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Nanoparticles-based Chemo-Phototherapy Synergistic Effects for Breast Cancer Treatment: A Systematic Review

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Abstract: Despite the promising outcomes, conventional therapies for breast cancer treatment suffer from apparent limitations, including systemic toxicity, adverse reactions, and tumor recurrence. In light of that, therapy that combines chemo-phototherapy with nanoparticles is of immense value as it provides an alternative that hope exerts better outcomes. This review systematically assesses publications between 2010 and 2022, focusing on the application of nanoparticles in chemo-phototherapy for breast cancer. A detailed search was conducted in Scopus, PubMed, and WoS, and relevant studies within the 11 years were selected. Final 18 out of 40 initial papers were selected, including studies on *in vivo* analysis. Detailed information on chemo-phototherapy effects, drug cargo design, the toxicity of nanomaterials, and immunomodulatory effects were extracted and discussed. This review demonstrates the promising anticancer activity of combined synergistic effects for breast cancer management.

Keywords: nanoparticles; drug delivery; chemotherapy; phototherapy; breast cancer.

1. Introduction

1.1. Breast cancer and risk factors.

Breast cancer is predominantly suffered by women worldwide and remains the second most lethal cancer among this group after lung cancer [1, 2]. According to the National Cancer Institute, breast cancer exists in three different types, including ductal carcinoma and lobular carcinoma, and inflammatory breast cancer, the rarest type [3-5]. Breast cancer can also be differentiated based on the molecular subtypes, which are defined by the absence or presence of estrogen or progesterone hormone receptors (HR-positive/HR-negative) and the expression of human epidermal growth factor receptor 2 (Her-2 positive/Her2- negative) protein [2]. In the non-invasive mode, breast cancer localizes mainly in the breast tissues comprised of glands for milk production or in the lobes [6]. Unfortunately, in their invasive mode, breast cancer cells eventually lead to cancer metastasis [7]. Metastasized breast cancer cells normally invade other internal organs such as bone, liver, lung, and brain via the vascular or lymphatic system [8].

In 2019, the National Cancer Institute outlined the common symptoms in early diagnosis of breast cancer patients, such as lump formation in the breast, abnormalities of breast shape, skin dimpling, disposition of non-milk fluids from nipples, inverted nipple, and red-patchy skin around the breast [9]. Detection of symptomatic cancer at an early stage is crucial to prevent further cancer invasion and metastasis [10, 11]. Nevertheless, the availability of cancer diagnosis is influenced by various factors, including the country's developmental status, time of diagnosis, and, most importantly, the quality of the healthcare system [12, 13]. It has been reported that patients from low middle-income countries (MIC) have a lower survival rate of breast cancer as compared to those from high-income countries (HIC) [14]. In this case, one of the reasons may be that patients suffer from long diagnoses and delayed treatments due to insufficient healthcare resources and sociodemographic influence [15]. Moreover, breast cancer risk factors include nulliparity, family history, non-breastfeeding mothers, and the usage of oral contraceptives [16]. Besides, some unique risk factors such as breastfeeding history and duration, level of soymilk and soy product intake, and level of routine physical activity are believed to have led to breast cancer occurrence [17].

1.2. Conventional and alternative therapies.

In breast cancer theragnostic, the implementation of cancer treatments depends on factors such as cancer stages, tumor prognosis level, and limitation of age [18]. Standard strategies for breast cancer management include both conventional and alternative therapies. Globally, countries that practice gold standard conventional approaches such as chemotherapy, radiotherapy, and surgery include the United States, Sri Lanka, India, China, and Germany [6]. Meanwhile, as reported by the World Health Organization, countries in Africa, Asia, and Latin America, blessed with abundant natural resources, tend to develop non-conventional remedies due to insufficient regular access to modern medicines [19].

According to the National Cancer Institute, conventional treatment is defined as the primary treatment practiced by most healthcare professionals [20]. Available conventional treatments include surgery, chemotherapy, radiotherapy, and endocrine therapy [20, 21]. In recent years, surgery remains the top option in referring to the condition of the tumor, but a series of follow-up treatments consisting of chemotherapy or radiotherapy is required to complement the post-palliative operation, mainly to prevent tumor recurrence [22]. However, conventional strategies are often associated with causing damage to normal (healthy) cells, systemic toxicity, adverse reactions (e.g., nausea, vomiting, and hair loss), multidrug resistance, and, most critically, tumor recurrence [23-25]. Hence, alternative therapies are developed and implemented due to demands for non-toxic approaches [26].

