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**Review Article**

# **EMERGING FRONTIERS: ADVANCEMENTS IN BIO-NONMATERIAL'S AND NON-INVASIVE STRATEGIES FOR COMBATING CANCER THROUGH PHOTO THERMAL THERAPY**

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# **ABSTRACT**

Cancer remained a global health challenge in 2020 and claimed approximately 10 million lives, thus rendering it the main reason for demise. Photo Thermal Therapy (PTT) has emerged as a promising approach among the various cancer therapies. PTT offers several advantages over traditional treatments such as surgery, chemotherapy, and Radiotherapy due to its precise tumor targeting and reduced damage to healthy tissues. Photo Thermal Agents (PTAs) are central to PTT and selectively kill cancer cells by converting near-infrared light into heat. However, some PTAs exhibit toxicity and remain in the body's Reticulo Endothelial System (RES), limiting their clinical utility. To address this issue, scientists are looking at putrescible nano-photothermal compounds. This study talks about the effects of PTT and other cancer treatment techniques on patient health, stares at the process beneath PTT, and highlights recent bio-nonmaterial's utilized in PTT. It also looks at how low temperatures and brightly coloured light might be used to improve PTT efficacy.

**Keywords:** Bionanomaterials, Cancer, Photo thermal therapy, Photo thermal agents

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# **INTRODUCTION**

In this review, we explore the latest advancements in biononmaterial's and their application in Photo Thermal Therapy (PTT) for cancer treatment. The search criteria for the literature review included sources such as PubMed, Scopus, and Web of Science. Key words used were "PTT," "bio-nonmaterial's," "cancer treatment, "near-infrared light," "near-infrared-II materials," "nanoparticle toxicity," and "synergistic cancer therapies." The search was restricted to articles published from 2010 to 2024, ensuring a focus on recent developments. Peer-reviewed articles and studies involving preclinical and clinical trials were prioritized. Cancer treatment remains one of the foremost challenges confronting the current wellness sector [1]. With its alarming ephemerality rates and rapid spread, cancer poses a grave threat to individuals worldwide, claiming nearly 10 million lives in 2020 alone, equating to almost solitary ephemerality for every hexadsubject, with a projected worldwide fresh case count of 19.4 million [2]. Throughout the centuries, scientists have tirelessly pursued effective cancer therapies. While current treatments such as chemotherapy, radiotherapy, and surgery yield limited success and come with severe side effects, newer technologies have emerged, including gene therapy, immunotherapy, PTT, and Photo Dynamic Therapy (PDT) that have garnered popularity due to their promising attributes [3]. PTT has mainly garnered attention among these modalities for its heightened specificity, reduced unwanted reactions, potent anti – euplastic efficacy, and reverse-invasive nature [4]. PTT induces a photo thermal effect (light energy is absorbed and transformed into heat via this process), elevating the temperature of cancer cells and triggering organism death, as cancer cells are less heat-tolerant [3]. PTAs with small-scale engineering can actively and passively target tumors, resulting in improved PTT specificity. Only exposing cancer cells to the laser does less damage to healthy tissues. Curing cancer intends to eradicate tumors while preserving healthy cells [5, 6].

A diverse range of organic and nanoparticles made of inorganic material, including photo thermal agents, comprise nonmaterial's that include platinum, gold, and silver carbon-based nonmaterial's, near-infrared dyes, conductive polymers, soluble proteins and peptides, and melanin-like polymers. On the other hand, PTAs with near-infrared absorbance possess downsides such as suboptimal pharmacokinetics, low immunogenicity, elevated toxic effects, and inflammatory side effects. They are also non-biodegradable. Investigating PTAs that exhibit strong clinical translational efficacy and optimize PTT therapeutic efficacy is imperative [7].

To solve the problem, scientists are creating biodegradable nonmaterials such as conducting polymers, melanin-like polymers, carbon-based tiny substances, and tiny molecular organic colors. These materials possess inherent biocompatibility and biodegradability, along with established degradation mechanisms and recognized metabolic pathways, making them promising candidates for enhancing the effectiveness of PTT. By leveraging the potential of these biodegradable nonmaterials, researchers aim to prevail over the constraints of recent PTAs and provide the most efficient, effective PTT treatments.

To ensure that PTAs used in clinical translation are successfully removed from the human body within a given timeframe, the Food and Drug Administration (FDA) of the United States emphasizes this matter. A clear advantage is provided by mechanisms that can stimulate the degradation of nonmaterial's [4]. Despite its considerable effectiveness in clinical therapeutics, PTT has drawbacks, especially when treating tumors at the periphery where light penetration is inadequate and partial removal of malignant cells results. This incomplete removal may facilitate tumor regret and metastasis to other body parts. Due to the previously mentioned limitations, PTT immunotherapy alone is currently frequently insufficient to achieve complete cancer eradication. Many complementary methods, including PDT, immunotherapy, gene therapy, and chemotherapy, are investigated to optimize PTT overall efficacy. These methods can lead to accurate tumor identification and management, providing a comprehensive plan to address a range of cancers and other conditions [8]. In addition to lowering the possibility of cancer cells spreading to all organs and unwanted reactions like inflammation, these combined approaches offer practical advantages over immunotherapy by reducing the chance of tissue injury, burns, and scarring from the heat near tumor locations [9]. Furthermore, nanozymes, a novel class of synthetic enzymes, have great potential.

Fan *et al.* made significant progress in creating a unique nanozyme with a characteristic yolk-shell structure in an innovative research study. With the help of this novel nanostructure, which combines a single gold nanoparticle core with porous hollow carbon shell

nanospheres, it is possible to see horseradish peroxides and oxidizelike functions in acidic environments. The gold nanoparticle core with porous hollow carbon shell nanospheres take full advantage of the photo thermal effect frequently used in tumor therapy by producing Reactive Oxygen Species (ROS) with remarkable efficiency, especially when exposed to 808 nanometer light. As demonstrated by extensive cellular and animal investigations, the combined effects of photo thermal therapy and light-enhanced ROS produce a highly effective tumor-eradication effect. These results highlight the potential for developing a novel tumor treatment strategy using nanozymes innate enzyme-like properties and photo thermal transformation. The research presents strong evidence for using nanozymes in catalytic PTT directed at tumors [10].

