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Review

Significance of Heat Shock Proteins on Hyperthermia-based Therapeutics

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Abstract

Numerous studies have shown that combining hyperthermia (HT) with other breast cancer treatment strategies can yield beneficial outcomes. Research indicates that HT may enhance tumor reduction, improve local tumor control, and potentially contribute to increased survival rates. Nonetheless, further investigations are essential to fully elucidate its therapeutic advantages and to establish the most effective protocols for its integration into breast cancer care. In response to hyper thermic stress, the body activates protective mechanisms, notably the upregulation of heat shock proteins (HSPs). These proteins help mitigate cellular damage and dysfunction by enabling cells to better withstand elevated temperatures. As such, understanding the behavior of HSPs under hyper thermic conditions is a vital area of research for exploring how cells cope with thermal stress and for identifying novel therapeutic targets. HSPs represent a conserved group of proteins present in both prokaryotic and eukaryotic cells. They are essential for maintaining protein homeostasis (proteostasis) and safeguarding cells from various stressors. Classified by molecular weight, HSPs act as molecular chaperones, facilitating the folding of newly synthesized polypeptides, refolding misfolded proteins, assembling multi-protein complexes, and degrading damaged proteins. In addition to their chaperone activity, HSPs play key roles in cellular signaling pathways, regulation of the cell cycle, and the initiation of apoptosis.

1. INTRODUCTION

Despite significant advancements in breast cancer treatment, the disease continues to be associated with high mortality rates. Breast cancer accounts for approximately 16% of all cancer cases globally, highlighting the urgent need for more effective therapeutic strategies [1]. To combat this widespread disease, researchers are increasingly focused on integrating both physical and biochemical approaches to prevent cancer progression. Among emerging therapeutic strategies, the combined use of HSPs has shown considerable promise. The regulation of HSP expression is critical in modulating cellular resistance to the elevated temperatures used in hyper thermic therapy. In this physical treatment modality, the temperature of cancerous tissues is typically raised to around 43 °C [2]. At such temperatures, key biomolecules—particularly cellular proteins—undergo denaturation. When HSP expression is insufficient, these proteins are irreversibly damaged and lose their functional integrity. This leads to enhanced cancer cell apoptosis and, consequently, a reduction in tumor size [3]. HT is an emerging therapeutic modality in cancer treatment, utilizing

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elevated temperatures to induce critical intracellular changes that disrupt cellular homeostasis [4, 5]. One of the primary consequences of HT is the denaturation and aggregation of proteins, which disturbs the cellular equilibrium **(Figure 1)** [6]. In addition to protein damage, HT adversely affects the cytoskeleton, cell membrane, essential enzymes, and various signaling biomolecules [7]. Both prokaryotic and eukaryotic cells express HSPs, which play a central role in managing cellular stress. These proteins aid in refolding misfolded proteins, facilitating the degradation of irreversibly damaged proteins, and restoring metabolic balance under stress conditions [5]. When cells are exposed to stressors such as elevated temperatures, ischemia, oxidative stress, mechanical forces, or ultraviolet radiation, the synthesis of protective proteins—primarily HSPs—is significantly upregulated [8, 9]. By considering their protective roles, HSPs have gained interest as potential targets for both anticancer drugs and physical treatment modalities such as HT [10]. However, HT itself can exert direct cytotoxic effects on cancer cells, even in the absence of adjunct therapies [11]. In comparison, HT in comparing with other techniques that generate heat such as radiofrequency or laser, this method which developed in the presence of magnetic fields, offers unique advantages. The corresponding method penetrates deeper into tissues, making it especially suitable for targeting solid tumors [12]. For applying high temperatures locally, magnetic nanoparticles could be employed in combination with HT. These nanoparticles when subjected to alternating magnetic fields, generate heat through mechanisms such as hysteresis loss (from cyclic magnetization and demagnetization) and relaxation losses (Néel or Brownian relaxation), resulting in localized temperature increases [13-15]. This magnetic HT approach has been applied in the treatment of various cancers, including brain, prostate, breast, and esophageal cancers [16]. When combined with chemotherapy, this technique offers enhanced tumor targeting while minimizing toxicity to surrounding healthy tissues [13]. HT is frequently administered in conjunction with conventional treatments like chemotherapy and radiation therapy to improve clinical outcomes [17]. There is a major controversial process leading into lower capability of HT in cancer therapy. The higher expression of HSPs prevents protein damages and finally, a lower degree of apoptosis will be occurred. To overtaking this issue, the combination of HT and inhibiting factors of HSPs, may result a better therapeutic strategy. Therefore, in this review, we explore the therapeutic potential of combining magnetic nanoparticle-mediated HT with targeted inhibition of heat shock proteins as a synergistic strategy against breast cancer.