On the other hand, an approach that has not been widely used in breast cancer treatment is known as non-conventional therapy. Examples of this type of treatment may include herbal, mental, and physical therapies [6, 27]. These therapies aim to resolve the problems that arise in conventional breast cancer treatments [6, 23].

1.3. Nanoparticles application for breast cancer therapy.

The urgency for more effective treatment in the clinical setting has prompted advances in cancer treatment modalities. Nanotechnology has gathered interests in the development of safe anticancer agents and of therapeutic benefits [28]. The American Society for Testing Materials and National Nanotechnology Initiative 2000 described nanotechnology in the

biomedical field as involving the usage of nanoparticles with the size ranging between 1 – 100 nm, either in two or three dimensions [29]. Various nanoparticles (NPs) have been designed to function for cancer nano therapy based on their physio-chemical properties. A large surface area is one of the advantages of nanoparticles [30]. Also, customized nanoparticles have adjustable particle size and shape, dual-function surface with improved permeability and retention effect, powerful electromagnetic radiation absorbance, and high thermal conductance [31-33]. Functionalized nanoparticles can be specially designed for photothermal therapy that can respond to externally applied fields such as magnetic, focused heat, or light favorable in specific cancer treatment [34, 35].

To an extent, nanoparticles are beneficial in cancer diagnostics, therapy, and imaging [36, 37]. For instance, Conti *et al*. [35] reported nanoparticles applications such as liposomes, which were the 'first generation' nanoparticles that deliver anticancer therapeutic agents to the target tumors. Furthermore, nanoparticles have successfully delivered specific drugs such as doxorubicin, actinomycin D, and camptothecin (CPT) in cancer chemotherapeutic applications.

2. Materials and Methods

2.1. Search strategy.

This systematically conducted review was performed to analyze articles related to the application of anticancer drug-loaded NPs with laser irradiation for breast cancer treatment. Generally, three established online databases were used to search for relevant studies; PubMed, Scopus, and WoS. The combination of keywords used were "Breast Cancer", “Chemotherapeutic Drugs”, “Nanoparticles”, “Photothermal Therapy” and “Not Review”.

2.2. Selection criteria.

Articles were limited to English-published articles and those published from 2010 to 2022 only. All databases were individually blasted, and relevant studies related to the keywords set were chosen. All identified titles and abstracts were screened carefully to prevent the selection of unrelated studies. Studies not related to the application of chemotherapeutic drugs loading on nanoparticles were excluded. All review articles, book chapters, news articles, editorial letters, and case studies were eliminated from the search.

2.3. Data extraction and management.

Two reviewers were involved in the data extraction process for each article. Several steps were endorsed in the screening process of the selected papers. Initially, all papers with irrelevant titles were filtered out. The abstracts were screened thoroughly. Papers that did not fit the criteria were excluded, and all duplicates were removed. Summary of data from the selected papers are presented in Table 1 with the publication year, authors, type of nanoparticles used, type of chemotherapeutics drugs, and results.

3. Results

3.1. Search results.

Initially, 40 articles were identified from the three search engines: 14 from PubMed, 25 from WoS, and 1 from Scopus. Further unbiased screening involves different reviewers to

select articles that fit the research criteria. Twenty-seven articles were excluded as they were either news, review articles, book chapters, editorial letters, or case studies. A more specific criterion was implemented in which selected studies must combine nanoparticles with chemotherapeutic drugs and photothermal therapy. A total of 3 more articles were eliminated. Further screening process by revising the abstract to confirm the criteria fulfillment where 2 duplicates were removed after parallel compilation was done between the 3 databases. The final selected articles were 18. The screening stages are portrayed in Figure 1.