An ultra small platinum nanozyme and a carbon nanozyme generated from a Metal Organic Framework (MOF) were combined by Yang *et al.* to create a highly efficient nanozyme. By boosting catalane activity and converting hydrogen peroxide to oxygen, incorporating platinum nanozyme improved the effectiveness of PDT. Additionally, including the platinum nanozyme improved the carbon nanozyme's inherent photo thermal performance. The notable Inhibition of tumor growth observed *in vivo* with the platinum carbon nanozyme is attributed to the combined benefits of increased photo thermal characteristics and catalane-like activity [11].

Nie *et al.* To minimize bleeding after surgery, a device called Surgiflo based palladium-copper nanoclusters is intended for efficient insertion into different tumor cavities. This technology employs dispersed palladium-copper nanoclusters to improve the antitumor immune response and kill glioma cells by producing ROS following exposure to near-infrared laser irradiation [12].

Zhang *et al.* introduced metal active sites scattered over a substrate stabilized by coordinating with elements known as Single Atom Catalysts (SACs). This approach has produced exceptional catalytic performance in various processes by maximizing the use of metal atoms. In disciplines like biology and nanotechnology, catalytic selectivity and activity are crucial factors to consider [13].

Under Zhang'sleadership, a research team has innovated a biodegradable hydro gel coupled with a bioadhesive to mitigate tumor recurrence post-surgery and mitigate skin damage from radiation therapy. This hydro gel facilitates oxygen release and drug delivery to combat cancer effectively, while the bioadhesive possesses antioxidant properties and fosters radiation wound healing. Animal trials have demonstrated the efficacy of this approach in suppressing tumor recurrence and mitigating radiation-induced skin heresy [14]. In this review, we have examined the most recent developments in biononmaterial used in PTT and the possible benefits of combining PTT with other therapeutic approaches. Additionally, we have provided insight into the role of mild hypothermia and Light Emitting Diode (LED) lights in enhancing the effectiveness of PTT.

#### **Mechanism of photo thermal therapy (PTT) action**

Over the past decade, there has been a remarkable surge in the utilization of PTT to eradicate solid tumors [15]. Towards PTAs at tumor locations, such as primary tumors and early local metastases, near-infrared light is directed. Heat is produced by this light-induced electron-to-electron relaxation within the PTAs, which causes hyperthermia and, ultimately, the death of cancer cells in the targeted areas (fig. 1) [16]. Several wavelengths are covered by PTAs, such as near-infrared-I (700-950 nm), near-infrared-II (1000- 1350 nm), near-infrared-III (1600-1870 nm), and near-infrared-IV (2100-2300 nm). Because of their effectiveness as irradiation sources, PTT research has concentrated chiefly on lasers operating in the near-infrared-I window. Furthermore, because of its improved tissue penetration and advantageous safety profile, near-infrared-II, especially the near-infrared-II window (1300–1400 nm), is more effective than near-infrared-I [17]. PTT induces three primary mechanisms of cell death: necrosis, apoptosis, and necroptosis.







**Fig. 2: Cell death mediated by photo thermal therapy (PTT) [70]**

Necrosis is characterized by unplanned cellular demise, resulting in cytoplasmic enlargement, extensive organelle damage, and eventual

plasma membrane rupture [13]. This process exposes the extracellular environment to intracellular materials, including Damage Associated Molecular Patterns (DAMPs), which can trigger detrimental immunogenicunfavourable mode of organism ephemerality [10]. Signals for phagocytosis are released during cell death, characterized by intact membrane integrity and membrane blebbing. Relative to the inflammatory reaction brought on by necrosis, it produces more significant results. It is possible to elicit necrosis without encountering resistance. Under ideal radiation circumstances, PTT can induce apoptosis. PTT induced apoptosis is facilitated mainly by the intrinsic route. It is interesting to investigate if the main pathway leading to cell death during apoptosis is the extrinsic or intrinsic pathway. Molecular signalling pathways linked to cellular responses to PTT offer insights into this matter. It is plausible that the primary mechanism of PTT induced cell death does not involve the extrinsic pathway, which is activated when specific ligands bind to "death receptors" on the cell surface. PTT probably causes membrane permeabilization and cytochrome c release from mitochondria by activating the intrinsic route. This outcome creates the apoptosome complex, which in turn causes a series of subsequent occurrences that culminate in cell death and phagocytosis by activating caspase-3, as depicted in fig. 2.

This is essential for highlighting the communication between the pathways leading to intrinsic and extrinsic apoptosis. When ligands engage death receptors, caspase-8 is activated and contributes to the cleavage of Bid into tBid. tBid then translocates to the mitochondria, releasing cytochrome c and activating Bax/Bak. This intricate interaction between pathways exemplifies the complexity of apoptotic signaling [15].

When cancer cells are subjected to high temperatures during PTT, typically exceeding 42 °C, they often undergo apoptosis or necrosis. The tumor cell ephemerality in PTT is known as necroptosis [18]. This mechanism shares similarities with a highly regulated cell death process and an uncontrolled, passive necrotic pathway. Reduced temperature can release heat-shock proteins, which prevent cancer cells from thermal burns. Irradiation with near-infrared light generates heat at 49 °C and below, which induces irreparable damage to tissue and necroptosis and cell death in cancer cells. Necrosis ensueswhen elevated temperatures disrupt the cancer cells membranes, releasing cytoplasmic contents and eliciting an inflammatory response. At 46 °C, protein denaturation and the disruption of cell membranes occur due to ischemia and micro vascular thrombosis, leading to cell death. Apoptosis, characterized by tightly controlled processes and the absence of inflammation, emerges as a suitable technique for eliminating cancer cells. PTT has acknowledged this distinction in cell death mechanisms for cancer treatment [14].

