

Utilizing Carbon Nanomaterials for Enhanced Photothermal Therapy in Breast Cancer Treatment

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Abstract. Breast cancer is the most often diagnosed cancer in women and the second largest cause of cancer mortality worldwide. Photothermal therapy (PTT) has emerged as a viable cancer treatment that uses near-infrared (NIR) light-absorbing chemicals to selectively heat and destroy tumor cells while sparing healthy tissue. PTT has advantages such as high specificity, little invasiveness, and efficient tumor ablation. Recent advances include developing imageable photothermal agents to aid in therapy planning. This review focuses on the function of carbon nanoparticles in PTT, investigating their processes and advantages and analysing *in vitro* and *in vivo* investigations. Carbon nanomaterials like carbon nanotubes (CNTs) and graphene have a large surface area, great electrical conductivity, and biocompatibility, making them ideal for PTT. Carbon nanomaterials absorb NIR light, enabling deep tissue penetration and targeted heating of tumor tissues, resulting in necrosis and apoptosis. Carbon nanomaterials also increase tumor vascular permeability, which promotes chemotherapeutic drug accumulation and improves treatment results. Repurposing carbon nanomaterials for increased PTT is a potential method because of its capacity to target various pathways, select cytotoxicity against cancer cells, and synergistic effects with other anticancer drugs.

Keywords: Breast cancer, Photothermal therapy (PTT), Carbon nanomaterials.

1. Introduction

Breast cancer is the most frequently diagnosed cancer in women and ranks as the second leading cause of cancer deaths among women globally [1]. Most recently, in 2022, approximately 2.3 million women worldwide had a breast cancer diagnosis in 2022, which resulted in 670,000 deaths. After puberty, women of any age can develop breast cancer, while older women are more likely to suffer from breast cancer. Human development levels (HDI) have a substantial impact on breast cancer mortality and rates. Approximately, a 1 in 12 diagnoses and a 1 in 71 death rate for women living in high HDI nations, compared to a 1 in 27 diagnoses and a 1 in 48 death rate in low HDI countries. Breast cancer results from uncontrolled cell growth in the breast, forming tumors in the milk ducts or lobules. Early-stage breast cancer is not life-threatening and can be detected early, but invasive cancer can spread to nearby tissue and organs, potentially becoming fatal [2].

Photothermal therapy (PTT) has developed as a potential cancer treatment technique that uses near-infrared (NIR) light-absorbing compounds to selectively heat and kill tumor cells while preserving healthy tissue. This approach has various benefits over standard treatments, including excellent specificity, low invasiveness, and effective tumor ablation. Recent improvements have focused on

generating imageable photothermal agents to improve therapy planning, as demonstrated by a new albumin-based nano-complex developed for multimodal imaging-guided PTT. This theragnostic technique uses Gd^{3+} -chelated human serum albumin and NIR fluorophores to precisely monitor and treat metastatic lesions, such as sentinel lymph nodes (SLNs), using focused laser irradiation. The albumin-based nano-complex method, which combines photothermal ablation with surgical resection, considerably improves survival results in preclinical animals, underlining its clinical cancer treatment potential [3].

This review summarizes the current advancements in utilizing carbon nanomaterials for enhanced photothermal therapy in breast cancer treatment. It explores the mechanisms and benefits of PTT, the role of various nanoparticles including carbon nanomaterials, and reviews both *in vitro* and *in vivo* studies, highlighting their potential and ongoing clinical trials.