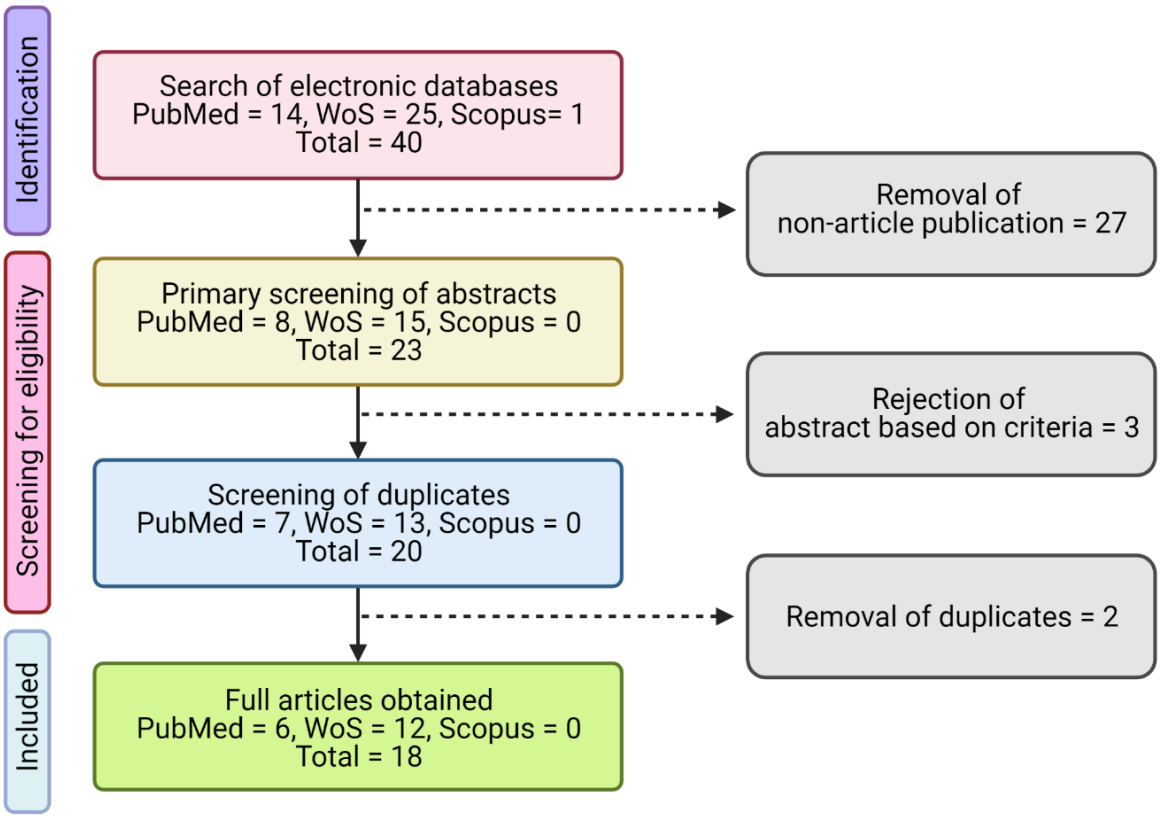

Figure 1. Flow chart of the article retrieval process in PubMed, WoS, and Scopus online databases.

3.2. Study characteristics.

All published articles extracted from the databases have proposed potential treatments specifically for breast cancer. All of the studies involve in vitro experiments using breast cancer cell lines; MDA-MB-231, MDA-MB-436, MDA-MB-468, MCF-7, MCF-7/ADR, EMT6, 4T1, and BT474. The extracted data consist of the types of nanoparticles, loaded materials, approached analysis, the cell line used, and results as listed in Table 1. Eight out of the 18 studies include *in vivo* studies as well. The type of materials used, the dosage of chemotherapeutic drugs, route of injection, power density, laser irradiation wavelength, and their treatment outcome were extracted from those articles. Information on the toxicity study was also included since the toxicity analysis was done in 6 out of 8 *in vivo* analyses, as listed in Table 2. Overall, the summary of the study characteristics is displayed in Figure 2.

Table 1. Summary and classification of the nanoparticles and their combination.