## **Bio-nanomaterials used for photo thermal therapy (PTT)**

Excellent photostability, minimal harm to normal tissues, exceptional biocompatibility, and excellent photo thermal conversion effectiveness at a particular wavelength is the ideal PTAs characteristics. Fig. 3 depicts various types of PTAs commonly employed, including organic nonmaterial's like conductive polymers and near-infrared dyes, noble metal nonmaterial's such as gold nanorods and gold nanospheres, and metal compounds like iron, copper, and molybdenum [19]. In recent years, a range of inorganic excellentphotostability, minimal harm to normal tissues, exceptional biocompatibility, and excellent photo thermal conversion effectiveness at a particular wavelength are characteristics of the ideal PTAs. PTAs has been synthesized and investigated in both *in vitro* and *in vivo* studies due to their surface plasmon resonance properties, which confer excellent near-infrared light absorbance [20]. However, despite their promising therapeutic efficacies, the drawback of these nonmaterials lies in their toxicity and nonbiodegradability, limiting their clinical translation and therapeutic applications [21].

In comparison, organic nonmaterials demonstrate higher biocompatibility [22]. To address this issue, various biononmaterials have been synthesized to enhance the photo thermal effect while ensuring biocompatibility, biodegradability, low cytotoxicity, and rapid clearance from the body. This biononmaterial's are discussed in the following section and are summarized in table 1 [70].

#### **Carbon–based nanomaterials**

#### **Carbon nanotubes (CNTs)**

These are cylindrical sp2 hybridized monolayer sheets of carbon atoms [23]. Due to these unique attributes, Carbon Nanotubes (CNTs) are currently at the forefront of scientific investigation. Serving as plasmonic nanoparticles, CNTs can infiltrate cells due to their remarkable thermal conductivity [42]. The thermal conductivity of CNTs offers several advantages, including even distribution of generated heat throughout tumor cells and confinement of heat exclusively to the targeted area, thereby reducing toxicity to off-target tissues. Furthermore, Magnetic Resonance Imaging (MRI) temperature mapping can verify targeted tumor tissue volume [23].

Nanotubes come in two primary varieties: single-walled and multiwalled. As the name suggests, Single-Walled Carbon Nanotubes (SWCNTs) consist of one layer forming a cylinder while the multiwalled nanotubes comprise several cylindrical layers each having a diameter greater than the other. The chemical bonding in the tubes is best described by orbital hybridization (sp2-hybrid carbon atoms) which accounts for the unique strength of CNTs [102].



**Fig. 3: Different biomaterials used for photo thermal therapy (PTT) [70]**

## **Single-walled carbon nanotubes (SWCNTs)**

Graphitic helical molecules, known as Single-Walled Carbon Nanotubes (SWCNTs), possess remarkably robust mechanical and physical properties [24]. Studies conducted by Liu *et al.* concluded that SWCNTs exhibit excellent biological stability, low toxicity, and

favourable water solubility [43]. Liang *et al.* similarly found that SWCNTs demonstrated high strength and minimal cytotoxicity in both *in vitro* and *in vivo* experiments. Incorporating Poly Ethylene Glycol (PEG) into SWCNTs prolongs their circulation time in the bloodstream. In a study by Li *et al.*, the addition of cyanine 5.5, which absorbs light at 808 nm, enabled cyanine 5.5 coupled SWCNTs to

mediate PTT in mice, resulting in systemic tumor ablation and improved therapeutic outcomes [99]. Virani *et al.* employed bladder tumor-specific SWCNTs followed by near-infrared light to treat superficial cancers and stop tumor recurrence. The bound nanotubes that are led to the tumor site by phosphatidylserine and annexin V are the main targets of the heat-based treatment [45]. Li *et al.* highlighted the SWCNTs exhibit remarkable Photothermal Conversion Efficiency (PCE), excellent water solubility, bio stability, and minimal toxicity. They can be coupled with dye and antibodies to give dye imaging-guided cytotoxic PTT that targets pancreatic cancers [46]. Mei *et al.* synthesized selenium based CNTs, which, when exposed to radiation, produce ROS and cause tumor cells to undergo apoptosis. By modifying signal transduction pathways, the nanosystem prevented Triple Negative Breast Cancer (TNBC) cells from migrating and invading [23].

Mckernan *et al.* introduced a novel therapeutic strategy for metastatic Epithelial Mammary Tumor 6 (EMT6) breast cancer in

BALB/c jackson mice that are syngeneic,integrating PTT with targeted SWCNTs and immunostimulation using a checkpoint inhibitor. This newly formulated approach enhanced the abscopal effect, relying on the cytotoxic T-lymphocyte associated antigen 4 blockade, showcasing remarkable synergy. As a result, there was a significant increase in the living probability of mice, reaching 60%. Moreover, this treatment regimen boosted the population of CD4+helper and CD8+cytotoxic T-cells, thereby enhancing the activity of anti-tumoral effector cells and inhibiting tumor spread [47]. Chen *et al.* developed an amylose derivative conjugated to modified SWCNTs. The amylose derivatives containing poly (L‐lysine) dendrons complex exhibits excellent water dispersion stability and demonstrate high p – Deoxyribo Nucleic Acid (DNA) transfection capacity. In both *in vivo* and *in vitro* studies, Tumor Necrosis Factor (TNF)/amylose derivatives containing poly (L‐lysine) based SWCNTs effectively inhibits tumor growth and prevents metastasis. The potent antitumor effects of near-infrared irradiation suggest its potential utility as a cancer therapy [24].





# **Multi-walled carbon nanotubes (MWCNTs)**

Multi-Walled Carbon Nanotubes (MWCNTs) exhibit diameters ranging from tiny to very small nanometers. They are increasingly recognized as promising candidates for applications in biological imaging, photo thermal tumor ablation, and tumor drug delivery [50]. Compared to other materials like SWCNTs, MWCNTs are anticipated to absorb a significantly more significant amount of near-infrared radiation, potentially leading to tumor thermal

ablation through localized heat generation upon near-infrared exposure. Cys-Arg-Glu-Lys-Ala peptide, PEG, MWCNTs, fibrin, and near-infrared irradiation are the therapeutic payloads of Zhang *et al.*'s drug delivery system, MWCNTs with PEG. It demonstrated efficacy in photo thermal therapy and had good tumor targeting [25]. Sobhani *et al.* covered MWCNTs with PEG and oxidized them to improve their water permeability. Tumor development and cytotoxicity decreased in CNTs onto PEG after PTT. A hightemperature conductivity and absorbance in the near-infrared range

have been achieved by combining CNTs with gold nanoparticles. The authors found MWCNTs with gold nanoparticles effective in cancer treatment [42]. These findings underscore the promising clinical and therapeutic potential of nano-agents despite the ongoing uncertainty regarding their long-term safety [21].

