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Disulfiram and cancer immunotherapy: Advanced nano-delivery systems and potential therapeutic strategies

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ABSTRACT

The initial focus of the clinical application of disulfiram was its efficacy in treating alcoholism. However, recent research has revealed its potential as an anti-tumor agent and even as an enhancer of cancer immunotherapy. Disulfiram has received safety approval from the FDA, indicating its safety advantages over other substances used for disease treatment. Although clinical trials have been conducted on strategies involving disulfiram or its combination with other anti-tumor drugs, the treatment outcomes have not yielded satisfactory results, thereby emphasizing the significance of addressing drug delivery as a crucial challenge to be resolved. The need to explore advanced nano-delivery systems and the potential immunotherapy enhancement effect of disulfiram in cancer treatment has increased. This review highlights various ways in which disulfiram can combat cancer and importantly, activate immune-related mechanisms. It also discusses obstacles related to delivering disulfiram and provides existing solutions in terms of drug delivery. These drug delivery strategies offer solutions to address various challenges encountered in diverse delivery methods and aim to achieve enhanced therapeutic effects. The focus is on recent advancements in disulfiram delivery strategies and the future potential of disulfiram in immune regulation.

1. Introduction

Tumor diseases, also known as cancer, are a type of disease caused by abnormal cells rapidly dividing and spreading in the body. Tumors are abnormal growths of cells in the human body and can occur in any tissue or organ. Tumors can be classified as benign or malignant (Mo et al., 2021). The development of tumors is the result of various factors, including genetics, environment, and lifestyle. Some tumors are associated with specific genetic mutations, while others may be linked to environmental factors such as smoking, alcohol habits, unhealthy diet, and prolonged exposure to carcinogens. In addition, certain infections are also related to the development of tumors, such as the association between human papillomavirus (HPV) and cervical cancer(van Huijgevoort et al., 2019). The treatment of tumors depends on the type of tumor, stage, and individual patient's condition. Common treatment methods include surgery, radiation therapy, and chemotherapy. Surgery is often used to remove surgically accessible tumors and prevent their spread to other tissues (Solares et al., 2021). Radiation therapy uses high-energy radiation to kill cancer cells or inhibit their growth. Chemotherapy involves the use of drugs to destroy cancer cells. In addition, there are other treatment methods such as targeted therapy and immunotherapy, which target specific molecules of tumor cells or stimulate the patient's own immune system to fight cancer(Lakes et al., 2023). Overall, tumor diseases are a serious illness that brings immense physical and psychological burdens to patients and their families. However, with scientific and medical advancements, the understanding and level of treatment for tumors continue to improve.

Currently, the field of cancer biology is transitioning from focusing solely on cells to a broader perspective that recognizes the interconnectedness between cancer cells and surrounding stromal cells. This includes fibroblasts, vascular cells, and inflammatory immune cells, which collectively make up the tumor microenvironment (TME) (Greten

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and Grivennikov, 2019). In addition, it is important to note that the field of cancer immunology focuses on using the immune system to target and eliminate tumors. This involves strategies such as redirecting or enhancing the immune system to recognize, suppress, and eliminate cancer cells. One approach in cancer immunotherapy is known as "immunological checkpoint blockade," which involves blocking certain immune checkpoints to enhance the immune response against cancer cells (Greten and Grivennikov, 2019).

Immunogenic cell death (ICD) refers to a specific type of cell death caused by stress, which stimulates an immune response against antigens from the dead cells. This activation of the immune system involves the participation of cytotoxic T lymphocytes (CTLs) and leads to adaptive immunity (Li et al., 2021; Ruan et al., 2020). ICD is defined as the organized release of a succession of damage-related molecular signals, which consist of various substances such as calreticulin (CRT) becoming visible on the surface of dying cancer cells, the secretion of adenosine triphosphate (ATP), the release of high mobility group box 1 (HMGB1), and the triggering of type I interferon (IFN) response. DAMPs have the ability to activate dendritic cells (DCs) and act as signals that prompt the cells to devour them. This process then leads to the attraction of cytotoxic T lymphocytes to the environment surrounding the tumor (Ahmed and Tait, 2020). Moreover, the combination of immune checkpoint blockade with ICD is expected to improve effectiveness (Gao et al., 2022).

Disulfiram (DSF) is a drug that was discovered in the 19th century. It works by inhibiting an enzyme called Aldehyde Dehydrogenase (ALDH). When alcoholics consume ethanol while taking DSF, it produces unpleasant symptoms. However, besides its use in alcoholism treatment, DSF has also shown significant anti-cancer effects. This has sparked renewed interest in repurposing DSF for cancer therapy. Multiple studies have revealed numerous anti-cancer effects of DSF (Ekinci et al., 2019). DSF is not only affordable at $20–40 for a daily dose of 250 mg taken orally in the USA, but it is also considered to be safe, allowing for long-term treatment at the same dosage. Combining it with radiation or chemo-radiation does not increase toxicity. Tumors and cancer patients have higher levels of copper (Cu) compared to normal controls. The progression of cancer is directly linked to high Cu levels. Hence, elevated Cu levels can be targeted specifically for treating cancer using DSF, which acts as a Cu-chelating agent. Additionally, DSF has the potential to function as an anti-cancer medication. When DSF is metabolized in the body, it produces a compound called diethyldithiocarbamate (DDC), which can bind with copper ions (Cu^{2+}) to form a complex called Cu $(DDC)_2$. This complex exhibits anti-tumor properties. On the other hand, DSF can be applied as a modular to reverse MDR (Kita et al., 2019). Nevertheless, more research is needed to explore the ability of DSF/Cu to induce ICD. Sun et al. discovered that DSF/Cu can enhance the effects of ionizing radiation and induce ICD in breast cancer (Sun et al., 2020). Similarly, Gao et al. demonstrated that DSF/Cu induces ICD by inhibiting the ubiquitin-proteasome system, thereby enhancing the anti-tumor effects of immunotherapy (Gao et al., 2022). In research, it was discovered that DSF has the ability to prevent the release of IL-1β and pyroptosis. This finding suggests that by inhibiting GSDMD, disulfiram can be used as a therapeutic option to combat inflammation, which is a contributing factor in various human diseases (Hu et al., 2020b).

Disulfiram is a promising anti-tumor drug. In recent years, nanomedicine delivery systems have been widely utilized as an emerging technology to enhance the therapeutic efficacy of disulfiram and mitigate its side effects (Zhang et al., 2022). The current development of nanomedicine delivery system for disulfiram includes the following: (1) Researchers can improve the solubility, stability, and targeting of the drug by loading disulfiram into nanocarriers like polymer nanoparticles, liposomes, and nano-emulsions, thereby enhancing the drug's effectiveness (Li et al., 2022).(2) Targeted delivery: through nanotechnology, specific delivery of disulfiram to tumor sites can be achieved to minimize damage to normal tissues and increase drug accumulation in tumor cells (Wang et al., 2020). (3) Controlled release system: designing nanocarriers with gradual release capabilities can ensure sustained release of disulfiram, extending the drug's duration of action in the body and enhancing efficacy (Huo et al., 2017). (4) Combination delivery: nanotechnology can facilitate the co-delivery of disulfiram with other drugs or treatment modalities to achieve a synergistic therapeutic effect, such as combined application with chemotherapy drugs or immunotherapy (Zhao et al., 2021). Ultimately, the nanomedicine delivery system for disulfiram represents a state-of-the-art technology that is poised to enhance the therapeutic efficacy, mitigate side effects, and introduce novel possibilities for tumor treatment. With continued technological advancements and further research, the nanomedicine delivery system will play an increasingly crucial role in the treatment of disulfiram in cancer therapy.

Disulfiram-based therapy holds great promise as a potential immunotherapeutic approach for cancer treatment. Its multifaceted anticancer mechanisms, including ALDH inhibition, disruption of copper-dependent enzymes, proteasome inhibition, inhibition of angiogenesis and metastasis, make it a versatile agent in combating cancer (McMahon et al., 2020). However, the limitations associated with its delivery, solubility, and off-target toxicity have prompted the development of innovative strategies to improve its clinical efficacy (Zhou et al., 2019). The use of nanocarriers, prodrug formulations, viral vectors, and combination therapies has shown tremendous potential in enhancing the delivery and effectiveness of disulfiram-based immunotherapy (Hu et al., 2020b). These approaches have the potential to overcome the limitations of disulfiram, enabling targeted and controlled release of the drug, minimizing systemic toxicity, and optimizing its therapeutic effects (Zhao et al., 2018).While significant progress has been made in the field of disulfiram-based cancer therapy, further research and clinical trials are warranted to fully explore the potential of this promising approach (Li et al., 2022). Continued investigation into the mechanisms of action, optimal delivery strategies, and combination therapies will contribute to the development of safe and effective disulfiram-based immunotherapeutic strategies for cancer treatment.

The most remarkable aspect of this paper is that, in comparison to other published reviews on disulfiram, the proposed mechanism of action by other authors may be limited to the action of disulfiram alone or in combination with other drugs, or the provided summary may be restricted to a summary of the mechanism or clinical application, or the type of delivery agent. However, our focus extends beyond solely examining the action of disulfiram to encompass its interactions with other drugs and adjuvants (e.g., PTT, PDT, etc.) within the present literature. It is noteworthy that there is often a lack of emphasis on immune effects caused by disulfiram in existing literature. Only a few primarily immune-related reviews have addressed this issue; however, they have not provided detailed elucidation regarding disulfiram's involvement. This paper serves as a comprehensive review suitable for researchers across various medical research fields seeking to obtain up-to-date advancements related to disulfiram.

2. Anti-cancer activity of disulfiram

Extensive studies have been conducted over the past two decades to understand the mechanism of action of DSF/Cu. These investigations have led to the identification of numerous molecular biology targets. Previous reviews have provided a summary of the mechanisms of action of DSF, DSF/Cu^{2+}, and its complex CuET (Ekinci et al., 2019). As indicated in Fig. 1, different anti-tumor mechanisms were involved as for DSF to combat tumors. We will then discuss each of them in next section to get a more comprehensive understanding of DSF's therapeutic potential.

DSF exhibits its anticancer effects by directly hindering specific protein molecules. This hindrance is achieved through a reaction between DSF and the sulfuryl group found in cysteine residues. As a result, a new disulfide bond is formed between DDC and Cys. Previous studies have shown that DSF employs various approaches to combat tumors. In

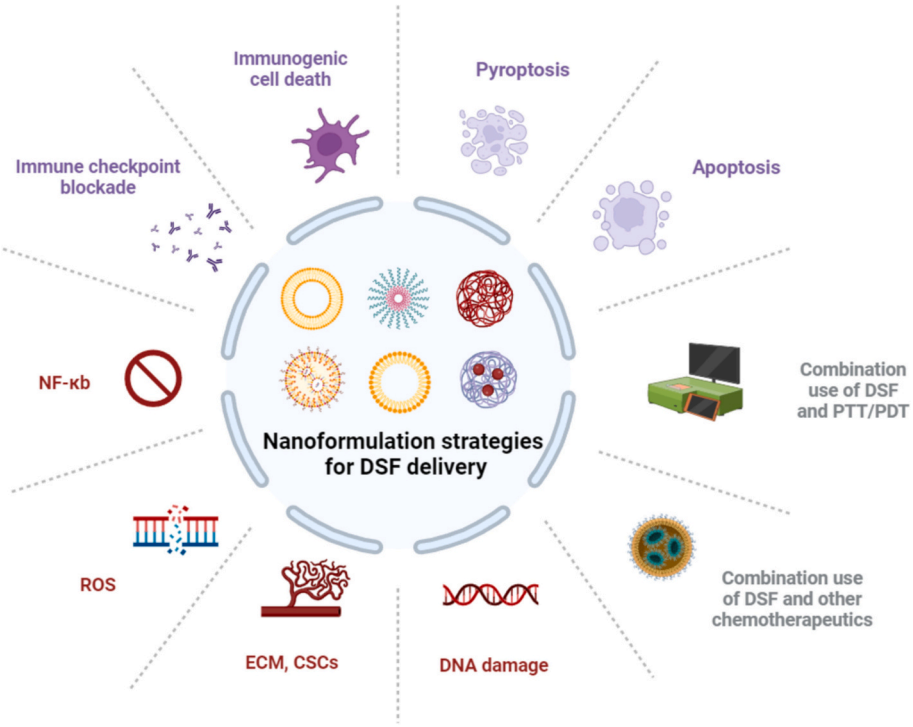

Fig. 1. The proposed anticancer mechanisms of DSF in tumor cells and tumor microenvironment.

