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Sonodynamic Therapy in the Treatment of Glioblastoma: Mechanisms, Challenges, and Insights

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Abstract

Sonodynamic therapy is a rapidly evolving approach in cancer treatment, which uses ultrasound waves and sonosensitizers, drugs which are sensitive to ultrasound. Stemming from photodynamic therapy, it works by exposing sonosensitizers in tumor cells to high-intensity ultrasound waves, generating reactive oxygen species that cause damage to tumor cells. Among existing therapies, it is minimally invasive with fewer side effects and has the potential to enhance treatment efficacy, especially when combined with other strategies as a secondary treatment. Glioblastoma multiforme has proven to be a hard-to-treat cancer, with many existing treatments having limited efficacy against it due to the presence of the blood-brain barrier. This novel adjunctive treatment is promising in the context of glioblastoma multiforme because it is less invasive than other treatments and potentially more effective in overcoming blood-brain barrier limitations. Nevertheless, sonodynamic therapy relies on sonosensitizers, which are currently limited in their efficacy, and the lack of real-time monitoring of parameters in this treatment can lead to uncontrolled cytotoxic effects. This paper addresses the mechanisms of sonodynamic therapy, its application in combination with other therapies, its disadvantages and, more importantly, suggests solutions to its drawbacks.

Keywords: translational medical sciences, disease treatment and therapies, sonodynamic therapy, ultrasound, glioblastoma (GBM), treatment monitoring

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1. Introduction

Cancer is characterized by the uncontrolled growth of cells, which may be able to invade nearby tissues. Over the past decades, cancer has become the second leading cause of global mortality (Siegel et al., 2024). Although current cancer treatment methods, such as chemotherapy, radiotherapy, immunotherapy and targeted therapies, have proven to be reliable, they are not always curative.

GBM is the most aggressive and common form of primary brain cancer in adults, classified as a Grade IV tumor by the WHO (Hanif et al., 2017). It can either arise de novo (primary GBM) or from lower-grade gliomas (secondary GBM). The main treatments for GBM currently are chemotherapy, surgery and radiotherapy. While Temozolomide chemotherapy shows signs of success, its median survival time is only 16 months (Parney & Chang, 2003). Major drawbacks of chemotherapy include its toxicity and side effects, such as myelosuppression and fatigue, as well as chemoresistance. As a result of chemotherapy's ineffectiveness, most patients relapse. Radiotherapy also shows limited efficacy in GBM treatment. Approximately 90% of GBM recurrences occur within 2 cm of the original tumor site post-radiotherapy, suggesting that it does not prevent the spread of the tumor (Fiveash & Spencer, 2003). Standard radiotherapy showed a median survival of 8-10 months, showing signs of low effectiveness. Chemotherapy and radiation therapy have poor tumor selectivity and can lead to increased therapy resistance through enhanced DNA repair mechanisms and increased production of hypoxia-inducible factor 1 (Q. Wu et al., 2014). This occurs when they cause hypoxic conditions in tumor cells, creating a pro-angiogenic and pro-stemness environment, which leads to therapeutic resistance. Immunotherapy has also proven to be ineffective against GBM due to the strong immunosuppressive tumor microenvironment of GBM tumors as well as the blood-brain barrier (BBB), which is impermeable to large molecules and immune cells (Rocha Pinheiro et al., 2023). Its heterogeneous nature and the protection from the BBB make it especially resistant to targeted therapies (Jain, 2018; Wirsching et al., 2016). The standard treatment for glioblastoma consists of surgery followed by radiotherapy and/or chemotherapy (Stupp et al., 2005). However, glioblastomas grow rapidly and are fatal. In treating GBM, existing anticancer strategies have relatively low effectiveness, with the five-year rate of survival for patients being only 6.9% (Dhermain & Barani, 2016; Glioblastoma Foundation, n.d.; Taal et al., 2015).

Sonodynamic therapy (SDT) is a novel cancer treatment which is minimally invasive (Mehta et al., 2023). It works by activating pre-administered sonosensitive drugs with ultrasound (US) and generating reactive oxygen species (ROS), which are responsible for cell damage. The US plays a role in temporarily opening the BBB, enabling larger molecules to enter the tumor more easily. The enhanced permeability and retention effect (EPR) enables sonosensitizers to selectively accumulate, making it less invasive than other therapies (J. Wu, 2021). SDT was inspired by photodynamic therapy (PDT), a method of treatment using visible light to induce tumor necrosis. In 1989, several photosensitizers, which were hematoporphyrin derivatives (HPDs), were found to be sensitive to US and had the ability to induce cell damage when activated (Yumita et al., 1989). Compared to using visible light to induce tumor necrosis, US was shown to be more effective, as a study found that sonodynamic therapy inhibited tumor growth in murine squamous cell carcinoma in mice by 77% (Jin et al., 2000). In contrast, photodynamic therapy caused tumor growth inhibition of only 27%. Light waves cannot penetrate beyond a few millimeters of soft tissue, while high-intensity focused ultrasound (HIFU) has a penetration depth of up to 12 cm in soft tissue (Hoogenboom et al., 2015; Stolik et al., 2000).