## **Carbon dots (CDs)**

Zero-dimensional Carbon Dots (CDs) are nonmaterial's with exceptional optical characteristics, biocompatibility, and little environmental effect. Because they can convert light into heat, they have significant promise for various applications, including photo thermal applications [48]. Shinde *et al.* demonstrated the utilization of Clitoria ternatea leaves in synthesizing hydrophilic lecithin-coated red fluorescent CDs with enhanced bioavailability and theranostic capabilities. With a hydrodynamic diameter of roughly 210 nm, soy lecithin-coated red fluorescent CDs are nanoparticles suitable for bioimaging and cancer therapy. They have assured PTT agents, which can cause significant cell death in 4T1 cells and damage neoblood vessels in Chorio Allantoic Membrane (CAM) assays [26].

#### **Graphene**

Recent interest in graphene-based nonmaterials has been driven by their unique structural, optical, thermal, electrical, and mechanical properties [49]. Graphene, a two-dimensional nanosystem of sp2 hybridized carbon atoms arranged in a hexagonal pattern, has garnered significant attention [43]. Because of its biocompatibility, adjustable surface structure, ease of formulation, and solubility, Graphene Oxide (GO) and reduced Graphene Oxide (rGO) are widely used in PTT [23]. Because of its intense near-infrared light absorption, graphene is a suitable nanoagent for PTT [21].

# **Graphene nanosheet (GN)**

The photo thermal properties of GO nanosheets exhibit remarkable performance and are characterized by a broad absorption spectrum. Additionally, the ample surface area of GO renders it a promising platform for drug loading. Dopamine hydrochloride was utilized by Liu *et al.* to generate polydopamine doped mesoporous silica-coated rGO. The photo thermal conversion efficiency and the release of medication at the tumor location are improved by this substance [27].

Furthermore, Wang Yijuan *et al.* conducted docking study utilizing methods of Monte Carlo, revealing an uneven distribution of nanosheets on the surfaces of cancer cells. This uneven distribution led to a rapid temperature increase, facilitating tumor cell death [100]. In another study by Li et al., manganese dioxide nanoparticles were incorporated into the rGO sheets mixture. The solid physical bond between methylene blue and doxorubicin with GO increased drug release at high temperatures [51].

## **Graphene oxide (GO)**

Graphene Oxide (GO) possesses several oxygen-based functional groups. These significantly reduce graphene's hydrophobicity [43]. Many GO small particle varieties utilized in photo thermal therapy are outlined in table 2 [70]. Leveraging extensive surface area for drug binding through hydrophobic, H-bonding, π-π, and electrostatic interactions [23]. By loading doxorubicin onto the nanocomposite, Liang *et al.* created GO nano complexes based doxorubicin-folic acid nanomaterial's. As a result of its large surface area, target selectivity, drug loading capacity, PCE, and photostability when exposed to radiation at 808 nm, this formulation works well [28]. Chang *et al.* engineered a flexible nano platform by binding barium hole-doped iron oxide fluoride 5 nanoparticles to GO. Leveraging the Enhanced Permeability and Retention (EPR) effect, the biocompatible GO/barium hole-doped iron oxide fluoride 5/PEG nanocomposite infiltrates lesions efficiently. This nano platform can be loaded with Heat Shock Protein 90 (HSP 90) NVP-AUY922 inhibitor to combat cancer and perform PTT upon irradiation with an 808 nm nearinfrared laser [29]. Qi *et al.* developed a Schiff base-cross-linked hydro gel using Carbonyl Methyl Chitosan (CMC) and aldehydemodified PEG. This injectable and self-healing hydro gel was designed to carry GO and nano hydroxyapatite inhibitors in needles,<br>enhancing tumor diagnosis accuracy while reducing enhancing tumor diagnosis accuracy while chemotherapeutic side effects. The hydro gel exhibited self-healing properties, improved injectability, and a porous structure [52]. Baipaywad *et al.* engineered a controlled *in vivo* drug delivery system by combining GO and poly N-isopropyl acrylamide in a nano hydro gel formulation. By strengthening PTT effectiveness in nano gel systems, GO and poly N-isopropyl acrylamide generated doxorubicin when exposed to near-infrared light [53].

**Table 2: The compilation of photo thermal therapy (PTT)-utilized graphene oxide (GO) nanomaterial's**

S. No.	<b>Formulation</b>	Curative marks	Reference
	GO and poly N-isopropyl acrylamide	Less toxic against tumors and biologically compatible	[53]
2.	PEG-CMC/hydroxyapatite/GO	Completely stop the cancer cell proliferation	[52]
3.	GO/BaHoF5/PEG	Positive PTT impact on cancer	[29]
4.	GO nano complexes based doxorubicin-folic acid	Outstanding possibilities for cancer treatment applications	[28]
	nanomaterial's		

#### **Reduced graphene oxide (rGO)**

Due to its high PCE in the near-infrared range, enormous surface area, and groups of molecules suitable for small interfering Ribo Nucleic Acid (RNA) and ligand attachment, reduced Graphene Oxide (rGO) is a promising 2D carbon nanomaterial for photo thermal therapy [54]. Regarding PCE, rGO demonstrates a two-fold improvement over GO as a PTT agent [29]. Various types of rGO utilized in PTT are outlined in table 3 [70]. Zhang *et al.* devised a straightforward method for putting medications into rGO that is nanoscale for breast cancer PTT, employing tamoxifen as the medication, resulting in significant tumoricidal activity with the combined tamoxifen nano rGO composition [30]. Gai *et al.* demonstrated that rGO derived from synthetic plant extracts exhibits minimal cytotoxicity towards cells and can be directly employed for PTT without additional surface modifications, effectively destroying Esophageal adenocarcinoma cell lines *in vitro* [31]. A tiny carrier combination for synergistic chemo PTT was created by Liu *et al.* (rGO@mesoporous silica), featuring an outer layer composed of mesoporous silica and an inner layer of rGO. This structure facilitates the easy release of doxorubicin into acidic environments, serving as both a near-infrared PTT agent and a pHinduced drug nanocarrier [55]. Lima-Sousa *et al.*, in collaboration

with other researchers, developed poly dopamine rGO by utilizing rGO as a reducing agent and dopamine. According to a study, poly dopamine rGO indicated considerable near-infrared spectrum absorption and kept distributed all over the cells. Thiolterminated poly(2-ethyl-2-oxazoline) was attached to enhance its stability and characteristics [42]. While remaining stable and compatible with organisms, this boosted poly dopamine rGO version exhibited intriguing properties. U87 glioblastoma cells showed uptake of this nanosystem. They developed an infrared-780/rGO/Hyaluronic Acid (HA) pH-responsive nano system loaded with doxorubicin for multimodal cancer treatment [chemotherapy/PTT/PDT] [56].

