Nanomaterials-assisted photothermal therapy for breast cancer: State-of-the-art advances and future perspectives


Published in:
Photodiagnosis and Photodynamic Therapy

Document Version:
Publisher's PDF, also known as Version of record
Nanomaterials-assisted photothermal therapy for breast cancer: State-of-the-art advances and future perspectives

Sagnik Nag\textsuperscript{a,b,c,1}, Oishi Mitra\textsuperscript{a,b,1}, Garima Tripathi\textsuperscript{a}, Israrahmed Adur\textsuperscript{a}, Sourav Mohanto\textsuperscript{d}, Muskan Nama\textsuperscript{a}, Souvik Samanta\textsuperscript{a}, B.H. Jaswanth Gowda\textsuperscript{d,c}, Vetriselvan Subramaniyan\textsuperscript{c,2}, Vino Sundararajan\textsuperscript{b,1}, Vinoth Kumarasamy\textsuperscript{1,2}

\textsuperscript{a} Department of Bio-Sciences, School of Bio-Sciences & Technology, Vellore Institute of Technology, Vellore 632014, Tamil Nadu, India
\textsuperscript{b} Pharmacology Unit, Jeffrey Cheah School of Medicine and Health Sciences (JCSMHS), Monash University Malaysia, Bandar Sunway 47500 Selangor Darul Ehsan, Malaysia
\textsuperscript{c} School of Pharmacy,Queen’s University Belfast, 97 Lisburn Road, Belfast BT9 7BL, United Kingdom
\textsuperscript{d} Department of Parasitology and Medical Entomology, Faculty of Medicine, Universiti Kebangsaan Malaysia, Jalan Yaacob Latif, 56000 Cheras, Kuala Lumpur, Malaysia

** Corresponding author.
* Corresponding authors.
** Corresponding author.
\textsuperscript{1} E-mail addresses: sagniknag234@gmail.com (S. Nag), subramaniyan.vetriselvan@monash.edu (V. Subramaniyan), svino@vit.ac.in (V. Sundararajan), vinoth@ukm.edu.my (V. Kumarasamy).
\textsuperscript{2} Equally contributing authors.

** Abbreviations:** BC, breast cancer; WHO, world health organization; CT, chemotherapy; PTT, photothermal therapy; PTN, photothermal nanotherapeutics; PDT, photodynamic therapy; RT, radiotherapy; FDA, food and drug administration; LSPR, localized surface plasmon resonance; PTEN, phosphatase and TENsin homolog; NF-\textsuperscript{B}, nuclear factor kappa B; pFAK, phosphorylated focal adhesion kinase; NIR, near-infrared; NPs, nanoparticles; IGD, immunogenic cell death; HOMO-LUMO, highest occupied molecular orbital- lowest unoccupied molecular orbital.; TNBC, triple-negative breast cancer; EGFR, epidermal growth factor receptor; ROS, reactive oxygen species; HSP, heat shock protein; Au@SiO\textsubscript{2}, amorphous silicon di-oxide; MTX, methotrexate; FA, folic acid; SWCNTs, single-walled carbon nanotubes; ANXAX5, annexin A5; CTLA, cytotoxic T-lymphocyte-associated; MWCNTs, multi-walled carbon nanotubes; PCE, photothermal conversion efficiency; EPR, enhanced permeability and retention; ICG, indocyanine green; AuNPs, gold nanoparticles; CDT, chemodynamic therapy; PINAs, polymer-inorganic nanoparticle assemblies; CMCINPs, cell membrane-camouflaged inorganic nanoparticles; HPD, hematoporphyrin derivative; TPF-G-FF, peptide–porphyrin conjugate; GNRs, gold nanorods; DOX, doxorubicin; MSNs, mesoporous silica nanoparticles.

\textsuperscript{1} Corresponding authors.
\textsuperscript{2} Corresponding author.

\textsuperscript{1} E-mail addresses: sagniknag234@gmail.com (S. Nag), subramaniyan.vetriselvan@monash.edu (V. Subramaniyan), svino@vit.ac.in (V. Sundararajan), vinoth@ukm.edu.my (V. Kumarasamy).

\textsuperscript{2} Equally contributing authors.

\textbf{ABSTRACT}

Breast cancer (BC) remains an enigmatic fatal modality ubiquitously prevalent in different parts of the world. Contemporary medicines face severe challenges in remediating and healing breast cancer. Due to its spatial specificity and nominal invasive therapeutic regime, photothermal therapy (PTT) has attracted much scientific attention down the lane. PTT utilizes a near-infrared (NIR) light source to irradiate the tumor target intravenously or non-invasively, which is converted into heat energy over an optical fibre. Dynamic progress in nanomaterial synthesis was achieved with specialized visual, physicochemical, biological, and pharmacological features to make up for the inadequacies and expand the horizon of PTT. Numerous nanomaterials have substantial NIR absorption and can function as efficient photothermal transducers. It is achievable to limit the wavelength range of an absorbance peak for specific nanomaterials by manipulating their synthesis, enhancing the precision and quality of PTT. Along the same lines, various nanomaterials are conjugated with a wide range of surface-modifying chemicals, including polymers and antibodies, which may modify the persistence of the nanomaterial and diminish toxicity concerns. In this article, we tend to put forth specific insights and fundamental conceptualizations on pre-existing PTT and its advances upon conjugation with different biocompatible nanomaterials working in synergy to combat breast cancer, encompassing several strategies like immunotherapy, chemotherapy, photodynamic therapy, and radiotherapy coupled with PTT. Additionally, the role or mechanisms of nanoparticles, as well as possible alternatives to PTT, are summarized as a distinctive integral aspect in this article.

\textbf{ARTICLE INFO}

\textbf{Keywords:}
Cancer
Breast cancer
Photothermal therapy
Near-infrared
Nanomaterials
Nanoparticles
1. Introduction

Breast cancer (BC) is a relatively frequent malignancy that annually concerns approximately 2 to 2.5 million females worldwide [1]. BC is the uncontrollable development and proliferation of the cells that arise from the breast and surrounding tissues [2,3], combination of various subtypes, each of which is characterized by a wide range of clinical consequences. A focused approach to cancer prevention and treatment requires a detailed understanding of this variability [4]. In accordance with World Health Organization (WHO) estimates, 170,000 women in India are anticipated to be associated with BC, which turns out to be 14% more than the country’s overall cancer incidence [1]. Despite significant advances in understanding the molecular pathways that drive malignancy and the introduction of molecular-based therapies, BC remains highly prevalent and lethal globally [5]. Premature BC is typically treated with a lumpectomy, partial or complete mastectomy, radiotherapy, as well as other kinds of adjuvant therapies, notably cytotoxic chemotherapy (CT), and immunotherapy, which are significantly associated with adversities, toxicities, and damage to healthy cells [5].

Photothermal therapy (PTT) has significant potential in treating tumors that utilize heat generated from light-absorbing agents to destroy cancer cells [6]. Thermal ablation is a nominally invasive technique for curing BC, as PTT utilizes laser radiation and heat generation around the site where the tumor is located [7]. PTT can significantly intensify treatment efficacy and diminish adverse effects when utilized with other conventional cancer treatments and not solely [8]. PTTs are entirely predicated on laser devices, by which endogenous tissue chromophores can be smoothly enhanced, and erosion of thermal tissue is accomplished. There is an obvious need for advanced diagnostic techniques and novel, efficient therapies with fewer adverse effects [9].

With the dawn of advances in material sciences and the subsequent advent of novel nanoscale biomedical materials, modern technological and engineering advancements have vastly enabled the integration of nanotechnology in medicine, owing to its remarkable physicochemical properties [10]. Cancer-targeted nanotechnology notably has put forth phenomenal strategies for the early detection, diagnosis, and treatment of the disease with lower toxicity and improved efficacy over conventional cancer treatments [11–16]. Along the same lines, nanotechnology can produce resources that humans manufacture at the nanoscale level, which is also the scale at which cellular and biological events occur [17–19]. The critical perspective of cancer nanotechnology is the ability to develop nano vehicles with various molecules that, due to their minute size, can specifically penetrate tumors with minimal associated risks [20]. The PTT approach to combat BC has been given new insight by nanotechnology. Several researchers are experimenting with different nanomaterials and nanostructures using near-infrared region (NIR) light absorption owing to their unique ability to target and penetrate malignant tissue, enhancing the efficacy of PTT and further coupling it with other therapies [21]. It is crucial to acknowledge that treating cancer is extremely challenging and requires the conjugation of different therapies and nanotechnology to combat the tumor [22]. Nanoparticles that strongly possess the ability to absorb light and aid in improving the rate of transforming light to heat can selectively destroy tumors by causing hyperthermia in the malignant cells [23]. Numerous photothermal nanotherapeutics (PTN) have been widely researched until now, i.e., noble polymeric nanomaterials, carbon-based nanoparticles, metal and metal oxide nanomaterials, and organic and inorganic nanoparticles [24]. The fact that nanoparticles can aggregate in malignant sites and have a high permittivity and longevity contributes to their increasing effectiveness in PTT [8,13,25].

