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REVIEW

A Minireview on Nanosized Hypericin-Based Inducer of Immune Cell Death Under ROS-Based Therapies

Chuanshan Xu[1,*], Xiaowen Cai[2,*], Lingran Du[1]

[1]Key Laboratory of Molecular Target and Clinical Pharmacology, State Key Laboratory of Respiratory Disease, School of Pharmaceutical Sciences, Guangzhou Medical University, Guangzhou, Guangdong, 511436, People's Republic of China; [2]School of Applied Biology, Shenzhen City Polytechnic, Shenzhen, People's Republic of China

*These authors contributed equally to this work

Correspondence: Lingran Du, Key Laboratory of Molecular Target and Clinical Pharmacology, State Key Laboratory of Respiratory Disease, School of Pharmaceutical Sciences, Guangzhou Medical University, Guangzhou, Guangdong, 511436, People's Republic of China, Tel/Fax +8620-37106238, Email dulingran@126.com

Abstract: Immunotherapy is emerging as a powerful strategy against cancer; however, its efficacy is often blunted by the immunosuppressive tumor microenvironment (TME). Immunogenic cell death (ICD) can tilt this balance by releasing tumor-associated antigens and damage-associated molecular patterns that enhance TME immunogenicity, promote antigen-presenting cell maturation, and activate effector T cells. Ionizing radiation and doxorubicin (Dox) are two types of the common ICD inducers. However, they have severe off-target toxicities and limited therapeutic indices. To overcome these challenges, safe and natural products are now drawing widespread attention. Hypericin, a naturally occurring photosensitizer derived from the traditional Chinese herb *Hypericum perforatum* (St. John's wort), has been used medicinally for centuries, and is now recognized for its potent antimicrobial, antiviral, anti-inflammatory, and anticancer properties. Recent studies have revealed that hypericin can modulate tumor immunity, and when employed in photodynamic therapy (PDT) or sonodynamic therapy (SDT) it generates reactive oxygen species that trigger endoplasmic reticulum stress-mediated ICD. Nanocarrier-mediated delivery further amplified these effects by enhancing hypericin solubility, tumor accumulation, and ROS yield upon light irradiation. This minireview synthesizes the current knowledge on the immunomodulatory actions of hypericin within the tumor microenvironment, evaluates its performance as a PDT/SDT-based ICD inducer, and highlights that nanosized formulations of hypericin may accelerate the development of novel ICD inducers and immunomodulators.

Keywords: hypericin, photodynamic therapy, sonodynmamic therapy, nanosizing technology, immunogenic cell death, tumor immune microenvironment, cancer immunotherapy

Introduction

Cancer remains a serious health challenge for humans. The International Agency for Research on Cancer (IARC) reported in 2022 that nearly one in five men or women developed cancer in a lifetime.[1,2] In the United States, there are an estimated 2.04 million new cases and 618,120 cancer-related deaths by 2025,[3] underscoring the escalating societal burden. Surgery, chemotherapy, and radiotherapy, as conventional modalities, achieve only transient responses with substantial side-effects.[4] Immunotherapy offers an alternative treatment that leverages the immune system to recognize and eliminate malignant cells with unprecedented specificity.[5–7] However, cancer cells frequently escape immune control by creating an immunosuppressive microenvironment and by presenting inadequate immunogenic cues.[5–9] Immunogenic cell death (ICD) can overcome these barriers by triggering the rapid release of tumor-associated antigens (TAAs) and damage-associated molecular patterns (DAMPs). This cascade enhances the maturation of antigen-presenting cells, activates cytotoxic T lymphocytes, and ultimately reprograms the tumor microenvironment toward an antitumor state.[10–13] Consequently, the research and development of safe and potential ICD inducers has emerged as a promising strategy to augment immunotherapeutic efficacy.

