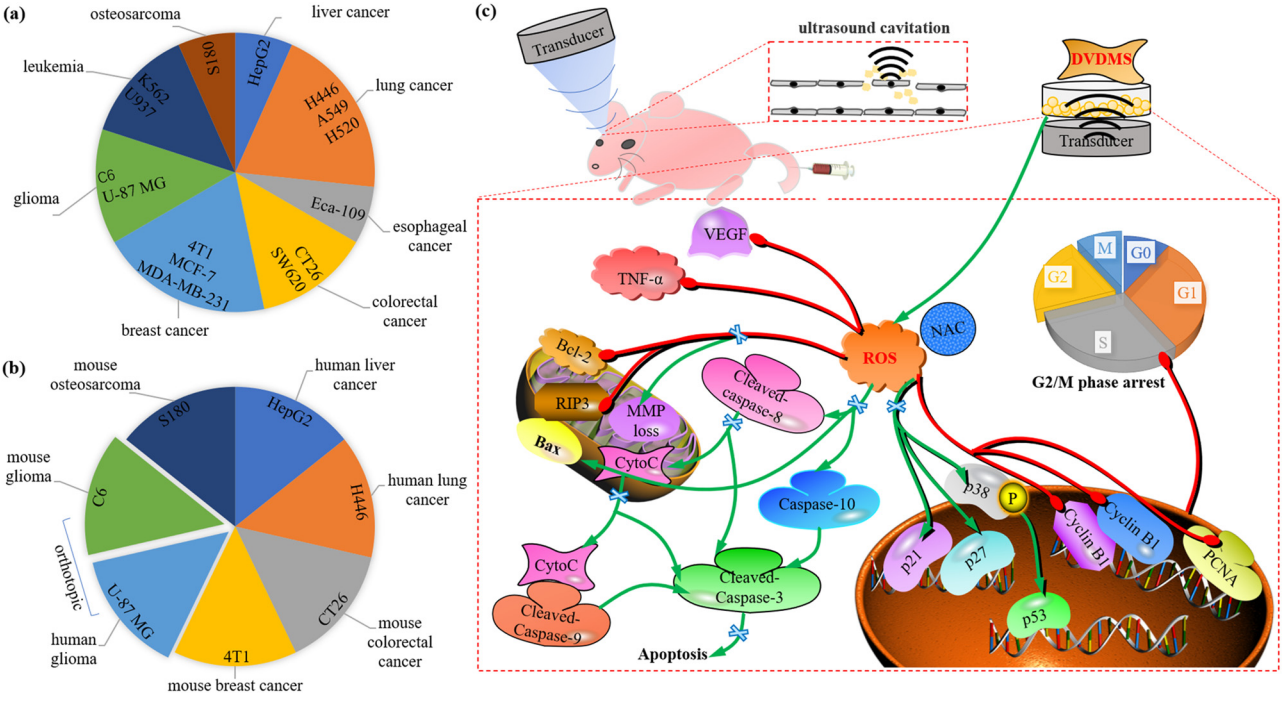

Figure3: Antitumor effects and mechanism of DVDMS-SDT. (a) Cell lines used *in vitro*. (b) Xenograft tumor models. (c) Mechanisms of DVDMS-SDT.

novel theranostic material greatly improved its imaging and PDT/photothermal therapy (PTT) effects. The antitumor capabilities and safety for treating glioma and lung cancer were investigated both *in vitro* and *in vivo*. Chu et al. [43] designed a tumor environment-triggered system using MnO_2 nanosheets as a DVDMS carrier and oxygen and DVDMS nanotheranostic (nanoDVD) generator. In this approach, MnO_2/DVDMS is reduced by glutathione (GSH) and H_2O_2, and then reassembled into nanoDVD, which has been shown to have improved antitumor efficacy in MCF-7 cells and xenograft tumors. Huang et al. [44] loaded DVDMS into RGD-modified ferritin (R-Fn) nanocages, and the resultant nanocomposite was successful for guided PTT/PDT co-therapy and showed good biocompatibility for treating breast cancer. Based on the above studies, a novel tumor microenvironment-induced ultrasmall nanodrug generation (TMIUSNG) strategy was designed to synthesize metal–organic nanodrug complexes (MONCs) through DVDMS, as well as the chemotherapeutic drug doxorubicin and ferric ions. MONCs produced more ROS than free DVDMS through energy transfer-mediated fluorescence quenching and proved to be more effective for treating MCF-7 tumors [45].

