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Review Article

Advances in Nanoparticle-Driven Drug Delivery for Targeted Breast Cancer Therapy: A Literature Review.

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Abstract

Background:
Breast cancer (BC) continues to be one of the most prevalent and deadly cancers affecting women, with current treatment modalities often leading to severe systemic side effects and reduced quality of life. Nanomedicine has emerged as a revolutionary approach to overcome these challenges by enabling targeted drug delivery, improving therapeutic efficacy, and minimizing damage to healthy tissues. This review focuses on recent advancements in nanoparticle-based strategies for breast cancer treatment and theranostics.
Methodology:
A systematic literature search was conducted using PubMed, incorporating MeSH terms and Boolean operators related to nanomedicine, cancer, therapeutics, and drug delivery systems. The search was restricted to English-language original research articles published between January 2022 and January 2025. After applying inclusion and exclusion criteria, 35 articles were selected for qualitative synthesis. These were analyzed for recurring themes and categorized accordingly.
Results:
The selected studies revealed a diverse range of nanoparticle designs and functions. Major themes included theranostic nanoparticles, nanoparticles that enhance existing chemotherapies such as DOX, light- and pH-responsive delivery systems, the inclusion of metallic elements (e.g., iron, gold, copper) to improve cytotoxicity, and the incorporation of biocompatible coatings to reduce immune rejection. Many nanoparticles also employed receptor-mediated targeting to improve tumor specificity and reduce off-target toxicity. Lastly, the models utilized for research in each study were assessed.
Conclusion:
Nanomedicine offers a transformative approach to breast cancer therapy by increasing precision and reducing systemic side effects. However, further in vivo studies, long-term safety evaluations, and scalable manufacturing solutions are essential for clinical translation.
Keywords:
Breast Neoplasms, Nanomedicine, Nanoparticles, Drug Delivery Systems, Targeted Therapy

Introduction

Breast Cancer (BC) was the most commonly diagnosed cancer in Canadian women in 2024, accounting for approximately 25% of women's cancers, with an incidence of 69.5 per 100,000 [1,2]. Alarmingly, it is estimated that 1 in 8 Canadian women will develop breast cancer in their lifetime and 1 in 34 women will die from BC [3].

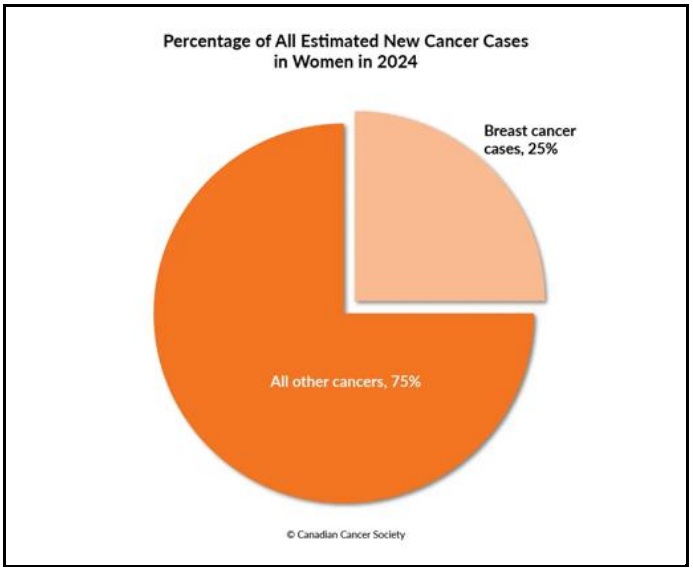

Figure 1: Breast cancer statistics 2024, Canadian cancer society [8].

In Canada, recommendations for BC screening differ between women at standard risk and those at increased risk due to a family history of breast cancer or the BRCA1/2 gene [4,5]. For women at standard risk, mammogram screening is recommended every two years from ages 40–74, and thereafter by referral after age 75 [4,6,7]. For women at increased risk, screening begins at age 30 with mammograms, along with MRI or ultrasound, which are recommended annually until age 70. After that, a mammogram every two years is recommended [4].

If BC is suspected, the diagnostic process includes further imaging, followed by a needle biopsy or mass removal with biopsy [8,9]. A pathologist then identifies the stage of the cells in the mass and determines tumor grade if cancerous, as well as investigates the presence of biomarkers such as estrogen, progesterone, and human epidermal growth factor receptor-2 (HER-2) to predict tumor progression and prognosis [10–13].