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ICD inducers, such as therapeutic modalities or drugs, can convert malignant cells into potent vaccines, eliciting robust tumor-specific adaptive immunity. This process is governed by three hallmark molecular events: (1) lysosome-mediated ATP secretion, which acts as ann "find-me" signal for dendritic-cell (DC) precursors; (2) pre-apoptotic translocation of calreticulin (CRT) to the plasma membrane, functioning as an "eat-me" signal; and (3) secondary necrosis–driven release of high-mobility group box 1 (HMGB1), which engages TLR4 on DCs to amplify antigen processing and presentation.[10–13] Together, these danger signals mature DCs, stimulate tumor-antigen cross-presentation to $CD4^+$ and $CD8^+$ T cells (Figure 1), and transform immunologically "cold" tumors into "hot" ones, thereby synergizing with immune-checkpoint inhibitors (eg, anti-PD-1/PD-L1) and adoptive T-cell therapies.[10–22] Ionizing radiation and doxorubicin (Dox) are commonly used ICD inducers (Table 1); however, their serious toxicity to normal tissues limits their therapeutic efficacy in clinical settings. Ionizing radiation typically induces myelosuppression. Dox is one of the most important ICD inducers and shows significant cardiotoxicity side effects, which seriously affect its clinical outcomes, leading to discontinuous Dox therapy in several cancer patients.[23–25] Recently, naturally derived agents are drawing widespread attention as an alternative to develop safer ICD inducers. Hypericin ($C_{30}H_{16}O_8$), a naturally occurring photosensitizer from traditional Chinese herb *Hypericum perforatum* (St. John's Wort), exemplifies this opportunity. It has been used for centuries as a herbal remedy for depression and infection and licensed by Commission E (Germany) for anxiety, depression, and insomnia. Pharmacological studies have revealed that hypericin exhibits broad pharmacological activities, including antimicrobial, anti-inflammatory, antidepressant, and anticancer effects.[26–28] Growing evidence shows hypericin-based photodynamic therapy (PDT) / sonodynamic therapy (SDT) generates cytotoxic reactive oxygen species (ROS) to provoke ICD and remodel the tumor immune microenvironment.[11,12,29–32]