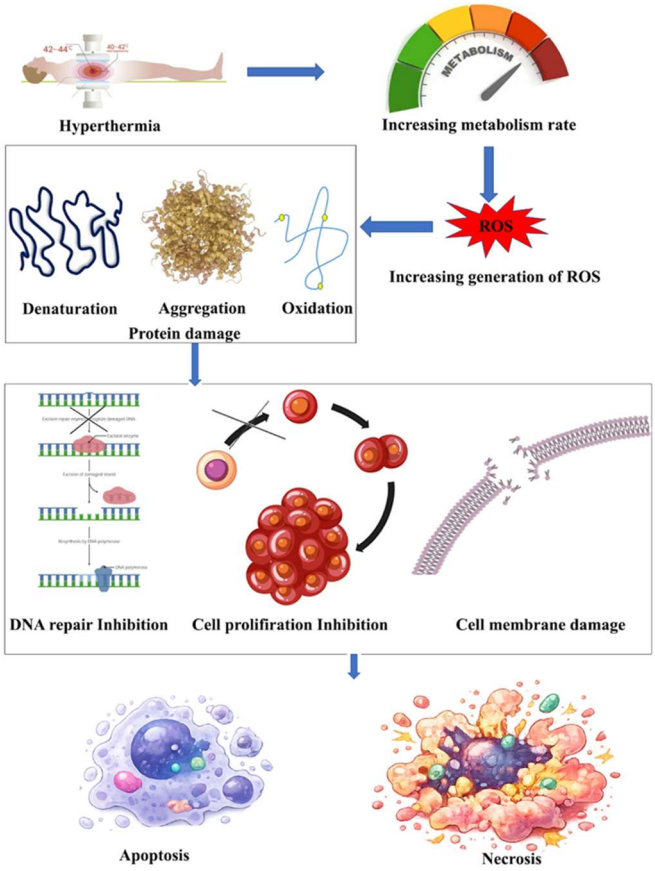

Figure 1. HT-induced signaling pathways which can cause tumor cell expiry.

2. HT AND CANCER THERAPY

HT is increasingly recognized as a valuable adjunctive therapy aimed at enhancing the efficacy of standard breast cancer treatments such as chemotherapy, radiotherapy, and immunotherapy. By inducing physiological and molecular stress, HT sensitizes tumor cells to these conventional modalities, thereby amplifying their therapeutic impact [18]. During HT, exposure to elevated temperatures disrupts cellular homeostasis, leading to the misfolding or unfolding of proteins within cancer cells, a process that can trigger programmed cell death or apoptosis [4]. In addition to protein destabilization, HT inflicts structural damage on critical cellular components, including membranes and DNA, impairing the cells' ability to repair themselves and survive [19]. The therapeutic potential of HT also extends to its vascular effects. Heat increases local blood flow, thereby enhancing oxygenation and improving the delivery of chemotherapeutic agents to the tumor site [20]. This improved perfusion has been shown to augment the effectiveness of commonly used breast cancer drugs such as doxorubicin and

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paclitaxel [21]. Moreover, HT plays a role in modulating the tumor microenvironment. It has been reported to suppress the expression of angiogenesis-associated factors, thereby inhibiting the tumor's capacity to generate new blood vessels—an essential process for tumor growth and metastasis [22].

One of the most established clinical applications of HT in cancer treatment is its integration with radiation therapy. This combined approach has been shown to enhance tumor control and improve therapeutic outcomes by increasing the tumor's sensitivity to ionizing radiation [23]. HT impairs the ability of cancer cells to repair radiation-induced DNA damage, thereby increasing their susceptibility to radiation-induced cell death [24]. Specifically, elevated temperatures compromise the repair mechanisms responsible for resolving DNA breaks, allowing radiation to exert a more lethal effect on tumor cells. Moreover, HT promotes increased blood flow within the tumor, which facilitates greater oxygen delivery—a critical factor for the effectiveness of radiation therapy. Tumor cells residing in hypoxic environments are generally more resistant to radiation; thus, enhancing oxygenation through HT can significantly improve radio sensitivity [25]. Clinical studies have demonstrated that the combination of HT and radiation therapy leads to more substantial tumor regression and improved local tumor control, particularly in superficial or clearly demarcated tumors that are suitable for external heating [26]. Additionally, this dual-modality approach has been associated with a reduced risk of tumor recurrence, especially in patients with recurrent or locally advanced breast cancer [27]. Another promising clinical application of HT is its use in combination with chemotherapy, a strategy referred to as thermal chemotherapy. HT enhances the effectiveness of chemotherapeutic agents through multiple biological mechanisms that sensitize tumor cells and improve treatment outcomes. One of the primary effects of HT is the increased permeability of tumor cell membranes, which facilitates improved intracellular uptake of chemotherapy drugs. The high temperatures can enhance the penetration of cytotoxic agents into cancer cells, which is particularly beneficial for drugs that typically encounter barriers to effective cellular entry under normal physiological condition [28]. In addition to improving drug delivery, HT has been shown to increase the cytotoxic potential of certain chemotherapeutic agents. Drugs such as doxorubicin, paclitaxel, and cisplatin exhibit significantly enhanced cytotoxic effects when administered in conjunction with high temperatures [29]. This synergy can lead to more efficient tumor cell killing compared to chemotherapy alone. Furthermore, HT can help overcome chemotherapy resistance, a major challenge in advanced cancer treatment. Studies have indicated that HT may downregulate the expression of drug efflux pumps—proteins responsible for transporting drugs out of cancer cells—thereby increasing intracellular drug accumulation and enhancing therapeutic efficacy [30]. Thermal chemotherapy has shown considerable promise in the treatment of both primary and metastatic cancer, particularly in recurrent cases where tumors have become resistant to single-agent chemotherapy. The combined approach offers improved tumor control, potentially fewer side effects, and better overall quality of life for patients.