Despite its potential advantages, SDT faces obstacles that must be overcome before it is fully recognized as a secondary treatment. Current sonosensitizers all have drawbacks, including poor bioavailability and selectivity, low reactive oxygen species (ROS) yield, and post-treatment side effects (Guo et al., 2022). Another challenge associated with SDT is the lack of real-time monitoring of ROS and temperature. Too high temperatures may cause excessive production of ROS, leading to unwanted cell damage, whereas temperatures that are too low may not produce sufficient ROS needed to cause apoptosis. Therefore, it is crucial to monitor ROS concentration and temperature during treatment (Gong & Dai, 2021).

This paper will cover the primary mechanisms which enable SDT to function, as well as evaluate the important types of sonosensitizers available. The challenges associated with SDT will be discussed along with its potential solutions, through reviewing their past and current approaches.

2. Mechanisms in Sonodynamic Therapy

The primary way that SDT leads to cell death is the production of ROS when a sonosensitizer is "activated" as a result of microbubble cavitation, which occurs when sound waves at a certain frequency range permeate through aqueous environments (Umemura et al., 1990). The first step in the mechanism involves the cavitation of microbubbles. Microbubbles are microscopic air/oxygen bubbles ranging from 1-100 µm, which have great potential in site-specific drug delivery (Rathor et al., 2021). These microbubbles already exist in aqueous environments, but can be deliberately administered intravenously to patients to increase the efficacy of SDT (McEwan et al., 2015). Under US exposure, they undergo cyclic expansion and contraction in a process known as cavitation, which induces rapid temperature and pressure changes. Cavitation can either be "stable" or "inertial," where microbubbles experience violent, uncontrolled oscillations at higher acoustic pressures (McNamara et al., 1999).

