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The evolution of integrated magnetic hyperthermia and chemodynamic therapy for combating cancer: a comprehensive viewpoint

Anjali Chauhan, †[ab] Anamika Saini†[ac] and Deepika Sharma *[a]

Magnetic hyperthermia therapy (MHT) and chemodynamic therapy (CDT) are emerging non-invasive cancer treatments that leverage reactive oxygen species (ROS) to induce tumor cell death. While MHT uses magnetic nanoparticles to generate localized heat under an alternating magnetic field, its efficacy can be limited by low ROS levels in hypoxic tumor microenvironments. CDT complements MHT by inducing toxic hydroxyl radicals through Fenton reactions, enhancing ROS production and antitumor effects. This mini-review discusses the synergistic potential of combining MHT with CDT using multifunctional nanomaterials, offering insights into enhanced ROS-mediated cancer therapy and future directions for clinical applications.

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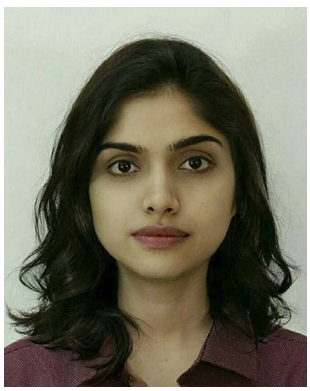
[a]*Institute of Nano Science and Technology, Knowledge City, Sector 81, Mohali, Punjab-140306, India. E-mail: deepika@inst.ac.in*
[b]*Lillian S. Wells Department of Neurosurgery, University of Florida, Gainesville, Florida 32608, USA*
[c]*School of Science, RMIT University, Melbourne, Australia*
† These authors contributed equally.

Anjali Chauhan

Anjali Chauhan is an assistant scientist in the Department of Neurosurgery at the University of Florida College of Medicine. She is part of the translational brain tumor immunotherapy laboratory, which is led by the renowned neurosurgeon and scientist Dr Maryam Rahman (MD, MS). Dr Anjali received her PhD from Jawaharlal Nehru University, India. As a doctoral student, she studied the synthesis and characterization of iron oxide nanoparticles for the treatment of cancer via magnetic hyperthermia therapy. She also studied the effects of magnetic nanoparticles on the neuronal survival and cognitive functions in the presence of an alternating magnetic field. Anjali has gained her post-doctoral experience in the field of magnetic hyperthermia mediated immunotherapy at the Institute of Nano-science and Technology (2021–2022), India. She also worked as a post-doctoral associate under the supervision of Dr Maryam at the University of Florida (2022–2023), where her work was focused on investigating the efficacy and underlying mechanism of a novel hydrogel-chemokine-mRNA (HCM) vaccine for GBM treatment. As an assistant scientist, she is working on the mechanistic evaluation of the HCM vaccine as well as laser thermotherapy against GBM.



Anamika Saini

Anamika Saini is currently a third-year PhD candidate at RMIT University, working in collaboration with the University of Melbourne and the Olivia Newton-John Cancer Research Institute. Her research focuses on biomedical science, with a particular emphasis on developing lipid nanoparticles for mRNA vaccine delivery. She specializes in formulating and optimizing nanoparticle systems for efficient mRNA encapsulation and studies their interactions with immune cells and biological systems to better understand their behavior and therapeutic potential. Through her work, Anamika aims to advance mRNA vaccine technology and contribute to the growing field of nanomedicine.

1. Introduction

Cancer remains a leading cause of death worldwide, with more than 2 million new cases and 0.6 million predicted deaths for 2024 in the US itself.[1] Despite advances in medical treatments, traditional cancer therapies such as chemotherapy, surgery, and radiation continue to have significant drawbacks, including severe side effects, high recurrence rates, and incomplete elimination of cancer cells. These limitations have prompted the search for more targeted and less invasive treatment options that can improve patient outcomes and reduce the overall burden of cancer.

Nanotechnology has emerged as a transformative approach in cancer therapy, introducing innovative treatments that utilize nanomaterials to target cancer cells more effectively. For instance, copper sulfide nanoparticles (NPs) have been developed for treating lymph node metastasis[2] and carbon dots have been used for gastric cancer.[3] Other advancements include the use of metal–organic frameworks (MOFs) for controlled drug delivery.[4] Several new therapeutic models have been developed based on these nanomaterials, including magnetic photodynamic therapy (PDT),[5] photothermal therapy (PTT),[6] magnetic hyperthermia therapy (MHT),[7] chemodynamic therapy (CDT),[8] sonodynamic therapy (SDT),[9] and so forth. Under the stimulation of light, heat, ultrasound, and other agents, these strategies intensify intracellular oxidative stress to impart therapeutic effects. The primary development trend in cancer treatment has been to reduce the adverse side effects associated with these non-invasive or minimally invasive treatment methods.

MHT has emerged as a viable alternative, utilizing magnetic nanoparticles (MNPs) to generate localized heat when exposed to an alternating magnetic field (AMF).[10,11] This heat induces tumor cell death through thermal stress and reactive oxygen species (ROS) production, offering advantages over other non-invasive therapies like PDT, PTT, and SDT, as mentioned in several reports.[7,12,13] MHT has shown effectiveness in enhancing the cytotoxic effects of anticancer drugs and radiation, as demonstrated in clinical studies involving bladder, breast, and cervical tumors.[14] However, MHT's efficacy can be compromised by low levels of ROS generation in the hypoxic tumor microenvironment and the adaptive mechanisms that tumors develop to resist oxidative damage. To overcome these challenges, chemodynamic therapy (CDT) can be combined with MHT. CDT relies on Fenton and Fenton-like reactions that convert hydrogen peroxide into highly reactive hydroxyl radicals within the tumor, significantly boosting ROS production and enhancing the overall antitumor effects.[15,16] The combination of MHT and CDT leverages the complementary mechanisms of these therapies to create a potent anticancer strategy. This dual approach enhances oxidative stress within tumor cells, leading to more effective cell death. Multifunctional nanomaterials, such as iron oxide NPs doped with catalytic metals, help to execute the dual MHT–CDT therapy, which not only generates heat under an alternating magnetic field (AMF) but also catalyzes Fenton reactions, amplifying ROS production directly within the tumor microenvironment.

Notably, tumors have adopted a variety of mechanisms to resist oxidative damage to protect themselves against death.[17,18] As a result, it is necessary to introduce significant levels of ROS to cause irreversible oxidative damage to tumor cells at low nanoparticle concentrations. The high efficacy and minimal adverse effects have made CDT an extensively preferred adjuvant with MHT in recent decades (Fig. 1). This mini-review explores the synergistic integration of MHT and CDT using multifunctional nanomaterials, highlights the mechanisms and benefits of combined ROS induction, and discusses the challenges and future directions for this dual-modality approach in cancer therapy.

Deepika Sharma

Dr Deepika Sharma is a Scientist-D at the Institute of Nano Science and Technology (INST), Mohali, India. She has over ten years of post-PhD research experience in cancer biology and cancer nanotherapeutics. Her research focuses on the development of advanced therapeutic strategies, including magnetic nanoparticle-based hyperthermia for the treatment of aggressive cancers such as glioblastoma multiforme, as well as the design of nanocarriers capable of traversing biological barriers like the blood–brain barrier. Her group also works on the early diagnosis of cancer, developing nanotechnology-based tools for timely detection and intervention. Additionally, she explores the therapeutic potential of plant-derived bioactives and microbial systems to complement conventional treatments. Dr Sharma has published over 43 peer-reviewed articles in leading journals including ACS Nano, ACS Applied Materials & Interfaces, Nanoscale, and Bioconjugate Chemistry, with over 2133 citations. She is a member of the Indian Association for Cancer Research (IACR), Indian Association for Hyperthermic Oncology and Medicine (IAHOM), Biotech Research Society of India (BRSI), and the Chandigarh Region Innovation and Knowledge Cluster (CRIKC).