While the integration of HT with chemotherapy or radiation therapy is generally well-tolerated, some adverse effects may occur. The most common side effects include skin irritation or mild burns, especially when external heating devices are used [31]. Pain at the treatment site is also frequently reported, ranging from mild to moderate intensity during or after the procedure [32]. As with many cancer treatments, fatigue is a common systemic side effect, particularly when HT is used alongside chemotherapy or radiation therapy [33]. Additionally, in the treatment of deep-seated tumors, there is a potential risk of unintended thermal injury to surrounding healthy tissues [34]. To mitigate these risks, precise monitoring and temperature control are essential. Recent advances in imaging technologies—such as MRI and ultrasound—have significantly improved the accuracy of HT application. These techniques ensure localized heating of the tumor while minimizing collateral damage to adjacent healthy tissues, thereby enhancing both the safety and efficacy of treatment [35].

3. HT TYPES AND CANCER THERAPY

Various HT techniques have been developed to target tumors based on their location, depth, and extent. These methods are categorized into local, regional, and whole-body HT:

- Local HT focuses heat on a small, specific area, typically where a tumor is located. It is suitable for superficial or accessible tumors.
- External HT is employed for tumors situated on or just beneath the skin. In this approach, heat-generating devices are positioned around or near the tumor to elevate its temperature.
- Intracavitary HT is designed for tumors within or near body cavities such as the rectum or esophagus. This technique involves inserting heat-producing probes directly into the cavity to deliver localized heating to the tumor.
- Interstitial HT is used for deeply embedded tumors, including those in the brain. During this procedure, conducted under anesthesia, probes or needles are inserted directly into the tumor to apply higher temperatures than

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external methods. Imaging modalities like ultrasound assist in precise probe placement [36].

- Regional HT targets larger anatomical regions such as an organ, body cavity, or limb. This category includes several techniques:
    1. Deep Tissue HT addresses internal tumors, such as those in the cervix or bladder, by positioning energy-delivering devices that raise the tumor's temperature.
    2. Regional Perfusion HT is suitable for malignancies in organs such as the lungs, liver, or for extremity tumors like melanoma. The process involves temporarily removing blood from the affected area, heating it externally, and then reintroducing it. Chemotherapy is frequently administered simultaneously.
    3. CHPP is used intraoperatively for tumors within the peritoneal cavity, which houses organs such as the stomach, liver, and intestines. While the patient is under general anesthesia, heated chemotherapeutic agents are circulated through the cavity, elevating local temperatures to 41–42 °C [37].
- Whole-Body HT is utilized in the treatment of a metastatic cancer. Patients are placed in specialized thermal chambers or wrapped in heated water blankets to increase their core body temperature to approximately 41–42 °C for a limited duration [38].

Among these methods, some are more popular than others. In the external HT type, heat is applied non-invasively using devices such as microwave or radiofrequency applicators. These systems are designed to direct heat from outside the body toward tumors located near the surface of the skin. This method allows for accurate tumor targeting while minimizing injury to surrounding healthy tissues. Superficial breast tumors, particularly those located close to the skin, are especially suitable for external hyperthermic treatment [35, 39]. For tumors situated deeper, interstitial HT is a more suitable option. This technique involves the insertion of small probes or needles directly into the tumor mass, allowing heat to be delivered precisely to the target area. Interstitial HT is particularly effective for treating deep-seated tumors that are not easily accessible by external heating techniques [40]. Another method is regional HT, which is employed when breast cancer has spread to surrounding tissues or is locally advanced. This approach involves heating a larger anatomical area, such as the entire breast or chest wall, using devices that distribute heat uniformly across the region. Regional HT is especially useful in the treatment of LABC or recurrent breast cancer, where tumors are extensive, unresectable, or resistant to conventional therapies such as chemotherapy and radiation. In such cases, HT can be applied to the tumor site to directly enhance treatment efficacy and improve local control [41, 42]. In recurrent cancer cases, HT not only contributes to tumor shrinkage but also helps in symptom relief, potentially making the tumors operable or more responsive to other curative interventions [43]. The ability to deliver controlled, localized heating while preserving adjacent healthy tissues, reinforces HT's value as a complementary tool in the management of challenging cancer cases.