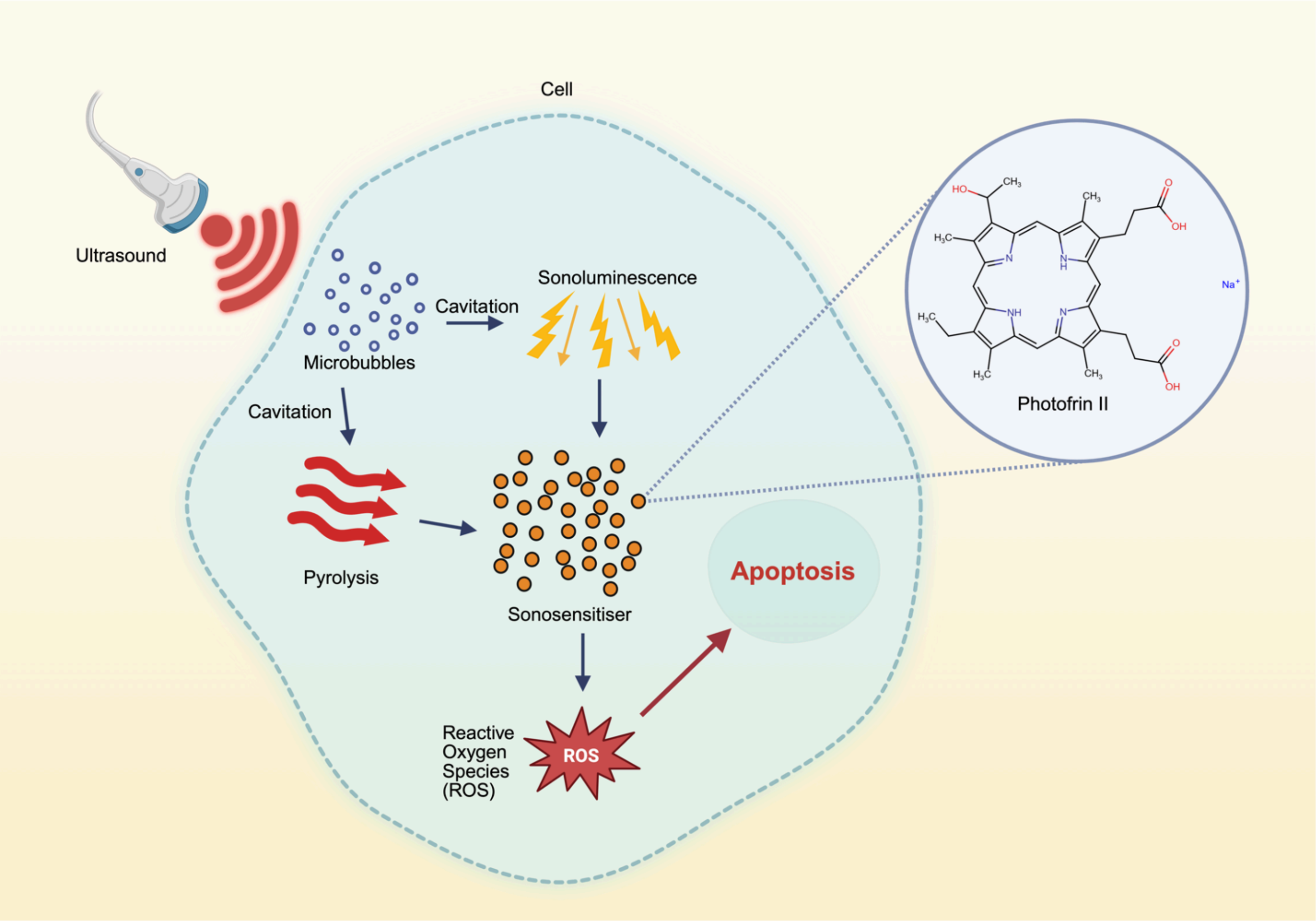

Figure 1: Schematic diagram to show microbubble cavitation leading to the generation of reactive oxygen species through sonoluminescence and pyrolysis, with Photofrin II as an example of a sonosensitizer. Figure created using https://BioRender.com and https://chemaxon.com/.

Inertial cavitation can subsequently cause sonosensitizers to rise to a higher energy state, leading to cytotoxicity through two possible mechanisms: sonoluminescence and pyrolysis. Sonoluminescence occurs when collapsing microbubbles release energy in the form of visible light (Didenko et al., 2000). Since most sonosensitizers are derived from photosensitizers, they are sensitive to light and will shift from their ground state to an excited state with higher energy. As they return to the ground state, they release energy to surrounding oxygen molecules to produce ROS, such as singlet oxygen, superoxide and hydrogen peroxide, which can damage intracellular DNA, promote lipid peroxidation, and result in apoptosis to targeted tumor cells, as shown in **Figure 1** (Ding et al., 2023). Pyrolysis is similar in many ways; the only difference is that microbubbles shift sonosensitizers to an excited state by generating extreme amounts of thermal energy, rather than light. It is believed that inertial cavitation produces shockwave effects which thermally dissociate water vapor into hydroxyl radicals and hydrogen radicals even without the presence of a sonosensitizer, which leads to cell death (Lafond et al., 2019).

Microbubbles have a greater role than cavitation alone; they can enhance BBB permeability to aid drug entry into tumors and increase tumor specificity. This is especially useful in GBM, where the presence of the BBB would otherwise prevent certain drugs from entering. The BBB is a highly selective barrier formed by endothelial cells surrounding the brain's capillaries. It controls which substances can pass from the blood into the brain, shielding the central nervous system from toxins, pathogens, and chemicals (Kadry et al., 2020). In fact, the BBB blocks all large molecules and 98% of micro-molecule drugs from entering the tumor (Pardridge, 2002). However, microbubble cavitation can cause significant shear stress on tumor cells and create ruptures in cell membranes in a process called cell lysis, thus enhancing the permeability of the tumor for sonosensitizers (Hernot & Klibanov, 2008; Ward et al., 1999). Another possible way microbubbles enhance permeability in tumor cells is through the generation of ROS, as mentioned earlier. Even without a sonosensitizer, microbubbles can generate ROS when in contact with US through pyrolysis, which is another possible explanation for increased tumor permeability (Juffermans et al., 2006).

Furthermore, microbubbles can improve targeted drug release. Glioma tumors are rich in vascular endothelial growth factor (VEGF). Fan et al. (2013) designed VEGF-conjugated BCNU-loaded microbubbles, which specifically bind to VEGF receptor two overexpressed in GBM tumors, thus allowing localized drug release at the tumor site and reducing damage to healthy tissue (Fan et al., 2013). This indicates that microbubbles further increase the efficacy of SDT by targeted treatment and increased permeability in the tumor. Sonosensitizers are another main component in SDT, and the following section presents both organic and inorganic sensitizers, as well as their advantages and drawbacks.

3. Organic Sonosensitizers

Sonosensitizers have a greater ability to selectively accumulate in tumor sites due to the enhanced permeability and retention (EPR) effect in tumors (J. Wu, 2021). When Yumita et al. (1989) found that several HPDs used in PDT were sensitive to US, they became the main focal point in sonosensitizer development, with Photofrin II and ATX-70 inducing severe cell damage when activated by US (Yumita et al., 1989; Yumita & Umemura, 2003). Organic sonosensitizers are mainly composed of carbon, particularly with carbon-hydrogen and carbon-carbon bonds. Despite having relatively good tumor specificity and ROS generation ability, even these commonly researched organic sonosensitizers have their downsides.