The latest investigations [8,26–30] discuss the utilization of diverse nanoparticles in PTT for the treatment of BC. The recent literature has examined the distinct category of nanoparticles or provided an overview of the different forms of nanoparticles, but without elucidating the significance of nanomaterials in BC therapy. This article explores the potential usage of various nanoscale materials in association with PTT and enduring advantages of their diverse physicochemical properties. Furthermore, this review precisely focuses on the portion that discusses the intent and usage of nanoparticles, as well as explaining the mechanism of PTT in the treatment of BC. The article explored numerous aspects of nano-conjugated PTT regimens, including photodynamic therapy (PDT), chemotherapy (CT), radiation therapy (RT), and immunotherapy (summarized in Fig. 1), further addressing the cellular toxicities, side effects, and safety concerns associated with nanomaterials and PTT. This study provides a comprehensive analysis of the potential applications of nanomaterials in combination therapies, with a focus on their prospects in clinical settings.

2. Rise in Nanomaterials for targeting Breast Cancer (BC)

BC is enlisted as one of the most fatal cancers, having a high mortality rate in women, continually raising concern about the upsurging burden on the healthcare sector. Different multimodality therapies are frequently used in the treatment of BC [31]. The effective treatment for BC, especially in advanced stages, is crucial for the well-being of BC patients. Cancer nanomedicine, an integrative field focused on the design and therapeutic applications of materials and technological advances at the nanoscale, has significantly advanced the evolution of cancer treatment over the past few years [32]. Conventional therapies, such as radiotherapy, surgical procedures, bone marrow transplant, and a combination of these therapies [33–35], pose a challenge to a smooth therapeutic intervention. Particularly considering the tumor cells, increasing chemoresistance associated with these treatments and the unchecked metastases cascades of incursion, intravasation, flow, exudation, and settlement also add to the array of challenges [36]. Evidently, each approach has certain drawbacks, including intrusiveness, lower solubility of medicine, inadequate chemotherapeutic blood circulation, cross-resistance, precise attacking, and systemic and local off-target adverse effects [37–39]. In order to overcome such limitations, several nanomaterial-based therapeutic agents, including biogenic nanoparticles, inorganic nanoparticles, carbon-based nanoparticles, polymeric nanoparticles, LSPR-based nanoparticles, metallic nanoparticles, and stimuli-responsive smart nanoparticles, have acquired approval from the Food and Drug Administration (FDA) [40]. These nanosystems have efficient roles like defending the initial dissolution of the medicines, augmenting the drug absorption into a chosen tissue, regulating the pharmacokinetics and dispersion of drugs into the tissue, increasing cellular absorption, ceasing drugs from interacting with the biotic ecosystem too soon, and lessen toxicity in the body [41].

Biogenic nanoparticles, including liposomes, have advantageous roles like biocompatibility, effective drug entrapment, size control, and simplicity in derivatization. The possibility of developing versatile, liposome-based nanoparticles with improved tumor site attacking arises from the simplicity of surface alterations [42,43], whereas the ability to encapsulate non-polar, water-soluble, and amphiphilic molecules, biodegradability, targeted and regulated pH-dependent controlled emission of bioactive fats are the characteristic roles played by cubosomes and polymeric nanoparticles [44,45]. Along the same lines, exosomes can cross cell membranes, regulate therapeutic agents, i.e., proteins or entrapped nucleic acids, and deliver contents at the target location for BC management [46]. Correspondingly, dendrimers have demonstrated a beneficial role in the nanosystems due to their effortless conjugation with targeting molecules, high water solubility, biodegradability, and compatibility [47].

Nanoparticles of gold are among the most stable metallic/ localized surface plasmon resonance (LSPR)-based nanoparticles that are readily surface-functionalized for molecular conjugation since they demonstrate enhanced binding abilities and strive at specificity improved targeting, quick transfer kinetics, lengthy half-life, size-enhanced tumor uptake, and biocompatibility with various targeting clusters [48,49]. Magnetic nanoparticles possess advanced imaging, therapeutic, and biocompatibility properties. The coating of polyarabic acid makes it
easier for BC cells to internalize and penetrate cell membranes. Additionally, the loading of the CT drug can be reversed [50]. A study attempted by Basu et al. to fabricate a novel nanosystem of metformin implanted with hyaluronic acid has shown that the combination has higher anticancer efficacy at lower doses. This nanosystem targets the microRNA-10b/ Phosphatase and TEnSin homolog (PTEN) axis via nuclear factor kappa B (NF-κB)-p65, causing cell death and hindering cell movement in triple-negative BC cells [51]. Additionally, it was uncovered that the treatment hinders cell migration by suppressing phosphorylated Focal Adhesion Kinase (pFAK) /integrin-1 expression, preventing the switchover of epithelial-mesenchymal cells, raising epithelial-cadherin expression, preventing the development of mammospheres, reducing the expression of stemness markers, and neutralizing the carcinogenicity the tumor had caused in nearby organs [52]. As a result, the utilization of these tumor-targeting nanosystems leads to the accumulation of drugs at the target location, intrusion in tumor cells, and augmented clinical benefit, increasing anticancerous activity against tumor tissues while minimizing toxicity in healthy tissues [53].

3. Mechanism of Photothermal Therapy (PTT) in Breast Cancer (BC)

The term "photothermal effect" refers to the heating of material due to the absorption of light of characteristic wavelength, especially in the near-infrared regions [54,55]. PTT has been investigated as a highly precise and less invasive cancer treatment technique, which uses PTT agents to destroy tumors by getting adequate hyperthermia (42 °C) under laser irradiation of near-infrared (NIR) light in the 700–1100 nm range [56,57]. Immunotherapy, radiation, CT, molecular-targeted therapy, and other anti-tumor therapies have too many systemic adverse effects, including long-term organ function degradation and significant immune system damage. Metal nanoparticles (NPs), especially gold, have been evidenced to be excellent PTT agents owing to their exceptional light absorption efficiency. Irradiation with electromagnetic waves causes coherent excitation of electrons in the NPs, which quickly return to the ground, generating heat. This heat energy generated is strong enough to lyse targeted cancerous cells [58,59]. PTT can efficiently induce immunogenic cell death (ICD) and switch on the autophagy button in tumor cells, thus enhancing immunogenicity [60,61].

The three main categories of photothermal conversion mechanisms are (a) Localized heating due to surface plasmon resonance, (b) Generation and relaxation of electron-hole pair, and (c) Highest occupied molecular orbital-lowest unoccupied molecular orbital (HOMO-LUMO) transition contributing to lattice vibration. These interactions between light and matter in different kinds of material are related to their bandgap structures and electronic configuration [62]. Metallic NPs, particularly those of gold and silver origin, have gained immense interest in a wide range of technology due to their characteristic interaction with visible and NIR light regions [63,64]. The property of heating by photothermal nanoparticles lies in their inherent characteristic of LSPR [65], further depicted via Fig. 2. The LSPR originates due to the excitation of free electrons on the metallic surface upon interaction with the light of an appropriate wavelength. At the same time, the electrons in the conduction bands oscillate collectively at the same frequency, providing elevation to the resonance [66]. The excited electrons in LSPR can bring themselves back to ground states by two distinct decaying processes: one is radiative decay that contributes to the plasmonic enhancement of the electric field, and the other is non-radiative decay characterized by intra-band and inter-band transitions giving rise to high energy electron that participates in particle heating. These are the basic principles of generating a photothermal effect by the different nanostructures of metallic origin, further illustrated in Fig. 2. One of the significant advantages of the photothermal effect imparted by nanomaterials is confining the thermal modulation within a nanoscale region instead of a broad area affected by heat generation [67,68].