2. Magnetic hyperthermia therapy (MHT)

Dating back to 1957, when Gilchrist and colleagues utilized magnetic particles with an alternating magnetic field to selectively heat tumors, MHT has a lengthy history. Since then, nanotechnology has advanced this approach into a well-studied field with the introduction of magnetic nanoparticles (MNPs). MNP-mediated MHT offers the significant benefit of deep tissue penetration and selective killing of cancer cells without harming adjacent healthy tissue.[19–21] By combining cell-targeting ligands with MNPs, intracellular hyperthermia can be enhanced, resulting in direct therapeutic heating of cancer

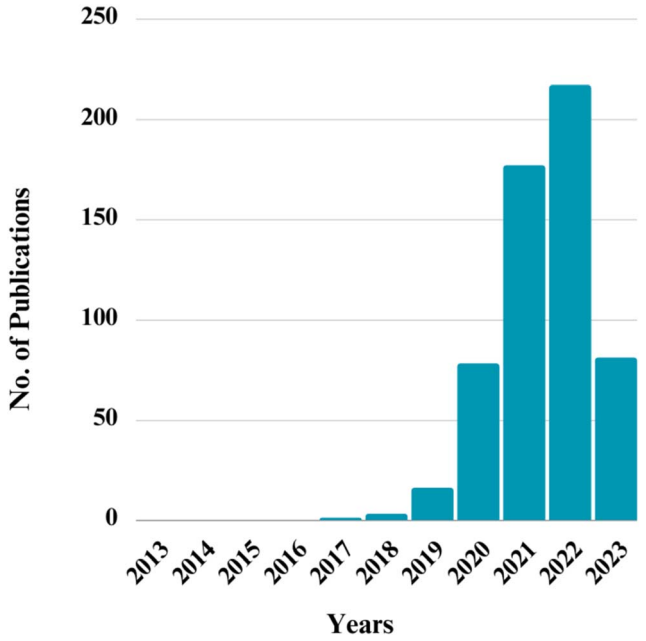


Fig. 1 Number of publications related to chemodynamic therapy combined with hyperthermia therapy in Google Scholar over the past decade (March 2023).

cells. This localized and homogeneous heat generation makes the treatment more effective and precise.

However, several non-invasive therapies have recently been introduced to the market for cancer treatment, including phototherapy and sonodynamic therapy.[12–14] Such treatments are reported to be useful to some extent but eventually have several shortcomings associated with them that make them ineffective for eradicating cancer completely.[15] Phototherapies such as PTT and PDT possess a non-invasive nature and high efficacy; however, there are limitations to phototherapy that prevent it from being used in clinical settings. PTT utilizes thermal energy generated by light-to-heat transformation materials to destroy cancer cells. The heat emitted by the energy transition zones or plasmon resonance raises the temperature of tumor cells that endocytose the photothermal materials without harming the normal cells. PDT is another approach for treating tumors that utilizes light activation and photosensitizing drugs. The irradiation of specific wavelengths on tumor sites activates the photosensitizing drugs that are specifically concentrated in tumor tissues, initiating a photochemical reaction to obliterate tumor cells. Regardless, these therapies cannot be used for clinical applications due to defects in photosensitive materials. The biggest disadvantage of PTT is its limited penetration depth of light that results in partial treatment of tumors that are within the radiation range and PDT has a short life span and short diffusion distance of ROS, which weakens the antitumor performance.[15,16] Meanwhile, SDT is also an evolving method that relies on a combination of specialized chemical agents called sonosensitizers and low-intensity ultrasound. By concentrating the ultrasound into small regions of the tumor, sonosensitizers are activated and serve as a non-invasive treatment for solid tumors.[17] However, a substantial amount of sensitizers is required to accumulate in the targeted lesion to obtain high efficiency of SDT and the large size of sensitizer molecules restricts the accumulation, resulting in low tumor penetration and SDT effectiveness.[18,19] Even with the high therapeutic effects of PTT, PDT, and SDT, their own limitations still result in incomplete elimination of cancer cells, which in turn leads to tumor recurrence and metastasis. To address the shortcomings of the above-mentioned therapies, MHT seems to be a viable option, which uses a small amount of MNPs to generate heat and is optimized with various coatings and targeting agents to achieve tumor site and type specificity.[20,21] The advantages of MHT over other non-invasive therapies such as PDT, PTT and SDT in the treatment of cancer have been confirmed by several reports.[8,21,22] MHT uses an AMF that penetrates deep into tissues (centimeters), unlike PTT and PDT that are limited by poor light penetration (typically <1 cm).

Therefore, it has been suggested that MHT can be an effective cancer treatment.[23,24] In the presence of an AMF, magnetic nanomaterials undergo Néel and Brownian relaxation, causing them to generate heat.[25,26] Various clinical studies undertaken on bladder, breast, cervix tumors, *etc.*, have revealed that MHT can enhance the cytotoxic effect of anticancer drugs and radiation on tumors.[27] In addition to the various clinical trials that have been conducted worldwide, NanoTherm Therapy (MagForce AG) has been launched as a commercial product. A magnetic nanomaterial most commonly used in therapeutic applications is magnetite (Fe_3O_4) nanoparticles, which are biocompatible and have a high heating efficiency. Despite being used for years, MHT still has its shortcomings. For example, MHT appears to be beneficial but lacks effectiveness due to low levels of ROS generation in the hypoxic tumor microenvironment (TME). In addition, tumors have adopted a variety of mechanisms to resist oxidative damage to protect themselves against death. As a result, it is necessary to introduce significant levels of ROS to cause irreversible oxidative damage to tumor cells at low nanoparticle concentrations. Furthermore, off-target accumulation of MNPs in organs such as the liver and spleen poses risks of non-specific heating during AMF treatment, raising concerns regarding systemic toxicity. Despite these limitations, advancements in magnetic nanoparticle engineering and targeted delivery strategies are likely to address these issues and broaden the clinical applicability of MHT–CDT.

The high efficacy and minimal adverse effects have made CDT with MHT an extensively preferred adjuvant therapy in recent decades, as shown in Fig. 1. Although MNP-mediated MHT cancer nanotechnology has been tested in clinical trials, further research and development are required to fully realize its potential. Specifically, a comprehensive study is needed to determine if it is feasible to overcome challenges such as the low therapeutic efficacy of this therapy modality in cancer therapy.

2.1 Mechanism of cancer cell death mediated *via* MHT: generation of ROS

The use of magnetic nanoparticles (MNPs) in magnetic hyperthermia therapy (MHT) for cancer treatment involves increasing

the temperature in the local tumor environment, leading to physiological changes in cancer cells and their eventual death through apoptosis or necrosis.[21,22] However, this localized heating effect can contribute to toxicity, as MNPs can have surface temperatures higher than the surrounding solution.[23] In addition to thermal effects, toxicity may also arise from chemical and mechanical damage due to the vibration and rotation of NPs, as well as surface-mediated reactive oxygen species (ROS) production.[24] ROS play a critical role in regulating apoptosis by inducing oxidative damage and are generated through various apoptosis pathways, including cytochrome C release in Granzyme B-induced apoptosis, which involves mitochondrial damage *via* Bid proteolytic cleavage.[25,26] Raising temperatures above the hyperthermia level can further increase ROS concentrations, leading to irreversible cell death, potentially due to increased Fenton activity or cancer cells' reduced ability to scavenge ROS at elevated temperatures. Recent research has shown that ROS can be generated more readily in alternating magnetic fields (AMFs), with significant increases observed even at NP concentrations that do not cause a temperature rise.[27]

MNPs affect cellular functions by influencing free radical activity, catalyzing ROS production in the tumor microenvironment (TME) through the Fenton reaction. Fe_3O_4 NPs (IONPs), which are commonly used in this context, act as Fenton nanoagents, generating toxic hydroxyl radicals ($^{\bullet}OH$) that damage DNA, cause lipid peroxidation, and trigger tumor cell apoptosis.[28] IONPs can enhance these processes when subjected to magnetic fields leveraging their intrinsic peroxidase-like activity discovered by Gao *et al.*[29] in 2007, which catalyzes the conversion of H_2O_2 into highly toxic $^{\bullet}OH$ radicals. This catalytic activity of ferrite NPs is central to ROS-mediated tumor therapy, facilitated by the enhanced permeability and retention (EPR) effect, which allows ferritin NPs to accumulate at tumor sites. In acidic environments within tumors, ferric and ferrous ions released from nanoparticles assist in the Fenton reaction with H_2O_2, producing $^{\bullet}OH$ radicals.[30] Research by Wydra *et al.*[31] demonstrated that IONPs generate free radicals more rapidly under AMF conditions, while theoretical analyses such as by Binhi[32] have shown that MNPs can enhance free radical formation even in static magnetic fields. MNPs generate strong magnetic fields around themselves, which can influence radical pair spin states and lower recombination rates, resulting in increased free radical generation.[33] The heat tension exerted by MNPs under an AMF also contributes to free radical production, as described by researchers such as Zhao *et al.*[34] and Yoshikawa *et al.*[35]

Despite the benefits of ROS production in tumor therapy, cells possess comprehensive antioxidant defense systems to counteract oxidative damage. When ROS levels overwhelm these defenses, an oxidative stress response is triggered. Heat shock proteins (HSPs) are crucial components of the cellular defense against oxidative stress, helping to prevent protein aggregation and supporting stress tolerance across various organisms, including humans. These proteins are upregulated in response to adverse conditions like elevated temperatures and oxidative stress, providing essential protection and aiding in the survival of cells under these challenging circumstances.[36–38]

2.2 Thermotolerance *via* generation of HSPs: less therapeutic efficacy

Elevated temperatures induced by MNP-mediated MHT ($\geq$41.5 °C) generally result in cytotoxicity that rises with the temperature. As a result of such high temperatures, proteins are denatured, enzymes are inactivated, and DNA repair mechanisms are inhibited, causing mitotic catastrophe and cell death.[39–41] However, when cells are subjected to high temperatures (41.5 to 45 °C) for a short time span (*e.g.* $\leq$1 h), or to low temperatures (39 to 41 °C) for a longer time period (*e.g.* 3 to 24 h), they build resistance against further cytotoxic heat treatments.[42–44] This process, known as thermotolerance, is closely linked with elevated expressions of cellular defences like heat shock proteins (HSPs).[45] In spite of cytotoxic aggressions and stress, these protective mechanisms enable cells to maintain their function. Therefore, MHT is less effective as a therapeutic strategy when thermostat tolerance is present, lowering its cytotoxic effects.