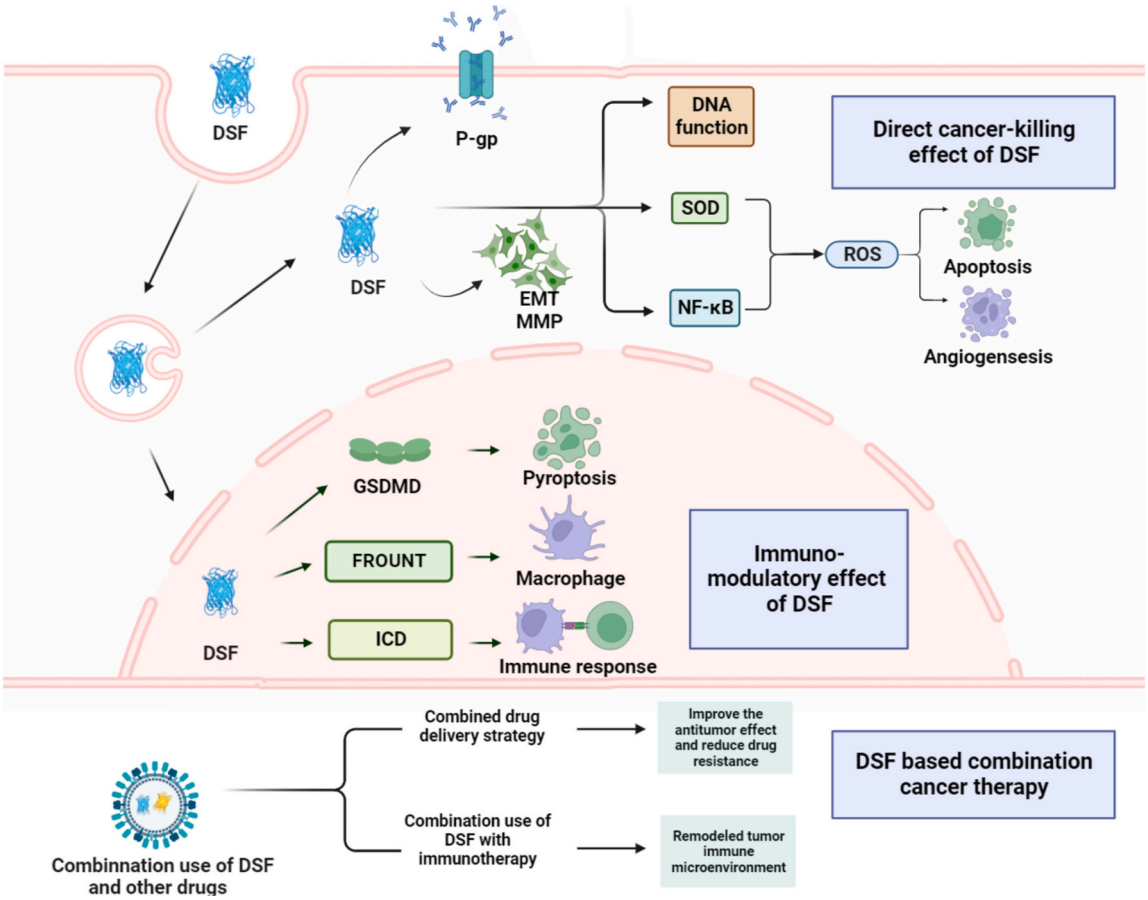

Fig. 2. The proposed anticancer mechanisms of DSF in tumor cells and tumor microenvironment.

addition, the anti-tumor effects of DSF are exerted through various mechanisms of action. Fig. 2 illustrates the mechanism by which DSF effectively treats tumors. Such as increasing the production of ROS, causing DNA damage, and impeding enzyme activity. Furthermore, DSF can target P-glycoprotein (P-gp) dysfunction, cancer stem cells (CSCs), and hinder the process of epithelial-mesenchymal transition (EMT). These actions assist in reversing drug resistance, preventing metastasis, and inhibiting tumor recurrence (Lu et al., 2022). And also, it has been reported that DSF stimulates the immune system and in the last few years there have been many studies on the effects of DSF on the immune system.[13] In addition, DSF can be combined with other medications to treat various types of cancer. Furthermore, the DSF-copper complex (DSF/Cu) has recently been recognized as a highly effective anti-cancer agent that enhances the effectiveness of radiotherapy. It can be combined with PTT or PDT to treat tumors.

2.1. Direct cancer-killing effect of DSF

Disulfiram has been found to be effective in tumor treatment. Despite the promising results observed in preclinical and early clinical studies, the use of disulfiram in cancer treatment is not without challenges. Table 1 showcases the current development and application status of DSF in clinical practice. One of the major obstacles is determining the optimal dosage and treatment duration (Greten and Grivennikov, 2019). Additionally, the treatment duration and long-term effects of disulfiram therapy in cancer patients are still being investigated.

The clinical application of disulfiram is not currently widely used beyond its use in treating alcohol addiction, but ongoing research is exploring its potential effects in other areas. In the following, I will introduce these potential effects individually.

2.1.1. ROS

Maintaining a balance in redox levels is vital for biological systems to carry out important cellular functions such as growth, differentiation, senescence, survival, and aging in humans(Kirtonia et al., 2020).Nonetheless, elevated formation of the different ROS leads to molecular damage, denoted ‘oxidative distress’(Sies and Jones, 2020).Cancer cells exhibit aberrant redox homeostasis, but while ROS are pro-tumorigenic, high ROS levels are cytotoxic. High ROS levels that would trigger senescence, apoptosis, or ferroptosis(Hayes et al., 2020). The one of anti-cancer mechanisms of disulfiram have been reported, though triggering oxidative stress by the generation of ROS, inhibition of the superoxide dismutase activity and activation of the mitogen-activated protein kinase (MAPK) pathway(Farooq et al., 2019). Metallothioneins are proteins rich in the amino acid cysteine that can bind to heavy metals like zinc and copper. They also have the capability to protect cells from oxidative stress. A new research study indicated that cells with low levels of metallothionein expression are susceptible to DSF, likely due to the correlation between the expression of metallothionein encoding genes MT1E and MT2A and the sensitivity to DSF (Corsello et al., 2020).

Table 1
The current clinical application of using disulfiram to treat diseases.

Drugs	Tumor type	Status	Identifier
Disulfiram	Germ Cell Tumor	Phase 2, Recruiting	NCT03950830
Disulfiram	Breast Neoplasm Female/ Metastatic Breast Cancer	Phase 2, Recruiting	NCT03323346
Disulfiram	Stage IV Melanoma	Phase 1/2, Completed	NCT00256230
Disulfiram	Breast Neoplasm/Metastatic Breast Cancer	Phase 1, Recruiting	NCT03323346
Disulfiram	Non-small Cell Lung Cancer	Phase 2/3, Completed	NCT00312819

2.1.2. DNA damage

Except inducing oxidative stress, DSF damages DNA to restrain cancer cell proliferation. Moreover, copper complexes have been shown to intercalate between the base pair of DNA owing to their planar conformation. It inhibits a variety of DNA-related enzymes, such as DNA polymerase, ribonucleotide reductase, DNA topoisomerases, DNA methyltransferase(Ekinci et al., 2019)and glutathione S-transferase P1 (Madala, 2018). DSF also investigated able to effect on human O^6-methylguanine-DNA methyltransferase (MGMT), a DNA repair protein and chemotherapy target that removes the mutagenic O^6-akyl groups from guanines, and thus confers resistance to alkylating agents in brain tumors. Besides, DSF was also a potent inhibitor of phosphoglycerate dehydrogenase (PHGDH), the first and limiting step of the so-called serine synthetic pathway (SSP), thus suggesting that DSF itself could display anticancer properties via alternative mechanism of action (Spillier et al., 2019).

2.1.3. ECM

In other study, which show that cell invasion and angiogenesis are crucial processes in cancer metastasis that require extracellular matrix (ECM) degradation. Additionally, DSF has been observed to decrease the formation of new blood vessels (angiogenesis) due to its ability to bind to metal ions, deactivate Cu/Zn Superoxide Dismutase (SOD), and hinder the activity of Matrix Metalloproteinases (MMP), MMPs seem to be primarily responsible for much of the ECM degradation. Furthermore, The presence of DSF hinders the function of superoxide dismutase (SOD), which is responsible for protecting against oxidative damage. This inhibition leads to an excess production of $O^{2\cdot-}$ (superoxide) and ultimately results in cell death due to oxidative stress.

2.1.4. CSCs

Recent findings support the concept that cells with the properties of stem cells are integral to the development and perpetuation of several forms of human cancer. Cancer stem-like cells (CMCs) can induce chemoresistance. Focus on the characteristics of these cells could yield new ways to thwart chemoresistance. Additionally, patient-derived bladder cancer cells produced an abundance of aldehyde dehydrogenase 1A1 (ALDH1A1), a stem cell marker. By inhibiting ALDH1A1, they repressed proliferation and spheroid formation (Namekawa et al., 2020). The DSF has been observed to have a significant role in inhibiting the activity of the ALDH enzyme and suppressing the expression of stemness-related transcription factors (Sox, Nang, Oct) in cancer stem cells derived from breast cancer cell lines in various studies (Yang et al., 2019). Nonetheless, DSF's anticancer activity is primarily caused by the aggregation of NPL4, rather than the inhibition of ALDH. This finding is important because it indicates that the viability of non-stem cancer cells is not significantly compromised by ALDH inhibition (Skrott et al., 2017). Further, other studies have found that ROS induce to CSC-associated resistance, a modest increase of ROS contributes to tumor promotion, whereas excessive levels of ROS induce cell death, apoptosis and suppression of tumor growth(Qian et al., 2018). DSF can active the ROS-p38 pathway contribution anti-cancer ability. Furthermore, the downregulation of Glypican3(GPC3) expression, which is caused independently of the ROS-p38 pathway, appeared to also be responsible for the anti-CSC effect of DSF.

2.1.5. NF-κB pathway

High NF-κB activity links inflammation and tumorigenesis. In many studies, it is concluded that previously observed antitumoral and NF-κB inhibiting activity of DSF could be attributed to their inhibition of the proteasome and degradation other regulatory redox-sensitive proteins. Besides, DSF also effectively abolished 5-FU chemoresistance, 5-FU promoted both NF-κB nuclear translocation and its DNA binding activity. In other studies, the DSF as an inhibitor of NF-κB is not only involved in epithelial-mesenchymal transition (EMT) and self-renewal of breast CMCs. They found that DSF inhibits EMT and stem-like properties in

breast cancer cells associated with inhibition of the ERK/ NF-κB/Snail pathway.

2.1.6. Reversal of drug resistance and recurrence by enzyme inactivation

Disulfiram forms chemical bridges with key cysteine residues found near the active sites of enzymes and proteins such as ALDH, MGMT, PHGDH, and P-gp. This bridging process is the chemical mechanism that leads to inhibition. P-gp is a membrane-bound efflux pump driven by adenosine triphosphate (ATP) that pumps various cytotoxic drugs out of the cell, leading to the development of multidrug resistance.An approach to inhibit P-gp would be to covalently modify cysteine residues within the NBDs. The results in that study indicate that metabolites of disulfiram can covalently inactivate P-gp due to modification of Cys1074 in NBD2.

The therapeutic effect of combining DSF with conventional cancer drugs like cisplatin and doxorubicin (DOX) has been proven to be enhanced. DSF conjugated with DOX showed significant accumulation in drug-resistant cells, effectively inhibiting the activity of P-gp and restoring cellular apoptotic signaling pathways. In addition, the simultaneous use of DSF and cisplatin (GC) altered the cellular distribution of the GC efflux transporter ATP7A, enhanced the formation of DNA-platinum adducts, and facilitated apoptosis (Kita et al., 2019). It is notable that while DSF has minimal toxicity without added copper, it functions as both an inducer of apoptosis and an inhibitor of P-gp when copper is present (Lu et al., 2022). Apart from this, $Cu(DDC)_2$ could induced cancer cell death through paraptosis, the paraptosis is caspase-independent cell death (Chen et al., 2018b).