Semiconductors are materials where electron-hole pairs are created and recombined in a typical manner [69]. The semiconductor materials absorb photons to create active electron-hole pairs when exposed to light with an energy ≥ band gap. In the conduction band, photoexcitation creates electrons; subsequently, in the valence band, it creates holes, i.e., a state of electron deficiency. Following the higher excited states, relaxation can occur radiatively or non-radiatively in photons or phonons, respectively [70]. Heat is generated when carriers transfer a part of the energy to the crystal lattice in the latter. As a result, the lattice’s thermal (vibrational) energy increases, resulting in a temperature rise [70]. Thus, a temperature distribution depends on light absorption and nonradiative bulk/surface recombination. The

![Fig. 1. Illustrative depiction of different nano-conjugated PTT approaches used in the current scenario. Primary conjugations involve radiotherapy (RT), photodynamic therapy (PDT), immunotherapy, and chemotherapy (CT); leading to efficient tumor degradation and ablation.](image-url)
The photothermal effect thus can be defined as forming a temperature distribution in the material charge by carrier diffusion and recombination [70,71]. Due to their powerful light-absorbing capabilities and capacity to convert photons into heat via lattice vibrations, carbon and other polymer-based materials have become the major research topic for their potential use as photothermal materials [72]. In such materials, \( \pi \) to \( \pi^* \) orbital transition is achieved by less input of energy as the electrons are held loosely in \( \pi \) bonds. The \( \pi-\pi \) or \( \sigma-\pi \) (conjugation) and \( \sigma-\pi^* \) (hyper conjugation) property contribute to \( \pi \rightarrow \pi^* \) transition when absorbing NIR light of appropriate wavelength. The excited electrons in \( \pi^* \) orbital in turn transit back to ground level by releasing the energy in the form of heat [73]. According to the principle of HOMO to LUMO transition, an electron in the ground state is promoted to an excited state (high energy) on the absorption of specific energy from the irradiating light that corresponds to a particular transitional energy gap [74,75]. The electron-phonon coupling mediates the transition from higher energy levels to lower energy. This relaxation process results in a rise in the temperature of the material because the energy obtained is transferred from the electrons in a higher excited state to the vibrational modes inside the lattices of atoms imparting the photothermal effects [76], further summarized in Fig. 3.

In a study by Zhang et al. demonstrated that triple-negative breast cancer (TNBC) can be treated using anti-epidermal growth factor receptor-antibody conjugated-gold nanorods combined NIR-PTT (anti-EFGR-GNs NIR-PTT). The mechanism is that anti-EGFR antibody causes autophagy in TNB cancer cells by inducing the class III PI3K/beclin pathway and inhibiting the class I PI3K/AKT/mTOR pathway. The GNs activated oxidative stress response genes and resulted in the generation of reactive oxygen species (ROS) and, subsequently, oxidative damage to the tumor cells. Moreover, treatment with anti-EFGR-GNs also resulted in upregulation of autophagy-related gene 5 (Atg5), degradation of p62, and enhanced conversion of microtubule-associated protein light chain 3-II (LC3-II), indicating autophagosome accumulation. In this investigation, NIR light at 1.5 W/cm\(^2\) was applied for 3 min to the anti-EGFR-GNs solutions, raising the temperature to 43\(^\circ\)C [77]. BC can be treated with the help of Cantharidin-Tellurium (CTD-Te) NP-induced PTT as Cantharidin inhibits the anti-apoptotic activity of heat shock protein (HSP70), and Te acts as the PTT photosensitizer. Formulating and designing this combined therapy utilizes heat shock proteins to prevent hyperthermia in eukaryotic cells. After receiving near-infrared laser irradiation, the temperature of CTD-Te NP quickly rose to 43.5\(^\circ\)C, which is high enough to cause cell membrane rupture and drug release. This

---

**Fig. 2.** Mechanistic illustration of NIR excitation of LSPR-based nanoparticles to generate photothermal phenomena using phonon-phonon coupling and rapid cooling.

**Fig. 3.** Different mechanisms of photothermal heat generation (A) Production of electron-holes and semiconductor relaxation mechanism (B) Illustration exhibiting HUMO-LUMO excitation and subsequent lattice vibration.
demonstrates that the NPs successfully exhibit hyperthermia-responsive release behavior. The combination therapy further resulted in up to 91.87 % cell death in 4T1 cells in the cytotoxicity assessment [78].

In another investigation, Dheyab et al. formulated a novel NP by sonication technique with Au-NPs as the shell and Fe3O4 NPs as the core. According to the findings of this work, after being illuminated with an 808 nm laser (200 mW, 10 min), the viability of MCF-7 cells treated with Au-Fe3O4 NPs was significantly reduced (73.9 % at 50 gFe/ml) [79]. In addition, Agabeig et al. designed yet another novel NP, amorphous silicon di-oxide (Au@SiO2) loaded with Methotrexate (MTX) and Folic acid (FA). This synergistic chemo-PTT with MTX and FA-loaded Au@SiO2 NPs showed a statistically significant increase in cytotoxicity and apoptosis of BC cell lines [80]. A vivid literature survey has also revealed that the photothermal-responsive technology can work with a laser to release local drugs while simultaneously inducing hyperthermia to lyse cancer cells in the area [81,82]. To increase the hyperthermia effect, Jia et al. have introduced a novel bimetal NP. The novel bimetallic mesoporous Dox loaded Pt-Pd-PEG FA-NP has not only been highly efficient against MCF-7 cell lines/tumors but also came up with high biocompatibility, Photoacoustic (PA) imaging, PTT, and high drug loading capacity [83]. Various inorganic semiconductor-based nanoparticles often have low biocompatibility and can cause side effects [7,17]. This adversity has been overcome by introducing endogenous materials such as nanoparticles (NPs), which are highly accepted in medicine. Melanin is one such endogenous material used in the formulation of NPs named M-NPs. M-NPs, being naturally black, absorb UV–visible wavelength of any range and have a high photothermal conversion when irradiated with 808 nm NIR light. PTT-induced ICD and other immunoblocking inhibitors prevent tumor immune escape and strengthen the anticancer immune response. Increased levels of CD8+ T lymphocytes and cytokines are produced due to this integrated approach based on natural M- NPs, ultimately leading to the successful treatment of primary and abscopal BCs [84].

Using PTT, single-walled carbon nanotubes (SWCNTs) specifically targeted, immunostimulation, and a checkpoint inhibitor, McKerman et al. have demonstrated a novel method of treating metastatic BC. They discovered that selective NIR photothermal ablation of primary orthotopic EMT6 breast tumors in syngeneic BALB/c mice, using an annexin A5 (ANXAX5) functionalized SWCNT biocongjugate, synergistically enhances an anti-cytotoxic T-lymphocyte-associated protein 4 (anti-CTLA-4)-dependent abscopal effect, leading to increased survival of 55 % at 100 days after tumor inoculation [85]. In a study conducted by Mohammad et al. multi-walled Carbon nanotubes (MWCNTs), which could increase their efficacy in treating cancer by PTT, were made using Au-NPs. The MWCNTs manufactured from walnut shells were examined using transmission electron microscopy (TEM), field-emission scanning electron microscopy (FESEM), atomic force microscopy (AFM), and Fourier-transform infrared spectroscopy (FTIR). On the BC cell line (i.e., MCF7), the effects of MWCNT-COOAu, MWCNT-COO, and MWCNT-Au at different doses (3.12, 6.25, 12.5, and 25 g/ml) and irradiation time intervals (30, 60, 90, and 120 s) were examined at 44.1 °C, demonstrated maximum temperature for MWCNT-COO, MWCNT-COOAu, and MWCNT-Au [86].

4. Different Photothermal Agents used in Breast Cancer Therapy

Photothermal agents are utilized in various PTT, including in combination with RT, immunotherapy, and CT for BC treatments [9]. An ideal photothermal agent should be able to target tumor cells and show a good amount of photothermal conversion efficiency (PCE) without exhibiting any spectral differences in the absorption bands from the chromophores while interacting In vivo [87]. The exhaustive ongoing research on PTTs has led to the development of various photothermal agents with varied degrees of targeting capability and enhanced permeability. There is a growth of nano-grade agents or nanohybrids in this realm, as it has an enhanced permeability and retention (EPR) effect that facilitates the easy targeting of the tumor cells [88]. Research is ongoing to develop nano-sized photothermal agents with enhanced PCE for different therapeutic applications and functions. However, photothermal agents are divided into various types based on their origin and function [89].

4.1. Organic dyes

The primary instances of organic compounds used in PTT for tumor diagnosis or treatment were first seen in the research conducted by Daimond and his colleagues [90]. Organic infrared dyes act as photothermal agents, exhibiting a robust absorption spectrum in the near-infrared region [91]. Significantly, the cyanine dyes exhibit sustainable amounts of biocompatibility and efficient phototherapy and imaging properties. IRReye800CW is a well-known analog of indocyanine green (ICG) dye, which has been used again in photo theranostics related to BC treatment [92]. The Indocyanine green (ICG), in combination with nanosystems, assisted in the organized development of targeted probes based on ICG complexes with conventional cancer therapies like daclizumab, trastuzumab, or panitumumab. In the case of BC, they are seen to interact with the HER1 and HER2 receptors and thus help in the diagnosis and treatment [93]. A recent study has demonstrated the working of lipo-polymeric nano-systems (DPDC)-AuNPs with the incorporation of IR780 dye. This system has shown a remarkable plasmon-enhanced fluorescence, alongside its novel property of inducing apoptotic cell death and increment of intracellular ROS, when tested with BC cells [94].