3.1 Photofrin II

Photofrin II is a family of oligomers where multiple hematoporphyrin molecules are bonded together, with the ability to retain in tumors longer than in healthy tissue selectively and has been FDA-approved as a photosensitizer in cancer PDT (Kuroki et al., 2007). A study on the effects of Photofrin II compared the survival rates of leukemic (MT-2) and normal peripheral mononuclear cells (PMNC). Using ultrasound (450 kHz, 0.3-0.5 W/cm^2), MT-2 cell survival decreased with higher sensitizer concentrations, while healthy cells showed no difference in survival rate between groups with and without Photofrin II administration. In patients with acute-type adult T cell leukemia, PMNC survival decreased from 69.4% ± 22.5% with ultrasound alone to 30.0% ± 23.0% with Photofrin (Tachibana et al., 1997). Although survival rates of leukemic cells are still relatively high, Photofrin II dropped leukemic cell survival rates by half. At the same time, healthy tissue showed no difference in survival rates, suggesting that Photofrin II has minimal toxicity to healthy cells. However, since porphyrins are photosensitive, they may cause post-administration side effects, including skin sensitivity to light and external burns, as shown in **Table 1**. Furthermore, their low water solubilities call for the use of nanocarriers to enhance accumulation in tumor tissues (Xing et al., 2021).

Table 1: Advantages and disadvantages of inorganic and organic sonosensitizers.

Type	Sonosensitizer	Advantages	Disadvantages
Organic	Photofrin II	• FDA-approved for PDT (Kuroki et al., 2007) • Significant tumor growth inhibition in vivo (Tachibana et al., 1997; Yumita & Umemura, 2003) • Good accumulation in tumors (Kuroki et al., 2007)	• High phototoxicity (Xing et al., 2021) • Low water solubility (Xing et al., 2021)
Organic	ATX-70	• Long phosphorescence lifetime (Nakajima et al., 1990) • Significant tumor growth inhibition in vivo (Nakajima et al., 1990; Umemura et al., 1993; Yumita et al., 1996, 2007) • Good accumulation in tumors (Nakajima et al., 1990)	• High phototoxicity (Xing et al., 2021) • Low water solubility (Xing et al., 2021)
Organic	Rose Bengal (RB)	• Good tumor growth inhibition. (Umemura et al., 1999)	• Requires higher concentration than porphyrins (Gong & Dai, 2021; Umemura et al., 1993; Yumita et al., 1989) • Easily captured by the liver (Sugita et al., 2010) • Poor accumulation in tumors (Sugita et al., 2010)

Inorganic	Titanium dioxide nanoparticles (TiO_2 NPs)	• Good tumor growth inhibition • Can be modified to improve circulation and ROS production (A. Harada et al., 2013; You et al., 2016)	• Aggregates and can be captures by the reticuloendothelial system (Chen et al., 2023; A. Harada et al., 2013; You et al., 2016) • Electron-hole recombination reduces ROS production (Sun et al., 2021)
Inorganic	Silicon nanoparticles (SiNPs)	• Medium tumor growth inhibition (Osminkina et al., 2016) • Hydrophobic SiNPs can carry microbubbles to increase ROS production (Chen et al., 2023)	• Antitumor effects are not as strong as those of porphyrins (Osminkina et al., 2016)

3.2 ATX-70

ATX-70 is a gallium porphyrin complex which showed the highest accumulation concentration in tumors out of the HPDs tested in this study by Nakajima et al. (1990). It also exhibits the longest phosphorescence lifetime among HPDs (Nakajima et al., 1990). In other words, ATX-70 absorbs and reemits sonoluminescent light the longest while also selectively accumulating in tumors. The efficacy of ATX-70 was studied using isolated sarcoma 180 cells, and findings demonstrated that an 80 μM concentration of ATX-70 increased the rate of damage to the mice sarcoma by four times under 2 MHz US, compared to the two times increased rate with hematoporphyrin (Umemura et al., 1993). This suggests that ATX-70 significantly amplifies US-induced cytotoxic effects, primarily through the generation of singlet oxygen radicals, and potentially has a greater effect than Photofrin II and other HPDs. The in vivo effects of ATX-70 in Sprague-Dawley rats with mammary tumors were examined, and it was shown that peak accumulation of ATX-70 in tumors was 24 hours post-administration, similar to Photofrin II (Yumita et al., 2007). 2 weeks after administration of ATX-70 and US radiation (3 W/cm^2), there was a mean reduction of tumor volume of 50%. With radiation of 5 W/cm^2, a further 18% reduction in tumor volume was observed compared to the control group (no treatment). ATX–70–mediated sonodynamic therapy significantly enhanced tumor regression and confirmed its efficacy as a sonosensitizer. Nevertheless, ATX-70 is a porphyrin derivative and shares the same downsides as Photofrin II, such as photosensitivity and low water solubility. Yumita et al. (2000) tested another HPD, known as ATX-S10, and found similar results to ATX-70 and Photofrin II, suggesting that HPDs share common characteristics and effects as a sonosensitizer (Yumita et al., 2000).