#### **Graphene quantum dots (GQDs)**

Solid quantum dots, abbreviated as Graphene Quantum Dots (GQDs), are nanostructures known for their photoluminescence and prominent edge effects. Leveraging an near-infrared laser, GQDs have found extensive application in PTT [49]. Because of their low level of toxicity and outstanding absorption in the near-infrared-II region, GQDs have tremendous potential for application in photo thermal therapy. Robust magnetic field tuning of hydrogen peroxide breakdown was achieved by Liu *et al.* [32].

**Table 3: The inventory of photo thermal therapy (PTT)-used reduced graphene oxide (rGO) nanoparticles**

S. No.	<b>Formulation</b>	<b>Curative marks</b>	Reference
	Infrared-780/reduced rGO/HA	For enhancing combined activity for [chemotherapy/PTT/PDT] treatment	[56]
2.	Poly dopamine rGO	PTT For the utilization in Ductal cancer	[57]
3.	rGO @mesoporous silica	For cancer treatment, it was the suitable platform	[55]
4.	Reduced nano GO	Kill Oesophageal adenocarcinoma cell lines	[31]
	Nano-rGO	Destroying of cancer cells	[30]

#### **Small molecular organic dyes**

Molecular dyes exhibit exceptional characteristics concerning surface modification and compatibility with biological systems. Tailoring molecular dyes to meet specific absorption wavelength requirements, particularly for targeted loading into tumor cells, can be achieved through seamless reshaping [58].

## **Indocyanine green (ICG)**

Indocyanine Green (ICG) has gained approval from the USFDA as a clinical diagnostic photosensitizer. As ICG comes into interaction with near-infrared laser radiation, it may trigger hyperthermia and generate ROS. However, due to its rapid clearance rates and poor stability, utilization in PDT is constrained. For a significant load of ICG, nanocarriers that include polymeric nanoparticles, calcium phosphate nanoparticles, and mesoporous silicon nanoparticles are being investigated [43]. Qing *et al.* produced monomethoxy PEGluteolin-bortezomib@ ICG, a pH-responsive gel incorporating chemotherapy medications and PTT/PDT to manage colorectal cancer. Through the synergistic action of bortezomib and ICG, this method successfully eliminated the tumor cells in both *in vitro* and *in vivo* trials [33]. Prussian blue nanoshells facilitated the absorption of ICG particles, forming fine aggregates that enhanced the cellular uptake of drugs. This combination exhibited improved histocompatibility, hemocompatibility, increased apoptosis, reduced toxicity, and effective tumor destruction [59]. ICG is a robust photosensitizer that booststhe production of ROS.

Additionally, its unique ability to absorb near-infrared light enhances the photo thermal effect, contributing to the degradation of tumor cells [60]. Wang and colleagues altered the surface potential of silicon dioxide-ammonium nanoparticles by incorporating ICG. This modification enhanced the targeting capacity of silicon dioxide-ammonium based ICG nanoparticles, making them stable enough to execute PCE. These silicon dioxide-ammonium based ICG nanoparticles absorb more light in the near-infrared spectrum after coating the ICG surface. According to this study, these nanoparticles significantly kill tumor cells [34]. To better the visible properties of ICG and enhance its uptake in 4T1 memory malignancies, Miranda *et al.* merged ICG to liposomes containing 1,2 dioleoyl-3-trimethyl ammonium propane. They examined the continued effectiveness of the combined formulation by using fluorescence and photoacoustic imaging approaches [61].

#### **Cypate**

Cyclapate, an indocyanine green derivative containing bis-carboxyl groups, exhibits heat production and fluorescence upon exposure to near-infrared radiation. Yin and colleagues developed Cypate-Poly Methyl Methacrylate (PMAA)-iron based Mesenchymal Stem Cells (MSCs) by coating PMMA nanoparticles with membranes derived from MSCs loaded with Fe and Cypate. This novel formulation demonstrates high PCE *in vitro* and *in vivo*, along with excellent tumor accumulation and stability, making it suitable for diagnosing lung cancer. Moreover, Cypate-PMAA-iron based MSCs serve as a platform for MRI bimodal imaging, fluorescence, and PTT enhanced radiotherapy [35].

## **Infrared-780**

Concerning ICG, infrared-780 dye is brighter but mixes more slowly in water and exits the body more quickly. The stability of infrared-780 dye in water may be boosted by wrapping it in micelle nanoparticles [48]. Biomolecule extracts' lipophilicity restricts the possibility of enhancing the therapeutic potential of several beneficial plants. In a study, Pemmaraju *et al.* used poly D-lactic co-glycolic acid to

encapsulate and distribute a hydrophobic extract from Anthocephalus cadamba. They added infrared-780 dye to the mixture as well. To create a cancer treatment that works, this strategy sought to increase the cells' absorption and the bioavailability of the Anthocephalus cadamba extract. HD of 177.3±85.5 was observed by infrared-780/Anthocephalus cadamba polymeric nanoparticles. At 20µg/ml concentrations, polymeric nanoparticles demonstrated enhanced cytotoxicity and selectivity for tumor cells, resulting in 53.2% of B16 cell lines collapsing [36]. Tutty, in addition. No cytotoxicity or damage to DNA was found when using liposomes loaded with the dye infrared-780 (Liplmage (TM) 815) for deep tissue imaging [2].