4.2. Nanoparticles and hybrid-based systems

4.2.1. Organic and in-organic nanoparticles

Organic photothermal agents are one of the primary agents used to destroy tumor cells and control metastasis. Functionalized organic nanoparticles have overcome the limitations of the non-specificity of the photosensitizers used conventionally in PTT and PDT. Organic liposomal nanoparticle composites with an inorganic core can be used for PTT for simultaneous and effective drug delivery of chemotherapeutic drugs [95]. Zeolitic imidazolate framework-8-capped Cu2XSe nanocomposites are developed for chemodynamic therapy (CDT) and PTT treatment of malignant BC bone tumors. Hyperthermia from PTT enhances the anti-tumorigenic effect of CDT [96]. Graphene oxide-magnetic (GO-Fe3O4) nanoparticles exhibit a high penetration power in carcinoma tumor cells [97]. They show better ROS production when irradiated with an infrared laser at 450 nm. Recent studies show that mitochondria-targeted organic nanoparticles (M-TD1 NPs) act as efficient photothermal agents by increasing the photothermal ablation of the BC cells, with simultaneous inhibition of the metastasis pathway [98].

Inorganic nanoparticles usually consist of an inner core and an outer shell that has been functionally modified [99]. The core consists of metals, quantum dots, or dyes, whereas the outer shell consists of polymeric composites. However, the inner core is responsible for the nanomaterials’ fluorescence, electromagnetic, and optical properties [100]. These attributes make the inorganic nanoparticles promising photothermal agents. Polymer-inorganic nanoparticle assemblies (PINAs) show synergistic effective properties for cancer therapy and imaging. The modulation of these nano-assemblies has been seen in photothermal imaging and magnetic resonance imaging; however, their therapeutic effects are explored by their effectiveness in PDT and drug delivery systems [101]. Recent research has shown the prominence of cell membrane-camouflaged inorganic nanoparticles (CMCNP), inspired by biomimicry techniques and promising results when combined with photodynamic and PTT. These inorganic nanoparticles can help deliver targeted drugs and extravasate toxic substances from the bloodstream [102]. Upconversion nanoparticles (UCNPs), with Ce6 PS and SiO2 (T-UCNPs@Ce6@mSiO2), are also further utilized for HER2
cell active targeting and PDT treatment on BC cells [103].

4.2.2. Metal and metal oxides nanoparticles

Metal and inorganic-based nanoparticles exhibit a more profound role in the modulation of intrinsic optical properties and show high photostability and efficiency [104]. Gold nanomaterials exhibit highly localized surface plasmon resonance and narrow emission spectrum, which can be utilized for surface modification and modulation of therapeutic properties [105]. Iron oxide-palladium (Fe$_4$Pd) Janus NPs have also amplified hyperthermic effects and enhanced ROS generation, which has been tested to be effective in BC treatment [106]. Further laser irradiation under a magnetic field can help enhance the function of the metal nanoparticles. Mesoporous platinum nanoparticles, synthesized using Pluronic F127, are surface-modified with polyethylene glycol (PEG) and loaded with doxorubicin (DOX). These nanoparticles show an increase of 84% efficiency in anti-cancer therapy, along with combinational therapy of photothermal and CT [107].

Gold nanoparticles (AuNPs) possess various properties, i.e., low toxicity, size tunability and biocompatibility which make it a prime fit as a drug carrier. They are being used in various biomedical application and theranostic techniques. Biosynthesized AuNPs are found to be more promising than chemically synthesized AuNPs with comprehensible anticancer property especially against BC cell line MDA-MB-231. Various plant extracts are being experimented for the rapid and stable biological synthesis of gold nanoparticles. One of the most researched involve mushroom extract [108]. Several *in vivo* and *in vitro* characterizations were done to ensure the physicochemical properties of the nanoparticles that were synthesised. The comprehensible structure and significant biological properties, make it an ideal topic for nanomedicine. The monodisperse AuNPs have different surface modifications and room for further functionalization [108,109]. This positions it as a highly promising instrument for both treatments and diagnostics, paving the way for broader applications in the medical field. Among the myriad applications of AuNPs, one of the most pivotal is their role in targeted drug delivery and localized hyperthermia for cancer tissues. Additionally, the exceptional optical properties exhibited by well-dispersed nanoparticles make them valuable as contrast agents in diverse optical imaging modalities, including CT and MRI. Ongoing research endeavors are actively exploring the mechanisms of cancer cell death contingent upon the presence and interaction with AuNPs [108,109].

4.2.3. Polymeric nanoparticles

Various polymers have been utilized as PTTs, either by getting incorporated into nanomaterials or by poised modifications in the given tumor environment. Polymers incorporating melanin polyphenol polymer-based agents act well in PTT and exhibit high biocompatibility and biodegradability. They show positive results in immunotherapy against BC and an excellent growing field of research that can be solely done to achieve the anticancer and antitumorigenic synergistic effects. Polymeric nanomaterials are a new realm of study for their multivariate nature and effect on tumor cells. One of the recent studies has confirmed the tetra(4-carboxyphenyl) porphine (TCPP) and isoliensine (Iso) encapsulated in PEG-b-PLGA polymer have resulted in the formation of polymeric nanomaterials with an astounding nature of drug delivery and anti-cancer property [110]. Several reports have shown how the drug targets the molecular signaling associated with BC developments. pH-sensitive photosensitizer-core copolymer, PDCZP, was entrapped with a hydrophobic derivative of ICG to form nanocarriers for anti-tumorigenic effects on BC melanoma cells [88]. Furthermore, injection of the polymeric nanocarrier resulted in increased cell apoptosis and inhibition of neovascularisation, demonstrating a positive photothermal effect [111].

4.2.4. Smart nanomaterials

In the world of cancer treatment, a silent revolution is underway, one that wields the power of nanotechnology to bring forth unprecedented precision and efficacy. Smart nanomaterials are revolutionary nanocarriers that show different sensitivities to temperature, pH, salinity, light, and other physical/chemical/biological parameters. At the heart of this revolution lie smart nanomaterials with stimuli-responsive behavior, poised to transform the landscape of therapies such as photothermal treatment. They have a unique structure and photothermal capabilities, which make them ideal tools for tumor treatments. Smart photosensitizers can be used for the enhancement of the conjugational therapies on the MCF-7 BC cells, along with gold nanoparticles [112]. Doxorubicin along with this therapy shows a synergistic effect on the tumor cells with the ability to ablate it up to 99.99 %. pH and photosensitive smart nanocarriers are used for photothermal starvation therapy in which iron nanoparticles, chemically attached to the glucose oxidase, are being used [113]. Photothermal and pH and photothermal sensitive chemotherapeutic nanoparticles are encapsulated in nano drug formulated platelets. They help in targeted drug delivery and photothermal agents are used for tracking the smart platelets nanodevices [114]. According to a study conducted by Howaili et al. Curcuma-loaded silver nanoparticle-based Chitosan-Poly(N-isopropylacrylamide) (PNIPAM) smart nanogel displayed 72 h sustained drug release with high efficacious response to temperature and pH gradient stimulation, thus eliciting PTT-CT response at 808 nm NIR irradiation. The *in vitro* evaluation against the MDA-MB-231 BC cell line revealed the endosomal internalisation of the smart nanogel composite [115]. Another prospective study conducted by Xu et al. revealed the triple stimuli guided behavior of gold nanorods conjugated with Glutathione-Hyaluronic acid for PDT-PTT regimen against MCF-7 cell lines with circulation half-life of 1.9 h and tumor tissue accumulation rate only as 12.8 % [116]. These smart materials can target cancer cells with unprecedented accuracy, optimize heat generation, reduce side effects, and allow for real-time monitoring of the treatment’s progress. As the boundaries of this field continue to expand, customization and combination therapies are becoming the norm, shaping a future where cancer treatment is as unique as the patient it serves [117,118] (Fig. 4). Furthermore, Table 1 represented various advanced categories of photothermal agents utilized in synergy with nanomaterials for BC treatment and diagnosis.

5. Different approaches of Photothermal associated Combinatorial Therapies in Breast Cancer

5.1. Photothermal therapy (PTT) in conjunction with photodynamic therapy (PDT)

The combinatorial approach of PTT and PDT is one of the most...
The enhanced property of this combination is preferred widely in the clinical setup and has been extensively studied realms. The enhanced property of this combinational therapy has been noticed with simultaneous excitation of near-infrared (NIR) laser [141]. PTT generates the heat from the nanoparticles required for the ablation of tumor growth, whereas PDT induces the formation of ROS and the growth of anti-tumorigenic factors. This combination is preferred widely in the clinical setup and has been comprehended for its minimal side effects and positive outcomes [121]. PTT corresponds to the photosensitive agent (PS). The anti-cancer effect of PDT is explored when the nano-grade interaction of the electric field is used to produce ROS, thereby aggravating cytotoxicity and reducing the half-life of tumor cells. These PS agents are of 3 primary kinds—(a) hematoporphyrin derivative (HPD): It is highly specific to tumor growth in breast, lung, and oesophageal carcinoma conditions [131], (b) benzene porphyrin, metal phthalocyanine, chlorophyll degrading agents have a stable structure, photosensitive ability, and a good curative effect [132], (c) growth factor receptor, magnetic and heat therapy, multifunctional photosensitizer [133]. Experiments have proven that organic molecules and PTT/PDT combinational therapy are one of the most ground-breaking setups for anti-cancer therapy. Supramolecular organic compounds with amphiphilic properties were more advantageous as they demonstrated better compatibility, endurance, and quick electron transfer. Mass accumulation and photosensitization were more efficient in small organic molecules [134].