The three types of breast cancer this paper will focus on are general breast cancer (with no specific mutations), HER2+ breast cancer, and triple-negative breast cancer (TNBC), which is the most aggressive form of breast cancer [10–13].

Treatments for breast cancer, depending on various patient and tumor characteristics, most often include some combination of surgery, radiotherapy, chemotherapy, hormone therapy, and/or immunotherapies [14,15]. However, these traditional treatments have many limitations that severely affect patients' quality of life. Specifically, chemotherapy, which targets rapidly dividing cells (e.g., cancer cells, hair, nail, and skin cells), has harmful effects on the immune system, leaving patients immunocompromised and vulnerable [16].

Radiation therapy, which targets treatment areas by attacking both cancerous and healthy cells, has similar systemic side effects, including fatigue, skin problems, nausea, loss of appetite, and others[17]. Surgery for breast cancer can be especially challenging for women, often involving procedures such as double mastectomy. Studies have shown that women may experience negative self-image, reduced feelings of femininity and attractiveness, social isolation, and increased post-surgical anxiety and depression [18,19].

However, surgery is rarely the only form of treatment, as at least one round of chemotherapy or radiation is typically administered afterward to ensure no cancer cells remain at the tumor margins. Additional treatments may be required if the cancer has metastasized prior to surgery. Other severe but common side effects of chemotherapy and radiation include infertility, bone thinning, heart damage, and significant emotional and psychological distress [20].

Over the past decade, research has focused on developing new treatments that are more effective and more targeted toward cancer cells to reduce systemic side effects. These include small molecule inhibitors, peptide drugs, monoclonal antibody therapy, antibody-drug conjugates (ADCs), and cell therapies [21–23]. Additionally, emerging approaches include genetic therapies, oncolytic viruses, immunological adjuvants and innate immunity activators, proton and carbon ion therapies, photothermal and photodynamic therapy, and anti-angiogenesis therapies [21–23].

However, challenges remain with many of these therapies, including short half-life, rapid clearance from the bloodstream, non-specific distribution into healthy tissues due to low molecular weight, and difficulties in achieving precise tumor targeting for a wider therapeutic index [16]. Therefore, research has increasingly shifted toward nanomedicine as a promising approach to overcome these limitations.

Nanomedicine refers to the application of nanotechnology for medical purposes, including disease diagnosis, monitoring, control, prevention, and treatment [24]. A wide range of nanomedicines, both approved and in development, leverage their nanoscale size (typically 1–1000 nanometers) to perform targeted and specialized functions within the body [25].

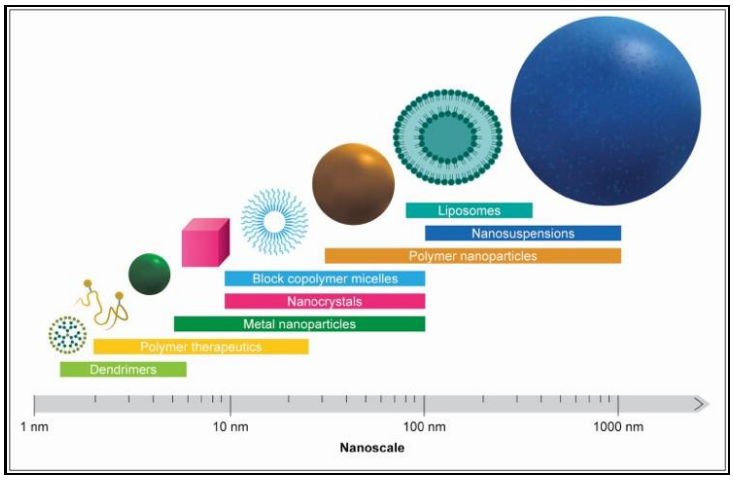

Figure 2: Different Nanomedicine forms and a comparison of their sizes on a 1-1000 nm scale [25].

Nanomedicine possesses unique properties that enhance traditional chemotherapeutic efficacy or enable novel therapeutic effects. These include small size, the ability to be engineered for biocompatibility, improved capacity to cross biological barriers, and controlled release of therapeutic agents [26].

General applications of nanomedicine include diagnosis, drug delivery, regenerative medicine, theranostics, and medical devices and biomaterials [27]. Various types of nanomedicines exist. Dendrimers are synthetically created, highly branched structures capable of delivering DNA, RNA, proteins, drugs, and imaging agents [28]. Polymeric nanoparticles are formed from natural or synthetic polymers and create colloidal particles that vary in size depending on their intended function [29].