Numerous other dyes besides infrared-780 also produce photo thermal effects, such as Pebam. In an investigation of malignant pulmonary cells, tiny polylactic acid particles comprising infrared-775 and an ethyl acetate extract of Terminalia chebula, a plant, were used. The results showed that near-infrared radiation elevated cell death decreased HSP70 and poly adenosine diphosphate ribose polymerase, and upregulated Phosphorylated Histone H2A Variant X [62]. A chitosan-coated Niosome has been proposed by Jogdand *et al.* as an approach to giving infrared-806 dye to inhibit the synthesis of mucin in breast cancer patients. When near-infrared radiation was utilized on Michigan Cancer Foundation-7 (MCF-7) cells, the nanosystem was activated and ablated cells by up to 93% [63].

#### **Proteins/Peptides-based nanomaterials**

While they are dissolved in water and exhibit an elevated level of biocompatibility, peptides and amino acids are excellent carriers for medicinal or diagnostics elements [7]. They may act as biotemplates for the synthesis of nanoparticles. Biomolecular hydrogels can target the delivery of medications, reduce cytotoxicity, and enhance drug release [64]. Subcutaneous carcinomas can now be eliminated with stable nanoparticles that do not trigger toxicity or stimulate tumor growth [37].

#### **Polymer-based nanomaterials**

A polymer of tiny particles was developed by Mudigunda *et al.* to treat retinoblastoma. Palladium(II) phthalocyanine nanoparticles were exhibited by Appidi *et al.* to induce DNA damage and cell division in tumor cells[ 66].

#### **Conducting polymers**

Conducting polymers, such as polyaniline and polypyrrole, have found widespread use in biomedical and bioelectronic applications. Due to their favourable optical absorption quality, they are particularly well-suited for PTT. Although conducting polymers are considered more biodegradable and less costly, they are often used as elimination agents in photo thermal treatments [67]. Poly-(3,4 ethylene dioxy thiophene):poly-(4-styrene sulfonate), a conducting polymer made from polythiophene, has been paired with PEG to improve biocompatibility. It can also be used as a polymer PTAs for cancer PTT [68]. Mice with 4T1 tumors were also employed to test double-acceptor polymers with conjugation [Tryptophan Tryptophyl Quinone (TTQ) and Diketo Pyrrolo Pyrrole (DPP)], enhancing photo thermal capacity and generating resilient near-infrared-II F1 signals. Therefore, they have vast potential for tumor eradication[69]. The work of Liu *et al.* and Chen *et al.* exemplify the possibility of conducting polymers in cancer therapy. Poly-(3,4-ethylene dioxy thiophene):poly-(4-styrene sulfonate), PEG and polymer-1 nanoparticles, in particular, have demonstrated excellent biocompatibility, photostability, and photo thermal capacity, which make them attractive candidates for future research and development in this field.

#### **Polyaniline**

The first documented photo thermal anticancer agent based on polymers is called polyaniline. A promising hydro gel Guar Gum (GG) based iron with polyaniline was created by Huang *et al.* Borax) through the doping of iron with polyaniline linked to GG moieties through borate/diol linkages. Guar gum chains were first used in this investigation as the main building component. GG based iron with polyaniline-borax demonstrated amendable sol-gel transformation, good injectability, and quick self-healing characteristics in response to heat or pH stimulation. Within the hydrogen Peroxide enriched tumor microenvironment, iron-doped polyaniline produced free ºOH radicals. The astonishing photo thermal characteristics and regulated release of pharmaceuticals in the near-infrared triggered range exhibited by hydrogels enable the establishment of combination PTT, radiation therapy, or PDT for *in vitro* and *in vivo* melanoma contexts [38]. An efficient polyaniline core-shell was created by Wang *et al.* Nanomaterial with an exceptional PCE administered at low doses for Photo Acoustic Image (PAI)-guided photo thermal therapy. HA modifies this PTAs without compromising its photo thermal effectiveness. Gold nanostar probe hydrogels demonstrate outstanding biocompatibility in PAI-guided PTT to removetumours [39].

#### **Polypyrrole**

Organic polypyrrole properties include improved biocompatibility and a high PCE. The polypyrrole-cantharidine was created by Cheng *et al.* Matériaux Institut Lavoisier-100 (MIL-100) based plasmonic core multimodel nanoparticles with coated macrophage cell membranes) successfully raised the PTT-based Fenton reaction rate. As a result, iron ions and polypyrrole cantharidine are released into the plasmonic core multimodel nanoparticles [101]. Near-infrared photosensitivity is present in polypyrrole. Polypyrrole-poly (ethylene imine)-silk nanoparticles were created by Xu *et al.* The combination of photo thermal and gene therapy was evaluated with this formulation. It reduced the invasive ablation of the malignancies and inhibited lymphatic metastasis [40].

## **Melanin-like polymers**

Antioxidant, radio-resistant, and anti-euplastic, this polymer is present in many plants, animals, and human tissues. Furthermore, melanin has intense near-infrared light benefits PTT [68]. In a biocompatible approach, Zhang *et al.* revealed that melanin PEG ylatednanoliposomes had good biocompatibility and clinical translation [41]. The prospective use of polyphenol-based PTAs and melanin-like poly dopamine substances as therapies for cancer is being investigated due to their sustainable production and biodegradable and biological compatibility [9].

## **Microspheres of MXene for photo thermal therapy (PTT)**

A novel two dimensional (2D) transition metal called MXene [1] was discovered in 2011 by Naguib *et al.* The parent metal, aluminium, carbon or nitrogen phase is printed to remove the element of the A-group, aluminium. As a result of their outstanding photo thermal conversion efficiency, enormous surface area, and simple functionalization, MXenes are intriguing substances for cancer research [3]. In breast cancer models, the full potential for tumor cells to respond to PTT has been explored; this has resulted in a reduction in the lifespan of cells and increased reactive oxygen species. In bioprinted models, PTT-mediated MXenes also impeded the growth of cancers [4].

#### **Naphthalocyanines (Nanonaps) and phathalocyanine**

Zhang *et al.* created nano-formulated naphthalocyanines, or nano-naps, exhibiting remarkable contrast in the near-infrared range for cancer theranostics. Multipurpose uses for nanonaps include lymphatic mapping and whole-tumor PAI. Additionally, they have inherent qualities that make them appropriate for Positron Emission Tomography (PET). A topical up conversion skin cream was developed using nanonaps for PTT against tumors. Molecules such as phthalocyanine and porphyrin have potential uses inimaging and medicine [71].