4. HT AND NANOTECHNOLOGY

Despite HT clinical potentials, its effectiveness in cancer therapy is often limited by challenges such as imprecise targeting of tumor cells and the risk of thermal injury to surrounding healthy tissues. Nanotechnology offers a transformative solution to these challenges by enabling the design and engineering of materials at the molecular and nanoscale level. This technology provides the means for highly controlled and localized heat delivery, significantly improving both the precision and safety of HT treatment [44]. Nanoparticles can be engineered with unique physical and chemical properties to enhance their thermal responsiveness and tumor-targeting capability. This enables more focused application of heat to tumor tissues, reducing collateral damage and increasing therapeutic efficacy. Among the most promising innovations, the use of magnetic and AuNPs is mostly interested to achieve localized HT. Conventional HT techniques often face limitations when treating deep-seated tumors due to the difficulty of uniformly heating tissues located far beneath the skin. This nanoparticle is a promising class of HT-enhancing agents. Engineered to penetrate deeper into tissue, these particles exhibit strong plasmonic behavior—absorbing NIR light and converting it into heat. Upon exposure to NIR light, gold nanoparticles generate localized heat within the tumor microenvironment, achieving therapeutic temperatures with minimal impact on healthy tissues. This makes them particularly valuable for photothermal therapy in breast cancer and other malignancies [41, 45]. In contrast, magnetic nanoparticles, such as superparamagnetic iron oxide nanoparticles (SPIONs) or their derivatives like cobalt ferrite, offer a more targeted approach. These particles can absorb energy from AMF and generate localized heat through a process known as magnetic HT. Once injected into the body, the nanoparticles can be directed to the tumor site via external magnetic fields. Their heating effect is confined to the tumor region, thereby reducing harm to adjacent healthy tissues. The magnetic properties of these particles allow for fine-tuned thermal control, improving both efficacy and safety [2, 44]. In a mouse model, the application of magnetic nanoparticles combined with chemotherapy

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significantly reduced tumor volume [46]. Another major advancement involves the use of targeted nanoparticles to increase the precision of HT. These nanoparticles can be functionalized with targeting ligands—such as antibodies or tumor-specific peptides—that bind selectively to cancer cells or tumor vasculature. This functionalization ensures preferential accumulation of nanoparticles in tumor tissues, thereby minimizing exposure of healthy tissues and increasing treatment specificity [34]. A further innovation lies in the development of drug-loaded nanoparticles that combine HT with controlled chemotherapy release. When these drug-carrying nanoparticles are exposed to high temperatures, they release their therapeutic cargo directly at the tumor site. This method, often referred to as thermal chemotherapy, enhances the uptake of chemotherapeutic agents by tumor cells and increases the overall effectiveness of treatment. Such synergy may be particularly beneficial in managing tumors that are resistant to conventional therapies [47]. Moreover, nanotechnology has enabled the design of biologically responsive nanoparticles that respond dynamically to the tumor microenvironment. These "smart" nanoparticles are activated by specific physiological triggers—such as low pH, hypoxia, elevated temperature, or metabolic stress—allowing for adaptive, tumor-specific HT. This responsiveness supports real-time adaptation to changes in the tumor environment, making treatments more precise and personalized [48]. Collectively, these strategies highlight the significant advancements made possible by integrating nanotechnology with HT. They not only address many of the limitations of traditional HT but also offer synergistic possibilities with chemotherapy, immunotherapy, and radiation therapy. The development of intelligent, targeted, and thermally responsive nanoparticle systems represents a critical step forward in improving the outcomes of breast cancer treatment.

The following table **(Table 1)** provides a simplified summary of key studies exploring the combination of nanoparticles and HT across various cancer types, including details on nanoparticle type, delivery method, and therapeutic outcomes.

Table1. Summary of Key Studies on Nanoparticle-Mediated HT in Cancer Therapy.

Nanoparticle	Cancer	Results	Year	Ref.
Fe_3O_4	Breast	The combination of HT and chemotherapy suppresses the growth of cancer cells and significantly decreases the metabolic activity of cancer cells.	2015	[49]
Iron oxide	Liver	The combination of thermotherapy and chemotherapy demonstrates a quicker thermal response to the applied AMF and greater treatment efficacy.	2018	[50]
Iron oxide	Pancreases	Hyaluronidase enhances the penetration of magnetic nanoparticles into pancreatic cancer models, thereby improving the effectiveness of thermal therapy and promoting cancer cell reduction.	2021	[51]
Magnetic nanoparticles conjugated with liposomes	Prostate	Tumor growth was reduced with some side effects on the central nervous system.	2008	[52]
Variable molecular weight nanoparticles	Colon	Induces cell death and enhances the effectiveness of chemotherapy in drug-resistant colorectal cancer cells.	2021	[53]