Micelles are another form of nanomedicine, self-assembling from amphiphilic molecules to form a drug-carrying hydrophobic core and hydrophilic outer shell, typically 10–100 nm in size [30]. Similarly, liposomes utilize lipids to form a cell-like concentric bilayer structure with hydrophilic heads facing inward and outward, and hydrophobic tails oriented internally [31].

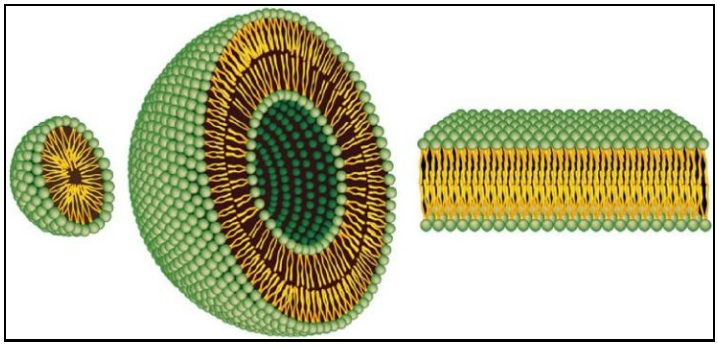

Figure 3: Representation of steric organization of a micelle (left), a liposome (center, and a lipid bilayer (right) [31].

Nanocrystals are another form of nanomedicine, typically used for poorly soluble drugs. These drugs undergo processes to form tiny crystalline particles, improving bioavailability [32].

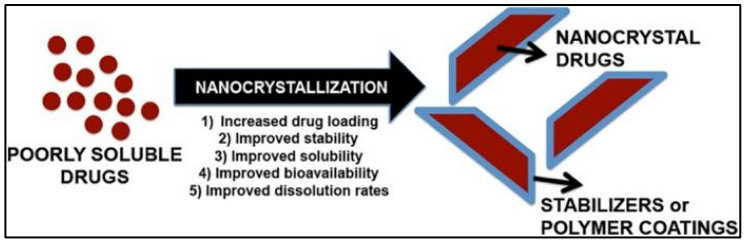

Figure 4: Brief visual process of the process of nanocrystallization, particularly the benefits to poorly soluble drugs [32].

Nanoemulsion techniques are also used for poorly water-soluble drugs. These systems utilize two immiscible fluids to create stabilized droplets (20–200 nm), enhancing drug bioavailability [33]. Nanocomplexes serve as a broader category encompassing nanomedicines not defined by other classifications, including metal-based nanocomplexes that enhance drug delivery or therapeutic activity [34].

Furthermore, organic and inorganic nanocomplexes have gained attention for their roles in improving drug efficacy and disease diagnosis [35]. Overall, nanomedicine offers several advantages, including increased precision, reduced side effects, improved biocompatibility, the ability to cross biological barriers, and high versatility [24,36]. Despite these advantages, nanomedicine is not entirely new, having been conceptualized in the 1960s. However, the first nanomedicine was only approved in 1990, and approximately 80 have since been approved by the Food and Drug Administration (FDA) [37,38]. Challenges remain, including high cost, limited accessibility, lack of dedicated regulatory frameworks, safety concerns, manufacturing difficulties, and translational gaps [24,39].

Ethical concerns also exist, including equitable access to treatment and the implications of diagnosing diseases without available treatments [24,39]. For example, Newborn Screening Ontario only screens for treatable conditions to avoid ethical issues associated with identifying untreatable diseases [40,41]. The current clinical landscape includes approximately 80 approved nanomedicines and hundreds more in development for various diseases. Several examples include Amphotec®, Arikayce®, Onpattro™, Rapume®, Ritalin®, Aristada Initio®, Injectafer®, Adynovate®, Copaxone®, and TriCor® [42–49].

In cancer specifically, nanomedicine has played a significant role in addressing the approximately 20 million new cancer cases annually worldwide [50]. Various nanomedicines have been developed and approved for different cancers, including Lipusu®, Genexol, Nanoxel, Mepact, Marqibo®, Oncaspar®, Vyxeos®, and others [42–55]. Some, such as Ontak®, have been withdrawn due to adverse effects, while others like DaunoXome® were discontinued due to logistical and efficacy-related reasons [44, 56–61]. For breast cancer, approximately 10–15 nanomedicines are currently approved [62–64]. These include Nanocoll, Doxil/Caelyx, Myocet, Abraxane, Lipusu, Genexol, Nanoxel, Kadcyla, Enhertu, Pazenir, and Trodelvy [62–75]. These therapies demonstrate improved targeting and efficacy, particularly in HER2+ and TNBC subtypes.