2.2. Immuno-modulatory effect of DSF

During the 1980s, DSF was documented to be a successful immune system booster (Johansson, 1992). In the past few years, researchers have discovered that DSF possesses the capability to trigger immunogenic cell death (ICD) in cancer cells, resulting in immune responses that target tumors. However, the exact mechanism by which DSF affects colorectal tumor cell death and regulates ICD is still not fully understood (You et al., 2019). ICD refers to any type of cell death that releases damage-associated molecular patterns (DAMPs) and stimulates anticancer immunity (Zhou et al., 2019). Research is required on the mechanism of cell death known as immunogenic cell death (ICD) induced by the drug disulfiram (DSF). Gao et al. conducted a study showing that treatment with DSF and copper led to the release of certain molecules associated with cellular damage, such as calreticulin, ATP, and high mobility group box 1. This in turn triggered the maturation and activation of dendritic cells. Furthermore, the combined treatment of disulfiram and copper improved the effectiveness of blocking CD47, a protein involved in immune evasion (Gao et al., 2022). Additionally, another study conducted in 2020 found that apart from directly causing cell death, DDC can effectively stimulate immunogenic cell death (ICD) in cancer cells, leading to the modification of the immunosuppressive tumor microenvironment (TME). This can potentially improve the efficacy of immune checkpoint blockade (ICB) therapy by triggering a systemic immune response (Li et al., 2022). Besides, Hu et al. find that DSF with copper also could combination significantly inhibits CRC cell viability and mainly induces autophagy by targeting ULK1 instead of apoptosis, a large number of studies demonstrates that antitumor drugs can effectively eliminate tumor cells by inducing autophagy (Hu et al., 2021).

The lack of FROUNT significantly slows down the advancement of tumors and reduces the activity of macrophages in promoting tumor growth. FROUNT is found to be abundantly present in macrophages, and when specifically deleted in these immune cells, it hampers tumor development. Furthermore, the study reveals that DSF has a strong inhibitory effect on FROUNT. DSF interferes with FROUNT's binding domain for chemokine receptors, resulting in the suppression of macrophage responses (Terashima et al., 2020). In 2022, Wang et al. found that DSF directly activates TCR signaling, activation of the T-cell antigen receptor (TCR)-CD3 complex is critical to induce the anti-tumor response of $CD8^+$ T cells. Mechanistically, DSF covalently binds to Cys20/Cys23 residues of lymphocyte-specific protein tyrosine kinase (LCK) and enhances its tyrosine 394 phosphorylation, thereby promoting LCK kinase activity and boosting effector T-cell function, interleukin-2 production, metabolic reprogramming, and proliferation (Wang et al., 2022a). Furthermore, Hu et al. proved that DSF as an effective inhibitor of GSDMD pore formation, cleaved GSDMD forms membrane pore lead to cytokine release and inflammatory cell death (pyroptosis) (Hu et al., 2020b). Moreover, in other study identified DSF could effectively inhibit NLRP3 inflammasome activation and suppress pyroptotic cell death. DSF prevented lysosomal cathepsin B releasing into the cytoplasm, which in turn inactivated the NLRP3 inflammasome (Deng et al., 2020).

To put it simply, DSF has various ways of disturbing the operations of cancer cells, including destroying the balance of redox reactions, triggering programmed cell death, overcoming resistance to drugs, and controlling the immune environment. These findings indicate that DSF could be a promising treatment addition. It is excellent that the synergistic or additive effects of multiple anticancer mechanisms will effectively kill the cancer cells by targeting multiple pathways and avoid or delay the emergence of acquired resistance (Kang et al., 2021).

2.3. DSF based combination cancer therapy

2.3.1. Combination use of DSF and other chemotherapeutics

The use of traditional chemotherapy drugs alone often leads to tumor cells developing multidrug resistance (MDR), which greatly limits the effectiveness of the treatment. To address this issue, a promising approach is to combine MDR modulators with chemotherapeutic drugs, as it proves to be an effective strategy in combating drug-resistant tumor cells. The use of DSF as an MDR modulator, when combined with specific chemotherapeutic drugs, can effectively overcome drug resistance and enhance their effectiveness through a synergistic effect. Multiple experiments and clinical evidence have demonstrated that this strategy of combining drug delivery improves the anticancer efficacy, while also reducing drug resistance and toxicity. In previous studies, the main focus was on summarizing the co-delivery strategies of DSF in combination with other chemotherapeutics.

Multiple studies have investigated the use of DSF in combination with other medications to treat various types of cancer. For breast cancer specifically, a combination of DSF with chemotherapy drugs like docosahexaenoic acid, paclitaxel, and cisplatin has been utilized. This combination aims to increase cellular oxidative stress, suppress the formation of mammospheres (clusters of breast cancer cells), and inhibit the activity of P-glycoprotein (a protein associated with drug resistance) (Yang et al., 2019). The effectiveness of doxorubicin (DOX) has been restricted due to the development of multidrug resistance (MDR). MDR occurs when excessive levels of P-gp on tumor cells lead to the expulsion of DOX, reducing its accumulation within the cells and diminishing its ability to fight against tumors. Table 2 provides a valuable insight into the combined use of disulfiram and other chemotherapy drugs in clinical practice. This approach has shown promising outcomes and holds immense potential for enhancing the efficacy of cancer treatment.

2.3.2. Combination use of DSF and immunotherapy

The combination use of DSF with immunotherapy has shown remarkable success in preclinical and clinical studies. In a study conducted on mice with breast cancer, the combination use of DSF and immune checkpoint inhibitors resulted in a significant reduction in tumor size compared to the use of either method alone. Another study conducted on mice with melanoma showed that the combination use of DSF with CAR T-cell therapy resulted in complete tumor regression in all mice treated with the combined therapy (Namekawa et al., 2020).

Those researches indicate that disulfiram has the potential to

Table 2
The current development of the combination of disulfiram and other drugs in clinical.

Drugs	Tumor type	Status	Identifier
Disulfiram/ Copper/ Alkylating Agents	Glioblastoma	Phase 2/3, Completed	NCT02678975
Disulfiram and cisplatin	Gastric Cancer	Not Applicable	NCT05667415
Disulfiram/ Copper/ Alkylating Agents	Glioblastoma	Phase 2/3, Completed	NCT02678975
Disulfiram/ Metformin	Glioblastoma	Early Phase 1, Terminated (Problems with including patients)	NCT03151772
Disulfiram/ Gemcitabine Hydrochloride	Metastatic Pancreatic Adenocarcinoma/ Refractory Malignant Solid Neoplasm/Stage IV Pancreatic Cancer	Phase 1, Recruiting	NCT02671890
Disulfiram/ Copper Gluconate/ Liposomal Doxorubicin	Relapsed Sarcomas	Phase 1, Recruiting	NCT05210374
Disulfiram/ Copper gluconate/ Temozolomide	Glioblastoma	Early Phase 1, Completed	NCT01907165
Disulfiram/ Copper Gluconate	Multiple Myeloma	Phase 1, Terminated (Closed at PI's Request)	NCT04521335
Disulfiram/ Copper gluconate	Prostate Cancer	Phase 1, Terminated (Study stopped due to lack of efficacy)	NCT02963051
Disulfiram/ Copper Gluconate	Solid Tumors Involving the Liver	Phase 1, Completed	NCT00742911
Disulfiram/ Copper Gluconate	Metastatic Pancreatic Cancer	Phase 2, Completed	NCT03714555

enhance and support the effectiveness of anticancer immunotherapy. The combination of Cu/DSF treatment with anti-PD-1 therapy can greatly improve the therapeutic effects of immune checkpoint blockade (ICB) therapy. This is achieved by enhancing the function and presence of immune cells in the tumor microenvironment (TME), which helps to counteract the immunosuppressive factors (Li et al., 2022). In other study, they found when the coloaded with regorafenib and Cu/DSF repolarized the tumor-promoting $CD206^{hi}$ TGF-$\beta1^{+}$ MΦ via inhibition of FROUNT and thus remodeled tumor immune microenvironment. The treatment efficacy demonstrated the macrophage-mediated innate immunity (Zhao et al., 2021). Komarova and her colleagues demonstrated that the utilization of DSF, a confirmed inhibitor of aldehyde dehydrogenase 2 (ALDH2), could be an effective method for activating bispecific antibodies derived from trastuzumab and pertuzumab plant biosimilars (bi-TPB-PPB), which have shown efficacy in treating breast cancer. Additionally, they found that DSF is able to induce cell death in breast cancer cells while causing the accumulation of formaldehyde (Komarova et al., 2019). Furthermore, the ALDH1A1 inhibitor DSF and chemotherapeutic agent gemcitabine cooperatively inhibited breast tumor growth and tumorigenesis by purging $ALDH^{+}$ TICs and activating T-cell immunity (Liu et al., 2021).

2.3.3. Combination use of DSF and PTT/PDT

The increasing evidence demonstrated the role of DSF in enhancing the role of DSF in enhancing the radiosensitivity of tumor cells in number of alternative mechanisms. Recent studies have also elaborated the advances of this drug in radiobiology (Wang et al., 2020). Extensive research has shown that DSF has a significant protective effect against radiation. In a study conducted half a century ago, Stromme et al. administered DSF to mice, which resulted in the drug being metabolized to DTC. As a result, all of the animals were successfully protected against the harmful effects of ionizing radiation. Since then, other findings have identified that radiation exposure could produce highly reactive free radicals, and DSF was a potent antioxidant that protected deoxyribose against damage in normal cells. Overall, the results of the DSF study show its potential as an effective radioprotector.

Recently, great progress has been made in the field of DSF with PDT and PTT, especially in the development of synergistic therapy strategies, such as the combination of PDT or PTT with chemotherapeutic modalities (Zhi et al., 2020). Furthermore, the breast tumor is a superficial mass of tissue that can be targeted for tumor ablation using photothermal therapy (PTT). In this study, ultrasmall CuS nanoparticles were used as both Cu^{2+} providers and photothermal agents. These nanoparticles were attached to the surface of hollow mesoporous organosilica nanoparticles (HMONs) through a linker. Meanwhile, the drug doxorubicin prodrug (DSF) was encapsulated within the mesopores and hollow interior of the HMONs (Zhang et al., 2021).The combination of chemotherapy and photothermal therapy(PPT) has become a hot topic in clinical research due to the high selectivity and excellent therapeutic effect. Herein, by taking advantage of the interactions between CuS and DDTC, a new multifunctional nanoplatform based on DDTC loaded CuS (CuS-DDTC) NDs is successfully fabricated, leading to the achievement of the synergistic effect of photothermal and copper enhanced chemotherapy (Tang et al., 2020). Currently, surgery is the only available and effective clinical strategy for treating malignant peripheral nerve sheath tumors. To solve this critical issue, DSF-CuO_2@DMSN nanoparticles were rationally designed. These nanoparticles have been engineered to exert high performance and synergistic sonodynamic/chemodynamic/chemotherapeutic tumor treatment under the stimulation of ultrasound by producing reactive oxygen species and dithiocarbamate-copper complexes in situ in response to the tumor-specific acidic and hypoxic microenvironment (Wang et al., 2023).

Researchers have conducted clinical and experimental trials to test new combinations of therapies, aiming to enhance the effectiveness of cancer treatment while reducing toxicity and drug resistance.