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5. HT AND ANTICANCER DRUGS

Chemotherapy remains as one of the most widely used and effective methods for treating cancer. However, despite its success, this approach is often limited by several challenges, including severe side effects, the development of drug resistance, and, in some cases, tumor recurrence following initial remission [54]. To address these issues, ongoing research efforts are focused on strategies to enhance the therapeutic outcomes and minimize the drawbacks of conventional chemotherapy. One promising approach involves the integration of HT with anticancer agents. This combination has been shown to significantly enhance drug sensitivity in cancer cells, thereby overcoming some of the key limitations of chemotherapy. When anticancer drugs or natural compounds are administered alongside HT, multiple cellular pathways are activated, contributing to enhanced cancer cell death. These mechanisms include increased generation of ROS, suppression of HSPs expression, induction of DNA damage, and disruption of MMP. Interestingly, the effects of HT used in isolation differ from those observed in combination therapy. When applied alone, HT primarily activates apoptotic pathways by modulating transcription factors, altering the cytoskeletal architecture, and inducing other cellular changes associated with programmed cell death [55].

Notably, while heat shock responses and the expression of protective HSPs typically counteract oxidative stress in HT-only treatments, the combination with anticancer agents shifts the cellular response. This synergy enhances apoptotic signaling and results in more pronounced cytoskeletal disruption—mechanisms that appear to play a more critical role in triggering apoptosis than ROS accumulation, HSP modulation, or DNA damage alone [9]. An illustrative example of this combinatory approach is the use of resveratrol, a naturally occurring stilbene found in grapes, berries, red wine, and other plant-based foods. In a study by Kuo et al., the combined effect of curcumin and resveratrol with mild HT (modulated electro-HT, at 42°C for 30 minutes) was investigated in CT26 murine colon cancer cells. Their findings support the enhanced efficacy of natural compounds when paired with controlled hyperthermic conditions. Their study demonstrated that the combination treatment effectively induced apoptosis and suppressed cell proliferation. In addition, a noticeable reduction in HSP70 expression was observed, alongside increased infiltration of $CD3^+$ T cells and $F4/80^+$ macrophages within the tumor microenvironment, indicating enhanced immune system engagement [56]. In a separate investigation, Zhang et al. assessed the impact of quercetin on PC3 prostate cancer cells. They found that co-treatment with HT (43°C for 1 hour) significantly amplified the anticancer activity of quercetin, resulting in marked tumor growth inhibition. Notably, the treatment also prevented the proliferation of DU-145 prostate cancer cells. Furthermore, quercetin suppressed the expression of HSP72, suggesting its role as a sensitizer for apoptosis and a potential inhibitor of tumor progression in vivo [57]. Similarly, Shen et al. reported that quercetin downregulated the expression of HSP70 and P-glycoprotein (P-gp) in K562/A human leukemia cells exposed to HT. Pre-treatment with quercetin led to an 8.3-fold increase in intracellular accumulation of doxorubicin compared to untreated controls. In addition, quercetin induced apoptosis and G2/M phase cell cycle arrest in a dose-dependent manner, reinforcing the concept that quercetin combined with HT produces a synergistic effect in promoting cancer cell death (**Figure 2**) [58]. Quercetin, a naturally occurring flavonoid, is known to inhibit heat-induced HSP expression across various cell types. In breast cancer cells, its effects appear to be cell-specific and may involve suppression of HSF transcriptional activity, rather than its DNA-binding function [59]. Tamoxifen, a selective estrogen receptor modulator (SERM), functions by competitively inhibiting estradiol activity in estrogen-responsive tissues. However, resistance to tamoxifen can develop when estrogen receptors or other critical transcription factors are lost or altered [60]. The anticancer efficacy and cytotoxic potential of tamoxifen are closely associated with PKC signaling pathways [61].

It has been shown that both quercetin and tamoxifen can reduce the expression of heat-induced HSP70 in melanoma cells. Piantelli et al. demonstrated that co-treatment with HT (42.5°C for 1 hour), quercetin, and tamoxifen synergistically enhanced apoptosis in human melanoma cell lines M10, M14, and MNT1 [62]. Zhou et al. proposed a tumor-targeted HT approach using AG-IR820, a conjugate of a photothermal agent and a tumor imaging compound. In their study, the combination of quercetin (an HSP70 inhibitor), lipopolysaccharide (LPS, a TLR-4 activator), and HT significantly inhibited the proliferation of TT human thyroid cancer cells, both *in vitro* and *in vivo*, compared to monotherapies. Additionally, AG-IR820 facilitated higher intracellular uptake of quercetin and improved tumor-targeting efficacy [63]. Collectively, these findings underscore the potential of HT as an adjunctive strategy to enhance the effectiveness of chemotherapeutic agents, particularly in overcoming limitations such as drug resistance and suboptimal therapeutic response.