2. Nanoparticle technology in PTT

2.1. Mechanism of PTT

PTT operates on the principle of converting light energy, typically NIR wavelengths, into heat through light-absorbing agents known as photothermal agents (PTAs) (Figure 1). These agents often nanoparticles like gold nanorods or carbon nanotubes (CNTs) selectively accumulate in tumor tissues due to enhanced permeability and retention (EPR) effects, minimizing damage to healthy cells while maximizing thermal effects on cancerous cells [4]. When exposed to NIR light, PTAs absorb photons, causing localized heating that induces several mechanisms of cell death within tumors, including direct cellular membrane disruption, denaturation of tumoral DNA and inhibition of angiogenesis [5]. The selective thermal destruction of cancer cells is advantageous over traditional therapies due to its high specificity and minimal invasiveness, thereby reducing systemic side effects [3]. Recent advancements in PTT include the development of theragnostic nanocomplexes that integrate imaging capabilities with therapeutic functionality, enabling precise monitoring and treatment of metastatic lesions like sentinel SLNs [6]. By combining PTT with other modalities such as chemotherapy or photodynamic therapy (PDT), synergistic effects can be achieved, enhancing overall treatment efficacy and potentially overcoming drug resistance mechanisms [4, 5]. Thus, PTT represents a promising strategy in oncology, offering improved therapeutic outcomes and paving the way for personalized cancer treatment regimens [6].

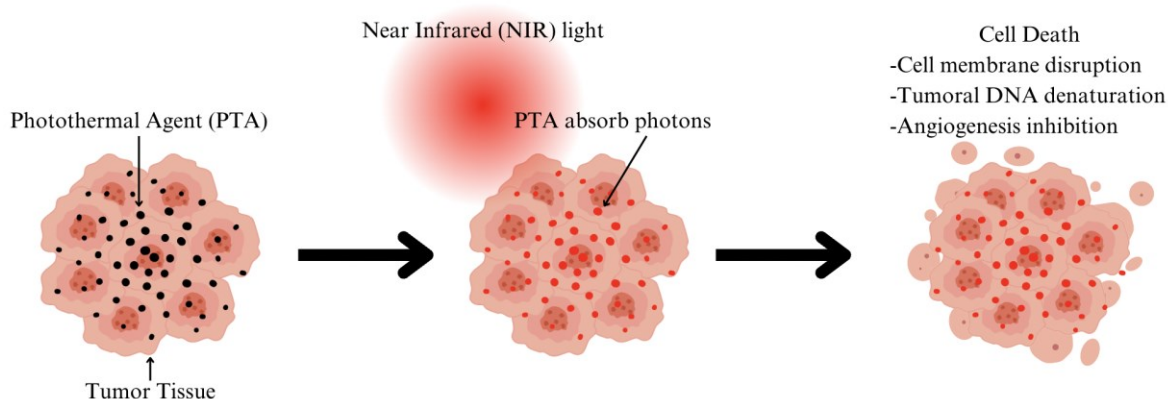


Figure 1. Mechanism of Photothermal Therapy (PTT). Figure created by Canva. Figure credit: original.

2.2. Nanoparticles in PTT

Nanoparticles have an important role in improving the efficacy of PTT in cancer treatment. PTT researchers take advantage of the unique optical and physical features of materials such as gold, iron oxides, silica, and carbon-based nanomaterials such as graphene to accomplish targeted tumor elimination. These nanoparticles are engineered to absorb certain wavelengths of light, often in the NIR region, allowing for deep tissue penetration while minimizing absorption by surrounding biological

molecules. When exposed to NIR light, these nanoparticles undergo plasmon resonance, which effectively converts light energy into heat, resulting in localized hyperthermia inside the tumor microenvironment. This heat production is critical because it causes permanent cellular damage and promotes tumor regression by increasing the local temperature. Furthermore, the tiny size and surface chemistry of nanoparticles allow for their circulation in the bloodstream and accumulation at the tumor site via the increased permeability and retention (EPR) effect, maximizing therapeutic efficacy while minimizing systemic adverse effects. Overcoming challenges such as tumor heterogeneity and inefficient nanoparticle penetration is an ongoing research focus, prompting innovations in nanoparticle design, such as surface functionalization and size optimization, to improve their delivery and therapeutic impact across a wide range of tumor types [4].

3. Carbon Nanomaterials

Carbon nanomaterials have garnered significant attention in biomedical applications due to their unique physicochemical properties. These materials, including CNTs and graphene, exhibit high surface area, excellent electrical conductivity, and biocompatibility [7]. They hold promise in diverse fields such as drug delivery, biosensing, and cancer therapy, owing to their ability to interact with biological systems at the molecular level [8]. The versatile nature of carbon nanomaterials allows for tailored modifications to enhance their functionality and application-specific properties, making them valuable tools in modern biomedical research [9].