Type of NPs	Materials loaded	Approach	Cell line	Result	Reference
Graphene oxide	Doxorubicin	In vitro	MD-MB-231	Encapsulated DOX (5μgmL^{-1}) possessed dual-mode: chemotherapy and photothermal action	[38]
Single-walled CNTs	Doxorubicin	In vitro & *In vivo*	MCF-7	The killing potency of the tumor was intensified when	[39]

Type of NPs	Materials loaded	Approach	Cell line	Result	Reference
				exposed to Gd/SWCNTs-HA-ss-DOX with NIR laser radiation	
Single-walled CNTs	Doxorubicin	In vitro	MCF-7 & L929	SWCNTs observed a significant photothermal effect, with a combination of chemotherapy, without causing toxicity to normal cells	[40]
Single-walled CNTs	Doxorubicin	In vitro	MCF-7/ADR	PEGylated DOX-SWCNTs ($40\mu gmL^{-1}$) caused endosomal disruption after being irradiated with NIR, thus resulting in the translocation of DOX to the nucleus	[41]
Magnetic mesoporous silica	Doxorubicin	In vitro & *In vivo*	MCF-7, MCF-7/ADR, HUVEC & EMT6	Tumor experienced significant thermal ablation, necrotized, and several structural damages	[42]
Gold nanorod	Docetaxel	In vitro & *In vivo*	4T1	Combined therapy suppressed 84.5% of tumor growth	[43]
Multi-walled CNTs	Platinum acridine (P3A1)	In vitro	MDA-MB-231, MDA-MB-468, MDA-MB-436, SUM159 & BT20	Treatment of P3A1-MWCNTs with laser was more effective than PTT with drug-free MWCNTs or P3A1-MWCNTs alone	[44]
Mesoporous magnetic gold	Doxorubicin	In vitro & *In vivo*	MCF-7, 293A & 4T1	DOX releases exhibited pH and laser irradiation dependence. IC_{50} of combined therapy is lower compared to another group	[45]
Single-walled CNTs	Doxorubicin	In vitro & *In vivo*	MCF-7	The combined treatment induces systemic toxicity under 808 nm NIR radiation. DOX release can be accelerated using a laser or low pH environment	[46]
Magnetic iron oxide	Doxorubicin	In vitro	MDA-MB-231	Fe3O4@DMSA/DOX recorded excellent temperature elevation with significant cell toxicity when irradiated with NIR	[47]
Poly (lactic-co-glycolic acid)	Docetaxel	In vitro	MCF-7	PTT by laser-produced a more significant effect compared to thermal therapy by water bath	[48]
Multi-walled CNTs	Organoselenium	In vitro & *In vivo*	MDA-MB-231	The number of tumor cells was reduced, and experienced necrosis. No acute toxicity was observed in combined treated mice	[49]
Single-walled CNTs	Doxorubicin	In vitro	MDA-MB-231	High DOX concentration was tracked in the nucleus. Combined treatment caused mitochondrial disruption, thus stimulating cell death	[50]
Zinc oxide	Doxorubicin	In vitro	MDA-MB-231 & HBL-100	The highest rate of cell death was recorded in DOX-FA-ZnO NS with NIR laser-treated mice compared to chemotherapy and photothermal therapy alone	[51]
Single-walled CNTs	Anti-Her2	In vitro	MDA-MB-231 & BTA474	Stable physiologic conditions of Mab-CNTs were observed and succeeded in generating	[52]

Type of NPs	Materials loaded	Approach	Cell line	Result	Reference
				specific photothermal killing of targeted B-cells	
Gold nanoparticles	Doxorubicin	In vitro & *In vivo*	MCF-7	Cell viability in chemo-photothermal therapy was lower than free DOX or NPs without laser irradiation. Significant results were recorded in chemo-photothermal synergistic therapy	[53]
Mesoporous copper sulfide	Doxorubicin	In vitro & *In vivo*	MCF-7 & NIH3T3	More apoptotic cells were discovered from cells treated with DOX/HMuCs-HA under NIR radiation. Significant tumor inhibition was recorded	[54]
Telodendrimer co-assembled nanoparticles	Imiquimod	In vitro	4T1	87% of cell death was recorded in the combined-treated group. Imiquimod activated NK cells, macrophages, and B-lymphocytes	[55]

Table 2. Details on *in vivo* study related to selected papers.