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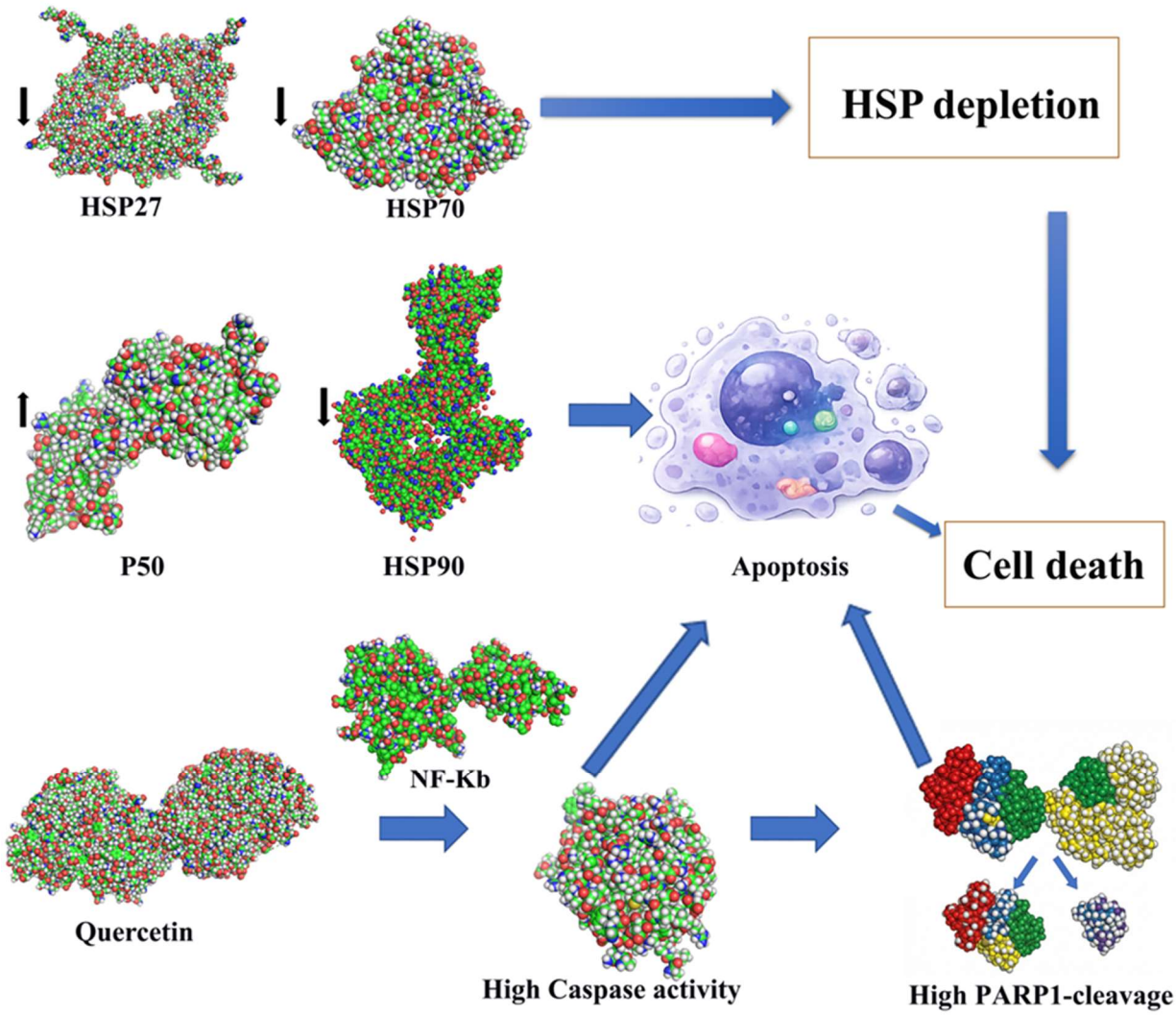

Figure 2. Quercetin acts as a heat shock protein inhibitor on apoptosis in human breast cancer cells.

6. HT AND CLINICAL TRIALS

Clinical trials have explored the use of HT both as a standalone treatment and in combination with other therapies. Among these, combining HT with chemotherapy or radiotherapy has shown the most promise in enhancing tumor destruction. In a Phase III clinical trial involving breast cancer patients, the combination of HT and radiotherapy was found to be more effective in controlling tumor growth compared to radiotherapy alone. This improvement was largely attributed to the increased permeability of cancer cell membranes in response to heat, which in turn heightened the tumor's sensitivity to radiation [28]. Similarly, combining HT with chemotherapy has demonstrated beneficial effects. By increasing cellular permeability, HT enhances drug uptake by tumor cells. In a clinical study on prostate cancer, the combination of HT and the chemotherapeutic agent docetaxel led to reduced tumor size and greater cancer cell apoptosis [64]. Comparable outcomes were reported in patients with melanoma and sarcoma, where the addition of HT to chemotherapy resulted in both tumor shrinkage and improved survival rates [41, 65]. HT has also been evaluated as a palliative treatment for cancers that cannot be surgically removed. In such cases—particularly with esophageal and head and neck cancers—when used alongside radiotherapy, HT was found to reduce tumor burden and alleviate pain, ultimately improving patient quality of life [32]. Despite these encouraging results, HT therapy is not without limitations.