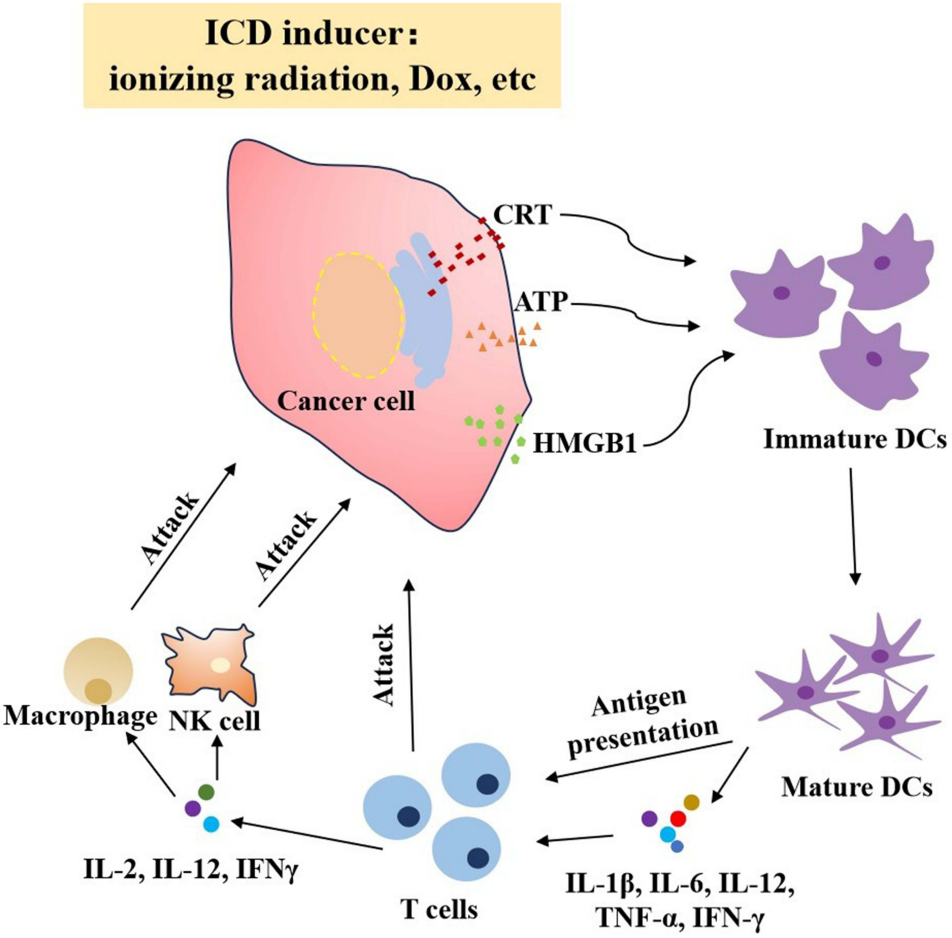

Figure 1 A schematic representation of ICD-induced antitumor immunity.

Table 1 Representative ICD Inducers

Category	Inducers	Cellular Target	The in vitro or in vivo Model Where the Result Has Been Observed	Reference
Type I ICD inducers	Ionizing radiation	DNA	In vitro and in vivo	[13]
	Anthracyclines (eg Dox)	DNA	In vitro and in vivo	[14]
	Shikonin	Mitochondria	In vitro and in vivo	[15]
	Cisplatin, oxaliplatin	DNA	In vitro and in vivo	[16]
	Cyclophosphamide	DNA	In vitro and in vivo	[17]
	Vorinostat	Histones	In vitro	[18]
	Cetuximab	EGFR	In vitro and in vivo	[19]
Type II ICD inducers	Hypericin-PDT	Endoplasmic reticulum	In vitro and in vivo	[20]
	Oncolytic Viruses	Endoplasmic reticulum	In vitro	[22]

In this review, we present the current knowledge on the immunomodulatory actions of hypericin within the tumor microenvironment, evaluate its performance as a PDT/SDT-based ICD inducer, and highlight that nanosized formulations of hypericin may accelerate the development of next-generation ICD inducers and immunomodulators. Our goal was to guide the further development of plant-derived agents and traditional Chinese medicines in photodynamic and sonodynamic immunotherapy.

Role of Hypericin in Tumor Immune Microenvironment

The tumor immune microenvironment dictates whether the cancer progresses or regresses. The TME mainly consists of malignant cells, stromal elements (fibroblasts and endothelial cells), and a heterogeneous immune infiltrate, including $CD8^+$ cytotoxic T lymphocytes (CTLs), regulatory T cells, dendritic cells, tumor-associated macrophages (TAMs), and myeloid-derived suppressor cells. In TME, CTLs are often sequestered at the tumor margin and blocked from the core by M2-polarized TAMs, resulting in an immunosuppressive microenvironment. Therefore, reducing M2 macrophages is an attractive strategy for "treating" cold tumors and prevent metastasis.[33,34]

Emerging data have shown that hypericin can re-educate the TME. In the dark, hypericin downregulates the M2 marker CD206 and other M2-associated signatures via PI3K/AKT inhibition, thereby impeding macrophage-driven proliferation, invasion, and migration of cancer cells.[35] In murine models, hypericin alone decreased intratumoral M2 macrophages, slowed tumor growth, and enhanced CTL infiltration into the tumor core.[35] In addition to myeloid cells, hypericin in the dark suppresses endothelial proliferation and angiogenesis, destabilizes hypoxia-inducible factors (HIF-1/2α), and diminishes the side population of chemoresistant cancer stem cells.[36]

Upon light exposure, hypericin generates ROS to trigger robust cytokine cascades including IL-1α/β, IL-6, TNF-α, IFN-γ, and multiple chemokines in HepG2 hepatocellular carcinoma cells.[37] A similar light-dependent upregulation of IL-6 mRNA occurs in CNE-2 nasopharyngeal carcinoma cells and xenografts,[38] whereas human dermal fibroblasts and keratinocytes exhibit light-dependent decreases in IL-8, MMP-1, IL-19, and IL-22, along with increases in IL-11.[39] These findings suggest that hypericin is a versatile, dual-mode immunomodulator, both in the dark and under illumination, that can reprogram the TME and augment anticancer immunity. PDT with hypericin could inhibit MMP-9 expression and the activity of nuclear factor kappa-B (NF-κB), a transcription factor that regulates the expression of pro-inflammatory cytokines and other genes involved in immune responses.[40] This inhibition of NF-κB downregulates tumor-promoting cytokines, thereby reducing the immunosuppressive environment within the tumor and enhancing the efficacy of the immune response. Moreover, PDT with hypericin can also modulate the tumor microenvironment by affecting the integrity of the tumor vasculature and promoting the infiltration of neutrophils and other immune cells into the tumor