Recent studies have demonstrated that the peptide–porphyrin conjugate (TPP-G-FF) nanodots can be used in photothermal and photodynamic combinational therapy for imaging and efficient In vivo and In vitro antitumor therapy [135]. Phthalocyanine (Pc) is a molecular dye used as a photosensitizer for photodynamic therapy (PDT), has been modified structurally and used in combinational PDT/PTT, proving to be a promising photo-theranostic agent [136], have been demonstrated in Fig. 5(i). The oxyhemoglobins present in RBC can be used as photosensitizers for PDT, which, combined with indocyanine green, can be used for PTT. They show efficient anti-tumorigenic properties against BC in combination with doxorubicin [137]. An amphiphilic porphyrin compound (TPA-Por nanoparticles), i.e., a combination of porphyrin and triphenylamine, exhibits excellent biocompatibility and can be used in PDT/PDT cancer therapy. This property of the concerned nanoparticle is attributed to its property of the redshift absorption spectrum [138].

In addition, gold nanodots excited up to a wavelength by a light source close to its LSP resonance wavelength, will result in a high-quality PTT effect. This PDT/PTT combination has been proven to be effective in the destruction of cancer cells [139]. Apoptosis induced via mitochondria is an essential segment of modulation during the growth of tumor cells. It has been seen that functionalized black phosphorus nanoscale (BPNGS) based nanosystems show high efficiency in the destruction of tumor cells when treated with combinational PDT/PTT [140]. Smart nanoparticles can now be used with combinational therapy like PTT/PDT/CT to induce rapid oxidative stress in BC tumor cells and control their proliferative property. This area of research has expanded due to the significant rise in BC cases in recent years [141].

### 5.2. Photothermal therapy (PTT) in conjugation with Chemotherapy (CT)

PTT is an effective cancer treatment that targets tumor cells with increased temperature sensitivity while leaving other somatic cells unharmed [142]. PTT typically necessitates direct access to the origin of light irradiation, as the extermination of large tumors is entirely challenging for standard PTT due to the vestigial mass of tumor at the treatment periphery, which not only prevents its assistance against promulgated metastases but also the effectiveness of PTT is restricted by
disparate heat installation and the feeble penetrating power of the laser [143]. Although chemotherapy is still a renowned method for cancer treatment and is immensely potent even when small doses are administered, it presents several obstacles, including vague delivery of the drug, heedless consequences, uneasiness to the patient, and complications in preserving the pertinent concentration of the drug [144]. Due to these drawbacks, an amalgamation of PTT with chemotherapy has come into existence by eliciting regionalized heat to the targeted sites and proffering anticancer drugs concomitantly. It is among the most enticing methods that proffer synergistic effects by reducing adverse consequences and boosting the effectiveness of cytotoxicity [145]. A novel drug delivery method involves using light-responsive fibers containing drug monomers. These fibers are then delivered to the target site using nano scaffolds. The enclosed drug monomers are released upon exposure to NIR rays, while the heat generated in the area effectively eliminates the tumor cells [146].

A novel functionalized niosome-based research was conducted by Khakbaz et al. Niosomes are vesicular formations made of zwitterionic detergents with tremendous potential as transporters in systems for delivering genes and drugs [147]. Numerous therapeutic agents, including photothermal agents, can be incorporated into these thermo-sensitive niosomes (TS-nio) as freight for specific multifunctional therapy to improve treatment efficacy while lowering drug dosage and adverse effects [148]. These niosomes have been structured with DOX serving as a cancer medication and carbon quantum dots (CQDs) serving as a photothermal agent. The formulation of the customized TS-nio was focused on adding phospholipids to a standard composition of niosome and adding folic acid to the top coating. Owing to the pre-loaded CQDs, niosomes exhibited photothermal action and controlled release of drugs by NIR. As a result, when MDA-MB-231 cells were treated with this remarkable PTT-chemotherapy, the cancerous cells ablated to the extent of 90% [149]. Another potential treatment was formulated by Yang et al. by utilizing gold nanorods (GNRs) linked with the drug. These nanorods consist of a positively charged ligand, responsible for increasing the solubility of nanoparticles in water and a site of drug linked with the water for hydrolysis [150]. The GNRs located in target areas emit heat on the specific site due to stimulation by extrinsic light, which kills nearby tumor cells and tissues and speeds up the hydrolytic discharge of drugs due to the increased temperature. Different hydrophobic and hydrophilic drugs can be delivered drug-independent because of functional groups of drugs conjugated GNRs [8].

An innovative MoS$_2$ nanosheet system for combination therapy (PTT-chemo) of BC was reported by Cai et al. In this study, DOX was loaded onto the PDA-coated nanosheets. To create the resultant product, i.e., DOX@Apt-PDA-MoS$_2$ nanosheets, the researchers modified the MoS$_2$ nanosheets using thiolate peptide AS1411 and polyethylene glycol. These modified nanosheets were introduced into MCF-7 breast carcinoma cells. The secretion of DOX from the nanocarriers was accelerated by NIR rays and the acid hydrolases present in the lysosomes of the tumor cells. Thus, the nanosystem synergy of PTT-chemo improved with the help of modified niosomes [151]. Tumor cells can efficaciously capture the exosome 4T1 coated mesoporous silica nanoparticles (MSNs), an invented nanosystem [152], which have been graphically represented via Fig. 5 (ii). These nanoparticles are capable of loading NIR dye (ICG) and DOX (ID@E-MSNs) concomitantly, can facilitate agglomeration of nanoparticles, and have the potential to accumulate in tumor tissue, precluding metastasis and growth. The process enhances drug delivery, which helps eliminate tumors [153]. To respond to the multiple stimuli, the mesoporous carbon nanoparticles (MCN) were used by Zhao et al. due to their high absorption and loading capacity. For developing the combination of PTT-chemo, human serum albumin (HSA) protein was used as a sentinel due to its pertinent molecular structure and biocompatibility by being disulfide-bonded to the porous apertures of MCN. This combination of PTT-chemo with the conjugate drug delivery system shows synergistic effects when exposed
to NIR rays. Based on the bioavailability of DOX, an NIR light can extend the duration of deceleration of DOX in tumor cells. Thus, it is considered the most effective In vivo treatment for 4T1 tumors in rodents [154]. In addition, in recent years, Chai et al. created hollow mesoporous silica nanoparticles that release DOX, which enhances PTT-chemo efficacy against BC [155]. A special type of nanoparticles has been developed that consists of gold nanorods as the core, a composite shell made of hydroxyapatite-doped mesoporous silica, and doxorubicin hydrochloride (DOX-HCl) as the drug inside. The gold nanorods at the core are highly efficient at converting light into heat, while the composite shell provides a means for drug storage. Due to the photothermal behavior of gold nanorods and the magnificent response to the pH of hydroxypatite, a steady and prolonged release of DOX is possible [95]. Through the impacts of intensified permeation and preservation, the modified nanoparticles specifically gather in the tumor and combine the effects of PTT-chemo. Guo et al. used an insightful nanoplatform for drug delivery to accomplish a PTT-chemo. The paramagnetic iron oxide nanoparticles were created and enclosed in Mcl-1-siRNA and DOX. The plasma membrane of the MCF-7 tumor was then applied to the encapsulated nanoparticles, enabling the primed nanosystem to attack MCF-7/ADR cells quickly. The study resulted in the activation of the drug nanocarrier by low pH and NIR laser rays enhanced DOX cytotoxicity on tumor cells, resulting in an 80% reduction in tumor growth [156]. A functionalized system was created for combinational therapy by loading curcumin onto nanographe and polyglycerol (PG). Because of the laser ablation, these primed nanohybrids produce high heat, high drug loading capacity, and endurability. As a result, these nanohybrids proffer the deterioration of MCF-7 cells [157]. Therefore, PTT in conjugation with chemotherapy provides a novel and vast gateway for BC treatment.