There is a growing body of evidence that HSPs have a broad variety of roles in apoptosis that, in most cases, suppress apoptotic pathways. Interestingly, stress triggers apoptosis, but HSPs are also released when these signals are activated. So far, many mechanisms have been proposed to explain the cytoprotective effects of HSPs; cytochrome c dimerization with Apaf-1 is one mechanism proposed to explain how HSPs work, hence blocking the assembly of apoptosome complexes, which is the defining characteristic of mitochondrial cell suicide.[28,46] Rane and colleagues have shown that HSP27 interacts with the serine/threonine (Akt) signaling pathway in a phosphorylation-dependent manner, thereby preventing apoptosis mediated by neutrophils.[47] However, more recent research indicates that another molecular chaperone, HSP70, directly binds to Apaf-1 and inhibits the growth of apoptotic cells through an ATPase-dependent mechanism, rather than *via* its traditional chaperone function.[48–50]

Researchers have found that HSPs prevent protein aggregation or target proteins towards proteolytic pathways.[51,52] HSP90, one of the most studied and well-conserved HSPs, is essential for the viability of eukaryotic cells.[53] It constitutively comprises 1–2% cytosolic proteins and its expression is further amplified when cells are brought to higher temperatures.[54,55] In eukaryotes, HSP90 serves dual chaperone functions, which are critical to nuclear hormone receptor maturation and to cellular stress responses.[56–58] A common feature of both of these processes is that HSP90 impedes protein aggregation and facilitates ATP-dependent refolding of denatured proteins from heat.[59,60] Moreover, there have been reports about HSP90 inhibiting caspase-3 activation *in vitro* and *in vivo*. In contrast to caspases-3, -6, -8, and -9, HSP90 adheres to Apaf-1 and hinders procaspase-3 activation. The findings also reveal that HSP90 prevents Apaf-1 oligomerization mediated by cyt c and subsequently activates procaspase-9. In short, studies have demonstrated that MHT-induced ROS generation activates HSPs,

which block caspase-3 and, in turn, reduce the effectiveness of the MHT treatment in killing cancer cells. Therefore, in order to achieve irrevocable oxidative injury to the tumor cells, combination with another modality like chemodynamic therapy (CDT) can be employed, which produces toxic hydroxyl radicals *via* Fenton's reaction.

3. Chemodynamic therapy (CDT)

A specific tumor microenvironment characterized by high levels of hydrogen peroxide, hypoxia, and mild acidity has been reported, which results from the unique metabolic pathways of tumor cells.[61] CDT has gained attention as a new therapeutic approach due to its ability to produce oxidative stress in a unique pattern.[62] CDT is based on Fenton and Fenton-like reactions that convert intracellular H_2O_2 into highly toxic hydroxyl radicals ($^{\bullet}OH$) in the tumor microenvironment, causing profound oxidative damage without external stimulation.[63,64] Unlike other clinical approaches, CDT only affects cancer cells, leaving normal cells unharmed, thus demonstrating tumor specificity.[65] Another advantage of CDT is its low energy requirement, minimizing energy attenuation during the treatment.[66] The combination of CDT with other modalities, such as hyperthermal treatment, can significantly improve the efficacy and sensitivity of antitumor therapy. Hyperthermal treatment can stimulate ROS production, and studies have indicated that combining it with CDT can inhibit tumor growth and present a promising treatment.[67–69] Therefore, the combination of MHT and CDT after surgical excision can synergistically kill remaining bone tumor cells, overcoming the disadvantages of single-mode therapy, such as non-specificity and heat damage to healthy cells.

3.1 CDT and its associated reactions

One of the main constituents of CDT is the Fenton reaction, for which dozens of mechanisms have been proposed. However, to simplify the discussion, we focus on the five reactions listed below[70] including the initiation reaction (eqn (1)), two propagation reactions (eqn (2) and (3)) that regenerate Fe^{3+} and liberate O_2, and two termination reactions (eqn (4) and (5)).

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^- + {}^{\bullet}OH, \quad (1)$$

$$^{\bullet}OH + H_2O_2 \rightarrow {}^{\bullet}OOH + H_2O, \quad (2)$$

$$Fe^{3+} + {}^{\bullet}OOH \rightarrow Fe^{2+} + H^+ + O_2, \quad (3)$$

$$Fe^{2+} + {}^{\bullet}OOH \rightarrow Fe^{3+} + HO_2^-, \quad (4)$$

$$Fe^{2+} + {}^{\bullet}OH \rightarrow Fe^{3+} + OH^- \quad (5)$$

Nanotherapeutics has mostly been reported to benefit from the effects of iron-based cations, but other metal cations are also demonstrated to cause CDT (Cu^{1+}, Mn^{2+}, and Sr^{2+}). As a general rule, the first initiation step is written as eqn (6),[71,72] where n is any integer and M is any metal that can exist as a cation in the n and n^{+1} oxidation states.

$$(M^{n+}) + H_2O_2 \rightarrow (M^{[n+1]+}) + OH^- + {}^{\bullet}OH \quad (6)$$

Therefore, iron and other Fenton-like metal cations can facilitate ROS production within cancer cells in the presence of sufficient levels of hydrogen peroxide (H_2O_2).

Another aspect of the Fenton reaction is the involvement of Fenton-compatible species and their resulting ROS with the glutathione (GSH) consumption that yields the oxidized and inactive form of glutathione (GSSG). This is accomplished *via* the following standardized reaction procedure:

$$GSH + (M^{[n+1]+}) \rightarrow M^{n+} + GSSG \quad (7)$$

Keep in mind that the mechanism given in eqn (7) is highly simplified and there are actually dozens of intermediate reaction steps.[73,74] In a similar fashion, the mechanism explaining how GSH reacts with ROS intracellularly is simplified as follows:

$$GSH + ROS \rightarrow GSSG + H_2O \quad (8)$$

Cells are significantly less able to cope with oxidative stress as GSH is consumed within them. Thus, the synchronous release of ROS and exhaustion of the cell's main antioxidant system result in excessive lipid peroxidation of the mitochondria and other cell components, compromising them and inducing cellular toxicity and apoptosis, as described in several CDT reports.[75–78]

CDT works by producing hydroxyl radicals that are highly toxic to cancer cells.[79] In order for CDT to be effective, Fenton or Fenton-like reactions must generate hydroxyl radicals that meet three conditions. Firstly, an ample amount of hydroxyl radicals must be generated within the tumor. An insufficient H_2O_2 concentration in tumor cells will result in a low concentration of hydroxyl radicals;[80] therefore, the main solution to this problem lies in enhancing the concentration of H_2O_2.[81,82] Secondly, the rate at which hydroxyl radicals are generated must be rapid, in order to cause continuous damage to cells within a short span of time. A catalyst's performance and the reaction conditions determine how quickly hydroxyl radicals are generated. As a result, there are two methods for increasing the generation of hydroxyl radicals: one is enhancing the effectiveness of Fenton or Fenton-like agents through the formulation of new catalysts and the modification of its composition and structure;[61,83–85] the other is optimizing the conditions of the reaction by raising the temperature or supplying an external energy source.[62,63] Finally, the produced hydroxyl radicals should be specifically targeted to tumor cells rather than other structures in the TME, for example, glutathione (GSH).[64,86] It has been well documented that antioxidants scavenge hydroxyl radicals, which compromises the efficacy of CDT.[61,87–89] Additionally, hydroxyl radicals have a short lifetime and a short diffusion distance, both of which limit their killing effect on cells.[89]

To circumvent tumor resistance and enhance chemodynamic efficacy, there is a high need for diminution of the concentration of intracellular antioxidant agents and the action distance in CDT.[89,90] Many chemodynamic agents have been developed to solve these problems, such as Mn^{2+}, Fe^{2+}, Cr^{4+},

Cu^{+}, Mo^{5+}, and Ti^{3+}-based nanomaterials[91,92] that have better CDT efficiency, but it is not enough to entirely eliminate tumors with only single therapy.[91] Therefore, combining CDT with other therapies serves as an essential development trend.