PDT has been proven to be effective against many malignancies, particularly lung, liver, stomach, esophageal, colorectal, cervical, breast, and nasopharyngeal cancers. However, for some specific tumors, such as glioma, PDT is not applicable, which may be attributed to two factors: the weak penetration and the blocking of photosensitizers by the BBB. Ultrasound has much stronger penetration than laser; therefore, DVDMS-SDT was recently used to treat gliomas. MBs are ultrasound contrast agents that have been shown to enhance the cytotoxicity induced by DVDMS-SDT [30]. Moreover, MBs are also good tools for drug loading and delivery, especially through the BBB. Li et al. [34] investigated the feasibility of using DLMBs, a liposome – microbubble complex loaded with DVDMS, as a possible candidate to enhance SDT against breast cancer. Shen Yuan-Yuan and Chen Xin et al. from Shenzhen University designed an ingenious strategy to treat glioma using DVDMS-SDT combined with MBs. First, FUS with MBs was used to open the BBB and enhance DVDMS delivery, and then another ultrasound irradiation was performed to activate DVDMS and kill the glioblastoma cells. An intracranial glioblastoma model proved the effectiveness of this therapeutic strategy [38].

Wang et al. [21] synthesized a ROS-producing liposome-based DVDMS-liposome (DL) and a PTX-liposome (PL). The composite DVDMS-PTX liposome (PDL) exhibited superior antitumor effects compared with DL and PL. Furthermore, multifunctional theranostic agent DVDMS-Mn-LPs were designed to integrate imaging and therapy into a single nanoplatform. DVDMS-Mn-LPs can produce ROS upon

Table 2: Experiment parameters of SDT mediated by DVDMS for treating cancers *in vitro* and *in vivo*

Ref.	*In vitro*						*In vivo*					
	Focused or planar	**Transducer diameter (mm)**	**Ultrasound frequency (MHz)**	**Load power (W)**	**Power intensity (W/cm^2)**	**Irradiation time (s)**	**Focused or planar**	**Transducer diameter (mm)**	**Ultrasound frequency (MHz)**	**Load power (W)**	**Power intensity (W/cm^2)**	**Irradiation time (s)**
Li et al. [13]	/	/	/	/	/	/	Focused	22	1.9	4	—	180
Xie et al. [14]	—	35	0.84	—	0.4	60	Focused	35	1.9	—	2.0	120
Liu et al. [15]	Focused	50	1.0	2–5	—	60	Focused	50	1.0	3	—	180
Hu et al. [28]	Focused	—	1.1	1–4	—	60	/	/	/	/	/	/
Wang et al. [29]	Planar	35	1.0	4		60–180	/	/	/	/	/	/
Wang et al. [30]	Planar	35	1.0	—	0.36–0.54	30–60	Focused	22	1.9	4	—	180
Xiong et al. [31]	Focused	—	1.1	2		30–90	—	—	1.9	4	—	30–90
Liu et al. [32]	Planar	35	0.84	—	0.25–1	60	Focused	—	1.9	—	1.6	180
Li et al. [34]	—	35	1.0	—	0.4	90	Focused	25	1.0	3	—	180
Sun et al. [35]	—	—	—	—	0.6	60	Focused	—	1.1	1	—	60
Liu et al. [36]	—	—	0.5	—	0.5	300	/	/	/	/	/	/
Liu et al. [37]	Planar	35	0.5	—	0.5	300	—	—	—	—	1.5	600
Pi et al. [38]	Focused	65	0.996	1.7	—	60	Focused	65	0.996	1.7	—	60
Li et al. [39]	Planar	40	0.84		0.25–0.75	120	Planar	30	1.1	—	1	600
Shen et al. [40]	—	35	0.5	—	0.5	—	Focused	—	1.1	—	—	300

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ultrasound irradiation and significantly inhibited glioma cell growth even in the presence of the skull; thus, they may be a promising candidate for MR and fluorescence imaging [37]. Sun et al. [35] used iRGD-Lipo-DVDMS, a liposome that combines UTMD and iRGD-modified DVDMS, to treat glioma. The orthotopically implanted C6 gliomas were greatly suppressed by UTMD followed by iRGD-DVDMS injection, and then FUS exposure. UTMD opened the BBB, the iRGD-modified liposomes showed enhanced tumor targeting ability, and strong antitumor effects were observed. Moreover, they designed a nanosonosensitizer by loading DVDMS onto tumor-derived exosomes (EXO-DVDMS). EXO-DVDMS were found to be ultrasound-responsive and could control the release of DVDMS to enhance SDT [15], which was very interesting and impressive.