3.3 Rose Bengal

Another organic compound, Rose Bengal (RB), a xanthene dye, has also been tested for its potential cytotoxic effects when exposed to US. Umemura et al. (1999) have shown that RB increased ultrasound-induced cell damage to isolated sarcoma 180 cells by a factor of 2-3 at a concentration of 160 μM (Umemura et al., 1999). At a US exposure of 5.9 W/cm^2, cell viability dropped to as low as 4% in the presence of 160 μM RB, but only to 38% with US alone after 60 seconds. However, after comparing the results of this study to results of previous studies, it was observed that to achieve similar cytotoxic effects, RB concentration needed to be at least double the concentration of porphyrins, suggesting that porphyrins have a slight advantage in efficacy in terms of cell damage (Umemura et al., 1990, 1993; Yumita et al., 1989). Another drawback of xanthene dyes is that the liver can easily capture and break them down, making them unable to accumulate in tumors (Sugita et al., 2010).

4. Inorganic Sonosensitizers

4.1 Titanium dioxide nanoparticles

Inorganic sonosensitizers are substances that are not primarily composed of carbon and hydrogen in a chain. They fall into two categories: metal and non-metal. Titanium dioxide (TiO) nanoparticles (NPs) are a class of metal-based sonosensitizers that also produce ROS when activated by US (Chen et al., 2023). As a superconducting material, it can produce electron-hole pairs when excited by ultrasound (Sun et al., 2021). These pairs interact with nearby oxygen and water molecules to produce hydroxyl radicals and superoxide anions. An in vitro study suggested that TiO_2 NPs or US alone had little effect on mouse melanoma C32 cells, with cell viability remaining above 92% after US exposure at intensities up to 1.0 W/cm^2 for 10 seconds. However, combining a TiO_2 solution (0.500% w/w) with US at 1.0 W/cm^2 for 10 seconds resulted in a decrease in cell viability to 53.6 ± 1.8%, and apoptotic cell levels were 2.73 times higher than those in the control group (no treatment). Additionally, microscopic analysis confirmed that the TiO_2 particles were responsible for cell membrane damage, indicating the production of ROS (Y. Harada et al., 2011).

Despite its potential apoptosis-inducing ability, TiO_2 NPs tend to aggregate in physiological environments, which enables them to be easily captured by the reticuloendothelial system (Chen et al., 2023). Therefore, research on carrier systems that can improve the dispersion stability of TiO_2 NPs under physiological pH conditions will significantly enhance the efficacy of TiO_2 NPs as sonosensitizers in SDT. You et al. 2016) encapsulated TiO_2 NPs in carboxymethyl dextran (CMD). This long-circulating hydrophilic TiO_2 NP still retained the ability to produce ROS when activated by US, but improved systemic circulation and uptake into cells (You et al., 2016). Another study used an encapsulation of TiO_2 NPs in polyion complex micelles to improve their dispersion stability while producing singlet oxygen (A. Harada et al., 2013).

TiO_2 NPs possess another drawback, namely, electron-hole recombination: As mentioned earlier, TiO_2 produces electrons and holes upon exposure to ultrasound. However, electrons and holes can recombine quite easily, resulting in reduced ROS production (Sun et al., 2021). Other metal-based sonosensitizers that include Manganese-based composites and Fe_3O_4-loaded sensitizers also show antitumor effects but may be limited in the complexity of their design and their reduced ROS production rate under non-acidic and hypoxic conditions. Therefore, more research should be done on overcoming these obstacles (Chen et al., 2023).

4.2 Silicon nanostructures

Non-metal sonosensitizers have also been widely used in SDT research. Silicon nanostructures, for instance, can cause an amplified sonodynamic effect, making them a potential sonosensitizer. A study found that silicon nanoplatforms (SiNPs) had a significant cytotoxic effect when paired with US: While US (0.88 MHz, 0.05 W/cm^2) alone only led to 50% Hep-2 cancer cell death in vitro, when combined with SiNPs (0.2 mg/ml), 90% of the cancer cells were destroyed (Osminkina et al., 2016). The researchers also conducted in vivo experiments on mice with Lewis lung carcinoma (LLC). The mice received injections of a SiNP suspension (1 mg/ml) into the tumor. When exposed to US, tumor growth was inhibited by 30 ± 5% over the course of 13 days, further suggesting that SiNP may be a possible sonosensitizer in SDT. Furthermore, Mesoporous silica nanoparticles (MSNs) have been modified in the past to alter their hydrophilicity, enabling microbubbles to be trapped in a hydrophobic MSN and increasing ROS production (Chen et al., 2023). However, despite showing some promise in vitro and in vivo, the efficacy and safety of SiNP in human clinical trials remain unclear (Zhao et al., 2021).