3.1. Types of Carbon Nanomaterials

CNTs represent one of the most studied forms of carbon nanomaterials [7]. These cylindrical structures exhibit extraordinary mechanical strength and electrical conductivity, ideal for applications ranging from nanoelectronics to biomedical devices [8]. Graphene, a two-dimensional carbon allotrope, has also gained prominence for its exceptional mechanical strength and high surface area [7]. Its single-atom thickness and unique electronic properties make graphene suitable for various biomedical applications, including tissue engineering scaffolds and biosensors [9]. Additionally, fullerenes, spherical carbon molecules like buckyballs, offer another class of carbon nanomaterials known for their antioxidant properties and potential in drug delivery systems [7]. Nanodiamonds are nanostructures with diamond-like crystallisation. Subsequently, nano-onions are made up of many layers of graphene [9]. These distinct types of carbon nanomaterials illustrate the breadth of their applications in biomedical research and highlight their ongoing exploration for innovative healthcare solutions [8].

3.2. Mechanism of Carbon Nanomaterial in PTT

Carbon nanomaterials, including CNTs and graphene oxide, offer promising prospects for PTT due to their efficient photothermal conversion and biocompatibility (Figure 2). They effectively absorb NIR light, allowing deep tissue penetration and selective heating of tumor tissues above 42 °C, which induces necrosis and apoptosis and enhances the permeability of tumor vasculature and cell membranes. This facilitates the accumulation of co-administered chemotherapy agents, thereby improving treatment outcomes. Additionally, carbon nanomaterial-mediated PTT can disrupt cellular homeostasis through DNA damage and protein denaturation within tumor cells, promoting cell death pathways [10].

Moreover, carbon nanomaterials exhibit the ability to modulate heat shock proteins (HSPs) like HSP70 in cancer cells, crucial for anti-apoptotic processes. By inhibiting HSP70 expression, these nanomaterials sensitize cancer cells to thermal stress induced by PTT, thereby reducing anti-apoptotic defenses and enhancing treatment efficacy. Furthermore, these materials can be engineered to target specific cellular pathways, such as the JAK/STAT signaling pathway, which regulates cell survival and apoptosis, thus augmenting the cytotoxic effects of PTT. The targeted approach synergizes effectively with other therapies like photodynamic therapy (PDT) or molecular inhibitors, offering a comprehensive strategy against cancer. The immune-modulatory properties of carbon nanomaterials further enhance their potential in combined therapies with PTT and immunotherapy, fostering a systemic immune response against primary tumors and residual/metastatic cancer cells [11]. This integration into

advanced PTT strategies highlights their versatility and potential as next-generation therapeutics in oncology, addressing both tumor ablation and long-term cancer management to prevent disease recurrence [10,11].