tissues.[41] This modulation is essential for the establishment of a pro-inflammatory environment that supports the activation of the adaptive immune system. The release of pro-inflammatory signals into the tumor-draining lymph nodes further enhances the systemic anti-tumor immune response.

Photodynamic Therapy with Hypericin: An Effective ICD Inducer

Cell death is an essential physiological process that maintains tissue homeostasis by balancing the cell proliferation and metabolic turnover. The 2018 guidelines of the Nomenclature Committee on Cell Death (NCCD) recognized 12 distinct modalities: apoptosis, parthanatos, necroptosis, ferroptosis, pyroptosis, mitochondrial-permeability-transition-driven necrosis, entosis, NETosis, lysosome-dependent death, autophagy-dependent death, mitotic catastrophe, cellular senescence, and ICD.[42,43] ICD is unique because it can convert dying cancer cells into de facto vaccines by simultaneously providing antigenicity (TAAs), adjuvanticity (DAMPs), and a microenvironment permissive to antigen presentation. Effective type II ICD typically requires ROS and endoplasmic-reticulum stress, which together drive the surface exposure or extracellular release of TAAs and DAMPs, thereby potentiating adaptive immunity and improving the efficacy of cancer immunotherapy.[20,30,31]

PDT is a clinically validated, minimally invasive strategy that exploits the photochemical interaction of three harmless components–light, photosensitizer, and tissue oxygen–to generate cytotoxic ROS.[44–47] Because both visible light and most photosensitizers are innocuous in isolation, PDT provides an exceptional therapeutic window for eradicating tumors while sparing normal tissues. The exact activated cell death modality depends on the subcellular localization of the photosensitizer, local oxygen tension, and light dose.[31] Upon light irradiation, photosensitizers localized in the endoplasmic reticulum (ER) generate large amounts of ROS and trigger ER stress to induce type II ICD. Hypericin is a natural photosensitizer that is predominantly localized in the ER of cancer cells. When hypericin accumulates in cancer cells, light activation produces a burst of ROS within the ER lumen, unleashing intense ER stress that drives bona fide ICD.[20,30,31] The underlying mechanisms of PDT with hyericin involve the generation of ROS predominantly in the ER, where hypericin localizes, leading to focused ER stress,[48,49] subsequently activating the PERK signaling pathway, which is crucial for the release of DAMPs such as CRT, HMGB1, and ATP. CRT, in particular, acts as an "eat me" signal, facilitating the phagocytosis of dying tumor cells by DCs. This process is essential for the maturation of DCs, which then present tumor antigens to CTLs, initiating a robust anti-tumor immune response. The release of DAMPs following PDT with hypericin not only promotes the maturation of DCs but also recruits T immune cells to the TEM. ATP acts as a "find me" signal, attracting T immune cells to the site of tumor cell death.[49–52] This recruitment is crucial for the establishment of an inflammatory milieu that supports the activation of the adaptive immune system. Additionally, the release of HMGB1 enhances the antigen-presenting capability of DCs, further amplifying the immune response against the tumor[53] (Figure 2). Consequently, PDT with hypericin not only destroys the primary tumor but also