Interestingly, a study reported an innovative approach to enhance CDT using non-metallic nanomaterials activated by ultrasound. Traditional CDT relies on metal-based catalysts to generate hydroxyl radicals through Fenton reactions, which can be limited by slow reaction kinetics and uneven H_2O_2 distribution within tumors. To overcome these challenges, the researchers developed $Bi_{0.44}Ba_{0.06}Na_{0.5}TiO_{2.97}$ (BNBT-6) nanocrystals that, upon ultrasound stimulation, create a piezoelectric-induced electric field. This field facilitates the simultaneous oxidation of water (H_2O) and reduction of H_2O_2, leading to increased $^{\cdot}OH$ production even in low H_2O_2 environments. Additionally, doping with electron-rich oxygen vacancies enhances the dissociation of H_2O_2 and H_2O, further promoting $^{\cdot}OH$ generation.[93]

3.2 Mechanism of cancer cell death mediated *via* CDT: lysosomal and endoplasmic reticulum damage

One of the pivotal mechanisms underlying CDT is the targeted disruption of lysosomes, which serves as a critical pathway for inducing tumor cell death.[94] The low pH in lysosomes provides an ideal site for Fenton and Fenton-like reactions catalyzed by transition metal-based nanoparticles used in CDT. Upon cellular uptake, these nanoparticles are frequently internalized through endocytosis and trafficked to lysosomes. Within this acidic milieu, metal ions (*e.g.*, Fe^{2+}) react with the abundant H_2O_2 present in tumor cells to generate highly reactive hydroxyl radicals. The localized production of these ROS within lysosomes leads to oxidative damage of the lysosomal membrane, a process known as lysosomal membrane permeabilization (LMP). LMP results in the release of cathepsins, proteases, and other hydrolytic enzymes into the cytoplasm, thereby triggering apoptotic or necrotic cell death pathways depending on the extent of membrane disruption. Additionally, the leakage of iron ions from damaged lysosomes can further catalyze Fenton reactions in the cytosol, amplifying ROS generation and promoting a feed-forward loop of oxidative stress.

In addition to lysosomal damage, the endoplasmic reticulum (ER) has emerged as a critical intracellular target in CDT-mediated tumor cell killing.[94] In CDT, transition metal-based nanomaterials, once internalized by tumor cells, can either localize near the ER or generate ROS that diffuse and disrupt ER function. The hydroxyl radicals generated *via* Fenton or Fenton-like reactions induce oxidative damage to ER membranes and luminal proteins, leading to an accumulation of misfolded or unfolded proteins. This disruption activates the unfolded protein response (UPR) transition from pro-survival to pro-apoptotic signaling.[95] The upregulated key mediators such as PERK (protein kinase R-like ER kinase), ATF4 (activating transcription factor 4), and CHOP (C/EBP homologous protein) trigger apoptosis by inhibiting protein synthesis, altering calcium signaling, and activating caspase-dependent pathways.

4. Mechanism of cancer cell death mediated *via* synergistic CDT with MHT

The strategic integration of MHT with CDT offers a powerful, synergistic platform for enhancing the therapeutic efficacy of nanomedicine-based cancer treatments. The mild hyperthermia serves multiple complementary roles in augmenting CDT. Firstly, the elevated temperature significantly accelerates the kinetics of Fenton or Fenton-like reactions catalysed by transition metal ions (*e.g.*, Fe^{2+} and Cu^{+}), thereby enhancing the generation of highly cytotoxic hydroxyl radicals.[96] This increase in ROS production promotes greater oxidative damage within the TME. Secondly, many of the nanoparticles employed in MHT inherently possess Fenton catalytic properties, enabling them to function dually as heat generators and ROS producers. More importantly, hyperthermia has been shown to sensitize intracellular organelles such as lysosomes and ER, rendering them more vulnerable to ROS-induced damage.[94] For instance, heat stress can destabilize lysosomal membranes and exacerbate ER stress, facilitating the release of pro-apoptotic factors and amplifying cell death signaling cascades. Consequently, the combination of CDT-induced ROS and MHT-induced thermal stress leads to profound organelle dysfunction, mitochondrial collapse, and activation of both apoptotic and immunogenic cell death pathways. This synergistic approach is particularly effective in overcoming therapeutic resistance, as it targets multiple intracellular vulnerabilities simultaneously. Overall, the dual action of MHT and CDT not only deepens the extent of tumor cytotoxicity but also provides a versatile and tunable framework for combination cancer therapies.

4.1 Nanomaterial-based nanoplatforms for combination therapy of CDT with MHT

Even though multiple potent chemodynamic agents have been introduced, CDT is still far from effective as a monotherapy in treating metastatic cancer. In recent years, the focus of CDT has shifted from optimizing the Fenton or Fenton-like catalytic effects of chemodynamic agents to developing combinations with other therapies, for example, PTT, PDT, SDT, ST, CT, and RT. The combination of therapies in many cases exerts a "1 + 1 > 2" synergistic effect, which is more than a simple addition, a synergistic promotion. The MHT–CDT synergistic cancer treatment effect has been observed in many magnetic nanomaterials combining the magnetic-hyperthermia effect and Fenton/Fenton-like catalytic activity[97] (Fig. 2).

It is fortunate that glucose consumption can decrease the amount of ATP produced, leading to downregulation of HSP expression, which makes combining MNPs with glucose oxidase (GOx) an effective method for enhancing MHT performance.[98] Combining enhanced MHT with CDT can further enhance cancer therapy, as demonstrated by Ying *et al.*[99] in their development of a nanocatalytic platform consisting of GOx-loaded hollow iron oxide nanocatalysts (HIONCs). These HIONCs contain Fe^{2+} that serves as a catalyst for generating ROS *via* the Fenton reaction and producing O_2 by decomposing H_2O_2, thereby alleviating hypoxia. GOx is catalyzed to break

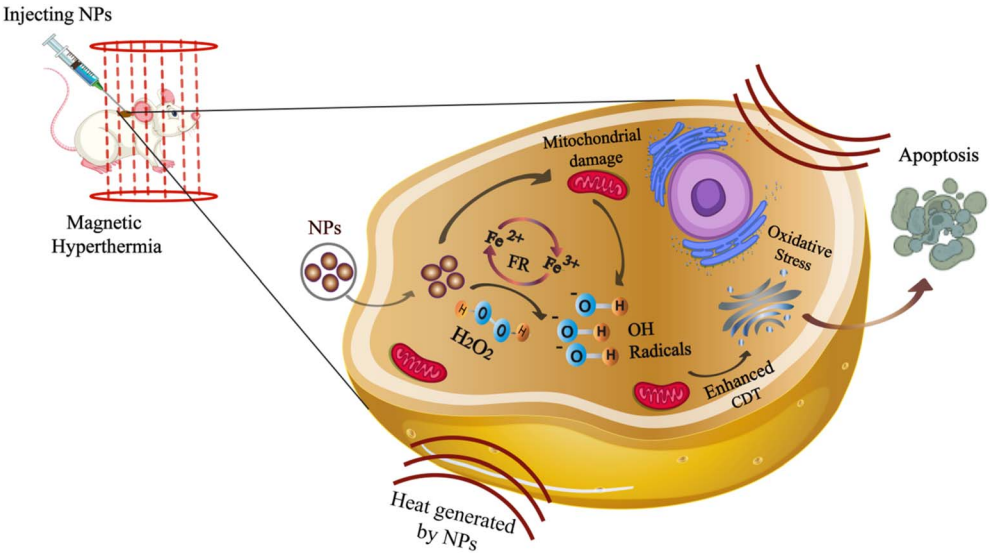


Fig. 2 A schematic illustrating the combined mechanism of magnetic hyperthermia and chemodynamic therapy, which work synergistically to enhance the therapeutic effect.

down intra-tumoral glucose into H_2O_2 and gluconic acid, consuming glucose and improving MHT efficacy. Ultimately, this leads to the downregulation of HSP expression.