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One major challenge is the difficulty in delivering heat uniformly throughout the tumor. Furthermore, it is problematic to reach deep-seated tumors without affecting nearby healthy tissues. To address these issues, new strategies such as interstitial HT—where heat is delivered directly to the tumor using probes or needles—have been developed [40]. Another critical concern is the need for precise temperature monitoring to prevent overheating, which could cause burns or cardiovascular complications. Ongoing clinical research is focused on overcoming these challenges and enhancing the benefits of HT. One promising avenue is the integration of nanotechnology. As discussed above, nanoparticles engineered for thermal sensitivity, can accumulate selectively in tumor tissues, thereby improving the localized heating efficiency of HT—a technique now commonly referred to as nano thermotherapy [66]. Among these, MNPs are widely studied. When subjected to an alternating magnetic field, MNPs generate heat through magnetic HT, enabling localized thermal treatment directly at the tumor site while minimizing damage to healthy tissue. In breast cancer, this method has been shown to improve tumor regression and increase cancer cell death [49]. MNPs can also be engineered as drug delivery systems, enhancing both HT and chemotherapy. By modifying the nanoparticle surface with targeting ligands, these systems can selectively bind to tumor-specific receptors, facilitating precise drug delivery and reducing systemic toxicity [67]. For instance, gold nanoparticles functionalized with tumor-targeting molecules can not only direct heat to cancer cells but also absorb NIR light, enabling photothermal therapy in addition to magnetic heating. This dual-modality approach offers a versatile treatment platform [68]. Other nanoparticle systems, such as lipid-based or polymeric nanoparticles, can encapsulate chemotherapeutic drugs, protecting them from premature degradation and enhancing their delivery to tumor sites. When combined with HT, these nanoparticles can release their drug payload in response to heat, increasing the cytotoxic impact on cancer cells. Ongoing clinical trials investigating HT coupled with nanoparticle-based drug delivery suggest that this strategy can improve local tumor control, minimize systemic side effects, and enhance overall treatment outcomes.

A table summarizing key clinical trials investigating HT in various cancers is provided below **(Table 2)** with general information.

Table2. Clinical Trials Investigating Nanoparticle-Assisted HT in Cancer Treatment.

Phase clinical	Cancer	Nano particle	HT condition	year	ref
phase I/II	Cutaneous metastatic melanoma	gold nanorods	Intra-tumoral gold nanorods and Near Infrared Light	2025	[69]
phase I/II	Glioblastoma Multiform	iron oxide nanoparticles	Nanoparticles for Cyclic HT and Adjuvant Therapy	2024	[70]
phase I/II	Pancreatic Cancer	Albumin-Stabilized Nanoparticle	Nanoparticles for Hyperthermic and Intraperitoneal Chemotherapy	2024	[71]

Despite encouraging findings, there are several challenges related to the use of nanoparticles in HT treatment for breast cancer. A major concern is the biocompatibility of nanoparticles, as some materials may trigger immune reactions or toxicity. Therefore, comprehensive testing is necessary to confirm the safety of nanoparticles for human applications [72]. Additionally, issues of scalability and cost-effectiveness continue to limit the broad clinical use of nanoparticle-based therapies [73]. In summary, combining HT with nanoparticles presents a promising approach to enhance breast cancer treatment. Nanoparticles improve the precision and efficacy of HT while enabling targeted drug delivery, multi-modal therapies, and reduced systemic side effects. As research advances, this method may become a key component of personalized cancer therapy, improving patient survival and quality of life [74].

Also, overexpression of heat shock proteins HSP70 and HSP90 is associated with resistance to chemotherapy, radiotherapy, and poorer prognosis, as these proteins help tumor cells withstand the stress caused by HT. Therefore, regulating HSP expression has become an important strategy to boost the effects of HT. Clinical studies indicate that combining HT with HSP inhibitors (such as quercetin or HSP90 inhibitors) can increase breast cancer cell sensitivity to

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heat-induced apoptosis by blocking the protective function of these proteins [75]. Furthermore, targeting HSPs alongside HT may overcome resistance and improve overall treatment outcomes in breast cancer patients, highlighting the critical role of heat shock proteins in both the efficacy and resistance mechanisms of HT in clinical breast cancer therapy [76].

The following table **(Table 3)** summarizes clinical studies that have investigated the relationship between HT and HSPs, focusing on HT's effectiveness and the impact of HSP modulation in various cancers, including breast cancer.