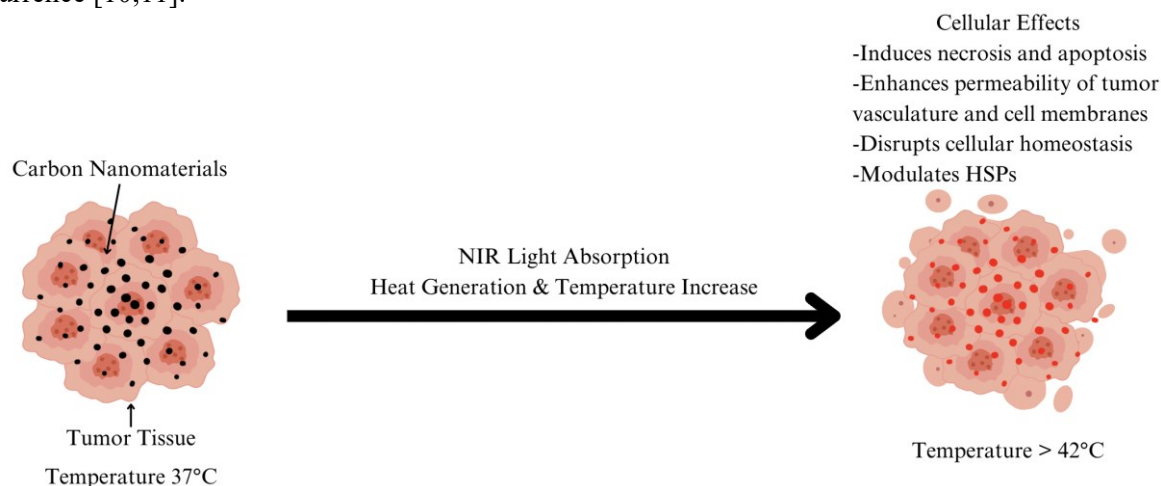


Figure 2. Mechanism of Carbon Nanomaterial-Mediated Photothermal Therapy (PTT) Effects. Figure created by using Canva. Figure credit: original.

4. *In Vitro* and *In Vivo* Carbon Nanomaterial for Breast Cancer

4.1. *Studies on CNTs in Breast Cancer*

In vitro studies have demonstrated the potential of CNTs in breast cancer research and treatment (Table 1). Oxidized graphene nanoribbons coated with folic acid and loaded with tamoxifen citrate, derived from multi-walled CNTs, showed effective drug loading and concentration-dependent death in breast cancer cells. The results showed preferential internalization into cancer cells, indicating a viable technique for the targeted delivery of therapeutic drugs such as tamoxifen to breast cancer cells. Furthermore, electrochemical immunosensors based on electrospun carbon nanofiber mats modified with Au nanoparticles, cysteamine, CNTs, and specific antibodies have shown promise for the precise and rapid detection of Her-2, a biomarker critical for breast cancer diagnosis and treatment decision-making [9].

In vivo, investigations into carbon nanotube-based therapies for breast cancer have demonstrated their potential to improve diagnostic and therapeutic approaches. Yang et al. developed an electronic nose utilizing carbon nanotube sensors that showed high sensitivity (86%) and specificity (97%) in distinguishing breast cancer through volatile metabolite analysis in breath samples [12]. This non-invasive diagnostic tool could aid in intraoperative decision-making and the identification of molecular subtypes, facilitating personalized treatment strategies for breast cancer patients. Furthermore, dopamine and mucin-1 functionalized electroactive CNTs have been utilized to construct electrochemical immunosensors capable of detecting MUC-1, with a high detection sensitivity *in vitro*. These findings suggest that carbon nanotube-based approaches hold promise for advancing both diagnostic and therapeutic aspects of breast cancer management in clinical settings [9].

4.2. *Graphene in Breast Cancer*

Several *in vitro* studies have proved the efficacy of graphene-based nanomaterials in treating breast cancer (Table 1). For example, when subjected to near-infrared (NIR) lasers, GO-SPION-MTX nanocomposites containing graphene oxide, superparamagnetic iron oxide nanoparticles, polyethylene glycol and methotrexate demonstrated significant cytotoxicity against folate receptor-positive breast cancer cells. The LBL Lipo-graph system, which consists of alternating layers of graphene oxide and poly(L-lysine) linked to graphene oxide coated on cationic liposomes containing doxorubicin, successfully kills MD-MB-231 cells following NIR irradiation. Furthermore, HA-GO-Met nanoparticles

loaded with metformin and grafted with hyaluronic acid was discovered to cause apoptosis and inhibit the migration of triple-negative breast cancer cells by targeting the miR-10b/PTEN axis through NFκB-p65. These findings demonstrate the effectiveness of graphene-based nanomaterials in improving cell uptake, boosting drug accumulation, and inducing cancer cell death *in vitro* [9].