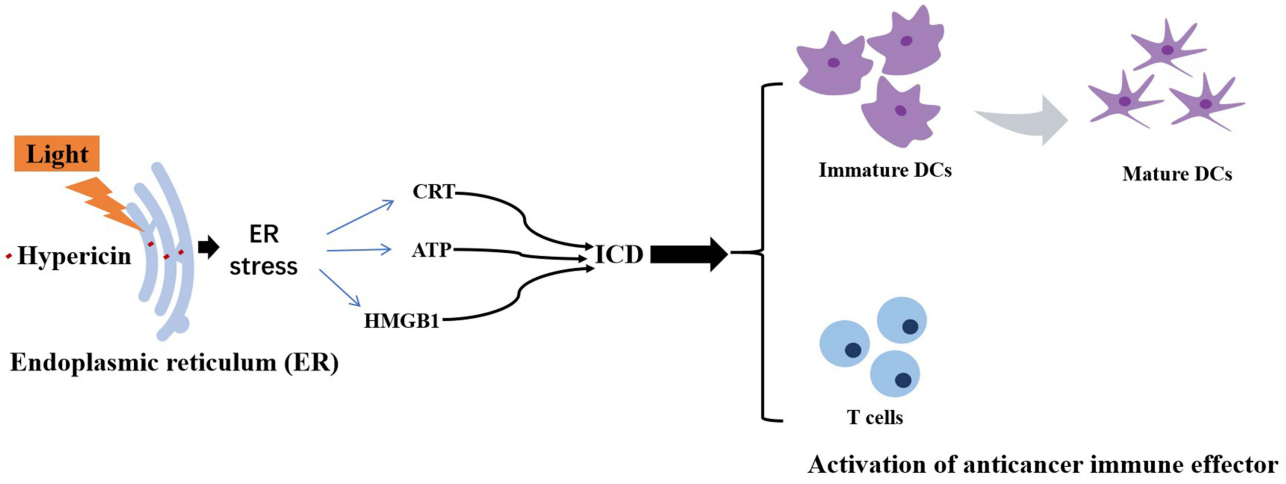

Figure 2 A schematic representation of photodynamic therapy with hypericin-induced ICD and antitumor immunity.

releases TAAs and danger signals that reprogram the TME and potentiate systemic antitumor immunity. Therefore, hypericin-based PDT is a safe, minimally invasive, and highly effective inducer of ICD.

Sonodynamic Therapy with Hypericin: An Innovative ICD Inducer

Similar to PDT, sonodynamic therapy (SDT) is a promising approach for inducing ICD. SDT employs a triad of sensitizers, oxygen, and ultrasound to generate cytotoxic ROS that triggers ER stress and mitochondrial dysfunction, ultimately releasing DAMPs that promote DC maturation and T cell infiltration. In addition, the cavitation effect of ultrasound can directly disrupt cell membranes and liberate immunogenic DAMPs, further enhancing ICD induction.[31,54]

SDT-induced ICD has been validated in various cancer models including glioblastoma and colon cancer. For example, temozolomide (TMZ), a first-line chemotherapeutic agent for glioblastoma (GBM), produces large amounts of ROS under ultrasonication. Zhou et al reported that SDT with TMZ elicited an ER stress response (ERSR), nuclear DNA damage, and mitochondrial permeability transition pore opening, releasing danger signals that trigger ICD and activate bone marrow-derived dendritic cells (BMDCs).[54] However, TMZ is burdened by substantial systemic toxicity and multi-drug resistance (MDR). More recently, SDT with hypericin has been investigated in two- and three-dimensional HT-29 colon cancer models. Hypericin-based SDT generated robust ROS-mediated anticancer activity and hallmark-specific DAMPs including CRT exposure and HMGB1 release. Notably, P-gp overexpression in HT-29/MDR cells did not compromise cancer cell responsiveness to hypericin-based SDT.[32] These data establish that hypericin is a potent sonosensitizer, and its SDT regimen effectively induces ICD and circumvents MDR. Unlike TMZ, hypericin is a naturally derived compound with tumor-selective cytotoxicity and minimal side effects, positioning hypericin-based SDT as a safe, non-invasive, and innovative ICD inducer.