3. Clinical applications

The translation of DSF (disulfiram)-based therapies into clinical practice is confronted with a number of challenges and limitations. The antitumour activity of DSF is contingent upon its chelation with Cu^{2+} to form the CuET complex. The efficiency and specificity of this process in vivo are pivotal to the efficacy of the treatment. However, the uneven distribution of Cu^{2+} in the human body and the potential toxicity issues associated with it restrict the applicability of DSF. Secondly, the pharmacokinetic properties and metabolic processes of DSF in vivo may influence its concentration and activity in tumor tissue, resulting in clinical outcomes that are not as optimal as those observed in laboratory conditions. Furthermore, the precise mechanism of action of DSF against tumors remains unclear, which increases the uncertainty of its clinical applications (Hulanicki, 1967). To surmount these challenges, researchers are investigating novel drug delivery strategies and drug carrier systems, including the utilization of nanoparticles as carriers for DSF, with the objective of enhancing its specificity and efficacy in tumor tissue. These nanosystems are capable of responding and releasing DSF within the tumor microenvironment, while simultaneously reducing the impact on surrounding normal tissues. Furthermore, combination strategies involving the use of DSF in conjunction with other ant-itumour drugs are being investigated with the objective of enhancing the therapeutic effect and reducing the incidence of drug resistance. For example, DSF can be combined with drugs such as alkylating agents, doxorubicin, and vincristine to enhance cytotoxicity and reverse drug

resistance (Stokes et al., 2024).

In conclusion, despite the potential anti-tumor effects of DSF, challenges in drug delivery, pharmacokinetic properties, mechanism of action and combination therapy strategies must be addressed for its successful translation into clinical practice.

3.1. Drug Characteristics and Pharmacokinetics

Disulfiram is an oral medication with a standard dosage of 250–500 mg per day, with a maximum recommended daily dose of 500 mg (Stokes et al., 2024). Following oral administration of disulfiram, approximately 80–90 % of the dose is absorbed via the gastrointestinal tract. Due to its high fat solubility, disulfiram and its metabolites are widely distributed in body fat tissue and readily cross the blood-brain barrier (Triscott et al., 2012). In a study employing the injection of radiolabeled disulfiram into rats, the drug was identified in the kidneys and pancreas (Faiman et al., 1980).

The pharmacokinetics of disulfiram remain poorly understood. A number of studies have examined the elimination of disulfiram and its metabolites in human volunteers and animals with half-lives. A comprehensive analysis of the pharmacokinetic data from these studies is lacking, partly due to the limitations of the detection methods employed and the lack of consensus within the field regarding the detection of disulfiram in samples (Hulanicki, 1967; Koppaka et al., 2012).

Dithiothreitol is extensively metabolized in vivo and rapidly biotransformed to metabolites, which provides the basis for its clinical use. Once dithiothreitol is reduced, all subsequent metabolism occurs via DDTC in humans, The initial dose of dithiothreitol (or DDTC) is rapidly eliminated from the plasma. In some instances, this rapid decline is succeeded by a longer terminal elimination phase (Faiman et al., 1984; Shen et al., 2001). The in vitro half-life of disulfiram following its addition to plasma is 2 to 4 min. The half-lives of disulfiram in studies with rats and mice have been reported to range from 10 to 87 min (Gaval-Cruz and Weinshenker, 2009). However, in the majority of studies, the half-life was below the level of detection. In human studies, the half-lives of disulfiram and DDTC were estimated to be 7 and 15 h, respectively (Fuller et al., 1986). This range demonstrates that there is considerable inter-subject variability in the disposition of disulfiram and its metabolites following oral administration (Mihic et al., 2017). Other studies have identified considerable and unexplained discrepancies in plasma dithiol levels between subjects. A study conducted in the 1970s utilizing gas chromatography revealed that following the administration of 250 mg of dithiol to human subjects, the mean plasma concentration was 590 $\pm$ 434 ng/mL, with a range of 30–1830 ng/mL. A follow-up study conducted in 1991 utilizing high-performance liquid chromatography revealed that following the administration of 200 mg of disulfiram to an individual, the median plasma DDTC-Me concentration was 15.02 ng/mL, with a range of 1.63–77.08 ng/mL. Although the two studies in question analysed different metabolites, both demonstrated that the metabolism of disulfiram exhibits significant inter-subject variability (Anton, 2001; Keane et al., 1984).

The considerable unpredictability of plasma dithiol levels presents a significant challenge to the practical application of dithiol in human therapy, as this variability has the potential to affect its efficacy and safety. This variability may explain the phenomenon observed in a study of 63 individuals, in which dithiol-ethanol reactions were not induced in nearly half of the alcohol-exposed individuals by a daily dose of 200–300 mg of dithiol (Bahji et al., 2022; Gaval-Cruz and Weinshenker, 2009). In some cases, even a dose of 500 mg was insufficient to induce such a reaction. Furthermore, differences in serum levels between patients may also explain the rare but serious risk of occurrence even at lower doses of 250 mg daily. The paucity of pharmacokinetic studies conducted in humans has resulted in ambiguity regarding inter-subject variability, which in turn has hindered our understanding of the effectiveness and safety of disulfiram (Koppaka et al., 2012).

3.2. Side effects and toxicity

The clinical application of disulfiram is constrained by its extensive range of adverse effects, most notably the disulfiram-ethanol reaction. The administration of disulfiram necessitates the complete abstinence from alcohol and the avoidance of various household products, which may prove onerous or impractical for a considerable proportion of patients. Furthermore, disulfiram can also cause rare but serious side effects, and thus doctors prescribing disulfiram must carefully assess whether there are any drug-drug interactions (Reagan-Shaw et al., 2008).

Disulfiram is a pharmaceutical agent utilized for the treatment of chronic alcohol dependence. Its adverse effects and toxicities have been extensively documented in the medical literature. The following section outlines the primary adverse effects and toxicities associated with this medication (Ito et al., 1999; Reinhardt et al., 2018). (1) Neurological adverse effects include: Peripheral neuropathy, characterized by numbness and tingling in the hands and feet, weakness, and reduced sensation to pain and temperature, may be caused by disulfiram. Furthermore, disulfiram and its metabolites traverse the blood-brain barrier, which may result in adverse reactions within the central nervous system, including confusion, hallucinations, and cognitive impairment. (2) Liver toxicity: Although uncommon, disulfiram has the potential to precipitate serious liver disease. In the event of the emergence of symptoms such as persistent nausea, vomiting, severe abdominal pain, dark urine and jaundice, it is imperative to seek immediate medical attention. (3) Dermatological reactions: Disulfiram has been observed to precipitate the development of acneiform eruptions and urticarial lesions on the skin. (4) The cardiovascular system may also be affected. The co-ingestion of disulfiram and alcohol may precipitate a constellation of symptoms, including flushing, headache, dizziness, nausea, vomiting, hypotension, tachycardia, cardiac arrhythmias, and dyspnea. In cases of severe toxicity, the potential for acute congestive heart failure, respiratory depression, loss of consciousness, convulsions, and muscle tremors exists. (5) Allergic reactions: Although uncommon, disulfiram has the potential to elicit severe allergic reactions, including dermatological manifestations such as rashes, pruritus, and oedema of the face, tongue, and throat. Additionally, it may precipitate symptoms such as dizziness, dyspnoea, and other forms of respiratory distress. (6) It is important to be aware of potential drug interactions when taking disulfiram. Disulfiram has the potential to inhibit the activity of cytochrome P450 enzymes in the liver, which may result in altered drug metabolism and an increased risk of toxic serum levels for other drugs. (7) Additionally, rare side effects may manifest as optic neuritis, myocardial lesions, and blood disorders such as methemoglobinemia.

4. Nanoformulation strategies for DSF delivery

A drug delivery system of DSF is a method of transporting drug substances to the area in need of treatment. Nano-delivery refers to a type of technology used in drug delivery systems. Nano-delivery systems can deliver drugs to the lesion through multiple pathways such as cell selectivity, drug hydrophobicity, and drug hydrophobicity, thereby enhancing efficacy and reducing side effects (Chen et al., 2018a).

In recent years, various nano delivery systems have been applied to the transfer and release of disulfiram (Lu et al., 2022). For example, researchers use lipid nanoparticles as carriers for disulfiram and used to improve its bioavailability and reduce side effects. This nano delivery system can regulate the distribution and release of nanoparticles in the body by changing their size, shape, and surface electrical properties. In addition, researchers have also explored other types of nanomaterials such as nanofibers, magnetic nanoparticles, quantum dots, as carriers to deliver disulfiram. These nanomaterials can be incorporated into disulfiram through various methods, such as electrochemical, physical adsorption, chemical modification, and released in vivo (Greten and Grivennikov, 2019). In addition, researchers have also explored other

types of nanomaterials such as nanofibers, polymeric NPs, MOF, as carriers to deliver disulfiram. These nanomaterials can be incorporated into disulfiram through various methods, such as electrochemical, physical adsorption, chemical modification, and released in vivo.

Overall, nanodelivery technology is an effective method for optimizing the efficacy and reducing side effects of disulfiram. However, there are still some issues with nanodelivery systems, such as the toxic side effects of drugs, the stability of nanomaterials, and the impact of surface modifications on biocompatibility (Chen et al., 2018b). Therefore, researchers need to continue exploring and optimizing nanodelivery systems to meet the growing medical needs. Here, we summarize the various DSF delivery strategies developed in previous research, including physical encapsulation methods (Table 3).

4.1. Liposome

Liposomes are bilayer vesicles composed of phospholipids, which were first discovered by a British scientist, Bangham. In the past 20 years, the interest in lipid vesicles, also referred to liposomes, to develop drug carriers has increased. All about that the simplicity of their preparation, there has been considerable interest to fabricate drug delivery systems, which sustain a good delivery without inducing any systemic reactions in human body as a classic dosage form for drugs.

Liposomes represent one of the most successful nanoparticle platforms with numerous products already approved by FDA (Wehbe et al., 2016). Zhang et al. have developed a new method to design lipid nanocapsules loaded with DSF with PEG-shedding ability (DSF-S-LNCs), which have oily cores and nonionic hydrophilic and lipophilic surfactant shells. Its excellent therapeutic action and targeting properties are shown in Fig. 3A-B. High loading of hydrophobic cargo in LNCs is effective in reversing multidrug resistance. To avoid capturing by the RES and enhance permeability and retention, PEG coating (hydrosterate-PEG660) is added. By responding to extracellular low pH and becoming exposed, TAT peptide conjugates with intracellular Cu in cancer cells. This results in the formation of $Cu(DCC)_2$ which can act on protease-mediated apoptosis, leading to increased toxicity on tumor cells (Wehbe et al., 2016). DSF can act as an active anticancer agent in the presence of copper, but recent research has focused on administering DSF as an anticancer drug by enhancing its accumulation and release in tumor tissues while reducing its exposure in normal tissues. However, clinical trials so far have been unsuccessful (Najlah et al., 2019; Wehbe et al., 2017). However, introducing external copper ions can also pose a risk of toxic effects on the body. As a result, researchers in another study created calcium phosphate nanoparticles (LCP NPs) that were modified with PEG to safely load both Cu^{2+} and DSF. Schematic drug design and other experiments for the treatment of tumor are shown in Fig. 3C-E. In this system, the inner core of calcium phosphate captured Cu^{2+} to minimize the leakage of heavy metal ions. The outer layer, loaded with DSF, a drug, not only stabilized the structure but also allowed for simultaneous delivery of DSF and Cu^{2+} through intravenous injection. This, in turn, improves the effectiveness of anti-PD-1 therapy, which targets the programmed cell death protein 1. Copper-LCP/DSF nanoparticles have the potential to function as an inducer of immunogenic cell death (ICD), thereby initiating a systemic immune response against tumors (Li et al., 2022).

In this part, we focus on the different liposome delivery of DSF in cancer therapy. It was stated separately that DSF-loaded lipid nanocapsules, DSF inside the aqueous core of liposomes, or co-encapsulating Cu and DSF in liposomes. Those nanomedicine formulations of DSF all would be a promising nano-therapeutic. Many factors contribute to the success of liposomes as a platform for drug delivery. The development of remote candidate drug loading process was significant (Wehbe et al., 2016).

Table 3
Delivery carriers for encapsulating DSF.