5.3. Photothermal therapy (PTT) in conjugation with Immunotherapy

Combination therapy of PTT with immunotherapy has gained prominence due to the limitations of monotherapy. PTT, which uses thermal energy, can contribute to the ablation and degradation of tumor cells. While chemotherapy is commonly used to treat tumors, it cannot guarantee that the tumor will not recur since its growth mechanism is immunologically engineered and can spread to other parts of the body. Immunotherapy can assist by targeting the immunocompromised tumor cells and creating an immune-suppressive tumor environment [158]. Photoimmunotherapy, also known as combinational PTT/immunotherapy, is a targeted treatment that delivers therapy to the affected area of the tumor. This process achieves a high level of tumor-specific targeting and protects the surrounding healthy cells. This therapy, combined with NIR-II radiation, can aid in preventing distant metastasis and disrupt the tumorigenic environment. Nanoparticles enhance and improve the biocompatibility of this therapy when used together [159]. One of the primary studies associated with the PTT/immunotherapy combination was conducted by Fernandez et al. where the application of Prussian blue assemble nanoparticle along with PTT/immunotherapy was studied with a neuroblastoma animal model, which showed prolonged life span and reduction of the tumor, as the therapy progressed [160]. Recent studies have found that photothermal agents like indocyanine green (ICG) and tripeptide sequence are multifunctional nanoparticles for PTT/immunotherapy therapy against BC. This exhibited a successful control of the BC tumor and its consequent side effects [161]. In another study, an amphiphilic molecule (PPhX-PEG8-KVPRQDWSL) with porphyrin was formed with the help of a PEG linker. These contributed to the nanoparticles’ self-assembly, which could be used in the tri-combinational therapy of PTT/PTT/immunotherapy, demonstrated a reduction in ROS levels in the vicinity of malignant melanoma cells [162].

TNBC is a very resistant and malignant form of BC. A multifunctional nanoplatform (CD@PP-CpG) along with PDT/PTT and docetaxel (DTX) -enhanced immunotherapy has been developed by Chen et al. It targets primarily the BC cells and suppresses the cytokine outburst, further described in Fig. 6(i) [163]. In the recent ongoing research by Yang et al. it was seen to be treated with photoimmunotherapy using mesoporous organo-silica nanoparticles (MONs) and Fe3+-loaded MON (MOF). This induced rapid activation of dendritic cells and T cells, further activating the tumor cells’ oxidative damage cascade [101]. One of the most recent developments in this line of research is the multimodal cancer therapy incorporating CRISPR/Cas9 development involving gene therapy, PTT, immunotherapy, and sonic therapy. The future clinical translation of this research can boost the development of individualized cancer therapy and treatment [164]. Recent research and findings show that FNPs/rGO-PEG (Fe3O4 nanoparticles (FNPs) with reduced-graphene oxide (rG0)) nanocomposites have the possibility of being used for magnetic resonance imaging (MRI), which might result in a new cancer treatment approach combining PTT and immunotherapy for metastatic cancers [165]. Treating BC with photothermal immunotherapy has been demonstrated to be effective using a peptide-photosensitizer conjugate (PPC). This PPC comprises a PD-L1 antagonist peptide and the photosensitizer Purpurin-18, which self-assembles into nanospheres. When injected into the body and exposed to laser light, it triggers the immune system to target and destroy cancer cells more effectively [166]. In the later stages of cancer development, laser immunotherapy and PTT have been administered to receive viable results in reducing primary tumors and controlling untreated metastases [167]. In a study by Li et al. photoimmunotherapy in 10 cancer patients of stages 3 and 4 was tested to show a significant reduction in the metastases and related side effects of the combinational therapies [168].

5.4. Photothermal therapy (PTT) in conjugation with Radiotherapy

Due to the low penetration of light, phototherapy as monotherapy is challenging for treating entrenched tumors in the breast. Therefore, PTT conjugated radiotherapy, a common non-virulent, adjuvant, cancer therapeutic approach, came into existence to treat sturdy breast tumors frequently that utilizes ionizing irradiation (i.e., X-rays and gamma rays) of high penetrating power to produce reactive oxygen species through the ionization of cellular components and water [169–171]. When this electromagnetic radiation of high penetrating capacity falls on tumor tissue, it destroys the ingrown breast tumor. The destructive dose of X-rays is reduced by boosting blood circulation and facilitating ROS formation with the high temperature persuaded by PTT [172]. In most instances, platinum, gold, bismuth, silver, gold, gadolinium, and hafnium oxide have been used adeptly as a sensitizer in radiotherapy due to their high atomic number to enhance the effectiveness of radiosensitization, an extrinsic irradiance [173–177]. In addition, new nanostructured Cu-Sb-S nanoparticles, which enhance the radiosensitivity of cancerous cells have also been reported in recent years. Nanoparticles of CuS and Au amalgamated, augmenting the impact of PTT, which is a consequence of the compelling conjugation between Au and CuS [178,179].

The unique combination of PTT-RT with gold decorated copper-antimony-sulfur (Au@Cu-Sb-S) multifunctional nanosystem had complementary antitumor effects, which was also demonstrated by Hue et al. When the breast tumors were administered with Au@Cu-Sb-S + NIR + RT, their size diminished, and the percentage of mortality was reported to be 97.6%. These findings supported the idea that Au@Cu-Sb-S nanoparticles demonstrate a synergistic radiotherapeutic effect with PTT. The toxicity level of Au@Cu-Sb-S NPs was minimal, was further demonstrated by the fact that when cells were cultured and incubated with the modified Au@Cu-Sb-S NPs, exhibited more than 80% survivability [180]. Another study was conducted in which hollow bismuth selenide (Bi2Se3) nanoparticles were investigated by Song et al. for the combined therapy, i.e., PTT/radiotherapy. When designing a modified version of hollow nanoparticles of Bi2Se3, Perfluoro hexane (PFC) was infused into them to serve as an oxygen storage tank. The final product was named PEGylated-Bi2Se3@PFC@O2. Upon exposure to NIR
tumor model showed inhibition against the Au-FeSe group compared to the control group. After 3 weeks, it was discovered that the 4T1 nanoparticles of alpha Fe\textsubscript{2}O\textsubscript{3}@Au nanoparticles rapidly release the oxygen stored in them, leading to an increase in the oxygenation status of the tumor [181].

This demonstrates the effectiveness of this nanoplatform’s photothermally stimulated oxygen supply. Whereas, Zhong et al. utilized the nanoparticles of alpha Fe\textsubscript{2}O\textsubscript{3}@Au for treating mice diseased with BC by using PTT conjugated with radiotherapy. These nanoparticles are a strong choice for bioimaging and treatment purposes [181]. A functionalized hollow microsphere of bismuth sulfide (Bi\textsubscript{2}O\textsubscript{3}) was developed by Zhang et al. which exhibits a rod-shaped structure. When these nanostructures are exposed to NIR rays of 808 nm, the high photo-thermal agent was examined for the first time. When nanoparticles of AuNPs are exposed under 808 nm photoexcitation, the high photothermal transformation efficiency of NCs efficiently destroys tumor cells [184]. In the meantime, tumor hypoxia in the tumor microenvironment could be circumvented by the local heat produced by the irradiation to improve the effectiveness of radiotherapy. Au-FeSe\textsubscript{2} nanocomposites have catalyzed the increased endogenous hydrogen peroxide amount throughout the radiotherapy, resulting in the surge of intracellular ROS. Eventually, after systemic administration and combinational therapy, the growth of tumor cells would be restricted due to the accrual of nanocomposites of PEGylated gold–iron selenide nanocomposites (Au-FeSe\textsubscript{2}) in tumor cells [185]. In another study, Lu et al. demonstrated how the combined treatment affected a 4T1 tumor mouse model by segregating the mice into five categories: the Au-FeSe\textsubscript{2} + NIR group, the Au-FeSe\textsubscript{2} + RT group, the Au-FeSe\textsubscript{2} + NIR + RT group, the Au-FeSe\textsubscript{2} group the control group. After 3 weeks, it was discovered that the 4T1 tumor model showed inhibition against the Au-FeSe\textsubscript{2} + NIR and Au-FeSe\textsubscript{2} + RT groups with a rate of 51.5 % for NIR and 67.3 % for radiotherapy [186].

Further, an investigation was conducted by Sears et al. to determine a multifunctional strategy built on integrated PTT, radiotherapy, and TNBC-specific cytotoxic activity employing silver nanoparticles that cure cells of TNBC. This decreases off-target repercussions on benign breast epithelial cells. Initially, apoptosis jumped from 0.28 % to 8.55 % and later surged from 1.66 % to 9.35 % when triangular silver nanoparticles (TAGNPs) were delivered to MDA-MB-231 BCcells [187]. On the contrary, MCF10A cells that are non-malignant, exposed to equal dosages of TAGNPs, exhibited minor modifications throughout the apoptosis. According to this research, the conjugation of TAGNPs’ apoptotic and heat-producing characteristics upon laser exposure may help treat TNBC without adverse side effects on normal breast tissue. Patients receiving breast conservation therapy and those with metastatic tumor lines close to the periphery would benefit most from this treatment. Therefore, phototherapy in conjunction with radiotherapy caused the most impactful tumor growth suppression with an inhibition rate of 82.8 % [187].