In this interesting finding, the authors also reported that decreasing HSP expression in tumors by over 70% was achieved by producing $^{\bullet}OH$. It is uncertain though whether $^{\bullet}OH$ radicals simply break down the expressed HSPs or instead actually inhibit their expression. There have been some speculations that depletion of ATP inhibits the expression of HSPs,[100] or the decline in the ATP : ADP ratio within a cell drastically alters the activity of the HSPs. No matter which mechanism was involved – inhibition of HSPs, destruction of HSP by ROS, or a change in HSP function – the authors found that the AMF increased the tumor's sensitivity to hyperthermia.

Shen *et al.*[90] developed a magneto-thermogenic nanozyme, known as Ir@$MnFe_2O_4$ NPs, that targets mitochondria using an iridium(III) complex (Ir) attached to the surface of MNPs. On AMF subjection, the Ir@$MnFe_2O_4$ NP complex yields a temperature increase because of the MHT effect, causing irreversible mitochondrial damage. Due to excellent optical and magnetic properties, this nanoplatform could be used both for two-photon microscopy imaging *in vitro* and MRI imaging *in vivo*. In addition, hollow Fe_3O_4 mesocrystals (MCs) were synthesized by Du *et al.*[101] *via* a revised solvothermal procedure, which involved ammonium acetate (NH_4Ac) as the structure-directing agent and ethylene glycol as the reducing agent. The magnetothermal conversion process is dominated by hysteresis loss; therefore, the magnetothermal conversion efficiency of Fe_3O_4 MCs was excellent, compared to Fe_3O_4 polycrystalline (PC) systems, as a result of the enlarged hysteresis loop leading to improved MHT.

Ma *et al.*[102] designed a versatile therapeutic nanoplatform with enhanced tumor treatment capabilities. In their research, they synthesised Fe_3O_4–Pd Janus nanoparticles (JNPs) that combine dual-mode magnetic resonance imaging (MRI) and photoacoustic (PA) imaging for simultaneous magnetic-photo hyperthermia and chemodynamic therapy. The magnetic-photothermal properties of Fe_3O_4 NPs, along with the plasmonic photothermal effect of Pd nanosheets, allowed the Fe_3O_4–Pd JNPs to achieve a synergistic heating effect that is greater than the sum of the individual effects (1 + 1 > 2). Beyond the enhanced heating, the Fe_3O_4–Pd JNPs also increased the generation of reactive oxygen species (ROS) due to the synergistic interaction at the interface. This effect is achieved through the Fenton reaction of the Fe_3O_4nanoparticles and the catalytic action of Pd nanosheets in the presence of H_2O_2 in an acidic environment. The study highlighted a novel strategy for cancer treatment by designing high-performance theranostic nanoplatforms tailored to the tumor microenvironment and leveraging distinct physiochemical characteristics of inorganic nanomaterials.[102]

The combination of the selective heat generating capability of MHT with the Fenton/Fenton-like catalytic properties of CDT can enable effective synergistic cancer treatment (Table 1).

5. Tumor resistance mechanisms and overcoming strategies

Like all cancer treatments, MHT and CDT can face tumor resistance mechanisms over time. Tumor cells are notorious for adapting to stresses, and the stresses induced by hyperthermia and intracellular ROS are no exception. One well-documented resistance mechanism in hyperthermia treatment is the upregulation of HSPs. HSPs such as HSP70 and HSP90 are molecular chaperones that help cells survive lethal conditions. When a tumor is heated (*e.g.* to 42–45 °C in MHT), surviving cells often show increased expression of HSPs, which can protect them from protein damage and apoptosis, thereby inducing thermotolerance.[106,107] For example, clinical studies on

Table 1 Nanomaterials for cancer treatment utilizing chemodynamic and magnetothermal therapy

Nanomaterials	CDT–MHT agent(s)	Nanomaterial size	Thermal profile and biocompatibility	Tumor eradication post-treatment	Mechanism rationale	References
Ir@$MnFe_2O_4$ NPs	Mn, Fe, Ir	11.24 nm	At a strength of 7.9 kA m^{-1} and a frequency of 598.0 kHz, the temperature rise was 43.8 °C and 85% cell viability was observed	14 days	Localized increase in temperature caused mitochondrial damage along with the release of toxic OH radicals by glutathione	90
Hollow Fe_3O_4 mesocrystals (MCs)	Fe	350 nm	The specific absorption rate of Fe_3O_4 MCs was 722 w g^{-1} and 85% cell viability was observed	15 days	Fe_3O_4 MCs elevated the levels of $^{\bullet}OH$ radicals and also reduced the expression of heat shock proteins (HSPs). Meanwhile, magnetic hyperthermia facilitated CDT with augmented temperature	101
Glucose oxidase (GOD)-loaded hollow iron oxide nanocatalysts (HIONCs)	Fe, GOD	295 nm	At a strength of 1.0 kA m^{-1} and a frequency of 513.0 kHz, the temperature rise was 50 °C and 85% cell viability observed	21 days	The Fe^{2+} present in HIONCs contributed to ROS generation *via* the Fenton reaction, relieving thermal resistance and inducing cell apoptosis by chemodynamic action	99
Nanosized zero-valence crystallized iron NPs (nZVCI NPs)	Fe	200 nm	At a frequency of 300 kHz, the temperature rise was 62 °C and more than 90% cell viability was observed	14 days	nZVCI-NPs generated heat from external incident light as well as an alternating magnetic field, which synergistically augmented the production of $^{\bullet}OH$ radicals for Fenton-based nanocatalytic therapy	103
Ellagic acid-Fe-bovine serum albumin NPs (EA-Fe@BSA NPs)	Fe	13.84 ± 2.53 nm	Temperature rose from 0 to 20 °C and 80% cell viability was observed	16 days	A rapid Fe(III)/Fe(II) conversion system was established by EA-Fe@BSA NPs, wherein highly active Fe(II) ions were continuously regenerated to improve the CDT efficiency	104
Fe_3O_4–Pd Janus nanoparticles (JNPs)	Fe, Pd	15 nm	At a frequency of 350 kHz under an 808 nm NIR laser (0.5 W cm^{-2}), temperature rose from 0 to 40 °C and 75% cell viability was observed	18 days	The magnetic properties of Fe_3O_4 nanoparticles and the plasmonic photothermal effect of Pd nanosheets provided synergistic heating effects of 1 + 1 > 2	102
Biocompatibility nano-truck (BMP NT)	Mn, GSH	21 nm	Under an 808 nm NIR laser (1 W cm^{-2}), temperature rose to 62 °C and 94% cell viability was observed	16 days	Mn^{2+} ions catalyzed a Fenton-like reaction and the ultrasmall Bi_2S_3@BSA nanoparticles generated local hyperthermia for PTT and accelerated the Fenton process	105

hyperthermic chemotherapy have observed that HSP70/90 levels peak around 18–20 hours after a heat treatment, potentially reducing the efficacy of a second hyperthermia or chemotherapy session if given too soon.[108] This suggests that tumors mount a transient defence after being heated. Other cellular changes, such as activation of pro-survival signalling pathways (*e.g. via* heat-induced phosphorylation events) and improved blood perfusion in the heated tumor region (which can act as a "heat sink" to dissipate thermal stress), may also contribute to resistance. There is evidence that certain genetic factors can modulate hyperthermia sensitivity; for instance, overexpression of integrin-linked kinase (ILK) or other stress-response mediators in tumor cells was found to significantly increase resistance to heat-induced cell death in experimental models.[109]