Carriers	Materials	Cancer type	Refs.
Liposome	PGA-g-PEG	Liver Cancer	[48]
	DOPA, DPPC, DSPE-PEG_{5k}	Cancerofcolon	[15]
Polymer nanoparticle	PEG, PLGA	Breast cancer	[54]
	PCL-b-PGLu-g-mPEG	Breast tumor	[56]
Micelle	$MPEG_{5000}$, PCL_{5000}, MCT	Liver Cancer	[59]
	PEG_{2000}, PLA_{1800}	Breast cancer	[41]
Metal nanomaterials	CuS	Glioma	[67]
	ZnO	Breast cancer	[68]
Metal-organic framework	ZIF-8	Brain tumor	[14]
	$HZIF_{Cu}$	Breast cancer	[73]
Hollow nanoplatform	CuS	Breast cancer	[45]
	Fe3O4	Breast cancer	[79]

4.2. Polymer nanoparticle

There has been significant research on using polymer nanoparticles as carriers for drug delivery systems (DDS). These nanoparticles have the potential to enhance the effectiveness of therapy and reduce the side effects of the drug. Moreover, it is easy to modify the surface and function of these nanoparticles using specially designed amphiphilic polymers. As a result, polymeric nanoparticles have gained considerable interest as carriers for DDS.

Encapsulating a chemotherapeutic drug in a nanoparticle offers a number of advantages, such as protection from degradation in the blood stream, improved drug solubility. Nanoparticles tend to be manufactured using biodegradable polymers like poly (lactic-*co*-glycolic acid) (PLGA) or polycaprolactone (PCL) and have been shown to have increased efficacy and reduced toxicity compared to conventional delivery of chemotherapeutic drugs (Najlah et al., 2017). Further improve the drug delivery performance, the study engineered passively-targeted DSF-nanoparticles (DSF NPs) using biodegradable monomethoxy (polyethylene glyc*o*l) D,L-lactic-co-glycolic acid (mPEG-PLGA) matrix. All because of PEG forms a hydrophilic coat over the hydrophobic PLGA core and protects the formulation from being engulfed by the reticuloendothelial cells (RECS) giving a stealth behavior and confers long circulation properties by acting ad steric stabilizer. PEG minimizes the ionic strength which stabilizes the nanoparticles from aggregation in physiological solution (Madala, 2017). The group that received the final injection demonstrated enhanced anti-tumor effects, resulting in a reduction in tumor volume (Fig. 4A). Further, combination therapy with different functional chemotherapeutic agents based on nano-drug delivery systems is an effective strategy for the treatment of breast cancer. In this study, PCL-b-PGlu-g-mPEG copolymer was designed and synthesized to develop a nanocarrier for the co-delivery of doxorubicin (DOX) and DSF (Fig. 4B-C). They successfully created the amphiphilic copolymer self-assembled into core-shell-corona structured nanoparticles with the hydrophobic PCL core for DSF loading (hydrophobic interaction) and anionic poly (glutamic acid) shell for DOX loading (electrostatic interaction) (Tao et al., 2018). This study shows that the final formulation exhibits enhanced anti-tumor effectiveness, as determined by evaluating the tumor size.

In brief, the delivery DSF though polymer nanoparticles (PNPs) have a number of key advantageous characteristics such as tissue-penetrating ability, high payload, a sustain drug release profile, drug protection from enzymatic digestion, passive targeting, etc. However, PNPs possess some limitations that include polymer degradation, drug release outside the diseased tissue.

4.3. Micelle

Self-assembly of amphiphilic polymers with hydrophilic and hydrophobic units results in micelles, where polymer concentrations are above critical micelle concentrations (CMCs). Recently, micelles with metal nanoparticles (MNPs) have been utilized in many bio-applications (Perumal et al., 2022). Micelles successfully used for the solubilization of various poorly soluble pharmaceuticals and demonstrate a series of

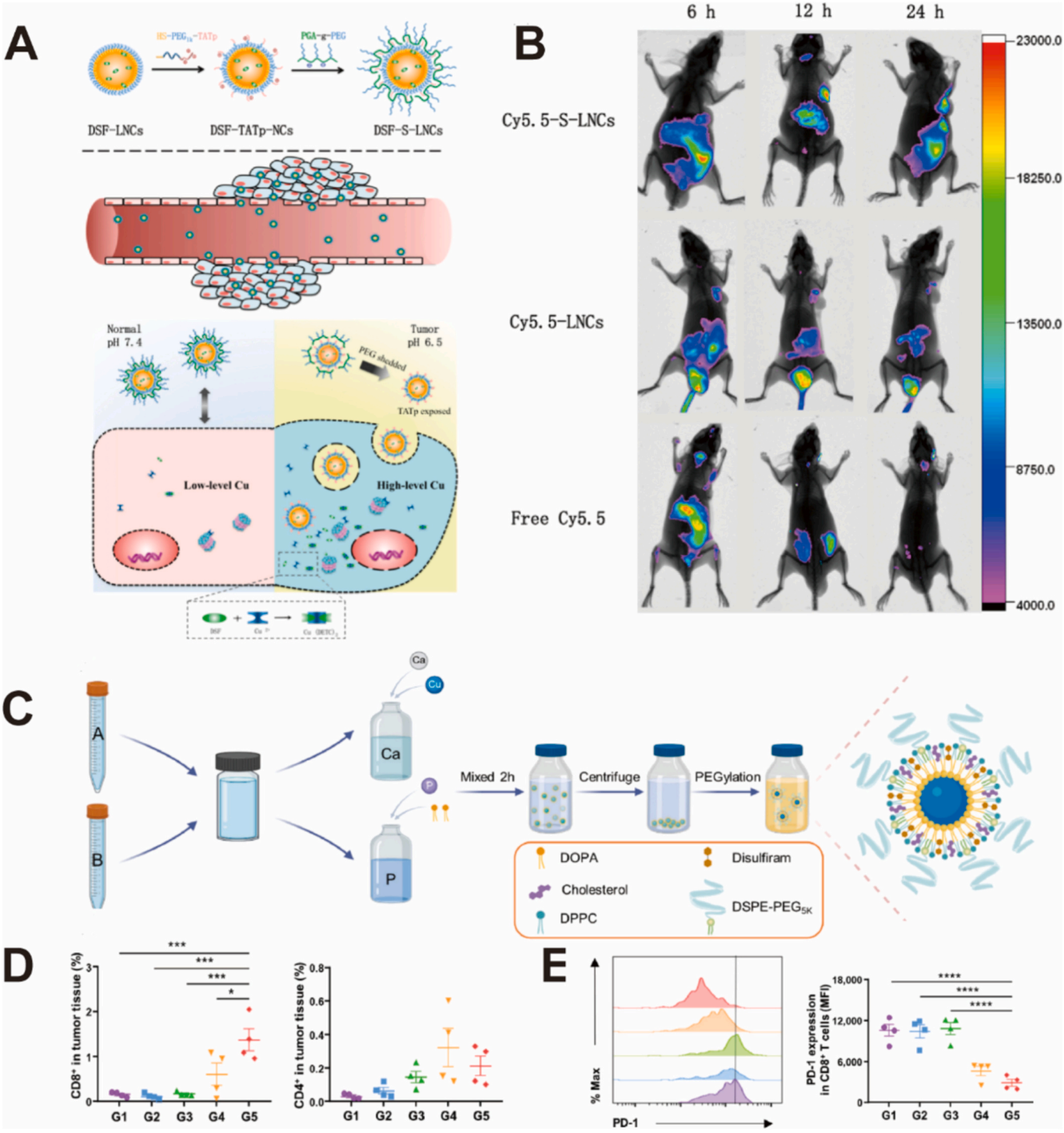

Fig. 3. (A) Structure and Treatment Strategy of DSF-S-LNCs. (B) NIRF imaging in tumor-bearing mice after the intravenous administration of Cy5.5-S-LNCs, Cy5.5-LNCs, and free Cy5.5. Reproduced from ref.(Nguyen et al., 2020) with permission from ACS Publications, copyright 2015. (C) Scheme illustrating the fabrication procedure of the Cu-LCP/DSF NPs. (D) Representative flow cytometric plots and corresponding quantification results of T cell infiltration within tumors. (E) PD1 expression on TILs after various treatments indicated. Reproduced from ref.(Li et al., 2022) with permission from Elsevier, copyright 2022.

attractive properties as drug carriers. Polymeric micelles, micelles formed by amphiphilic block *co*-polymers possess high stability both in vitro and in vivo and good biocompatibility.

Several studies prepared micelle-based DSF delivery systems where DSF was loaded in the hydrophobic region of micelles. In this studies, DSF was successfully encapsulated in pluronic micelles and which in vitro release studies showed that DSF was slowly released from the micelles (Tawari et al., 2015). Further improvement the more effective cellular up take ability of tumor cancer of drugs, and the unstable of micelles is a significant problem for their in vivo application (Huo et al., 2017). To improve DSF of drug-loading and plasma stability, Zhuo et al. develop an injectable formulation, DSF was encapsulated into mixed DSF-NPs($mPEG_{5000}$-PCL_{5000}/PCL_{5000} + 20 %MCT) through a high-pressure homogenization method. mPEG5000-PCL5000 were blended to reduce the leakage of DSF during preparation, as well as increase the stability of the nanoparticles. Apart from the hydrophobic

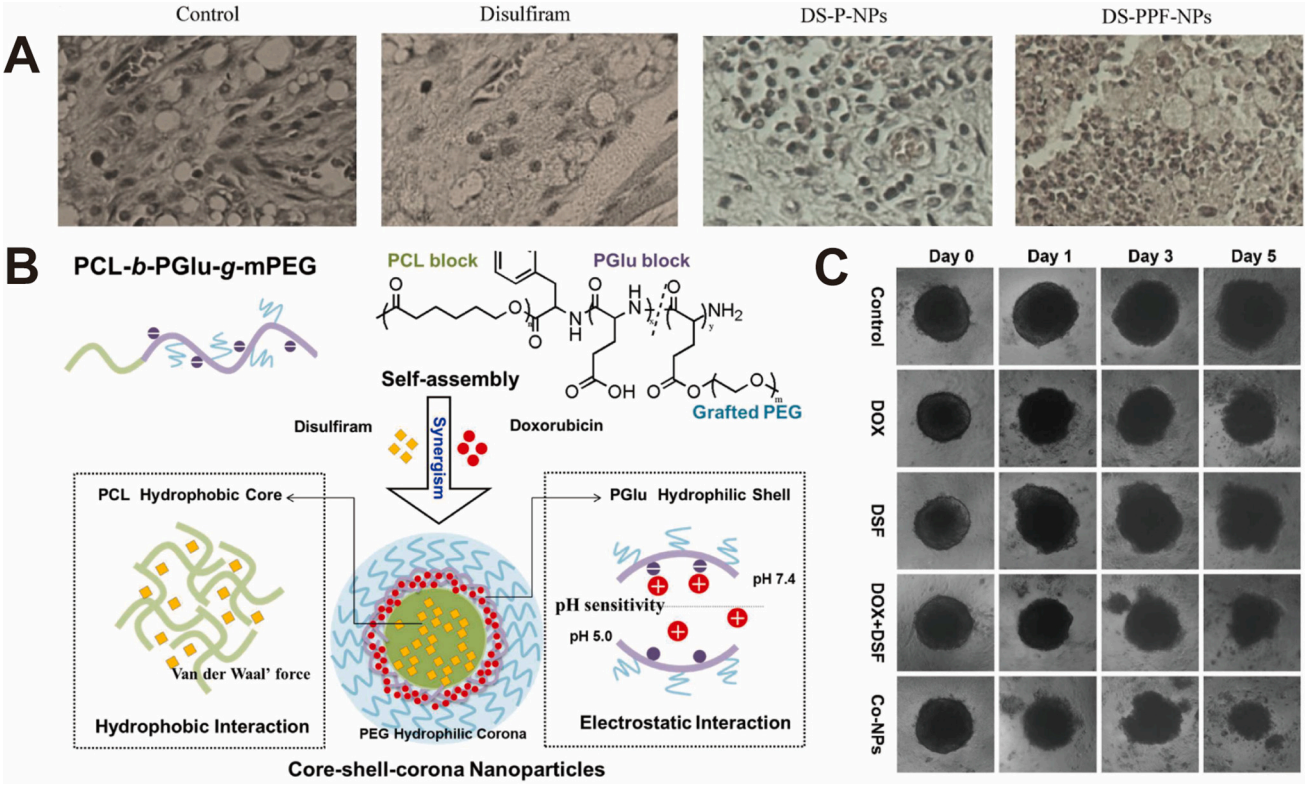

Fig. 4. (A) The comparison between tumor volume of control, disulfiram, DS-P-NPs and DS-PPF-NPs injection groups. Reproduced from ref.(Madala, 2017) with permission from BMC, copyright 2016. (B) Schematic illustrations of DSF and DOX loading. (C) Inhibition of 3D tumor cell spheroid growth. Reproduced from ref. (Tao et al., 2018) with permission from RSC, copyright 2018.