Materials	Dosage	Route of Injection	Power density (W/cm^2)	λ (nm)	Result	Toxicity analysis	Reference
Gd/SWCNTs-HA-ss-DOX	4.0 mg DOX/kg	Intravenous	2.5	808	Combined treatment with laser showed the most efficient tumor growth inhibition. There were almost no intact tumor cells with obvious necrosis	*N/A*	[39]
M-MSN(Dox/Ce6) /PEM/P-gp shRNA	*N/A*	Intravenous	2	660	Combined treated mice achieved significant tumor ablation. More structural damage and apoptotic cells were observed	Histological analysis of vital organs showed no abnormalities. No significant changes in body weight	[42]
GDTX/p65	0.06 mg DTX/kg	Intratumoral	0.4	665	84.5% of tumor growth was suppressed compared to other groups. Higher cellular apoptosis percentage was analyzed in DTX/p65 group compared to drug-free NPs or laser alone	Unobvious body weight changes were recorded	[43]
DOX-loaded MMGNCs	2.5 mg DOX/kg	Intravenous	2.5	808	Most of the tumor cells disappeared at the tumor site. Apoptosis and necrosis activities were recorded in combined treated mice	*N/A*	[45]
SWCNT-PEI/DOX/NGR	7.5 mg DOX/kg	Intravenous	*N/A*	808	SWCNT-PEI/DOX/NGR showed the	No weight loss was observed.	[46]

Materials	Dosage	Route of Injection	Power density (W/cm^2)	λ (nm)	Result	Toxicity analysis	Reference
					strongest antitumor effect. NGR peptide allowed more SWCNTs to be transferred to the tumor. Tumor cells experienced fragmentation, necrosis, and cell lysis	No significant cytotoxicity of combined NPs to mice. All major organs exhibited a normal condition	
Se@CNTs	2.0 mg/kg	Intravenous & Intratumoral	3	808	Relative tumor volume of i.t combined with laser showed a more significant effect compared to i.v injection. Combined treatment inhibited tumor growth	No fluctuation in body weight. Blood biochemical indexes showed no differences in tumor-bearing mice compared to healthy mice	[49]
Gold 3D-PAs	*N/A*	Intravenous	1.5	808	Tumors from combined treatment shrank and disappeared 24 days post-treatment	The average body weight of mice was increased during treatment, indicating no toxicity was observed	[54]
DOX/HMCuS-HA	4.0 mg DOX/kg	Intravenous	2.0	808	An 88.9% inhibition ratio of mice in the combined treated group was observed. Treatment remarkably enhanced antitumor efficacy	No obvious sub-chronic toxicity was observed	[55]

All studies retrieved from the databases are related to the synergistic effects of three major elements: chemotherapeutic treatment, integrated nanoparticles, and laser irradiation. The studies were specifically designed for breast cancer treatment, with the ultimate goal being the application of combined conventional therapy with drug delivery for combating breast cancer. Hence, this review aims to assess the implications of chemo-phototherapy effects on breast cancer. In addition, the designing of compatible NPs with emphasis on their drug loading capacity and bioavailability and antitumor and immunomodulatory effects post-administration are extensively discussed.