Table3. Clinical Studies on the Role of HT and Heat Shock Proteins (HSPs) in Cancer Therapy.

clinical	cancer	HSPs	Ref
Phase II	Gastrointestinal Stromal Tumors	HSP70	[77]
Phase II	Metastatic Ocular Melanoma	HSP90	[78]
Phase I	Metastatic Pancreas	HSP90	[79]
phase I-II	breast cancer	HSP90	[80]
Phase I	Advanced or Metastatic Gastric Cancer	HSP90	[81]

7. PROSPECTS OF HT IN CANCER THERAPY

The future of HT as a cancer treatment appears highly promising. Although its current clinical use faces limitations—such as challenges in treatment precision, side effects, and effective tumor targeting—ongoing technological advancements and research are expected to significantly improve its efficacy and broaden its therapeutic applications. A major focus for the future of HT is enhancing its accuracy and effectiveness through emerging technologies. These include nanotechnology, advanced imaging modalities, precise temperature control systems, and improved methods for targeting cancer cells specifically. Nanoparticles, for instance, can facilitate the direct delivery of heat to tumors, making HT a highly precise and potent therapy. MNPs, gold nanoparticles, and other nanomaterials can be engineered to selectively accumulate in tumor tissues. Once localized, these particles can be activated by external stimuli—such as alternating magnetic fields or laser light—generating controlled, localized heating. This precision reduces damage to surrounding healthy tissue. Research has shown that nanoparticles enhance spatial control over HT, improving treatment outcomes for deep-seated tumors, including breast cancer, prostate cancer, and glioblastomas [82]. As nanoparticle technology evolves, HT treatments are likely to become more targeted and efficient, potentially lowering the temperatures required and thereby minimizing side effects like skin burns and systemic toxicity. In addition to nanotechnology, advances in imaging techniques such as MRI and PET enable real-time monitoring of heat distribution within tumors. Methods including MRI-guided thermometry, ultrasound, and infrared thermography allow clinicians to precisely tailor treatments by continuously measuring temperature and adjusting protocols accordingly. These imaging tools also help identify tumor heterogeneity, ensuring uniform heating across complex tumor regions. Furthermore, integrating HT with imaging can improve tumor delineation, which is especially important when treating intricate, multilayered tumors [83].

Another exciting avenue for HT is its combination with other treatment modalities, notably immunotherapy. HT has been shown to stimulate the immune system by inducing stress responses in tumor cells and the surrounding microenvironment. It can promote the release of tumor antigens, thereby enhancing immune recognition and attack. Moreover, HT can boost the effectiveness of immune checkpoint inhibitors and other immunomodulatory treatments, potentially improving patient outcomes. For example, a 2021 study by Zhang et al. demonstrated that combining HT with immune checkpoint blockade significantly enhanced antitumor immunity and slowed tumor growth in mouse models [84].

Personalized medicine is also poised to play a critical role in the future of HT. Advances in genomics, proteomics, and biomarker discovery will allow HT treatments to be tailored to the unique molecular profiles of individual tumors. Such personalized approaches could optimize HT in conjunction with other therapies, based on the tumor's genetic characteristics and its sensitivity to heat stress. This strategy may enhance therapeutic efficacy while reducing unnecessary adverse effects [85]. Ultimately, large-scale clinical trials and the development of innovative HT technologies are crucial to establishing HT as a standardized and effective cancer treatment. In summary, the outlook for HT is very positive—ongoing technological progress and expanded research efforts

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promise to significantly improve cancer therapy and enhance patients' quality of life.

8. DRAWBACKS OF HT

Despite the significant advantages of HT in cancer treatment, this method also presents various challenges and limitations that must be addressed to enhance its effectiveness and broader application. Some of the key drawbacks include:

- The need for advanced, costly, and highly specialized equipment, including precise temperature control systems and imaging technologies, which may not be widely accessible in all healthcare settings.
- Limited efficacy when used as a stand-alone therapy.
- Accurate temperature regulation is critical; failure to adjust the temperature based on the characteristics of different tissues can result in unintended damage to healthy tissue.
- Local side effects may include swelling, bleeding, blood clot formation, and harm to surrounding normal tissues. Whole-body HT can cause additional side effects such as diarrhea, vomiting, and nausea, and in rare cases, more severe complications like cardiovascular problems [86, 87].

9. CONCLUSION

The future of HT in cancer therapy is highly promising. By integrating advancements in nanotechnology, sophisticated imaging techniques, immunotherapy, and personalized medicine, HT is poised to become a more precise, effective, and multifaceted treatment option against cancer. Ongoing research, clinical improvements, and technological innovations will continue to propel the development of HT, likely establishing it as a central pillar in cancer care. Consequently, HT is expected to evolve from its current status as primarily an adjunct therapy to a vital and strategic component of comprehensive cancer treatment regimens.

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Conflict of interest

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Ethical statement

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