6. Challenges and Toxicity associated with Nano-PTT regimens

Conventional cancer therapy predominantly includes systemic drug surgery coupled with CT and radiotherapy, having inadequacies like multidrug resistance, non-targeting, poor bioavailability, and systemic toxicity. Recently, the emergence of gene therapy, immunotherapy, PTT, and PDT have paved the way through \textit{In vivo} and \textit{In vitro} trials [188]. These invasive techniques and selective therapies are well discussed and are under clinical trials at low cost. As discussed, the PTT conjugation with CT, radiotherapy, and immunotherapy, with novel nanomaterials, has elucidated better BC treatment than the single conventional therapies. However, certain drawbacks need to be addressed, including the mechanism of synergistic effects and how it can be optimized with minimal dose during therapy, such as combined PTT and CT. Studies have shown that a single treatment is unlikely to eliminate a tumor. Therefore, it is essential to integrate PTT with other combinational therapies to improve their therapeutic effectiveness against malignancies [83]. A multidisciplinary approach may be used to improve anticaner outcomes. Until now, PTT was preclinically tested in a 2D cell culture system and animal models, which fails to mimic the 3D complex tumor microenvironment [189].

Since the emergence of nanotechnology, nanomaterials have been designed for drug delivery, tissue engineering, and stem cell therapies. Though Photo-Nano thermal therapy is found to be efficient in
conjugation with conventional therapies in terms of drug delivery, we are still uncertain about the potential threat to patients and the environment [189]. However, these innovative nano-system-based therapies have specific limitations, including drug leakage, poor stability and biocompatibility, short blood circulation time, and NIR light penetration depth. In addition, there is an adverse effect on healthy tissues due to the accumulation and aggregation of nanomaterials, which could lead to cytotoxicity on long-term exposure. The nanoparticle causes cytotoxicity through the skin, blood vessels, and cell membranes, producing inflammation or ROS [190], depicted in Fig. 7. There are several nanomaterials introduced into the PTT. These materials are mouldable, and their pharmacokinetics and biodistribution of particles can be altered in size, shape, and surface area. The surface area of the nanomaterial can be altered to enhance the effect of photosensitizers in PTT and PDT. However, the challenge includes non-biodegradability, non-biocompatibility, and high photothermal efficiency, along with a lack of traceability of the nanomaterial in the patient after treatment [163]. Moreover, due to the variation in an individual’s body and the complex microenvironment, control over an internal stimuli-responsive system becomes difficult during the treatment. In addition, it is essential to optimize specific parameters to ensure efficient management of the patient’s pain and PTT. These parameters include using painless nanoparticle delivery, selecting the appropriate wavelength during laser exposure, and determining the most effective exposure time. Additionally, body cooling strategies should be employed during treatment to enhance nanoparticle flow, accumulation, and retention [187].

The cytotoxicity of gold nanoparticles is primarily dependent on their particle size. Therefore, any heterogeneity in their size or shape can alter the photothermal effect. The biggest challenge is achieving a homogeneous distribution of nanoparticles at the tumor site, which is hindered by their solubility, hydrophobicity, and tendency to aggregate [183]. This can be achieved by PEG-coating, a laser source with safe power, and other parameters to achieve better treatment efficiency and fewer complications in patients. Additionally, the PEG coating lowers cytotoxicity, improves the PTT effect, and helps detect excretion and metabolism. However, the diameter of the nanomaterial is critical in determining its clearance by the reticuloendothelial system and its excretion through the kidney [191]. Therefore, to synthesize an ideal nanomaterial, there is a need for nano-controllable technology. It is critical to evaluate ablation agents’ safety power and limit to optimize the preclinical data and not underestimate the long-term side effects of the nanomaterial. The rise of antibacterial nanomaterials to reduce the effect of antibiotics that cause toxicity has led to the emergence of antibiotic-resistant bacteria in the host. However, the therapeutic efficiency can be increased by using such antibacterial nanomaterials [192].

In biomedical research, inorganic nanomaterials have been proven to be optimistic. However, considering certain drawbacks in clinical application, it requires more actuation and stability due to the complex environment of living organisms. For instance, according to Zhou et al. nanoparticles are more likely to be transferred to the reticuloendothelial system of the spleen and liver instead of the target tumor cells, thereby causing hepatotoxicity in the liver [193]. Recently, the PTT has been enhanced to specifically detect and kill MCF-7 BC cells by bio-conjugation of gold nanobioparticles with surface-enhanced Raman scattering [194]. Unfortunately, these gold nanomaterials remain inside the body without degradation. Therefore, organic conductive polymers like polypyrrole are considered the better alternative to treat BC due to their outstanding stability, strong Near infrared absorbance, and conductivity [188]. Although metal nanoparticles of gold, iron, sulfide, silica, palladium, and natural polymers like hyaluronan, and chitosan, synthetic polymers like poly (lactic-co-glycolic acid), polyaniline are widely used, there have been a recent intriguing nano system called hybrid nanomaterial which is a combination of two or more organic or inorganic components were found to be promising nanosystem in treating BC in synergy with PTT [189].

7. Conclusion and Future Perspectives

The growing burden on the healthcare sector and successive progress in the biomedical paradigms have witnessed immense progress in the

---

**Fig. 7.** A visual diagram that illustrates the numerous hurdles and complexities associated with the delivery of nanotherapeutics for cancer treatment. This figure elucidates the toxicity mechanism of nanoparticles through the mediation of reactive oxygen species (ROS) generation. It portrays a comprehensive model highlighting two primary pathways in this process. The upper part of the figure demonstrates extracellular sources of ROS, showcasing the environmental routes through which engineered nanoparticles are exposed. Engineered nanoparticles, upon exposure, can initiate the generation of ROS in the extracellular milieu. ROS act as intermediaries in the toxicity mechanism. The lower segment of the figure focuses on intracellular ROS generation. In particular, it highlights the role of mitochondria as one of the chief sources of ROS within cells, reproduced with permission from Ref. [195], Copyright 2020, Springer.
development of nanomaterials, optical equipment, and laser facilities to counteract the lethality associated with cancer [196]. It is evident that nanoparticles are efficient drug delivery agents with higher efficacy and bioavailability in target tissues and organs. However, there are many challenges in development of an efficient nanomaterial considering the factors of toxicity and metabolism, and specific targeting [197]. The challenge lies in designing a smart biocompatible nanomaterial by optimizing their physiochemical properties to reduce biological toxicity [198]. Additionally, the internal structure and external components are crucial for nanoparticles' efficacy, toxicity, targeting ability, and biocompatibility. Biocompatibility cannot be compromised; therefore, nanoparticles like extracellular vehicles (EVs) are designed to evade immune surveillance for efficient targeting [199]. In addition to overcome the challenges of the toxicity and biocompatibility, the surface modification was achieved by PEGylation [83]. Also, tackling toxicity of antibodies and antibacterial resistant bacteria, antibacterial effect can be considered as one of the intrinsic properties while developing a nanomaterial in order to prevent infection in cancer patients [200].

Nanoparticles are widely used in biomedicine, and hence different types of functionalisation can be done on these nanoparticles for enhancing the outcome of these materials, during a particular biomedical application. These modification on the surface of a polymeric nanoparticle may impose some cytotoxicity, which can be one of the limitations for the associated functions [201]. Inorganic or metal NPs can be reactive with various compounds and different environment. Hence, the functionalization, via any surface modifications, should be regulated according to the reactivity of the material used, so that it does not cause any further toxicity in the system, it is being administered in. NPs can be personalized and multi-functionalized, according to the specific stimuli and requirement of the In vivo condition [202]. This quality makes the smart NPs and hybrid NPs, one of the promising mode of treatments in biomedicine. Furthermore, the exploration of PTT research with these nanomaterials ought to focus on enhancing the restricted selectivity of PTT agents towards tumor tissue. This is imperative due to the diminished concentration of PTT agents within tumors, necessitating elevated PTT doses for effective therapeutic outcomes [203]. Several investigations have delved into the functionalization of nanomaterials through the incorporation of PEG and targeting ligands, such as antibodies and RGD peptides. This approach aims to augment structural stability, biocompatibility, and the precision of these agents specifically for tumor tissues [204].