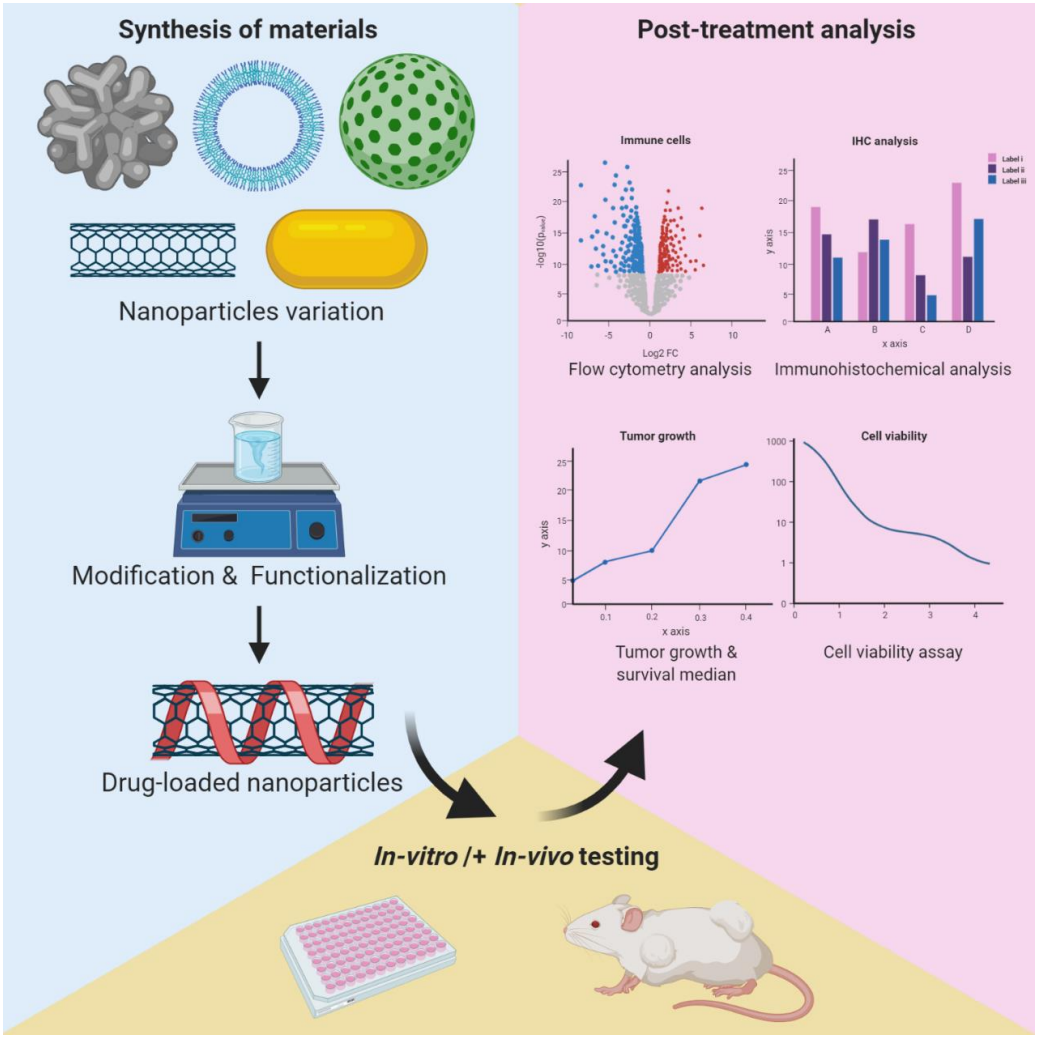

Figure 2. Illustration of the overall procedures involved in related studies. Nanoparticles were modified and loaded with the desired drug. The drug-loaded nanoparticles were tested in vitro and/or *in vivo* on breast cancer cell lines. Test material performance was analyzed.

4. Discussion

4.1. Chemo-phototherapy synergistic anticancer effect.

Advancement in cancer therapeutics for breast cancer includes the development of alternative or adjunctive treatments [27]. In this case, combining both conventional and alternative treatments provides new hope for improving breast cancer management. Standardized conventional treatments routinely practiced worldwide have been reported to cause severe systemic toxicity, hypoallergic, and inflammation [23]. Due to these, alternative treatments have been regarded as a complementary medium for conventional therapy [56]. Such therapy includes photothermal-mediated therapy (PTT), for example, hyperthermia (HT) and thermal ablation. PTT has been associated with certain benefits such as deep penetration, minimally invasive, and low toxicity, which may increase the effectiveness of the antitumor activity of the patient [57, 58].

Furthermore, PTT is thought to be a safer procedure that is less invasive and thus prevents breast cancer patients from traumatic injuries [59]. Available PTT strategy such as HT is classified as adjunctive therapy, which works by directly or indirectly killing the tumor cells with immune system activation [60]. Thermal therapy can also be coupled with conventional chemotherapeutic drugs [39, 61]. While other alternative therapy, such as herbal

therapy, might be effective for treating breast cancer, its effect when used in combination with other therapy remains elusive. Hence, PTT has been demonstrated as the best candidate for use in combination with chemotherapy based on the in vitro and *in vivo* reports on breast cancer, as demonstrated from all the articles extracted.

The excellent synergistic effect of laser irradiation used in photothermal therapy has also contributed to the antitumor efficacy. Near-infrared (NIR) radiation used in HT treatment at 700 – 850 nm provides maximum depth penetration through the tumor tissue [61]. Furthermore, a study by Zhang *et al*. [55] found that NIR light can limit the interference with blood and tissue while avoiding photodamage conditions to normal adjacent tissue [62]. In addition, NIR could also stimulate the liquid phase transition temperature of the plasma membrane, thus aiding drug delivery to target the intracellular environment, as stated by Hashemi *et al*. [38]. Major studies have revealed that the release of chemotherapeutic drugs is more efficient in higher temperatures mediated by thermal radiation. Wang *et al*. [46] described the Doxorubicin release profile as being increased at the higher intracellular temperature, indicating that the drug release activity is temperature-dependent [63].