These material advances of DVDMS have led to stronger antitumor effects and more widespread use, such as treating gliomas with PDT and SDT; however, in some studies, much higher doses of DVDMS and laser or ultrasound irradiation were used. Although the authors claim them to be safe, more evidence and systematic evaluations are needed.

5 Metabolism and safety evaluation of DVDMS

The safety and pharmacodynamics of several photosensitizers including DVDMS were evaluated using a technical platform that evaluated the safety and phototoxicity of photosensitizers. These studies revealed the photobleaching characteristics of DVDMS using four solutions *in vitro* and in normal and psoriatic nude mice *in vivo* [46]. They also investigated the metabolism of DVDMS in Sprague – Dawley (SD) rats [47] and evaluated the safety of repeated intravenous DVDMS infusions with and without PDT in SD rats [10] and Beagle dogs [12].

The results showed that the no observed adverse effect levels (NOAELs) for repeated administration of DVDMS with and without PDT were 2 and 6 mg/kg, respectively, in SD rats. Liver injury was the primary toxicity observed in the study, and elevated white blood cell and neutrophil counts were observed in both groups (with and without PDT); only one out of a total of 270 SD rats died after PDT treatment with 60 J of 630 nm laser illumination and 18 mg/kg DVDMS administration. The death occurred during the fifth PDT treatment (7 days for 5 cycles followed by a 14-day recovery period), and rats in the DVDMS groups (2, 6, and 18 mg/kg, i.v.) and PDT groups (2 and 18 mg/kg DVDMS, i.v. with 60 J of 630 nm laser illumination) survived [10]. Similarly, the NOAEL of DVDMS in Beagle dogs was 1 mg/kg; no deaths were observed after DVDMS administration at the doses of 1, 3, and 9 mg/kg. However, dogs in the PDT group (1 and 9 mg/kg DVDMS i.v. with 630 nm laser illumination for 10 min) showed skin swelling and ulceration. Additionally, changes in blood coagulation were observed in several groups. An accumulation of DVDMS in plasma was not found; however, slight or mild brown-yellow pigmentations were observed in the liver, spleen, local lymph nodes, and bone marrow of dogs in the mid- and high-dose groups (3 and 9 mg/kg) [12].

Metabolic dynamics studies found that DVDMS photobleaching occurred both *in vitro* and *in vivo* after 630 nm laser irradiation [46]. Phase 1 metabolism was the main pathway of DVDMS in SD rats; a total of 10 metabolites, including products of the ether bond cleavage and further hydrogenation, were detected in the blood, urine, and feces of rats [47]. Further pharmacokinetic studies of tumor-bearing mice were performed by Zhu et al. [48], who determined the main pharmacokinetic parameters, including C_{max} (24127.59 ± 1415.23 ng/mL), t_{max} (0.083 h), $t_{1/2}$ (9.59 ± 1.25 h), $MRT_{0-\infty}$ (11.77 ± 1.73 h), and $AUC_{0-\infty}$ (34775.83 ± 6185.43 h ng/mL). These results provide references for dose selection in clinical and preclinical studies. Li et al. [49] evaluated the pharmacokinetics and tissue distribution of DVDMS in tumor-bearing mice, and found that DVDMS accumulated in tumor tissue to a greater extent than adjacent tissues.

6 Uses of DVDMS in non-neoplastic diseases

The antibacterial effect of DVDMS-PDT on *Staphylococcus aureus* was evaluated and it was found that the fluorescence intensity of DVDMS in bacteria peaked at 75 min after co-incubation; more than 90% of the bacteria were effectively killed by DVDMS-PDT (2 mM DVDMS with 10 J/cm^2 light irradiation). ROS generation and biofilm disruption were found to be the potential mechanisms of action [50]. The efficacy of DVDMS-mediated photodynamic antimicrobial chemotherapy (PACT) for treating normal and multidrug-resistant *S. aureus in vitro* and *in vivo* was also proved. DVDMS-PACT significantly inhibited bacterial proliferation, intracellular ROS levels, and the expression of bFGF, TGFβ1, and VEGF was increased in the PACT-treatment group [51]. These studies might provide a strategy for nosocomial and medical

device-related infections and antibiotic resistance. Wang et al. [52] prepared a sonoactivated TiO_2–DVDMS nanocomposite. The nanocomposite was proved to improve the antibacterial activity of DVDMS. Mai et al. [53] developed a hydrogel-based nanodelivery system with antibacterial activity and skin regeneration function, and the system was mainly composed of DVDMS and poly(lactic-*co*-glycolic acid) (PLGA)-encapsulated basic fibroblast growth factor (bFGF) nanospheres, which mediated PACT provided a promising strategy of burn infections.