The nanoparticle targeting tumor, interaction with blood proteins, and removal from the system is another significant encumbrance. The passive targeting of nanoparticles during drug delivery causes enhanced permeability and retention (EPR), thereby accumulating in the tissue. To overcome this, active drug delivery and targeting produce a better outcome than passive nanoparticle targeting. The cancer tumor is heterogeneous in patients; therefore, all approaches must be reconsidered while designing a nanoparticle. While these nanomaterials are conjugated with PTT, the difficulty lies in biodistribution, target accumulation, pharmacokinetics, healthy tissue localization, therapeutic efficacy, and drug release kinetics. For instance, graphene and gold nanoconjugate nanomaterial emerged as an optimistic material for cancer PTT with a unique design as a multifunctional nanosystem bearing attributes of temperature/pH-dependent drug/gene delivery abilities for multimodal cancer therapy [205]. It is essential to closely monitor the long-term degradability and toxicity of 2D nanomaterials. These concerns have been validated through studies in animal models with real-time imaging. Understanding the interaction of nanomaterials and drugs during PTT is vital [120,206].

In this article, we focus on the role, mechanism, and recent approaches of various nanoparticles involved in the influence of PTT while treating BC. The nano systems in conjunction with PTT are proven to have enhanced therapeutic outcomes [206]. PTT has proven safe for patients with fewer side effects. However, so far, nano-based PTT has only been tested on tumor models in preclinical studies (both In vivo and In vitro), and more inducement is needed for its use in clinical applications [207]. The use of nanomaterials in PTT allows for precise and localized heating of tumor cells, reducing damage to healthy tissues. Overall, nanomaterials have revolutionized the field of PTT and show great promise in the treatment of BC.

In each conjugational therapy discussed, the synergistic effects due to each are unique, where the nanomaterial with adequate drug release protects normal cells from intrinsic toxicity in a controllable and efficient manner [8]. PTT outperforms radiotherapy on radiation-treated tumors, while radiotherapy outperforms PTT on hypoxic cancer cells with hyperthermia-induced oxygenation. In tumor-associated antigens induced by PTT and immunoadjuvants coupled with nanomaterials, the immune system strengthens for combined PTT and immunotherapy [208,136]. Although this review presents some promising aspects for nanoparticles in PTT in conjunction with RT, immunotherapy, and CT to simultaneously treat BC, extensive research is required to enter the clinical trials.

The future prospect of nano system-based PTT lies in developing a biodegradable, bioinert, biocompatible, multifunctional, innovative material. Considering the advancement in nanomaterial technology, we believe a nanoparticle in the future must be multifunctional, targeting the metastatic tumor with high photothermal conversion efficiency, targeting specific tumors and long-term retention [209]. The employment of a sonochemical approach in mediating PTT represents a cutting-edge method with promising implications for therapeutic applications [210]. Iron oxide (Fe3O4) nanoparticles and iron oxide/gold (Fe3O4/Au) nanocomposites have a significant role as an imaging agent, therapeutic material and to some extent in drug delivery [204]. These organic and inorganic coating of these nanoparticles is also responsible for the functionalisation and enhancement of properties [211,212]. Various methods of synthesis are considered to bring out the best outcome possible for its application in biomedical sphere. In the recent researches, attempts are being made for the intrinsic modularity of the synthesis processes of the Fe3O4/Au and Fe3O4/glue/Au nanocomposites [211]. Further modifications in the physicochemical properties of these nanocomposites can help us to achieve the specific requirements for the varied applications. In recent research by Dhejay MA et al. the MRI efficacy of Fe3O4 is harnessed within its inner core, while the gold shell (Au-shell) achieves photothermal effects through near-infrared absorption, resulting in the targeted destruction of cancer cells. The nanoparticles synthesized in their as-prepared state exhibit significant capability for photothermal ablation on MCF-7 cells In vitro when subjected to near-infrared laser irradiation. Therefore, the Fe3O4@AuNPs developed in this investigation hold immense promise as an optimal candidate for both MRI and PTT [203,213]. The advance ment in 3D printing of dopamine-modified alginate and polydopamine (PDA) biomanomaterial was effective for treating BC with PTT [209]. Also, the preclinical studies in 2D cell culture do not provide an accurate tumor tissue microenvironment. Therefore, the advancement lies in 3D models to understand NP-based drug discovery, screening, and development, which is cost-effective and has a more significant potential for high scalability than animal models. Despite the success of protein-based biomimetic nanocarriers, there are enormous challenges in understanding target host recognition in cancer diagnosis and prognosis [214]. Therefore, enhancing proteomics studies of cancer via high therapeutic techniques can help in developing potential anticancer nanocarriers.

The outstanding application of Artificial Intelligence (AI) in regulating nanomaterials has paved the path for a promising future for nanosystems. AI is used in adverse event prediction, real-time monitoring, optimized dose, and predictive modeling. The AI and Machine learning (ML) systems are developed and can be made more efficient by training the systems with previously performed data of therapies to predict a better outcome [215]. This training bridges the gap using pattern analysis and classification for more precise diagnoses and treatment. A Trojan-horse-like nanoparticle was designed, which had a
better retention time at the tumor site due to the imaging control strategy causing an artificially controllable aggregation leading to enhancement of PTT in NIR-II [216]. Similarly, according to Adir et al. [217], and Kesharwani et al. [218], gold nanoparticle is an ideal nanocarrier in cancer therapy which can be controlled by AI and mathematical modeling due to their ideal shape, size. The favourability is due to its high electronic content, optical characteristics like strong scattering and absorbance in the visible-near-infrared region, and low chemical reactivity. The future of nanomedicine with AI looks innovative as one can operate on body Nano sensors via mobile phone and Bluetooth. The smartphone-based operating nanodevices can be easily operated by patients, saving energy and resources of patient and burden of medical teams [217]. However, there is a challenge in the standardization of data due to heterogeneity in the population to enter clinical trials using AI. To reduce the overdose and improve treatment outcomes, the AI is used to optimize the dose and release by nanoparticle based on the patient’s weight, age, metabolism, and medical history. The use of deep machine learning can aid in developing nanoparticles with optimal parameters to accurately target the nanoparticles to the cancer cells, assessing the toxicity of the drug simultaneously [219]. Using optical coherence tomography to generate high-resolution images of tumors and surrounding tissues, AI imaging techniques can track drug delivery and distribution. During PTT, AI-based monitors can help minimize collateral damage to healthy cells due to hyperthermia. AI image analysis software can also control critical optical parameters, such as light intensity during photothermal and photodynamic therapy [220]. The algorithms predict the best heating patterns to maximize the effectiveness of hyperthermia therapy while minimizing collateral damage to healthy tissues. In contrast, AI-based image analysis software has visually monitored PTT or PDT cancer treatment to examine images of the treatment area and help determine the optimal location and intensity of the light during light-based cancer treatment techniques [221].

This article strives to discuss extensively the different combination therapies available to combat BC and provide better individualized management alternatives through marginally invasive techniques that facilitate BC diagnosis and treatment. To achieve enhanced cancer treatments and surgical intervention, multipurpose nanoplatforms that integrate visual and clinical imaging methods will be developed and utilized. A meticulous therapeutic management strategy that involves preoperative assessment, examination, adjunct therapy treatment, real-time multimodal image analysis during surgery, multi-drug coupled treatment, post-surgical adjunct therapy, relapse protection, and tissue repair are all parts of tumor therapeutic. Therefore, establishing several reliable conjugate therapeutic interventions that can manage and encompass the entire spectrum of BC management is a feasible and convenient approach, with nanotechnology playing a significant role in making it a reality.

Data and code availability
Not applicable.

Funding
Not applicable.

Ethical approval
Not applicable.

CRediT authorship contribution statement
Sagnik Nag: Writing – original draft, Resources, Data curation, Conceptualization. Oshi Mitra: Writing – original draft, Data curation. Garima Tripathi: Writing – original draft. Israrahmed Adur: Writing – original draft. Sourav Mohanto: Writing – review & editing, Writing – original draft, Visualization, Resources, Formal analysis. Muskan Nama: Writing – review & editing, Data curation. Souvik Samanta: Writing – review & editing, Formal analysis. B.H. Jaswanth Gowda: Writing – review & editing, Visualization, Validation, Formal analysis. Vetriselvan Subramaniyan: Writing – review & editing, Supervision, Software, Resources, Project administration. Vino Sundararajan: Writing – review & editing, Supervision, Project administration, Formal analysis. Vinoth Kumarasamy: Project administration, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest
The authors declare that they have no conflict of interest.

References


C. Tao, L. An, J. Lin, Q. Tian, S. Yang, Surface plasmon resonance

J. da S. Oliveira, E.J. Guidelli, Multitherapeutic nanoplatform based on


J. de S. Oliveira, E.J. Guidelli, Multitherapeutic nanoplatform based on scintillating anthracene, silver@anthracene, and gold@anthracene nanoparticles for combined radiation and photodynamic cancer therapies, Mater. Sci. Eng. C. 126 (2021) 112122.