Nevertheless, HT at higher temperatures was found to be associated with the exposure of tissue to a toxic environment [48]. While higher temperature irradiation proved to generate significant tumor inhibition, high energy irradiation might also lead to cell necrosis, resulting in the formation of damage-associated molecular patterns (DAMPs) [48]. Subsequently, DAMPs are likely to trigger the inflammatory response at the injury site, thereby reducing the efficacy of treatment, albeit not at a significant level [64]. Therefore, suitable carriers need to be considered to allow drug delivery and amplified heat irradiation which are vital for optimum anticancer efficacy [34, 65].

4.2. Cargo design for intracellular uptake.

The application of nanoparticles in drug delivery and combination with PTT for breast cancer therapy depends on the type and characteristics of the chemotherapeutic drugs and the route of administration [66]. Thus far, only certain chemotherapeutic drugs such as Doxorubicin, Docetaxel, and Paclitaxel have been tested for drug loading on nanoparticles. NPs used for drug delivery with a combination of PTT for breast cancer include graphene oxide [67], mesoporous silica [28], carbon nanotubes [68, 69], gold nanorods [70], mesoporous gold [71], iron oxide [72], zinc oxide [73], copper sulfide [74] and Poly (lactic-co-glycolic acid) [75]. To ensure suitability for drug loading and PTT procedures, it is very important to consider the material selection for NPs. Materials with high thermal stability are required as PTT involves heat induction [76, 77]. Moreover, NPs must also be equipped with high photothermal conversion ability [48], which would ease the conversion of laser frequency into heat energy. Studies by Xia *et al*. [53] and Wang *et al*. [43] claimed that gold nanoparticles possessed strong longitudinal surface plasmon resonance (LSPR), which is efficient enough to convert NIR light into local heat. Meanwhile, a study by Marches *et al*. [52] claimed that CNTs absorbance at 700 – 850 nm provides deep penetration while avoiding the destruction of normal tissues as these tissues do not strongly absorb frequency of that range.

In the context of drug loading and cargo release capability, Oh *et al*. [50] have enunciated three main focuses of the drug design study: controlled drug release, drug effective nucleus accumulation, and cell cytotoxicity. Other studies have concluded that the released capacity of chemotherapeutic drugs can be pH and temperature-dependent [42, 45, 46]. Therefore, the main goals are the successful delivery of drug-loaded NPs into intracellular

cancer cells and the release of the drugs from the designed NPs [78]. To achieve both goals, one needs to design biocompatible NPs, specifically targeting the tumor site and internalization by the cancer cells [79, 80]. Therefore, functionalization and modification of NPs surface and interior are made to create the best NPs.

Nonetheless, this also involves specific fabrication processes on the type of NPs and drugs to be loaded. On another note, to increase the NPs, hyaluronic acid (HA) coating onto the NPs surface was done [39, 54]. The presence of HA on the NPs surface aids in increasing their specificity since HA specifically binds to the CD44 receptor, which is highly expressed in cancer cells. NPs were also fabricated with the incorporation of folic acid (FA) since FA acts as a targeting moiety that can recognize the folate receptors on cancer cells, including those of breast tumors [40, 53]. Several other strategies, such as the coating of NPs with polyethylene glycol (PEG) and poly (ethylene imine)-grafted-B-cyclodextrin (PEI-g-CD) were also being investigated [24, 81]. The coating of PEG, for example, on the surface of carbon nanotubes (CNTs) has displayed prolonged survival of mice bearing breast tumors and remarkable tumor necrosis. Importantly, special features such as high drug-carrying capacity, elongated circulating time, and unique cell membrane permeability may increase the efficacy of the combined therapy [82]. Also, CNTs are reportedly excellent in fulfilling both the requirements of chemotherapeutic drug delivery and PTT protocols, as they are known for their safe transport of drugs and strong optical absorption in the NIR region [83-85].