In the context of CDT, the primary challenge is the tumor's antioxidant capacity. Chemodynamic therapy relies on producing lethal hydroxyl radicals (·OH) *via* Fenton reactions inside cancer cells. Cancer cells, however, often adapt by elevating their antioxidant defences, especially glutathione (GSH). GSH is the most abundant intracellular antioxidant and can readily neutralize ROS. Tumors with high metabolic activity frequently have high GSH levels as an adaptive response to endogenous oxidative stress.[110] While this helps the cancer survive under its own growth-induced stress, it directly counteracts CDT – excess GSH can scavenge the hydroxyl radicals generated by Fenton chemistry, thereby blunting the therapeutic effect.[111] Additionally, if the tumor microenvironment is extremely hypoxic or low in H_2O_2, Fenton reactions may be insufficient; some aggressive tumors consume hydrogen peroxide and other peroxides quickly or upregulate enzymes like catalase and peroxidases to break down H_2O_2. Such tumors would be inherently less responsive to CDT unless these conditions are modified. Other potential resistance factors include upregulation of metal-binding proteins or efflux pumps; for example, cancer cells might increase expression of ferritin or metallothioneins to sequester catalytic metal ions, or pump out the introduced nanoparticles, thereby reducing CDT efficacy over time. Understanding these mechanisms has led researchers to develop counter-strategies. One approach to mitigate thermotolerance is to pharmacologically inhibit heat shock proteins. In experimental models, using an HSP90 inhibitor alongside hyperthermia prevented the tumor cells from mounting an effective heat shock response and enhanced DNA damage and cell killing.[112] Such HSP inhibitors (several of which are in clinical trials as anti-cancer agents themselves) could be combined with MHT to sensitize tumors to heat. Another practical tactic, as clinical data suggest, is to optimize the timing of sequential treatments. Since HSP levels return to baseline about 24 hours after a heat exposure,[108] scheduling repeated MHT sessions or follow-up chemotherapy courses may avoid the peak of thermoresistance. A number of studies are investigating GSH-depleting strategies to accompany CDT. These include designing NPs that release GSH scavengers or inhibitors once inside the tumor. For instance, NPs can be coated or co-loaded with compounds that react with GSH (such as disulfide bond-containing molecules or buthionine sulfoximine, a GSH-synthesis inhibitor). By lowering intracellular GSH, the Fenton-generated ROS are less likely to be neutralized.[110,113]

It is worth noting that combination therapy can pre-empt or overcome resistance as well. Using MHT and CDT together is itself a strategy to tackle resistance: MHT-induced heat can disrupt cancer cell membranes and proteins, potentially impairing the function of efflux pumps or DNA repair proteins, which might make cells more susceptible to ROS damage from CDT. Conversely, CDT's ROS burst can sensitize cells to heat shock.[114] Additionally, combining these modalities with immunotherapies or radiotherapy could help eliminate any resistant cell populations. For example, residual tumor cells that survive MHT/CDT might become more immunogenic (due to heat or ROS-induced protein denaturation and release of damage signals), making them better targets for immune attack – ongoing research is examining if MHT/CDT can induce immunogenic cell death that a checkpoint inhibitor or CAR T-cell therapy could exploit.[115,116] In summary, tumors may resist MHT *via* thermal adaptation (HSPs and other stress responses) and resist CDT *via* chemical adaptation (antioxidants and metabolic changes). Researchers are actively developing methods to block these defences. Careful scheduling, HSP inhibitors,[112] and redox modulation approaches such as GSH depletion[117] have shown promise in restoring tumor sensitivity to hyperthermia and CDT. By integrating such strategies into treatment protocols, the efficacy of MHT and CDT can likely be significantly improved, turning the tumor's adaptive tricks against itself and ensuring cancer cells have nowhere to hide from the heat and oxidative assault.

6. Comparative analysis with emerging therapies

Emerging cancer therapies like CRISPR-based gene editing and personalized cancer vaccines offer fundamentally different treatment strategies compared to MHT and CDT. CRISPR-based treatments (for example, CRISPR-Cas9 edited T-cells or CAR-T cells) aim to reprogram a patient's cells at the genetic level to better fight cancer. Early-phase trials have shown that CRISPR-edited immune cells can be safely infused and persist in patients. In one landmark Phase I study, T-cells were edited to knock out PD-1 and insert a cancer-specific T-cell receptor; the modified cells engrafted and survived up to 9 months *in vivo* with manageable side effects.[118] These trials demonstrate feasibility, but clinical efficacy (tumor responses) has so far been modest. A major advantage of CRISPR therapies is their precision – they can, in principle, permanently disable oncogenic genes or enhance immune cell function. This could yield durable remissions if successful. However, safety and delivery remain concerns. Off-target gene edits and unforeseen immune reactions (such as anti-Cas9 immune responses) need to be carefully monitored, and CRISPR treatments currently require complex *ex vivo* cell engineering for each patient.[119] By contrast, personalized cancer vaccines (*e.g.* neoantigen-targeted mRNA vaccines) leverage the patient's immune system to seek and

destroy cancer cells. Recent trials have reported encouraging results; for instance, an individualized mRNA vaccine combined with immunotherapy (pembrolizumab) in high-risk melanoma patients reduced the risk of recurrence or death by 44% compared to immunotherapy alone.[120] These vaccines are highly specific (each vaccine is custom-made to target mutations in the patient's tumor) and generally well tolerated, with side effects mostly limited to immune reactions like injection-site inflammation or flu-like symptoms.

In terms of efficacy, MHT/CDT and CRISPR/vaccine approaches have different strengths. MHT and CDT act locally and rapidly – heating and *in situ* chemical generation of ROS directly kill tumor cells in the targeted region, which can lead to immediate tumor debulking. This local aggressiveness can be very effective for accessible tumors and can synergize with other treatments (*e.g.* radiation or chemotherapy). However, on their own they may not address distant metastases or microscopic disease outside the treatment field. CRISPR and vaccine therapies, on the other hand, aim for systemic and long-lasting immunity or tumor suppression. A personalized vaccine can stimulate T-cells that patrol the entire body, potentially attacking metastatic lesions and providing memory against relapse.[120] Similarly, CRISPR-edited T-cells or NK cells can circulate and continuously seek out cancer cells. The trade-off is that these genetic/immunologic therapies often take time to induce an effect (weeks to months to generate an immune response), whereas MHT/CDT can destroy tumors within a single treatment session.

When comparing safety, MHT and CDT tend to have more localized side effects. Magnetic hyperthermia's reported toxicities are mostly related to the procedure (*e.g.* minor surgical risk of nanoparticle injection, transient inflammation or edema in the heated tumor area) and some mild systemic effects like fever. The biocompatibility of iron-oxide NPs used in MHT has been good in trials,[121] although long-term tracking of particle biodistribution is still needed. CDT uses chemical catalysts (often metal-based NPs) to produce ROS, and its specificity for tumor conditions (high H_2O_2 and acidity) helps spare normal tissue; however, there is a risk of off-target oxidative damage if the catalysts distribute to healthy organs. Overall, because MHT/CDT are applied locally, they avoid the widespread toxicities of chemotherapy. In contrast, CRISPR and vaccine therapies engage the immune system or alter cells throughout the body, which can cause distinct side effects. CRISPR-edited cell therapies can provoke cytokine release or graft-*versus*-host-like responses if the edited cells are reactive, and there is the theoretical risk of unintended mutations leading to secondary malignancies[122] (though none reported to date in trials). Personalized vaccines can cause immune-related adverse events; for example, excessive immune activation might trigger autoimmunity or systemic inflammation. Thus far, trials of neoantigen mRNA vaccines have reported mostly grade 1–2 immune side effects (fatigue and fever), indicating acceptable safety.[120] Availability and practicality also differ. MHT is partially available in specialized centers – for example, the NanoTherm MHT therapy is approved in Europe for brain tumors and can be offered at equipped hospitals.[123] It requires hardware (an AMF generator) and trained personnel, but once set up, each treatment is relatively quick. CDT formulations are still experimental, but many utilize materials or drugs that could be mass-produced if approved. Personalized vaccines and autologous CRISPR cell therapies, however, face scalability challenges. Each personalized vaccine involves sequencing a patient's tumor and manufacturing a bespoke vaccine (often taking 4–8 weeks), and thus is currently available only through clinical trials at major centres. CRISPR cell therapies likewise require harvesting a patient's T-cells or hematopoietic cells, engineering them in a specialized lab, and re-infusing them – a labour- and cost-intensive process. Off-the-shelf approaches (*e.g.* allogeneic CRISPR-edited CAR-T cells) are under study to improve accessibility.[124] In summary, MHT and CDT represent locally focused therapies that can be deployed with existing medical technology (if available) and may be especially suitable for patients with isolated tumors or as adjuncts to surgery/radiation. CRISPR-based treatments and personalized vaccines offer a precision medicine paradigm, potentially attacking cancer at the molecular level across the whole body, but they are in earlier stages of development with significant technical and regulatory hurdles to overcome before widespread use. As these modalities evolve, it is conceivable that they will not be mutually exclusive – for instance, local therapies like MHT/CDT could debulk tumors and release antigens, while a personalized vaccine or adoptive T-cell therapy cleans up residual disease, combining immediate tumor destruction with long-term immune surveillance.