Nanosized Hypericin-Mediated PDT/SDT: Novel and Promising ICD Inducers

Hypericin exerts potent immunomodulatory effects in cancer therapy by suppressing M2 macrophage polarization, reshaping the cytokine/chemokine milieus, and eliciting ICD. However, its clinical translation is hindered by severe hydrophobicity. In aqueous media, hypericin rapidly self-aggregates through hydrophobic interactions, diminishing water solubility, systemic bioavailability, and ultimately ROS yield upon light activation or ultrasound sonication, which significantly reduces its immunotherapeutic impact.[55] Nanotechnology offers a versatile solution for this problem. The use of inorganic or organic materials encapsulating or conjugating hypericin within engineered nanocarriers,[47] dispersibility, and tumor-directed delivery has markedly improved. These nanoformulations can be fabricated through straightforward physical encapsulation or covalent attachment, thereby providing a scalable platform to unlock the full immunomodulatory potential of hypericin-based PDT/SDT.

Among inorganic nanomaterials, mesoporous silica (eg, SBA-15) stands out for its large, tunable pores that accommodate both hydrophilic and hydrophobic cargos. Guo et al and Pevná et al exploited this feature to construct SBA-15-hypericin nanoparticles that remained biologically inert during circulation, yet released hypericin in a sustained manner inside cancer cells, providing a safe, targeted depot.[56–58] Metal-organic frameworks, such as MIL-101(Al)-NH_2 have also been loaded with hypericin, yielding MIL-101(Al)-NH_2-hypericin composites with simultaneous anticancer, antibacterial, and antiviral activities.[59] Graphene oxide functionalized with hypericin has been engineered to potentiate anticancer activity of Dox.[60,61] Upconversion nanoparticles (UCNPs) further expand the utility of hypericin; CS-UCNP @P(DMA-AEA)-Ale-hypericin can induce substantially more apoptosis upon light irradiation than free hypericin, while enabling deep-tissue imaging and NIR-triggered PDT.[62,63] Gold nanoparticles (AuNPs), prized for their biocompatibility and facile surface chemistry, have been covalently conjugated with hypericin to create AuNP-hypericin hybrids, which display enhanced solubility, prolonged circulation, and superior photodynamic activity.[64–66]

Recently, organic nanocarriers have been developed to overcome the poor aqueous solubility of hypericin and sharpen their phototherapeutic index. The oil-in-water nanoemulsions prepared by Salawi et al remained stable for months and retained their antidepressant activity in vivo.[26] The amphiphilic block copolymer Pluronic F127 self-assembles into nanomicelles that encapsulate hypericin (F127/HYP), increasing its circulation time and driving preferential

accumulation in the endoplasmic reticulum (ER) and mitochondria. Upon light irradiation, the F127/HYP micelles generated localized oxidative bursts that caused necrotic cell death in a dose-dependent fashion.[67] Similarly, hypericin-loaded nanoparticles assembled from biodegradable amphiphilic copolymers exhibit markedly elevated ROS production and superior photodynamic potency compared with free hypericin.[68] Gradient copoly(2-oxazoline)s engineered by Huntošová et al delivered hypericin for simultaneous tumor imaging and PDT, thus validating the versatility of self-assembled polymeric systems.[69]

Lipid-based vectors offer an additional clinical translatability. Liposomes and solid-lipid nanoparticles have been widely adopted to package hypericin, improving its solubility, tumor targeting, and safety by minimizing off-target photosensitization.[70–74] More recently, the FDA-approved maize protein zein was used to formulate zein-hypericin nanoparticles, which demonstrated potent photodynamic eradication of hepatocellular carcinoma cells.[75] These organic platforms provide tunable, biocompatible, and scalable solutions for next-generation hypericin-based cancer immunotherapy.