4.3. Safety and toxicity of integrated NPs.

In clinical settings, the safety and efficacy of the designed treatment remain the main priorities. The application of NPs warrants the validation of their toxicity to ensure their relevance in clinical application. According to Burke *et al*. [31], factors that can contribute to the toxicity of NPs include type, size, shape, surface characteristics, and concentration administered. Therefore, pre-modification of drug carrier design such as surface modification and functionalization of NPs is believed to reduce their toxicity. *In vivo* studies with combined therapy concluded that all NPs and protocols administered were safe by observing specific parameters such as average body weight, behavior, histological analysis of vital organs, and serum biochemistry analysis [54, 55]. Other studies on pharmacokinetics also revealed that 18 out of 21 patients expressed negative toxicity and hepatotoxicity when treated with nanoparticles [86]. Moreover, the use of CNTs in breast cancer treatment showed that only a small number of CNTs entered the systemic blood circulation. It was reported that CNTs were eliminated from the body through urinary and biliary systems within 60 days [23]. On the other hand, hyperthermia treatment using CNTs demonstrated complete tumor elimination without any toxicity effects after six months post-treatment [49, 87].

NPs administration *in vivo* showed the potential to avoid acute and systemic toxicity. However, more detailed and long-term investigations to avoid any side effects of NPs and proper risk bias assessment on both pre-clinical and clinical reports are needed to be done. Since more interest has been gathered in the application of NPs in recent years, future predictions on the effects of NPs on their consumption, economic growth, and the ecosystem should be put into consideration.

4.4. Immunomodulatory stimulation in the tumor microenvironment.

Immune response, be it innate or adaptive, plays a great role in combating breast cancer. Unfortunately, none of the studies on chemo-phototherapy synergistic effects have investigated the immune system's role in the breast tumor microenvironment post-treatment. Therefore, the mechanisms of anticancer activity stimulated by the immune system are poorly understood. However, knowledge of immunomodulatory effects post-independent treatment, either chemotherapy or PTT has been well documented. For example, paclitaxel (PTX) for breast cancer therapy has shown improvement in immune system activation, although PTX has been associated with high hydrophobic properties [88]. In a study conducted by Esteva *et al*. [89], a standard dose of PTX triggered immunosuppression in the tumor microenvironment, inhibiting several types of immune cells such as macrophage, effector T, and natural killer (NK) cells. In contrast, a lower dosage of PTX has been reported to promote antitumor immune response [89, 90] actively. It is also reported that PTX may be present in the form of a ligand to toll-like receptor 4 (TLR4), which is available on the surface of the macrophage. However, it was reported that Tumor-Associated Macrophages (TAMs) induced tumor chemoresistance against PTX [91].

On the other hand, PTT, such as HT treatment, has been widely studied, including its advantages on immune-related anticancer activity. Through these temperature-inducing cancer cells, studies have reported that the elevated temperature has stimulated the production of heat shock protein (HSP) extracellularly within the tumor microenvironment [92, 93]. Hsp70 released from the irradiated cells known as TKD peptides was predominantly recognized by antigen-presenting cells (APCs). The uptake and cross-presentation of TKD peptides by APCs to immature CD4 T cells could lead to the activation and proliferation of CD4+ and CD8+ T cells. Furthermore, Hsp70 is said to have an epitope that is sensitive to NK cells, in which the detection of the epitope will activate the proliferation and cytotoxic activity of NK cells [94].

5. Conclusions

Currently, available breast cancer treatments are hampered by flaws and limitations, thereby drawing efforts to develop other alternative treatments that are more patient-friendly. Chemo-phototherapy has been proven to produce consistent positive outcomes through in vitro and *in vivo* analyses. Importantly, the safety of the chemo-phototherapy application is extensively described and proven, but the effect of the treatment might vary between individuals. Nevertheless, this designated synergistic treatment might reduce our sole reliance on chemotherapeutic drugs in managing the tumor burden by chemotherapy. Integration of the drug delivery system with nanoparticles can also improve the specificity of drug administration, thus reducing adverse reactions.

However, studies on the immunomodulatory effects of chemo-phototherapy synergistic effects are limited. Such data are needed to understand the uncertainties of the body responsible for avoiding adverse outcomes in clinical trials. In addition, while there have been studies delineating the immunological effect of the individual treatment of chemotherapeutic drugs or PTT, information on the combined therapy in antitumor mechanisms involving the immune response is yet to be collected. Therefore, more targeted and niche studies need to be conducted before applying this synergistic treatment in a clinical setting.

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Conflicts of Interest

The authors declare no conflict of interest.

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