7. Clinical trials and translational progress

Early-phase clinical trials are probing the combined use of MHT and CDT in cancer treatment. In recurrent glioblastoma multiforme (GBM), a Phase I trial in 14 patients demonstrated the feasibility, safety, and potential efficacy of intratumoral magnetic hyperthermia.[125] Building on this, a Phase II study in 65 GBM patients is underway,[126] and a post-marketing trial[127] is comparing NanoTherm® MHT (with or without radiotherapy) against radiotherapy alone. In prostate cancer, a Phase 0/I trial (NCT02033447) with 12 patients established that injected iron-oxide NPs could be safely retained and heated in the tumor, informing a larger US trial in intermediate-risk prostate cancer (MagForce, stage 1 completed in 2019).[128] Notably, a separate Phase I study in Japan (6 patients with refractory tumors) achieved intratumoral temperatures of ~43 °C *via* MHT and observed >33% tumor cell necrosis in resected specimens with no significant adverse events,[129] indicating robust tumor responses with the MHT–CDT approach.

These trials span gliomas, prostate tumors, and advanced pancreatic cancers, reflecting growing translational progress. The iron-oxide NPs used in MHT also act as Fenton catalysts, converting tumor-endogenous hydrogen peroxide into cytotoxic hydroxyl radicals – essentially a CDT effect – which is amplified under an alternating magnetic field.[125] This dual modality has shown powerful synergy in preclinical models: for example,

magnetothermal heating combined with nanocatalytic CDT completely halted breast tumor growth in mice without added toxicity.[129] Clinically, MHT gained EU approval in 2010 for recurrent GBM after promising Phase IIa results (improved survival) and the EU "NoCanTher" program recently launched a trial integrating MHT–CDT for advanced pancreatic cancer.[130] Across studies, combined MHT–CDT has been well-tolerated and yields encouraging efficacy (tumor shrinkage/ablation and prolonged disease control), leveraging synergistic tumor heating and ROS-mediated cytotoxicity to overcome thermoresistance.[131,132]

7.1 Economic considerations and cost-effectiveness

The adoption of any new cancer therapy depends not only on efficacy but also on economic feasibility. Magnetic hyperthermia and chemodynamic therapies pose unique cost considerations compared to traditional treatments. On one hand, they could reduce downstream costs by improving local tumor control (potentially lowering recurrence rates and the need for prolonged chemotherapy). On the other hand, they require specialized materials and equipment that can be expensive. For example, the magnetic nanoparticle formulation and AMF generator used in MHT have a significant upfront cost. MagForce's NanoTherm therapy, as applied in European clinics, was reported to cost roughly €23,000 per patient for a full course of treatment.[123] This figure includes the cost of synthesis of NPs, the procedure to administer them, and the hyperthermia sessions. By comparison, standard chemotherapy regimens can vary widely in cost but often run into tens of thousands of euros as well, especially when factoring in management of side effects and hospitalizations. Traditional hyperthermia (using microwave or radiofrequency devices) has historically been considered a relatively cost-effective adjunct, especially in resource-limited settings. Clinical experts note that hyperthermia is a "unique multifaceted modality" with few side effects and can be delivered at moderate cost, making it attractive for low- and middle-income countries when used to boost radiotherapy or chemotherapy outcomes.[133] The same logic could apply to MHT/CDT: if these therapies substantially enhance the effectiveness of existing treatments, the incremental cost might be justified by better tumor control and potentially fewer treatment cycles of expensive drugs.

However, there are economic barriers to widespread adoption. The need for specialized equipment (magnetic field generators, NP manufacturing facilities, *etc.*) means an initial capital investment that many hospitals may not afford without clear evidence of benefit. Operating an MHT suite also requires trained personnel (interventional radiologists or surgeons for NP delivery, physicists to run the AMF device, *etc.*), which adds to operational costs. Analyses estimate that a single hyperthermia treatment session (not specifically MHT) can cost on the order of $20,000–50,000, which has limited its use globally to larger cancer centres.[134] If MHT or CDT can be shown to significantly improve cure rates or enable reductions in expensive systemic therapies, a cost-benefit balance could be achieved. For instance, if adding MHT prevents a cancer from recurring, the savings from avoiding second-line chemotherapy or extended immunotherapy could offset the MHT procedure cost. Additionally, magnetic nanoparticles are relatively inexpensive to produce in bulk (iron oxides are cheap raw materials), and if demand grows, economies of scale might lower the per-patient cost of nanoparticles. One study projected that if NP-mediated therapies are accepted, the NP material costs could be on the order of only a few hundred dollars per treatment,[123] with the main costs coming from clinical delivery and equipment amortization. From a health economics perspective, it is also important to consider patient quality of life and indirect costs. MHT and CDT are generally associated with milder systemic side effects, which could translate to less time off work and fewer supportive care medications, improving cost-effectiveness. In one analysis of hyperthermia combined with chemotherapy, the addition of hyperthermia was found to be cost-effective due to improved response rates, which reduced subsequent treatment needs.[133] Still, thorough cost-effectiveness analyses specific to MHT and CDT are scarce at this time, given that these modalities are still emerging from research phases. As clinical trial data accumulate, formal studies should evaluate the incremental cost per quality-adjusted life year (QALY) gained with MHT/CDT *versus* standard care.

Feasibility and scalability will also influence economics. If CDT, for example, relies on complex nanocarriers or combination with expensive drugs, its cost could be prohibitive without refinement. Simpler, bioinspired CDT agents such as NPs made/coated with endogenous substances might be cheaper and easier to approve.[96] MHT is being integrated with existing treatment suites (for instance, combining magnetic hyperthermia with MRI machines for real-time guidance)[135] – such dual-use equipment could spread the capital cost over multiple uses (imaging and therapy). In summary, while current MHT and CDT therapies involve non-trivial expenses, there is potential for them to be cost-effective if they deliver superior outcomes. Ongoing clinical trials will not only clarify the medical benefits but also provide data to model whether those benefits outweigh the costs compared to conventional surgery, radiation, or drug therapy. Addressing cost and manufacturing challenges early will be important for the widespread adoption of these nanotechnologies in oncology.

7.2 Ethical and regulatory challenges in nanotechnology-based cancer therapy

The use of nanotechnology in cancer treatment raises important ethical and regulatory considerations that go hand-in-hand with the scientific and clinical challenges. One major ethical aspect is ensuring informed patient consent in trials and eventual clinical use. Because MHT and CDT are novel therapies with mechanisms unfamiliar to most patients, clinicians must take care to clearly explain the potential risks, benefits, and unknowns. In early-phase trials, the risk/benefit profile is still being determined, which complicates the consent process. Researchers have cautioned against the "therapeutic misconception", where patients might misconstrue a research

intervention as a guaranteed cure due to excitement around new technology.[136] To counter this, consent documents and discussions should be conducted in plain language, candidly stating that nanomedicine approaches are experimental and that outcomes (both good and bad) are uncertain. It is essential that investigators neither overhype the potential success nor underplay possible risks during consent.[136] Patients should also be informed about the long-term follow-up plans, since any long-term risks of nanoparticles may not be fully understood at trial entry. For example, most clinical studies of drugs or devices last only a few months to a couple of years and may miss late effects.[137,138] With nanomaterials, there is a possibility of delayed impacts such as particles remaining in organs for years. Ethically, patients should consent to, and be informed of, plans for extended monitoring even after the formal trial to track any late-emerging safety issues.[139,140]

Regulatory agencies like the U.S. FDA and European EMA face the challenge of evaluating therapies that are not easily classified as a conventional "drug" or "device".[141] Magnetic hyperthermia, for instance, involves a combination of a device (the magnetic field generator) and NP formulation (which could be seen as a drug or device depending on its primary mode of action). This necessitates a coordinated review process. In the US, such combination products may undergo joint evaluation by device and drug centres of the FDA. Regulators require that the manufacturing quality of NPs meets pharmaceutical standards – consistency in particle size, coating, purity, and dose is critical for approval.[142] Establishing these standards is part of the translational challenge, since slight changes in nanoparticle synthesis can alter the therapy's behaviour. Moreover, regulatory frameworks insist on a demonstration that the risks are reasonable relative to the benefits for the intended patient population.[143] One regulatory challenge lies in evaluating combined modalities: if MHT is always used with radiation or chemotherapy, agencies must determine how to credit outcomes to the new component. The FDA generally expects that a new therapy demonstrate a contribution to efficacy in combination (or superiority to standard care). This was seen in the case of magnetic hyperthermia for glioblastoma, where trials compared outcomes to historical controls to argue that adding MHT improved survival.[121]

From an ethical standpoint, equity and access constitute another pillar of discussion. If MHT and CDT prove successful, will they be accessible to all patients or only those in specialized centers? The complexity and cost could limit availability initially, raising fairness concerns. It is important for policymakers to consider strategies to avoid a scenario where only patients in wealthy regions or academic hospitals can get these advanced treatments.[144] Finally, public perception and trust are crucial. Nanotechnology in medicine has occasionally been met with public skepticism or misconceptions (the term "nano" sometimes evokes unfounded fears of futuristic risks). Transparent communication and regulatory oversight can help maintain trust. Regulatory bodies have published guidance on nanotechnology products, emphasizing that existing frameworks are applicable but might need case-by-case tailoring.[145–147] Ensuring that nanotherapies meet the same rigorous efficacy and safety standards as other treatments is the surest way to address ethical concerns.