crystallization inhibitor medium chain triglyceride (MCT) was added in order to increase the drug loading and stability of DSF-NPs by reducing the core crystallinity of the nanoparticles (Fig. 5A-B)(Zhuo et al., 2018). However, this method has drawbacks such as low stability and inconsistent drug loading and release kinetics between different batches (Kolishetti et al., 2010). To address the aforementioned issues, a smart pH-sensitive polymeric micelles system was developed. This system was designed to deliver both hydrophilic DOX and hydrophobic DSF simultaneously. Initially, DOX was linked to a derivative of poly (styrene-*co*-maleic anhydride) (SMA), using adipic dihydrazide (ADH) and an acid-cleavable hydrazone bond. Subsequently, DSF was enclosed within the micelles formed by the self-assembly of the SMA-ADH-DOX (SAD) conjugate (Zhuo et al., 2018). There are reports stating that DSF can cause cell death by various means. These include blocking proteasome activity, stopping NF-κB from moving to the cell nucleus, and triggering the production of reactive oxygen species (Duan, 2013). Moreover, Kang et al. developed a novel [copper sulfide nanoparticle (CuS NP) + disulfiram prodrug (DQ) micelle + near infrared (NIR) laser](CDL) combination therapy. An advance of the CDL therapy can effectively induce immunogenic cell death (ICD), the induction of ICD will bolster adaptive anticancer immune responses to suppress cancer metastasis and potentially enhance the efficacy of immune checkpoint inhibitors. By analyzing the biomarkers associated with immune checkpoint dysfunction (ICD), it can be shown that the formulation has anti-tumor effects by influencing the immune system (Fig. 5C) (Kang et al., 2021).

In conclusion, the development of biocompatible and biodegradable drug carriers possessing small size, high loading capacity, extend circulation time, ability to accumulate in required pathological sites in the body, and capable of carrying poorly soluble pharmaceuticals still has many unresolved issues. The availability of such micelles is especially important on the background of the fact that therapeutic application of hydrophobic, poorly water-soluble agents is associated with various serious problems.

4.4. *Metal nanomaterials*

Metal-containing nanomaterials have garnered significant interest in recent times due to their distinctive biological, physical, and chemical characteristics that manifest upon entry into tumor cells, commonly known as the biological effect (Lei et al., 2023). Metal-based nanomaterials are recognized for their distinctive benefits and are categorized into five main directions: enhancing the efficacy of radiotherapy, catalytic therapy, promoting ferroptosis, inducing pyroptosis, and enhancing immunotherapy through metal-based approaches (Yaqoob et al., 2020).

In recent times, numerous sonosensitizers have been created with the goal of improving the effectiveness of sonodynamic therapy (SDT) by enhancing the production of reactive oxygen species (ROS)(Lai et al., 2022). Metal-organic complexes, also known as MOCs, are formed when metal ions or clusters coordinate with organic ligands. These complexes have high potential for use in Sonodynamic Therapy (SDT) applications because of their distinct ability to respond to sound and efficiently diffuse Reactive Oxygen Species (ROS). The researchers created a convenient method called one-pot coordination-crystallization to produce platinum nanoparticle-anchored metal-organic complexes (Pt-MOCs). This study aimed to directly demonstrate the anti-tumor effect of the formulation by utilizing the degree of reaction between H_2O_2 and the final formulation as a measure, which results in an increase in reactive oxygen species (ROS)(Sun et al., 2023). Another research study discovered that for glioma therapy, they developed nanotherapeutics using DSF and copper sulfide (CuS) which were modified with transferrin (Tf). This modification of Tf on the surface of the DSF/CuS nanocomplex improved targeted delivery specifically for glioma treatment, thus enhancing treatment effectiveness. (Fig. 6A-B) The DSF was introduced and worked together to effectively eliminate cancer cells by triggering programmed cell death (apoptosis) and cellular recycling (autophagy)(Lan et al., 2021). To improve the degradability and

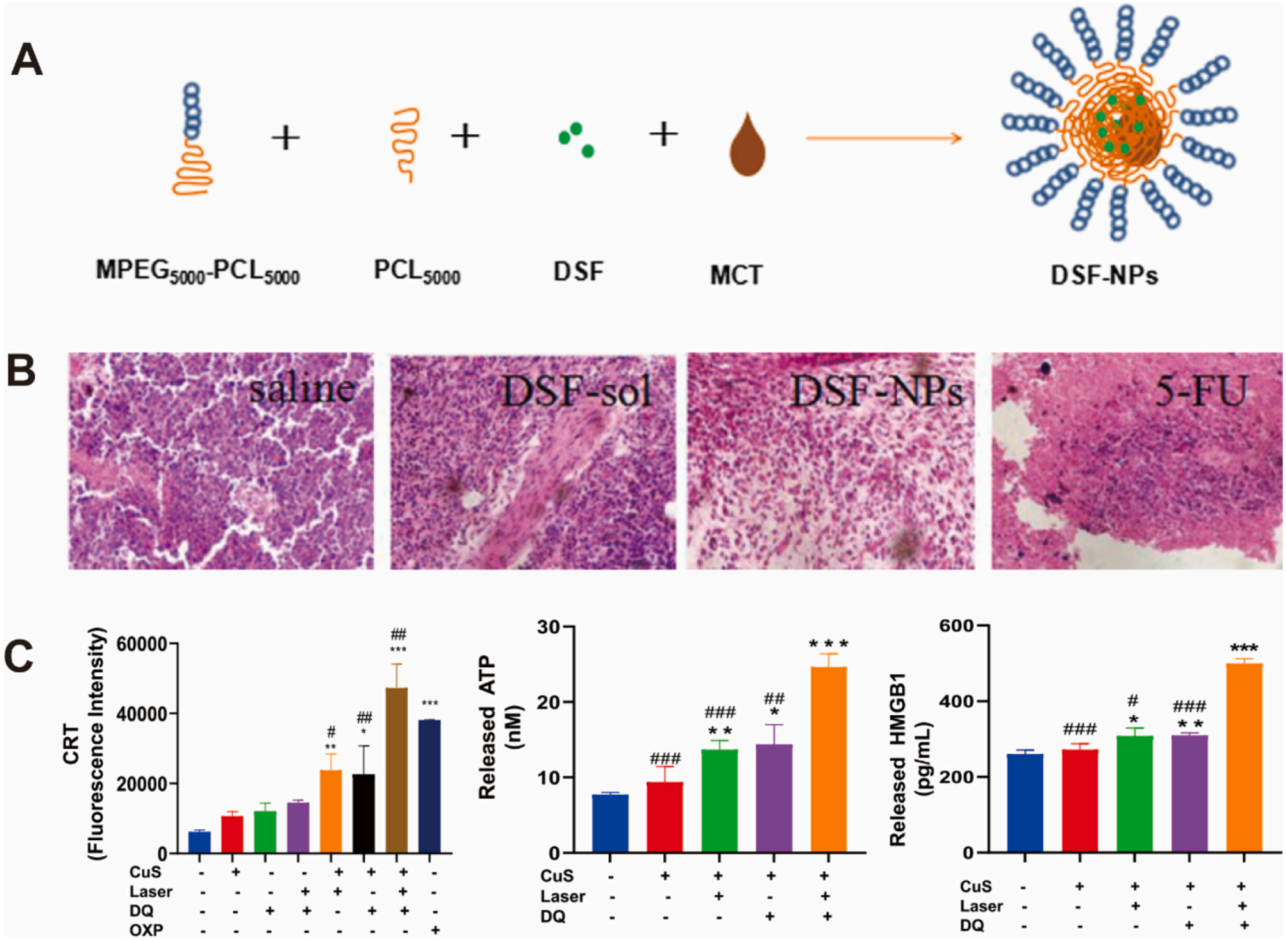

Fig. 5. (A) Schematic illustration the compositions and structure of the DSF-NPs. (B) Images of H&E staining tumor tissues in H22 tumor-bearing mice after injection of saline, 5-FU, DSF-sol, and DSF-NPs. Reproduced from ref.(Zhuo et al., 2018) with permission from Elsevier, copyright 2018. (C) Biomarkers of ICD. Reproduced from ref.(Kang et al., 2021) with permission from Elsevier, copyright 2021.

biocompatibility of drugs. In other study, they have successfully created a silk fibroin modified disulfiram/zinc oxide nanocomposite (SF/DSF@ZnO). This nanocomposite aims to deliver disulfiram (DSF), trigger the release of zinc ions under certain pH conditions, and ultimately exhibit a synergistic anticancer effect. This process is accompanied by the production of a high amount of ROS (reactive oxygen species). The presence of Zn^{2+} enhances the cell-killing effect of DSF. Moreover, the ROS generated by ZnO also contributes to cell death (Zhao et al., 2020). The article provides evidence of the significant antitumor effect of flow cytometry by demonstrating its ability to promote cell apoptosis. (Fig. 6C-D).

Metal-based nanomaterials demonstrate strong biological effects in radiotherapy sensitization. These nanomaterials enhance their deposition at tumor sites and increase the radio-sensitization of the tumor. Additionally, they improve tumor hypoxia by generating O^2 directly from H_2O_2 in the tumor microenvironment or by increasing blood flow to tumor sites (Xu et al., 2020). Consequently, metal-based nanomaterials have the potential to effectively enhance the therapeutic effect of tumor treatment while reducing damage to normal tissues. This innovative approach offers a promising avenue for improving traditional tumor radiotherapy (Wang et al., 2020).

4.5. Metal-organic framework

Metal organic frameworks were first reported in 1989 by Hoskins (Chen and Wu, 2018). In general, a MOF is a crystalline network of a single metal ion or metal cluster connected to multidentate organic linkers, which are themselves linked by strong covalent bonds. MOFs are a relatively new type of materials with high surface areas and permanent porosity that show great promise for such applications (Chedid and Yassin, 2018).

Recently, some research has identified MOF nanoparticles as a promising delivery carrier for drug molecules and transition metal ions (Guo et al., 2019). Zeolitic imidazolate framework-8 (ZIF-8) nanoparticles, a typical MOF structure, confer advantages of high hydrolytic stability and sensitive pH responsibility over other MOF nanoparticles. In a study, a PEG-modified, DSF-loaded, Cu-doped ZIF-8 (PEG-DSF-Cu/ZIF-8) nanoparticle was synthesized as a TME-selective nanodrug for cancer treatment. The PEG-DSF-Cu/ZIF-8 exhibited desirable dispersity and high hydrolytic stability in normal physiological conditions (Fig. 7A-B). While this nanoparticle was featured with high TME-specificity and thus effectively induced cancer cell death (Zhang et al., 2022). In order to further improve the nanoparticles for the treatment of tumor to supplement the shortage of Cu^{2+} dose. Zhao et al. report that Cu^{2+} doped hollow zeolitic imidazolate framework nanoparticles ($HZIF_{Cu}$) as the carrier and equipped with DSF and indocyanine green (ICG) and targeted by folic acid (FA) (D&I@$HZIF_{Cu}$-FA) could effectively supply Cu^{2+} by a buffet-style, assisting the "DSF-to-CuET" transformation in the tumor. In this study, 4 T1 cells showed more significant cell death under the same conditions, proving that D&I@$HZIF_{Cu}$-FA has better anti-tumor effects (Fig. 7C). Furthermore, ICG achieves hyperthermia for tumors under laser irradiation (Zhao et al., 2022). In order to enhance the stability nanoparticles and achieve better tumor treatment effect. Pan et al., presented a disulfiram prodrug (DQ)-loaded and