Phthalocyanine is an organic PTAs that is highly flexible and environmentally acceptable. Its chemical structure is well-defined and exhibits significant absorption in the near-infrared spectrum [72]. It made a novel cruciform phthalocyanine pentad that forms water-soluble nanoparticles with unique absorption capabilities in the near-infrared region. With a phenomenal PCE of 58.3%, these nanoparticles produce a robust photoacoustic signal [73].

#### **Combinatorial effect of photo thermal therapy (ptt) with cancer therapy**

PTT has become increasingly popular in recent decades due to its increased therapeutic efficacy. PTT still has a lot of drawbacks, though. Factors that prevent its use in many clinical situations (such as high temperature, a shallow depth of light penetration, thermal injury to normal tissues, and heat-shock response) (fig. 4) [74]. To circumvent these constraints to deliver effective cures for cancer, combination therapy-which combines concurrently co-targeting substances or combining medical treatments in various forms-is needed. It is true that combination therapy significantly improves the prognosis for a wide range of illnesses [33].



**Fig. 4: Advantages and limitations of photo thermal therapy (PTT) [70]**

## **Photo thermal therapy (PTT) combined with chemotherapy**

For advanced-stage tumors, chemotherapy is an effective cancer treatment. For many cancer patients, it extends their life expectancy. This therapy is difficult to use, nevertheless, due to issues like limited drug penetration in tumor locations, significant cytotoxicity, and non-specific distribution. Better outcomes have been achieved by adapting a combination of chemotherapy and PTT to get around these constraints [16].

Synergistic PTT/chemotherapy action were created by Liu *et al.* Epoxide Iron(III) Chloride Nanoparticles (EICN) is a tremendous therapeutic drug for chemotherapy/PTT because of its dualacid/near-infrared-responsive qualities. EICN is very stable and has a diameter of 90 nm [75]. Li *et al.* developed a novel nano agent that delivers the chemotherapeutic medication Paclitaxel using polymeric nano micelle-based technology. When this nano agent is exposed to an 808 nm laser, site-specific hyperthermia is quickly achieved. It is an efficient tumor treatment because of the temperature increase and site-specific medication delivery [76].

A novel approach utilizing chemo-PTT generated by near-infrared light is used to manufacture doxorubicin-Bovine Serum Albumin (BSA)– rGO nanosheets. They have shown promise in addressing brain tumor cells. The ensuing nanosheets were evaluated with X-

ray Photoelectron Spectroscopy (XPS) and an Ultra-Violet (UV) visible spectrophotometer [77].

#### **Photo thermal therapy (PTT) combined with immunotherapy**

While PTT is less intrusive on surrounding tissue, its effectiveness in stopping tumor recurrence is short-lived and results in cytotoxicity. PTT agent biodegradation is sluggish [78]. Immunotherapy is a potentially effective treatment method that stimulates the host's immune system to fight the tumor. Restricted immune cell penetration, restricted immunity, alteration rate, and a wrong host immune response are some of the disadvantages of immunotherapy. For it to fight cancer, a combination regimen, including PTT-induced immunotherapy, releases immune responses that are adaptive as well as innate (fig. 5) [16].



**Fig. 5: Photo thermal therapy (PTT) combined with immunotherapy [70]**

Immune checkpoint inhibition paired with photo thermal therapy leads to focused cytotoxicity and improved immunogenicity, improving cancer patients' clinical outcomes [79, 80]. In addition, gellan gum hydro gel, polyoxometalate, and localized ablative immunotherapy have shown positive results in boosting the anticancer defenses against breast tumors [78].

## **Photo thermal therapy (PTT) combined with radiotherapy**

For improved clinical translation outcomes, Radiotherapy is a frequently employed approach combined with radio sensitizers [81]. Some restrictions exist, like weakening the ability to destroy and arming the surrounding solid tissues. Consequently, to maximize radiotherapy effectiveness, it is imperative to combine it with other medications, including PTT (fig. 6) [82].

Using Poly (thiodi-ethylene malonate) and PEG), both packed with radiosensitive Suberoyl Anilide Hydroxamic Acid (SAHA), Liu *et al.* constructed a nano-phototherapeutic system. The equipment demonstrated its capacity to carry out morphological changes and generate therapeutic effects in responses to near-infraredirradiation and X-ray radiotherapy. As compared with radiation treatment alone, a combination of therapy diminished the ability to survive breast cancer cells [81]. Radio therapy, PDT/PTT effects, nearinfrared imaging, and preferential tumor accumulation are all displayed by the multifunctional bioactive small molecule infrared-83. It was built with intrinsic tumor penetration and phototherapeutic efficacy using 2-nitroimidazole, a radio sensitizer, in the core of heptemethine cyanine dyes [82].



**Fig. 6: Photo thermal therapy (PTT) combined with radiotherapy [70]**

## **Photo thermal therapy (PTT) combined with gene therapy**

Gene vectors improve gene therapy therapeutic application of nucleic acids DNA, small interfering RNA and micro RNA [83]. The negative aspects of gene Therapy include allergic reactions, poor clinical trials, and safety issues. Odda *et al.* utilized an unusual photo thermal nanocarrier to combine PTT in gene therapy. Small interfering RNA-B cell lymphoma 2 was employed to capture and load the surface-modified iron oxide based poly (3,4-ethylene dioxythiophene) nanoparticles into breast carcinoma cells. Compared to other iron oxide based poly (3,4 ethylene dioxythiophene) nanoparticles, this core-shell surface-modified iron oxide based poly (3,4-ethylene dioxythiophene) nanoparticles have demonstrated intense near-infrared irradiation, biocompatibility, and water dispersibility. They demonstrated improved photostability and PCE (η=54.3%) in the area. The combination treatment of gene therapy and PTT, as opposed to either therapy alone, showed superior tumor cell death, according to the results [84]. Liu and colleagues generated HA-coupled. It Is anticipated that this will accelerate the body's nanoformulation circulation time. These composites showed improved targeting of tumor tissues, stability, biocompatibility, and a longer retention time in the Physique [85].