7.3 Patient selection and personalized therapy

Not every cancer patient will benefit equally from MHT or CDT; identifying the right candidates and personalizing the treatment plan are crucial for optimal outcomes. Generally, patients with localized, solid tumors that are accessible to NP delivery are the best candidates for these therapies. For magnetic hyperthermia, this has meant focusing on tumors like glioblastomas (where NPs can be injected or infused into the resection cavity), prostate tumors (accessible *via* transperineal injection), or liver/pancreatic tumors (*via* catheter-directed delivery). In trials, MHT has been used for patients with high-grade gliomas that recur locally after standard therapy[148] – a scenario where the tumor is confined and can be targeted by the NanoTherm NPs. Similarly, the ongoing pancreatic cancer trial explicitly targets locally advanced tumors that are unresectable but not yet metastatic, because those patients have limited options beyond palliative chemotherapy.[130] This illustrates a key selection criterion: MHT/CDT are most useful when the disease burden is primarily at one site (or a few sites) that can be reached by the treatment. Patients with widespread metastatic disease may be less ideal candidates for a primarily local therapy, unless used in a palliative manner to ablate one or two dominant lesions.

Perhaps one of the most important personalization aspects is treatment planning for each patient. Before administering MHT, the medical team typically performs imaging studies to map the tumor and plan NP delivery. Advanced techniques like MRI combined with magnetization measurements can confirm that nanoparticles have distributed adequately in the tumor. Treatment planning software can overlay pre-treatment MRI/CT scans with post-injection scans to model the expected heat distribution during MHT.[121,149] This ensures that the correct dose of particles is delivered and that the alternating magnetic field settings (frequency and field strength) are optimized for that patient's tumor size, location, and particle load. Personalization also extends to the nanoparticle design in some cases. Researchers are developing multifunctional NPs that can be customized with targeting ligands for a patient's tumor markers (for example, attaching antibodies or peptides that bind to antigens overexpressed on that patient's cancer cells).[150,151] If a patient's tumor highly expresses, say, EGFR or HER2, NPs can be functionalized to target those receptors,[152,153] improving uptake by the tumor cells. Such targeting could enhance the specificity of CDT (delivering catalysts more selectively to cancer cells) or MHT (concentrating heat within cancer cells rather than the stroma). Another personalization avenue is using a patient's own biomaterials to coat or formulate nanoparticles – for instance, some experimental approaches use a patient's tumor cell membranes or exosomes to cloak NPs, making them more biocompatible and immune-stealth.[154,155] While still in early research, using autologous biological coatings could reduce the clearance of the nanoparticles by the immune system and increase tumor accumulation, effectively tailoring

the delivery to the patient's physiology. Finally, once a patient is selected, the therapy can be personalized in execution. For instance, the number of MHT sessions required, intervals between sessions and monitoring systemic biomarkers of oxidative stress (for CDT) can be tailored for each patient based on tumor volume.

In summary, therapy personalization in MHT–CDT therapy involves multi-level customization: selecting appropriate patients, tailoring the delivery and dosing of NPs and heat/oxidative stimuli to the patient's tumor characteristics, and adjusting the treatment plan based on real-time feedback and the patient's tolerability. As experience grows, it is conceivable that clinicians will develop formal guidelines or nomograms to aid in patient selection – for example, a scoring system incorporating tumor size, location, and molecular features to predict MHT/CDT benefits. The ultimate vision is that MHT and CDT could be integrated into precision medicine frameworks, where along with genomic and proteomic data, the physical and chemical phenotype of a patient's tumor guides the inclusion of these therapies. This patient-specific approach should maximize effectiveness while minimizing unnecessary risk, aligning with the broader trend in oncology toward personalized treatment regimens for each individual's cancer.

8. Conclusion and future perspectives

Incorporating CDT with MHT in combination techniques has displayed immense potential for supplementing existing therapeutic protocols and integrating synergistically with other therapies such as PDT, PTT, and SDT, thereby enhancing anticancer effects and immune responses. Combining it with immunotherapy can yield impressive therapeutic results, including tumor ablation, metastasis inhibition, recurrence prevention, and prolonged survival. Technological advancements in nanomaterial carrier systems have improved control over various qualities, such as drug loading, selective tissue accumulation, and release kinetics. With the rapid advancement of nanotechnology, materials science, oncobiology, and physics-based therapeutics, the field of cancer theranostics is poised for a transformation. The trend in the future will be to combine therapy techniques, as synergies and mutual promotion enhance therapeutic efficiency when used in conjunction with other modalities. Therefore, we anticipate positive clinical outcomes for CDT–MHT as a combination therapy. However, certain factors must be considered for CDT–MHT to successfully transition into clinical cancer therapy.

To begin with, in order to develop precise CDT–MHT therapy, the long-term biosafety of the agents needs to be heavily scrutinized. Even if the nanomaterials show excellent biocompatibility and biosafety *in vivo*, their chronic toxicity and side effects still need to be systematically studied. It is imperative to establish the safety of these agents before they can be used further. The focus should be on optimizing the physical and chemical properties of CDT–MHT agents to increase their Fenton/Fenton-like catalytic efficiency, heat transfer ability to deep tissues, and regulation of the TME for improved effectiveness. Furthermore, a thorough understanding of the structure–activity relationship between therapeutic agents and procedures is necessary for the CDT–MHT therapy to progress towards clinical trials.

To begin with, the long-term safety of CDT–MHT agents must be thoroughly investigated to ensure precise therapy development. Even if they demonstrate excellent *in vivo* biocompatibility and biosafety, their chronic toxicity and side effects should still be systematically examined. The optimization of the physical and chemical properties of CDT–MHT agents is also critical to enhance their Fenton/Fenton-like catalytic efficiency, heat transfer ability, and regulation of the tumor microenvironment. Understanding the structure–activity relationship is also important for CDT–MHT therapy to advance to clinical trials. Secondly, nanoplatforms for combination therapies should be tailored with specific components and efficacy for different cancers, and it is the synergistic mutual promotion of various therapeutic agents that enhances the curative effect. However, as the composition becomes more complex, ensuring stability and toxicity becomes more difficult. Designing high-quality, simple composition CDT–MHT drugs is therefore a crucial step in advancing therapy. Lastly, the potential increase in biological toxicity must be considered, and the composition and structure of nanomaterials should be determined based on the various conditions of the human body. Endogenous substances can be used to load, modify, or synthesize therapeutic agents for cancer treatment.

The generation of low levels of ROS in the hypoxia TME presents another challenge associated with MHT and CDT therapies. The hypoxic environment induces metabolic adaptations in tumor cells, such as a shift towards anaerobic glycolysis. This metabolic reprogramming not only supports tumor survival but also contributes to an environment less susceptible to ROS-mediated damage. Additionally, under hypoxic stress, tumor cells can upregulate DNA repair pathways, making them more adept at fixing damage caused by ROS, thus leading to increased resistance to therapies that induce oxidative stress. Moreover, hypoxic conditions can elevate the levels of antioxidants like glutathione within tumor cells. These antioxidants neutralize ROS, further reducing the efficacy of ROS-dependent treatments. Addressing these challenges necessitates innovative strategies to enhance the effectiveness of ROS-based therapies in hypoxic tumors. In this direction, approaches such as nanoparticle-mediated oxygenation of the TME, development of hypoxia-activated prodrugs, and utilization of nanoparticles designed to modulate the hypoxic environment are being explored to overcome these obstacles.

In summary, constructing nanoplatforms for multimodal therapies is a complex process and requires the involvement of researchers with a wide range of backgrounds and expertise. Research interest in combining therapies has grown in recent years due to their benefits. More targeted endeavors aimed at addressing the challenges encountered by combination therapies will aid in their translation to clinical practice. Nanomaterial-based platforms are anticipated to have a crucial

role in forthcoming clinical cancer therapies based on CDT–MHT.

Data availability

All data generated or analyzed for the preparation of this review are included within the manuscript. Further inquiries can be directed to the corresponding author.

Author contributions

A. C. and A. S. share equal contributions to the manuscript for their efforts in conceptualisation, literature collection, methodology, drafting of the article, and data analysis. D. S. contributed towards the conceptualisation, final drafting and editing of the manuscript. All authors read and approved the final version of the manuscript.

Conflicts of interest

The authors declare no conflict of interest.

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