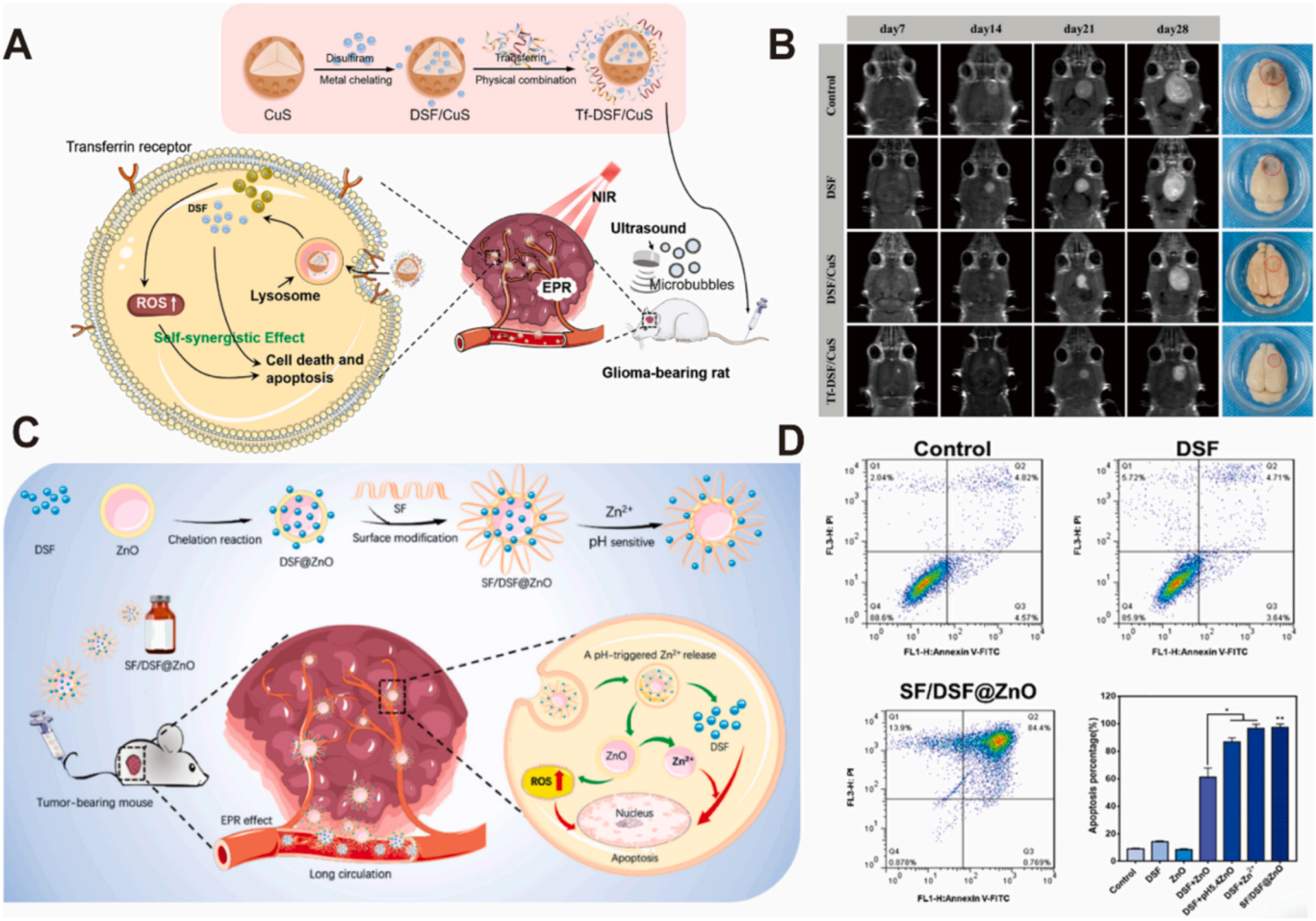

Fig. 6. (A) Development of Copper sulfide-based disulfiram nanoparticle (Tf-DSF/CuS) and mechanisms for self-synergistic anti-glioma therapy. (B) MRI images of brains of glioma rats. Reproduced from ref.(Lan et al., 2021) with permission from Elsevier, copyright 2021. (C) Schematic Design of Silk Fibroin Modified Disulfiram/Zinc Oxide Nanocomposites (SF/DSF@ZnO) for Cancer Therapy (D) Cells were stained with Annexin V − FITC and PI for cell apoptosis analysis using flow cytometry after treatment. Reproduced from ref.(Zhao et al., 2020) with permission from ACS, copyright 2021.

glucose oxidase (GOD) conjugated copper (II) -based nanoscale MOF, MPDG, for tumor-specific, enhance chemo-chemodynamic therapy. Copper MOF, MOF-199, played a dual role of drug nanocarrier of DQ and copper ion reservoir for sufficient generation of CuET. GOD improved the stability of Cu(II) nano-dept and enabled catalytic generation of H_2O_2 in response to high concentration of glucose in cancer cells. In this design, Cu-MOF enable improved chemotherapy and CDT effect. Besides, Glucose oxidase modification further rendered the Cu-MOF improved stability and catalytical generation of H_2O_2 for enhanced anticancer effect by harnessing the abundant glucose in tumor (Pan et al., 2022).

To conclude, MOF structures possess the advantage of a variety of organic linkers/inorganic built units, infinite arrangements, fine-tuning potential (Wang et al., 2022b). However, there are challenges that still exist before clinical applications. At first, the toxicity of MOFs is complex, not only related to its composition, but also the morphology, size and degradation; there still no conclusion about the toxicity of MOFs.

4.6. Hollow nanoplatform

Simple organic-inorganic hybridization by surface conjugation of nanoparticles (NPs) cannot change the intrinsic physiochemical/physiological features of initial nanocarriers. Only homogeneous hybridization within the framework is effective for endowing the nano-systems with new biological effects (Huang et al., 2017). Compared to other inorganic nano-systems, biocompatible hollow mesoporous organosilica nanoparticles (HMONs) that are a combination of organic and inorganic materials have demonstrated excellent performance in molecular imaging and drug delivery. Besides, hollow nanoplatform (HNP) has attracted tremendous attention owing to their hierarchically porous structures, ultrahigh surface area, small diffusion blockage, and high drug loading capacity (Xu et al., 2023).

Organic and inorganic nanoplatforms possess multiple functions, are highly compatible with the body, exhibit good stability in bodily fluids, and can release therapeutic agents in specific locations, particularly targeting tumor cells (Cao et al., 2017). Zhang et al., reported that a based on the employment of HMONs to integrate ultrasmall photothermal CuS particles onto the surface of the organosilica and the molecular drug DSF inside the mesopores and hollow interior. The ultrasmall CuS acted as both photothermal agent under near-infrared (NIR) irradiation for photonic tumor hyperthermia and Cu^{2+} self-supplier in an acidic tumor microenvironment to activate the nontoxic DSF drug into a highly toxic CuET for enhance DSF chemotherapy (Fig. 8A-B)(Zhang et al., 2021).To enhance targeting of nanoparticles, Solak et al., found that a drug carrier system based on magnetic mesoporous silica nanoparticles (Fe_3O_4@SiO_2 MNPs).The Fe_3O_4 MNPs were coated with mesoporous silica (Fe_3O_4@$mSiO_2$) to achieve MNPs. After DSF loading to the Fe_3O_4@SiO_2 MNPs folic acid conjugated polyethyleneimine (PEI-FA) was used for encapsulation of DSF-loaded MNPs (Fe_3O_4@$mSiO_2$-DSF@PEI-FA, mMDPF) to increase both the dispersibility of drug-loaded MNPs in water and the selective cellular uptake of NPs by cancer cells. This study demonstrates that cells show a

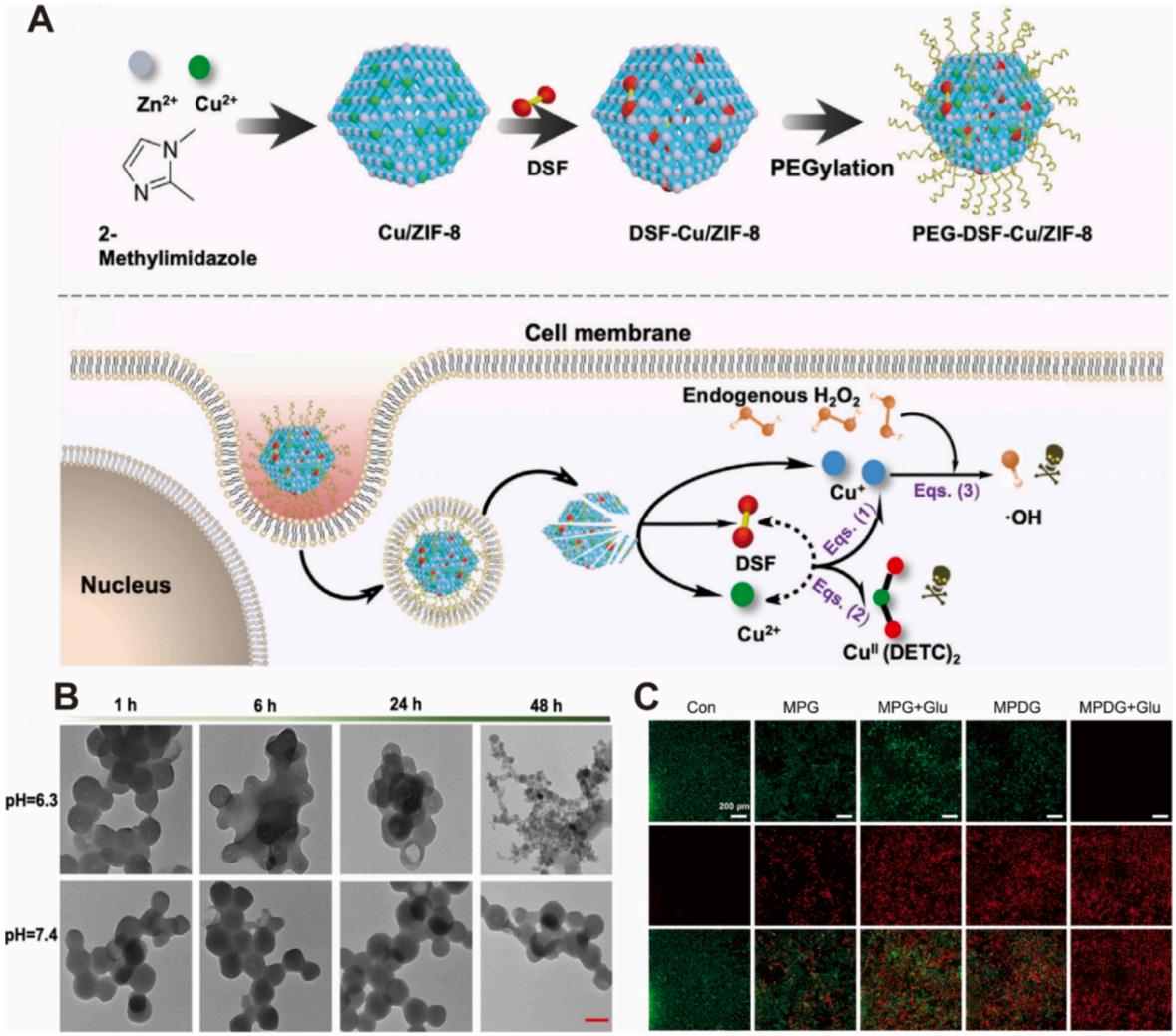

Fig. 7. (A) Schematic illustration of the synthetic procedure of the PEG-DSF-Cu/ZIF-8 nanohybrids and the tumor microenvironment-responsive generation of cytotoxic compounds CuII(DETC)$_2$ and hydroxyl radicals through the nanohybrids.(B) TME-responsive biodegradation performance, drug release behavior. Reproduced from ref.(Zhang et al., 2022) with permission from Elsevier, copyright 2022 (C) Fluorescence images of 4 T1 cells upon different treatments and staining by calcein AM (green, live cells) and propidium iodide (red, dead cells). Reproduced from ref.(Zhao et al., 2022) with permission from Elsevier, copyright 2022. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

higher uptake of the final NPs (Fig. 8C)(Solak et al., 2021). Besides, to further increase therapeutic efficacy and reduce undesired off-target effect. In a study, found that cuproptosis is a recently discovered from of programmed cell death and show great potential in cancer treatment. Herein, a copper-dithiocarbamate chelate-doped and artemisinin-loaded hollow nanoplatform (HNP) is developed via chelation competition induced hollowing strategy for cuprptosis-based combination therapy. The HNP is prepared via an insitu chelation competition-induced hollowing (CCIH) strategy by using CuT nanoplatform (NP) as a template to simultaneously produce hollow structure and CuET complex (Xu et al., 2023).