In vivo studies demonstrate the therapeutic potential of graphene-based nanoparticles in breast cancer therapy. HA-GO-Met nanoparticles have demonstrated considerable anticancer effectiveness in triple-negative breast cancer cells, both *in vitro* and *in vivo*, lowering tumour burden and eradicating tumour-borne toxicity in peripheral organs. The multifunctional CePO₄/CS/GO scaffold, which includes graphene oxide nanoparticles, CePO₄ nanobars and bioactive chitosan, shows promise in photothermal treatment for killing tumour cells, inducing macrophage polarisation and promoting bone and blood vessel development. This scaffold has the potential to treat breast cancer bone metastases by killing leftover tumour cells and promoting bone repair. These *in vivo* results suggest the viability of graphene-based techniques to enhance breast cancer treatment outcomes [9].

4.3. Fullerenes in Breast Cancer

In vitro research has shown that fullerenes have the potential to improve breast cancer therapy techniques. Molecular coupling experiments have demonstrated that letrozole, a medication used in breast cancer treatment, has more biological activity when paired with graphene and fullerenes in self-assembled structures than when used alone (Table 1). This synergistic method shows more efficacy in preventing breast cancer cell growth. Additionally, the application of fullerene-based arrays for targeted hyperthermia has been investigated *in vitro*, with the goal of optimizing therapeutic effects while minimizing injury to neighboring healthy tissues [9].

In vivo studies have found intriguing possibilities for fullerene-based treatments in breast cancer therapy (Table 1). Studies using fullerene-based arrays for targeted hyperthermia have shown controlled super-radiance processes with external electric fields, which might improve treatment accuracy while minimizing collateral harm to healthy tissues. Furthermore, molecular coupling experiments using letrozole, graphene, and fullerenes have demonstrated improved therapeutic efficacy *in vivo*, indicating a role for fullerene-based techniques in optimizing drug delivery and treatment results for breast cancer. These findings highlight fullerene-based techniques as a possible route for enhancing breast cancer treatment [9].

Table 1. Applications of Carbon Nanomaterials in Breast Cancer.

Method	Result	References
Carbon Nanotubes (CNTs)	— Effective drug loading and concentration-dependent death in breast cancer cells	[9,13]
	— Preferential internalization into cancer cells for targeted delivery of therapeutic drugs	
	— Detection of Her-2 biomarker for breast cancer diagnosis	
	— Distinguishing breast cancer through volatile metabolite analysis in breath samples	
Graphene	— Significant cytotoxicity against folate receptor-positive breast cancer cells	[9,14]
	— Killing MD-MB-231 cells following NIR irradiation	
	— Inhibiting migration of triple-negative breast cancer cells	
	— Treating breast cancer bone metastases	
Fullerenes	— Improving breast cancer therapy techniques when paired with graphene and letrozole	[9,15]
	— Optimizing therapeutic effects while minimizing injury to healthy tissues through targeted hyperthermia	
	— Enhancing therapeutic efficacy <i>in vivo</i>	

5. Clinical Trials

Although laboratory studies indicate the therapeutic role of carbon nanoparticle-based diagnoses and therapeutic approaches in breast cancer cells, future clinical trials are required to verify the role. Currently, a prospective, multicentre study aims to apply nano-carbon to mark preoperative axillary lymph nodes in Breast Cancer Patients before neoadjuvant chemotherapy (ClinicalTrials.gov ID NCT05512468). This clinical trial is currently recruiting patients with invasive breast cancer, and to be treated with neoadjuvant chemotherapy.

6. Conclusion

Research has shown the potential of PTT in selectively targeting and destroying breast cancer cells by using NIR light-absorbing chemicals. Carbon nanomaterials, for example, CNTs and graphene, improve PTT because of their large surface area, good electrical conductivity, and biocompatibility. These materials may absorb NIR light, and cause localized heating, resulting in tumor cell necrosis and death. *In vitro* and *in vivo* research showed that carbon nanomaterials improve PTT results and medication distribution and reduce harm to healthy tissues in breast cancer, including CNTs, Graphene, and Fullerenes. The clinical trial to apply PPT to breast cancer is still recruiting patients. Future research should concentrate on improving carbon nanomaterial characteristics and performing clinical studies to confirm their therapeutic potential and incorporation into routine breast cancer treatment regimens.

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