Psoriasis is a chronic inflammatory skin disease that is difficult to cure. Photochemotherapy (Psoralen ultraviolet A, PUVA) has been recommended for refractory psoriasis; however, there are many adverse reactions to PUVA, especially phototoxicity and burns [54,55]. Applying PDT to psoriasis treatment has been given more attention in recent years. Liu et al. [56] evaluated the inhibitory effects of DVDMS-PDT on the abnormal proliferation of skin cells *in vitro* and *in vivo*, and considered it a potential strategy for treating psoriasis.

Moreover, Li et al. [57] found that DVDMS-SDT could significantly inhibit the proliferation of fibroblast histomorphology in humans, which might be related to increased intracellular ROS, calcium ion concentrations, and membrane damage. This could be beneficial for treating diseases such as scar tissue after hand trauma. Yao et al. found that DVDMS-SDT could suppress neovascularization in atherosclerotic plaques via macrophage apoptosis-induced endothelial cell apoptosis.

Non-neoplastic diseases are important applications for PDT and SDT. However, there are few studies of DVDMS in this respect. In the future, more studies of DVDMS-PDT treatments for skin diseases like psoriasis, actinic keratosis, Bowen disease, and port wine stain should be performed. Additional evidence has indicated that PDT is also effective for fungal infections [58]. The use of DVDMS-PDT to treat fungal infections like onychomycosis and tinea of the feet and hands should be better tested in the future.

7 Clinical trials of DVDMS

Two phase I clinical trials of DVDMS were registered as early as in 2015. The first aimed to evaluate the tolerability and pharmacokinetics in patients with esophageal cancer who did not respond to standard treatment (No. CTR20150690). This study was presided over by Dr Li Zhao-Shen, a chief physician of Changhai Hospital (Shanghai, China). The target for patient enrollment was 34, but they have yet to be recruited to date. The second clinical trial of DVDMS was for treating advanced solid tumors (CTR20150725). This was directed by Dr Shen Lin, a chief physician of Beijing Cancer Hospital (Beijing, China). The first recruitment started on August 31, 2017, with a target of 12–35 patients; however, none are yet to be recruited.

The difficulties faced during DVDMS clinical trials are primarily due to the difficulty in patient recruitment and the uncertainty of clinical effects. This is also reflected in the dilemmas facing photosensitizer researchers. Despite thousands of years of history and over a century of modern medical research, only a few photosensitizers have been successful in clinical applications. As an emerging therapy from the 1990s, SDT has not been used in the clinic, and not even one drug has started a phase 1 clinical trial.

8 Conclusion and prospects

The preclinical applications of DVDMS have been fully studied, especially regarding the antitumor effects of DVDMS-mediated PDT and SDT. In the future, efforts may be needed for applications in non-neoplastic diseases, selection of treatment parameters, and understanding the mechanisms that underlie PDT and SDT. PDT has become an option for dermatologic conditions such as psoriasis and nevus flammeus [59]. However, the effects of DVDMS-PDT for treating dermopathy need more proof. In addition, DVDMS-PDT has demonstrated good antibacterial properties in the early stage, which may greatly expand its application field [50]. SDT is considered a potential treatment strategy for atherosclerosis in recent years [60]. DVDMS-SDT might be used for treating atherosclerosis, but this needs to be further confirmed. The therapeutic parameters of both PDT and SDT mediated by DVDMS are very tanglesome in the current preclinical studies. which might be due to the differences in instruments and conditions in different laboratories, and which is very detrimental to the clinical application. For now, the most urgent thing is to focus on how to promote clinical trials and other applications of DVDMS. And in the clinical trials, standardized therapeutic parameters must be formulated with full reference to the previous researches about the pharmacology, toxicology, and pharmacokinetics of DVDMS. Available evidences suggest that the potential mechanisms of DVDMS mediated PDT and SDT mainly involving in ROS and apoptosis signaling pathways, the role of autophagy in the process were revealed recently; however, many more potential mechanisms such as regulation of different signaling pathways and the effect on cell pyroptosis and necrocytosis have not been discovered. Besides,

advances in the materials and methods of drug delivery may bring opportunities for the application of DVDMS, and the combination of multiple therapeutic strategies (such as SPDT and PACT) may also provide more possibilities [61].

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