Nanotechnology endows hydrophobic hypericin with "stealth" blood-circulation properties. Amphiphilic block copolymers self-assembled into nanomicelles that cloaked hypericin from reticuloendothelial clearance, sheltered it from premature degradation, and exploited the enhanced permeability and retention (EPR) effect to preferentially accumulate in tumors. To confer active targeting of hypericin, lactose-decorated magnetic iron-oxide nanoparticles (Lac-PHM) have been engineered to deliver hypericin to asialoglycoprotein-receptor-positive HepG2 cells.[76–78] Hypericin-loaded transferrin nanoformulations (HTfNPs) were prepared to deliver hypericin to transferrin-receptor–overexpressing colorectal cancer cells. In the presence of light irradiation, HTfNPs induced significant BMI1 degradation and robust tumor retardation.[79] Folate-receptor-targeted P123 nanomicelles delivered hypericin to melanoma cells with high selectivity and photoinactivation efficiency.[80,81] More recently, plant-derived exosome-like nanovesicles from *Hypericum perforatum* were shown to naturally ferry hypericin, achieving superior photodynamic efficacy against multiple malignancies.[82]

Lipoprotein shuttles further refine the targeted delivery of hypericin. LDL-hypericin nanocomplexes are internalized 2-fold more rapidly by glioma and breast cancer cells than HDL-hypericin, resulting in stronger photodynamic killing action on malignant cells.[83–85] Smart stimuli-responsive nanoparticles now add temporal and spatial precisions. pH-, redox-, and enzyme-cleavable nanophotosensitizers can amplify ROS generation by photosensitizers within the acidic, glutathione-rich, or protease-abundant tumor milieu.[86–89] A pH-responsive metal–drug nanocomplex integrating hypericin, apigenin, PVP, and $Fe^{3}+$ has recently demonstrated markedly enhanced PDT potency and metastasis suppression.[90] These nano-enabled hypericin systems not only improve solubility and enhance targeting ability but also induce widespread ICD, positioning nanosized hypericin as a next-generation ICD inducer and immunomodulator for photodynamic immunotherapy.

Recently, nanosized sonosensitizer-mediated SDT using phase-transformation nanoparticles or folate-targeted systems has been shown to induce ICD and stimulate DC maturation, resulting in increased $CD8^{+}$ T-cell activation and tumor growth inhibition.[91,92] Yuan et al used a hematoporphyrin monomethyl ether (HMME)-based liposomal nanosystem as a sonosensitizer for colon cancer treatment. They found that SDT extensively induced ICD, causing enhanced T-cell recruitment and infiltration to improve the immunosuppressive TME and promote antitumor immunity. Both in vitro and in vivo results demonstrated that SDT with an HMME-based liposomal nanosystem induced ferroptosis, apoptosis, and ICD via ROS generation during SDT and reprogrammed the TME.[93] Tian et al also reported that the aggregation-induced emission (AIE) nanosonosensitizers under sonication produced abundant ROS-mediated mitochondrial oxidative stress to trigger significant ICD.[94] Huang et al used the thin-film hydration method to prepare lipid nanobubbles (NBs) loading chlorin e6 (Ce6) and anti-PD-L1 Ab (Ce6@aPD-L1 NBs). They found that Ce6@aPD-L1 NBs in the presence of ultrasound sonication effectively induced ROS generation and ICD, thereby activating DC maturation.[95] Moreover, red blood cell membrane-camouflaged nanoparticles (SB-IR-PLGA@RM) encapsulating the sonosensitizer IR780 and ER-targeting iridium(III) nanosonosensitizers were shown to effectively induce ICD in cancer cells, remodel the immunosuppressive TME, and amplify antitumor immunity.[96,97] Although there are no reports on the direct study of nanosized hypericin-based SDT on ICD, the inspiring findings on nanosonosensitizers-mediated SDT inducing ICD induction and immunomodulation indicate that nanosized hypericin has great potential for developing an innovative ICD inducer and immunomodulator for sonodynamic immunotherapy.