5. Sonodynamic Therapy and Glioblastoma

In vitro experiments have demonstrated the potential of SDT in combating GBM. 5-Aminolevulinic acid (5-ALA), a precursor of porphyrins, has been extensively researched for its application in treating GBM. 5-ALA, at concentrations of 10 μm/mL, coupled with US at a power of 6 W, significantly reduced cell viability in rat RG2 glioma cells in vitro (Bilmin et al., 2016). Similar observations were found in mouse cells in vitro as well as human U87 GBM cells (Sheehan et al., 2020; Suehiro et al., 2018). Other sonosensitizers, including RB, sinoporphyrin sodium and PpIX have also shown apoptotic effects in glioma cells (Endo et al., 2015; Nonaka et al., 2009; Y. Shen et al., 2021). Though SDT may not be a likely primary treatment in the future, it has high potential to become a supporting treatment. To date, research has shown that SDT can be combined with other therapies such as chemotherapy and PDT to yield synergistic effects (H. Hu et al., 2023; S. Shen et al., 2015).

Chemotherapy is a mainstream therapy used in GBM treatment. In the case of brain tumors, SDT can aid chemotherapy in a few ways. A major challenge associated with brain tumors is the presence of the BBB, which restricts molecules from entering the tumor site (Pardridge, 2005). As mentioned earlier, cavitation of microbubbles can facilitate the entry of sonosensitizers into tumors (Trendowski, 2014). By improving the selective uptake of chemotherapeutic drugs in cancer cells, SDT thereby reduces toxicity in normal cells and tissues (J. Wang et al., 2022). SDT also enhances the sensitivity of cancer cells to chemotherapeutic drugs by inducing apoptosis and inhibiting ATP-binding cassette (ABC) transporters, including ABCG2. These transporters actively efflux chemotherapeutics, which would normally lead to tumor resistance to chemotherapy. However, SDT disrupts mitochondrial function and activates the mitochondria-caspase apoptotic pathway, both of which contribute to reduced ABC transporter expression (Xu et al., 2013). Hence, the role of US and sonosensitizers can theoretically be used alongside chemotherapy to enhance treatment efficacy. When Wang et al. (2015) investigated the potential synergistic cytotoxic effects of PpIX-mediated SDT combined with the chemotherapeutic drug doxorubicin (DOX), their findings demonstrated that SDT significantly enhanced the efficacy of DOX by inducing apoptosis and increasing intracellular drug uptake. When SDT was coupled with DOX, the ABC transporter P-glycoprotein was inhibited by 21.3%, leading to an increased uptake of the drug in K562/DOX cells, a multi-drug-resistant human leukemia cell line. While DOX alone caused apoptosis rates of 7.9%, and US and PpIX caused apoptosis rates of 13.9%, the researchers found that together, SDT and chemotherapy caused the highest apoptosis rate of 39.6%, suggesting the synergistic effects of SDT and chemotherapy (X. Wang et al., 2015).

SDT stems from PDT, and along with it, sonophotodynamic therapy (SPDT) emerged with the combination of SDT and PDT. PDT, however, relies on light, which has less penetrating power in bones and tissue, while SDT relies on US waves, which can be passed through the body through water molecules. US waves propagate through water molecules through a series of compressions and rarefactions. Therefore, activating sonosensitizers with a combination of US and light allows targeting tumors at different depths (Wood & Sehgal, 2015). Photosensitizers can be excited by using light with a certain wavelength, much like sonosensitizers with sound (Correia et al., 2021). By activating sensitizers using both light and ultrasound simultaneously, SDPT exploits the synergistic effects of the two therapies to produce mechanical, sonochemical and photochemical activities, leading to apoptosis. Liu et al. (2016) conducted both in vitro and in vivo studies on the benefits of SPDT in human breast cancer cells and mouse mammary cancer cell lines, and found that SPDT was more effective than SDT or PDT alone (Liu et al., 2016). While SDT alone caused a loss of cell viability of 27.36%-34.88% and PDT resulted in a loss of 36.69%-40.16% in vitro, the SPDT group exhibited a loss of cell viability ranging from 80.49% to 85.01%. Further analysis revealed a 12.68% survival rate for SPDT-treated cancer cells, which is substantially lower than that of SDT and PDT (68.78% and 59.51%, respectively). The evident synergistic effects of SPDT can be attributed to the increased generation of ROS. Specifically, the SPDT group produced intracellular ROS in mice 4-5 times more than SDT or PDT alone, suggesting that the heightened levels of ROS caused apoptosis in SPDT (Liu et al., 2016).

SPDT's effects on squamous cell carcinoma (SCC) tumor models were investigated (Miyoshi et al., 2016). While it was found that PDT alone resulted in a 40% reduction in tumor volume and PDT combined with TiO_2 sensitizers achieved 55% growth inhibition, the SPDT group exhibited an 80% tumor suppression. Increased ROS generation caused this increased effectiveness; however, more electron spin resonance (ESR) measurements showed that specifically hydroxyl radicals were most prevalent in SPDT tumors, being three times higher than in SDT or PDT alone (Miyoshi et al., 2016). The results of these studies indicate a synergistic effect when SDT is combined with PDT. Though PDT and SDT alone may have mild effects, when combined together, SPDT has the ability to treat deep-lying tumors that light would not reach, such as bowel and ovarian cancer, or metastatic cancer that spreads to bone, lung and liver tissue (Sadanala et al., 2014). SPDT is still a newly emerging combination, and its effects have still not been optimized in GBM treatment. A study found that in C6 rat models, its effects were initially promising, but its long-term impacts were less effective than PDT alone (Park et al., 2023). SDT surprisingly contributed to tumor growth, and a possible reason for this was that the US was incorrectly applied. Although the effects of SPDT were small, ROS production in the SPDT group was far greater than in the SDT or PDT group (Park et al., 2023). Further research into sustaining SPDT's effects will be crucial for putting it into use in clinical settings.