In this part, either HMONs or HNP, this drug delivery system of hollow nanoparticles enhances biocompatibility and biodegradation behavior to traditional delivery system (Huang et al., 2017). They also can preferentially accumulate in tumor tissues (Xu et al., 2023). On the other hand, carbon based nanomaterials often have NIR absorption and have drawn considerable attention for PAI and PTT (Zhang et al., 2017). It was mentioned that hybrid nanomaterials (HMONs) were created with a deliberate design to improve and combine the therapeutic effects of external photon-based irradiation and internal activation of chemo-therapeutic drugs in response to the tumor microenvironment (TME). The goal was to achieve enhanced and synergistic therapeutic outcomes while minimizing the adverse effects on healthy cells when treating cancer.

4.7. Nanoparticles stimulate the tumor immune response

In this review, some of the nano delivery systems for disulfiram have been summarized, and disulfiram has been shown to potentially exert immunomodulatory functions. In addition, it is noteworthy that some nanoparticle delivery systems themselves have immunomodulatory effects. This provides a great deal of inspiration for our subsequent design of disulfiram delivery systems.

A new study presents a nanodrug-delivering-drug (STNSP@ELE) strategy using 2D stanene nanosheets and β-Elemene to reprogram tumor-associated macrophages (TAMs) from immunosuppressive M2-like to M1-like, enhancing chemo-immunotherapy. This approach has shown to boost antitumor responses by repolarizing TAMs and increasing the presence of M1-like TAMs, CD4$^+$ and CD8$^+$ T lymphocytes, and mature dendritic cells in B16F10 melanomas in mice, promoting a robust antitumor response (Zanganeh et al., 2016). Ferumoxytol, an FDA-approved iron supplement, has shown therapeutic effects on early mammary and lung cancers, and liver metastases. In vitro, it increased caspase-3 activity in adenocarcinoma cells and pro-

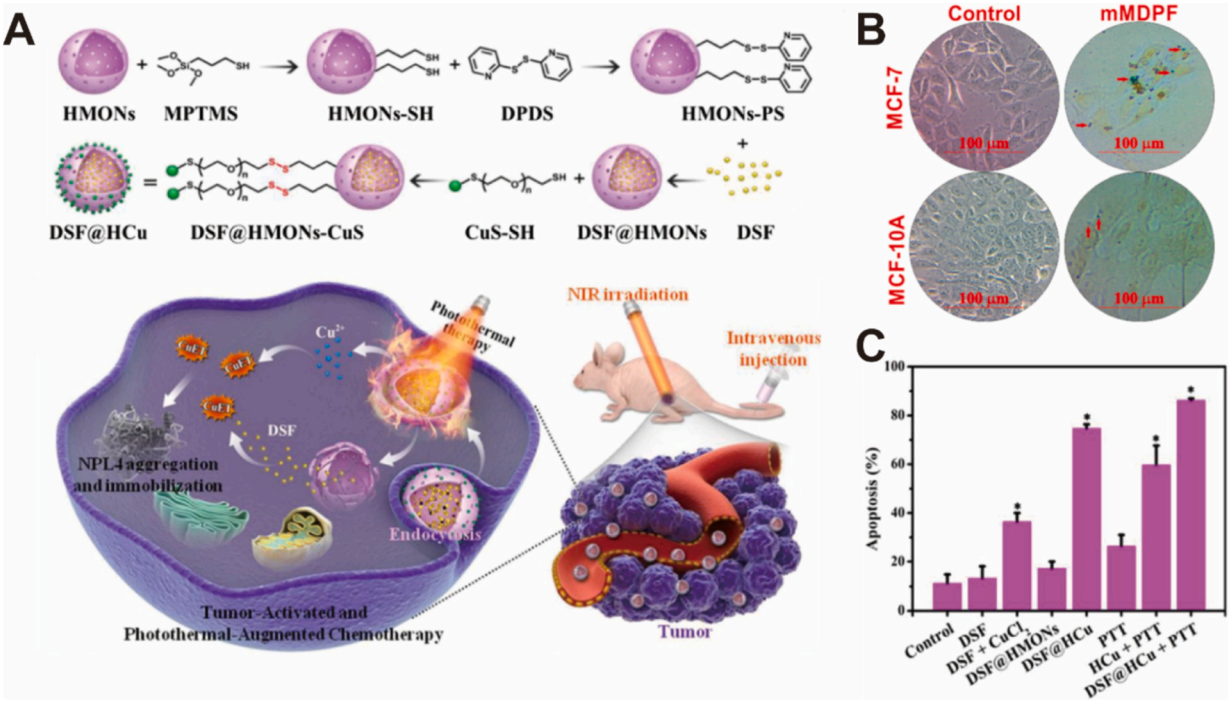

Fig. 8. (A) Schematic illustration of the stepwise construction of DSF@HCu nanomedicine (B) Flow-cytometry apoptosis assay of 4 T1 cancer cells after different treatments followed by staining with Annexin V-FITC/PI. Reproduced from ref. (Zhang et al., 2021) with permission from BMC, copyright 2021 (C) Prussian Blue dye is used to detect the presence of iron nanoparticles in cells. mMDPF contains an iron core and Prussian Blue gives blue colour in the presence of iron. Reproduced from ref.(Solak et al., 2021) with permission from Elsevier, copyright 2021. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

inflammatory Th1 responses in macrophages. In vivo, it inhibited tumor growth and prevented liver metastasis in mice, possibly by promoting M1 macrophages. This suggests ferumoxytol could enhance cancer immunotherapies (Chen et al., 2023).

The immune response of the nanoparticles themselves is conducive to our future design concepts when designing disulfiram nanoparticles. Although the immune response of the nanoparticles themselves has a beneficial effect on disease control, on the other hand, the toxic effect of the nanoparticles may be enhanced. How to control the amount of nanoparticles while ensuring the drug loading of disulfiram is a question worth considering.

5. Conclusion and future prospects

Drug repurposing is a valuable strategy for finding new cancer treatments. DSF, originally used for alcoholism, has shown promise as a potential anticancer drug. The focus of this article is to explore the possible aspects of DSF and its metabolites that can be targeted for cancer treatment. Several studies have revealed that DSF and its metabolites can regulate the activity of metal-dependent enzymes and proteins like metallothionein, SOD, and MMP by competing with limited metals in the cell. Another important aspect of DSF's biological effects is its ability to react with cysteine residues of proteins and enzymes such as ALDH, P-gp, MGMT, NF-κB, and others. Although DSF can increase reactive oxygen species levels in cells, inhibit tumor-promoting signaling pathways, and have immunomodulatory effects, it extremely low toxicity limits its use to that of a therapeutic adjuvant.

In recent years, there has been a significant increase in research focused on DSF-based treatment strategies. This is evident from the growing number of innovative studies being published. Analyzing various system designs, we have observed a clear progression in the delivery systems used. Initially, DSF was delivered alone, followed by separate delivery of DSF and Cu. Subsequently, delivery of CuET and co-delivery of DSF/Cu became prominent. This evolution underscores the importance of precise temporal and spatial interaction between Cu and DSF, as well as the consideration of enhancing biocompatibility while reducing toxic and side effects. These delivery strategies of DSF/Cu (and CuET) can potentially be applied to other copper complexes and metal-based anticancer drugs. TME responsive and versatile drug delivery systems act like skilled hands, effectively targeting treatment areas and offering various anti-cancer patterns.

We identified several captivating obstacles that impede progress in this field. (1) Currently, the majority of DDSs developed to combat tumor growth solely focus on observing the superficial aspect of cell death, disregarding the diverse effects of different modes of cell death. Apoptosis(Wu et al., 2019), paraptosis(Chen et al., 2018b), autophagy (Zhang, 2019), ICD(Zheng et al., 2020), and ferroptosis(Li et al., 2020) were found in DSF/Cu treatment, but there is no obvious regularity. Studying the in vivo experiments that uncover the process of cancer cell death can provide insights into how treatments affect organisms. Understanding the mechanisms of cell death, such as immunogenic cell death (ICD), can have long-term benefits by reducing the chances of tumor recurrence and metastasis. In particular, Hu et al. made a groundbreaking discovery that DSF has the ability to inhibit inflammation, which has potential applications in treating various inflammatory diseases, including tumors (Hu et al., 2020b). Mice with sepsis experienced reduced mortality when administered with DSF-loaded lactoferrin nanoparticles, as evident from a recent study that demonstrated the effective inhibition of induced pyroptosis (Ou et al., 2021). The DSF exhibits unexpected capability in promoting inflammatory cell death and enhancing immunogenic cell death. (2) There is growing evidence suggesting that DSF and DSF/Cu may have immunotherapeutic potential. Unlike current drug delivery systems, which typically rely on adding immunomodulators or modifying the carrier's surface, they often overlook the potential role of DSF/Cu itself. We believe that investigating the effects of DSF, DSF/Cu, or CuET on tumor immunity would be an important research area. (3) Moreover, the emerging knowledge about the connection between the human gut microbiota and the

immune system suggests that these microorganisms may have a significant impact on tumor elimination in certain patients. DSF and its byproducts have been found to possess antibacterial properties, and a recent investigation indicates that a combination of antibiotics and DSF/Cu can decrease pro-inflammatory cytokines in tumors and enhance the presence of beneficial gut bacteria (Hu et al., 2020a). (4) Despite the advent of numerous nano-formulations based on disulfiram, the primary obstacles to their clinical application include safety concerns pertaining to the use of nano-drugs in preclinical and clinical studies, which have resulted in an approval rate of less than 10 %, and mounting concerns about biosafety (Wang et al., 2024). The challenge of identifying suitable preclinical research models that accurately reflect the human condition, coupled with the dearth of validated analytical techniques for characterising nanoparticles, represent significant obstacles to the advancement of nano-drugs. The quality control of the preparation process and the scale-up of production represent significant challenges encountered during the clinical application of nano-drugs. Further research is required to gain a deeper understanding of the physicochemical properties of nanomedicines, including their composition, structure, storage method, and route of administration. Additionally, the rationality and accuracy of analytical characterization methods, as well as the controllability and quality standards of the preparation process, require further investigation. Nano-bio interactions: The presence of a multitude of proteins in the blood can bind tenaciously to the surface of nanoparticles, forming a 'protein crown', which alters their physicochemical characteristics and stability, thereby impeding the specific binding of target molecules to receptors (Ito et al., 1999). The design of clinical trials for nanomedicines is a complex process that requires careful consideration of several factors, including patient selection, the choice of model drug, and the combination with existing therapies. This approach can facilitate the accelerated development of nanomedicines. One of the key factors in achieving the clinical translation of nanomedicines is the development of specific and unified regulatory protocols. These challenges must be addressed through interdisciplinary collaboration and technological innovation to facilitate the widespread clinical application of nanomedicines.

Despite the existence of numerous published reviews on disulfiram, this paper provides a unique contribution by summarizing the classical literature from a formulation science perspective and presenting an isolated description of each dosage form. In comparison to other reviews focusing on disulfiram delivery, this paper offers a more comprehensive categorization of dosage forms. This is particularly valuable for researchers seeking up-to-date information on nano delivery. Additionally, this review includes a comparative summary of different formulations, their constituent materials, and the diseases they are utilized to treat. The classification of nano delivery systems in this review not only serves as an informative summary but also presents a thorough analysis of the advantages and disadvantages associated with various dosage forms used in applications. Consequently, readers can obtain guidance regarding the selection of appropriate dosage forms for nano preparations from this literature. While considerable headway has been made in investigating this field, several pivotal issues remain unresolved. These obstacles impede our comprehension of the diverse treatments for DSF and its clinical applications. By optimizing drug formulations, the efficacy of DSF in cancer treatment could be markedly enhanced. A multidisciplinary approach will facilitate a more comprehensive understanding of the biological activity of DSF.

CRediT authorship contribution statement

Di Huang: Writing – original draft. **Yinsha Yao:** Writing – original draft, Validation, Formal analysis. **Yifei Lou:** Validation, Formal analysis. **Longfa Kou:** Writing – review & editing. **Qing Yao:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization. **Ruijie Chen:** Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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