Summary and Future Directions

Hypericin is the only FDA-approved natural photosensitizer with anticancer, antiviral, and immunomodulatory activity. Recent studies have confirmed that it elicits robust ICD upon light activation and reshapes the TME. However, hypericin's hydrophobicity, which causes aggregation in aqueous environments, reducing bioavailability and ROS production. Nanoformulations could improve its solubility and targeting, systemic half-life, and ROS yield, positioning nanosized hypericin as a highly promising ICD inducer. For example, superparamagnetic iron oxide nanoparticles (SPIONs) as an inorganic nanoformulation enable magnetic-guided targeting of hypericin. Hypericin-loaded SPIONs enhanced the amount of hypericin in the tumor tissues under an external magnetic field, which resulted intratumoral hypericin accumulation, boosted ROS production, and amplified ICD via DNA damage and DAMP release.[77] Mokoena et al found that Gold nanoparticles improved hypericin's hydrophobicity and colloidal stability, allowing deeper tumor penetration and prolonged retention in tumor interstitial spaces.[64] Organic nanoformulations, such as glyconanoparticles or polymeric systems, also enhance hypericin solubility and targeting. For instance, polymeric carriers also facilitate prolonged blood circulation and controlled release. Hypericin-entrapped glyconanoparticles improve aqueous solubility and tumor-specific delivery by leveraging surface ligands like folic acid, which binds to tumor-overexpressed receptors, enhancing cellular uptake and photodynamic efficacy.[76] Lipid-based nanoformulations, particularly liposomes, effectively solubilize hypericin within their lipid bilayers, preventing aggregation and ROS loss. Olszowy et al found tetraether liposome-encapsulated hypericin exhibits superior tumor vasculature targeting due to passive tumor targeting via the enhanced permeability and retention (EPR) effect, thereby improving biodistribution and hypericin delivery.[98] Surface modifications of nanoformulations using antibody or ligand can endow the active targeting of hypericin. Sardoiwala MNet al prepared a hypericin-loaded transferrin nanoparticles (HTfNPs) and found the improvement in half-time ($t_{1/2}$) of hypericin from 2.16 to 4.29 h using transferrin nanocarrier, indicating the prolonged circulation time of hypericin for better distribution to its target site. And HTfNPs also show a significant photodynamic efficacy against colorectal cancer by inducing PP2A-mediated BMI1 ubiquitination/degradation.[79] These encouraging findings indicate a great potential in developing nanosized hypericin-based PDT as an innovative ICD inducer. Nevertheless, the current proof-of-concept is largely derived from conventional in vitro and small-animal models; rigorous demonstration that nano-hypericin triggers bona fide ICD and remodels the TME in clinically relevant settings remains limited. Moreover, the multistep synthesis and batch-to-batch variability of existing nanocarriers hinders scalable translation, highlighting the need for a sustainable, eco-friendly preparation method and large-scale clinical trials to establish safety and efficacy.

A second hurdle of hypericin-based PDT in the clinic application is the limited tissue penetration of the 595 nm light required for classic PDT. SDT replaces light with ultrasound waves and offers an elegant solution to overcome some of the limitations of PDT. Similar to PDT, sonosensitizers can generate cytotoxic ROS to induce ICD upon ultrasound sonication; however, ultrasound penetrates centimeters deep with negligible systemic toxicity. Emerging evidence has demonstrated that hypericin retains its sonosensitizing capacity,[31,32,99–107] producing ER-localized ROS under ultrasound sonication that provoke ER stress-mediated ICD. Therefore, nanosized hypericin engineered for SDT could overcome the depth restriction of light, showing a promising opportunity to induce ICD for the treatment of deep-seated malignancies. However, rigorously engineered quality-controlled nanohypericin-SDT systems require intensive investigation to develop nanohypericin-based SDT as a novel next-generation ICD inducer and immunomodulator.

Beyond delivery and activation issues, the clinical translation of ICD inducers like hypericin faces validated biomarkers and standardization challenges. There is a critical need for validated biomarkers to consistently measure ICD induction in patients, and the current lack of uniform evaluation metrics, such as standardized assays for DAMP release, hinders the clinical assessment of therapeutic efficacy.[108] To bridge these gaps, future research must prioritize the development of innovative nanoformulations designed to improve hypericin's solubility, stability, and tumor-specific targeting, thereby enhancing its pharmacokinetic profile.[109,110] Developing ultrasound as an activating sources will potentially overcome the depth limitation of traditional PDT. Ultimately, a multidisciplinary effort combining advanced drug formulation, refined ultrasound delivery, and rigorous biomarker-driven clinical trial design is imperative to fully realize the potential of hypericin as a clinically viable ICD inducer.

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Disclosure

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