5.1 Current Limitations and Insights of Sonodynamic Therapy

Sonosensitizers are a critical component of SDT, yet their development is still in progress. Due to a range of issues, including low stability, poor bioavailability, and selectivity, the current generation of sonosensitizers requires further research before SDT can become a more widely used treatment (Gong & Dai, 2021). Some organic sonosensitizers, such as RB, for instance, have the ability to be triggered by US but are limited in their tumor accumulation ability. The lack of accumulation ability in some sensitizers has inspired research into the synthesis of their derivatives and investigations of their properties. For example, Sugita et al. (2007) investigated the development of tumor-accumulating derivatives of RB for SDT and PDT to overcome RB's poor tumor accumulation (Sugita et al., 2007). Several RB derivatives (RBD) were tested, including RBD1 (2, RB, C-2' alkyl ester, C-6 sodium salt), RBD2 (3, RB, C-2′ ω-carboxyalkyl ester, C-6 molecular form) and RBD3 (4, RB, C-2′ R-carboxyalkyl ester, C-6 molecular form). While all three derivatives behaved similarly to other sonosensitizers, RBD3 with longer alkyl chains significantly improved tumor accumulation, accumulating 1.5 times more in tumors than ATX-70 and 40 times more than RB. The researchers successfully engineered tumor-targeting RBDs by optimizing amphiphilicity and showed that these modifications make RBDs promising sonosensitizers for SDT (Sugita et al., 2007). To further combat the low selectivity of sonosensitizers, Xiong et al. (2015) isolated a novel porphyrin derivative from Photofrin known as sinoporphyrin sodium (DVDMS), which showed strong potential in SDT due to its water solubility (Xiong et al., 2015). The results of this study demonstrated that DVDMS concentrations in tumors in vivo reached approximately 98.77% and 70.37% of the maximum concentration in the tumor at 6 h and 24 h, respectively. In S180 xenografted mice, DVDMS-mediated SDT also significantly decreased tumor growth rates (Xiong et al., 2015); It outperforms other porphyrin-based sonosensitizers due to its superior tumor selectivity, effective ROS generation and strong tumor inhibition, deeming it a promising solution, particularly when compared to the current sonosensitizers and their individual disadvantages.

The role of microbubbles can also be expanded in SDT. As mentioned earlier, microbubbles facilitate the activation of sonosensitizers through cavitation and pyrolysis. A promising potential of microbubbles was investigated by Nomikou et al. (2012), when they covalently attached RB to a lipid microbubble to form a conjugate, which showed heightened cytotoxicity in tumor cells and a greater reduction in tumor growth compared to the use of RB alone (Nomikou et al., 2012).

First, microbubble conjugation provides site-specific, precise drug delivery, as US selectively collapses microbubbles, activating only sonosensitizers around the tumor site. Second, the close spatial proximity of RB to the microbubble enhances the effectiveness of ROS production. In fact, when the cytotoxic potential of the MB-RB conjugate was assessed, it was found that exposure to US (1 MHz, 1.5 W/cm^2 for 30 s) decreased cell viability by 72% in RIF-1 murine fibrosarcoma cells in vitro (Nomikou et al., 2012). The results also indicated that the MB-RB conjugate had a significantly enhanced production of singlet oxygen compared to unconjugated RB, supporting the potential of MB-RB conjugates as a highly effective approach in SDT. Furthermore, microbubbles can be used to identify tumor locations more accurately (Ibsen et al., 2013). Zheng et al. (2012) developed hematoporphyrin-encapsulated poly(lactic-co-glycolic acid) microbubbles, which acted as a contrast agent for ultrasound imaging both in vitro and in vivo (Zheng et al., 2012). This suggests that microbubbles may have a greater use, not only in SDT delivery, but also in cancer diagnosis.

Another possible function of microbubbles in SDT is to combat hypoxia levels usually associated with tumors. A compromised and anisotropic blood supply in tumors leads to inadequate oxygen and nutrient delivery to tumor cells (Vaupel et al., 1989). As a result, SDT, which relies on oxygen acting as a substrate for the generation of ROS, becomes less effective and limited in its cytotoxic potential. To combat hypoxic environments, oxygen-loaded MBs (OxyMBs) conjugated with RB (OxyMB-RB) were investigated (McEwan et al., 2015). A series of in vitro and in vivo experiments was conducted. However, notable findings in the in vivo experiments revealed that OxyMB-RBs resulted in a 45% reduction in tumor volume over 5 days with US (1 MHz, 3.5 W/cm^2, 30% duty cycle, 3.5-minute exposure). In contrast, a non-oxygen-loaded MB conjugate (SF6MB-RB) resulted in a 35% increase in tumor volume. The significant difference in tumor growth between OxyMB-RB + ultrasound and SF6MB-RB + ultrasound indicates that the oxygen delivery is crucial for SDT efficacy in hypoxic tumors(McEwan et al., 2015).