#### **Photo thermal therapy (PTT) combined with photo dynamic therapy (PDT)**

In recent years, PDT has become a very appealing alternative therapy. When exposed to laser light, it produces ROS by employing photosensitizers to impact the cancer cells' death [44]. Numerous benefits of this therapy include its excellent selectivity, reduced invasiveness, exceptional healing abilities, and reduced adverse effects. However, tumor hypoxia or reduced tissue penetration limits its application in clinical translation. The combinatorial impact of PTT with PDT yields the intended result and fixes the problem [16]. Fig. 7 explains the PTT and PDT combinatorial mechanism.



**Fig. 7: Photo thermal therapy (PTT) combined with photo dynamic therapy (PDT) [70]**

Spinacia oleracea co-assembled on a polydopamine core was the source of the multifunctional chlorophyll-rich fluorosomes that Rajalakshmi *et al.* proposed to enhance the process of photo thermal transmission. Using a combination of PDT and PTT, Spinacia oleracea co-assembled on a polydopamine core nanoparticles were assessed the proliferation of cancer cells under normoxic and hypoxic conditions. Synergistic PTT and PDT improved physiological stability and tumor regression in Spinacia oleracea co-assembled on a polydopamine core nanoparticles, which measured 176±10 nm. When Spinacia oleracea co-assembled on a polydopamine core nanoparticles were used to treat MCF-7 cell spheroids, they effectively targeted the tumor and overcame resistance, angiogenesis, and metastasis. The spheroids' centres were severely damaged [86]. Another therapeutic strategy, using liposomal gold nanoparticles to encase curcumin, was described by Alvi *et al.* Cur nanoparticles) to treat acne that has returned after developing antibiotic resistance. It used a dual light-mediated treatment with a size of 100–120 nm. By exerting a positive zeta by iontophoresis, these nanoparticles take advantage of targeted follicular delivery [87]. Li and colleagues have effectively created ICG based molybdenum disulfide nanoparticles. With this formulation, the PTT-PDT combinatorial action is achieved, and successfully pglycoprotein, protein is inhibited. By removing anticancer medications from the cell and inhibiting P-glycoprotein, this pump can increase the PDT impact and ultimately lead to Multi Drug Resistance (MDR) [88]. Guo *et al.* developed a novel method in their investigation by creating a hybrid material from folic acid and chlorin e6 functionalized GO. This combination of PDT and PTT was intended to work in concert.

Interestingly, the mixture demonstrated a fantastic capacity to enter macrophages efficiently. PTT-PDT was found to have a higher combinatorial effect when destroying cancer cells [89]. Using an easy two-step procedure, Liu *et al.* created ICG-encapsulated HA

surface coated with polydopamine nanoparticles. These synthesized nanoparticles display strong PCE and single oxygen radicle generation. Research revealed that cancer cell growth is inhibited by combining PTT and PDT. A novel photo thermal-photodynamic compound for cancer treatment showed great promise when applied to ICG-encapsulated HA surface coated with polydopamine nanoparticles [90].

## **Effect of light emitting diode (LED) in photo thermal therapy (PTT)**

Because LED light sources are less expensive and have fewer side effects, it focuses on LED light sources for photo thermal therapy. For clinical institutions and research labs, LED lighting. However, the newest LED light sources are excellent at reducing the hazards usually associated with lasers while still producing near-infrared light that is both longer-lasting and of higher intensity. The therapeutic applicability of tiny LED light sources is enhanced when they are developed to illuminate a more extensive treatment area than lasers [94].

# **Effect of mild hypothermia in photo thermal therapy (PTT)**

This differs from traditional laser therapy, which requires a long-term and intensive procedure because of its limited ability to reach deep tissue and lower photo thermal conversion efficiency. Increased laser power to achieve effective tumor death while causing some nonspecific damage to the cytoskeleton and vasculature of bystander cells and the host's antitumor immunity. To sensitize cells to mild temperature rise and, ultimately, stop the proliferation of cancer cells, researchers have focused on using PTT and PDT therapeutic modalities at mild temperatures (42–45 °C), either alone or in combination with other strategies that modulate HSP expression, generate ROS, supervise autophagy, and target specific organelles [95– 98]. Huang *et al.* transformed cool tumors into hot tumors using a

temperature-sensitive lipid gel depot. Plate number 1 and an antiprogrammed death ligand 1 antibody were added to the centre, and near-infrared radiation was employed to accelerate the infiltration of tumor-infiltrating cells. Optimizing the approach, *in vivo* tests on mice verified the presence of lymphocytes, increased T-cell activity against cancers, and elevation of programmed death ligand 1 in tumor cells [89].

## **Future perspective**

In the upcoming years of research, safety concerns regarding PTT usage as an anticancer treatment will be closely examined and hopefully resolved. Further study will concentrate on how PTT might be combined with other cancer medications to improve therapeutic outcomes and clinical efficiency. Mild hypothermia will be used to decrease the adverse consequences of PTT, and LED lights rather than laser will be encouraged because of their affordability.

# **CONCLUSION**

This review discusses the development of selective biononmaterial's for PTT in cancer treatment. Despite their biocompatibility and biosafety, the long-term toxicity of these materials remains under investigation due to non-biodegradable nanoparticles causing cell toxicity. By optimizing exterior features, bio-nonmaterial's can convert photon energy into thermal energy, enhancing their therapeutic properties. Research aims to identify the best agents for PTT and synergistic therapies like PDT, gene therapy, radio therapy, chemotherapy, and immunotherapy. PTT is beneficial for eradicating primary tumors or lymphatic metastases in superficial tissues. However, the penetration depth of nearinfrared light is limited. To improve cancer treatment, PTT must be integrated with other therapies. Near-infraed-II materials, with higher PCE potential and radiation limits, offer better tissue penetration. Although contrast-enhanced PTT is still under investigation, non-contrast PTT medical devices show promise. Clinical trials continue to explore laser ablation systems without external contrast agents, focusing on practical applications and integration into cancer treatment.

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Jalaniy V: Writing-review and editing, Validation.

#### **CONFLICT OF INTERESTS**

The authors declare that there are no conflicts of interest in this article.

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