As stated earlier, the cavitation effect of microbubbles can temporarily open the BBB and improve drug uptake by tumors in the brain. However, the ability of US to open the BBB also poses risks. Excessive exposure of microbubbles to focused US can significantly reduce the energy threshold for brain lesion creation, causing vascular injury and hemorrhage (McDannold et al., 2006). Compromising the BBB could allow cells to escape the tumor and may lead to an increased risk of metastasis. However, under a certain threshold, there is the possibility of a 100% BBB opening rate without any hemorrhage or vascular damage (Kung et al., 2020). More research and in vivo studies are needed to verify the effects of microbubble cavitation on the BBB. To mitigate the possibility of rupture and hemorrhage, O'Reilly and Hynynen (2012) tested a real-time feedback-controlled focused US system which monitors inertial cavitation in the body and adjusts the ultrasound pressure according to the feedback data. They found that this system could be a reliable way to prevent excessive exposure to US, ensuring the BBB remains open temporarily with minimal rupture and vascular damage (O'Reilly & Hynynen, 2012).

In both clinical applications and future studies, providing real-time monitoring of treatment parameters, such as ROS concentration, is crucial. Extreme concentrations of ROS generated may lead to temperatures too high, and can result in damage to surrounding healthy tissue; therefore, more research on optimizing and standardizing SDT parameters is beneficial (Gong & Dai, 2021). A proposed insight into quantitatively measuring ROS concentration is through chemiluminescence, where probes detect the emission of light from chemical reactions occurring in SDT. Several researchers have developed chemiluminescence probes: Hu et al. (2011) developed a near-infrared area charge-coupled device, which detected chemiluminescence in 2-dimensional imaging in vivo, showing a linear relationship between singlet oxygen concentration and chemiluminescence, making quantification of ROS concentration possible in vivo (B. Hu et al., 2011). Zhen et al. (2016) engineered chemiluminescent semiconducting polymer nanoparticles which were sensitive to chemiluminescent irradiation by hydrogen peroxide, and they were able to detect concentrations as low as 5 nM in vivo mouse models (Zhen et al., 2016).

6. Conclusion

SDT has been developed to treat various cancers, including GBM, where conventional ways of treatment, such as chemotherapy, are not as efficient. It is initiated by inducing microbubble cavitation through ultrasound, leading to ROS generation from sonosensitizers. ROS is responsible for cell damage and apoptosis of tumors. Numerous sonosensitizers have been researched and tested. Currently, Photofrin II, an organic sonosensitizer, is being used in clinical applications for PDT. While it shows good antitumor effects, it is limited in its low water solubility and side effects on the patient. Inorganic sonosensitizers, however, show weaker antitumor effects but can be more easily modified to increase their efficacy. SDT has a high potential in treating GBM due to its ability to open the BBB for a higher accumulation in tumors, especially when combined as an adjunctive treatment to other therapies, such as chemotherapy or PDT. However, more research and in vivo experimentation are needed to optimize this newly emerging therapy; it is limited by current sonosensitizer development and a lack of real-time monitoring of parameters, such as ROS concentration. Recent studies have revealed that microbubbles may have a greater role in optimizing SDT since they can be conjugated to sonosensitizers to improve tumor accumulation or combat hypoxia conditions, which decrease the efficacy of SDT. Furthermore, utilizing chemiluminescent probes in real time may improve the effectiveness of SDT in clinical applications, as well as enabling future studies to quantify ROS concentrations. SDT, however, will only be used in clinical applications through more experimentation and collaboration among researchers.

7. References

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Author Biography

Aidan Chan is a year-13 Academic Scholar and Prefect at Eton College, United Kingdom. He previously attended SummerFields School, Oxford, where his passion for research in the scientific field began.

Aidan pairs research acumen with decisive leadership. At school, he was elected to the STEM Committee and serves as Chief Editor of the Engineering & Design Magazine. At the same time, his academic distinction earned him appointment as an Academic Scholar and Academic Prefect. Beyond the classroom, he is committed to widening access: he co-founded Farrer Academy, a non-profit that supports under-resourced pupils in Science, Math and English, and he regularly volunteers in local schools, delivering GCSE Mathematics tuition to Year 10 and Year 11 students. Together, these roles have equipped him with essential skills to achieve impact, motivating him to continue to do so in the future.

Passionate about biomedical systems and robotics, Aidan is curious about recent advancements in the field, with hopes to pursue higher education in biomedical engineering. He aims to innovate and bring about new ideas to solve existing problems.