Despite these advancements, current nanomedicines still face several limitations. Rapid clearance from circulation, potential toxicity, off-target effects, immunogenicity, and nanoparticle aggregation remain significant concerns [76–78]. Additionally, tumor heterogeneity and limited long-term safety data further complicate clinical translation [79].

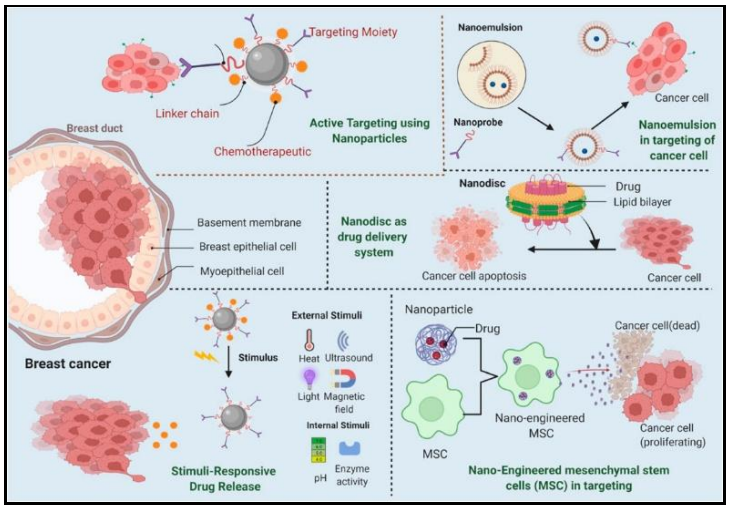

Figure 5: Mechanisms of nanocarriers as drug delivery system in breast cancer [80].

Manufacturing challenges, including scalability and reproducibility, also hinder widespread adoption80. These limitations highlight the need for continued research and innovation in nanoparticle-based therapeutics.

This literature review explores journal articles published between January 2022 and January 2025 that investigate the use of nanoparticles for targeted drug delivery and theranostic applications in breast cancer.

Methodology

Search Strategy

A structured literature search was conducted using the PubMed database to identify relevant studies on nanoparticle-based drug delivery systems in breast cancer. The search strategy incorporated Medical Subject Headings (MeSH) terms alongside keyword variations combined with Boolean operators (AND, OR). Core search terms included "nanomedicine," "nanotechnology," "cancer," "neoplasm," "therapeutics," "drug delivery," and "delivery systems."

To ensure the relevance and recency of the literature, results were limited to articles published between January 2022 and January 2025. Additional inclusion criteria required studies to be (i) original research articles, (ii) available in full text, and (iii) published in English. Review articles, editorials, conference abstracts, and non-peer-reviewed content were excluded.

The initial search yielded 482 records. Following a preliminary screening of titles and abstracts from a subset of articles, it was observed that the majority of relevant studies focused specifically on breast cancer and nanoparticle-based systems. Based on this observation, the search strategy was refined to include breast cancer–specific terminology, resulting in 541 records.

Subsequent screening involved the removal of duplicate records and exclusion of studies that did not meet the predefined inclusion criteria (non-English publications, lack of full text, studies outside the date range, and non-original research). After full-text assessment, a total of 35 studies were deemed eligible and included in the qualitative synthesis.

Data Extraction and Synthesis

Data extraction was conducted using an iterative, theme-based approach. Initially, the 10 most recent studies were reviewed in full to identify recurring patterns and emerging research themes. These preliminary themes included:

- theranostic nanoparticle systems,
- nanoparticles enhancing conventional chemotherapeutics,
- stimulus-responsive delivery platforms (e.g., pH- or light-triggered systems),
- incorporation of metallic components,
- strategies to improve biocompatibility,
- receptor-mediated targeting mechanisms,
- nanoparticle interactions with immune cells, and
- experimental model design (in vitro, in vivo, or combined approaches).

Following this initial thematic framework, the remaining studies were systematically reviewed and categorized according to these predefined domains. Additional subthemes were incorporated where necessary to capture emerging innovations. The synthesized data were then qualitatively analyzed to provide a comprehensive overview of current advancements in nanoparticle-driven breast cancer therapeutics and drug delivery systems.

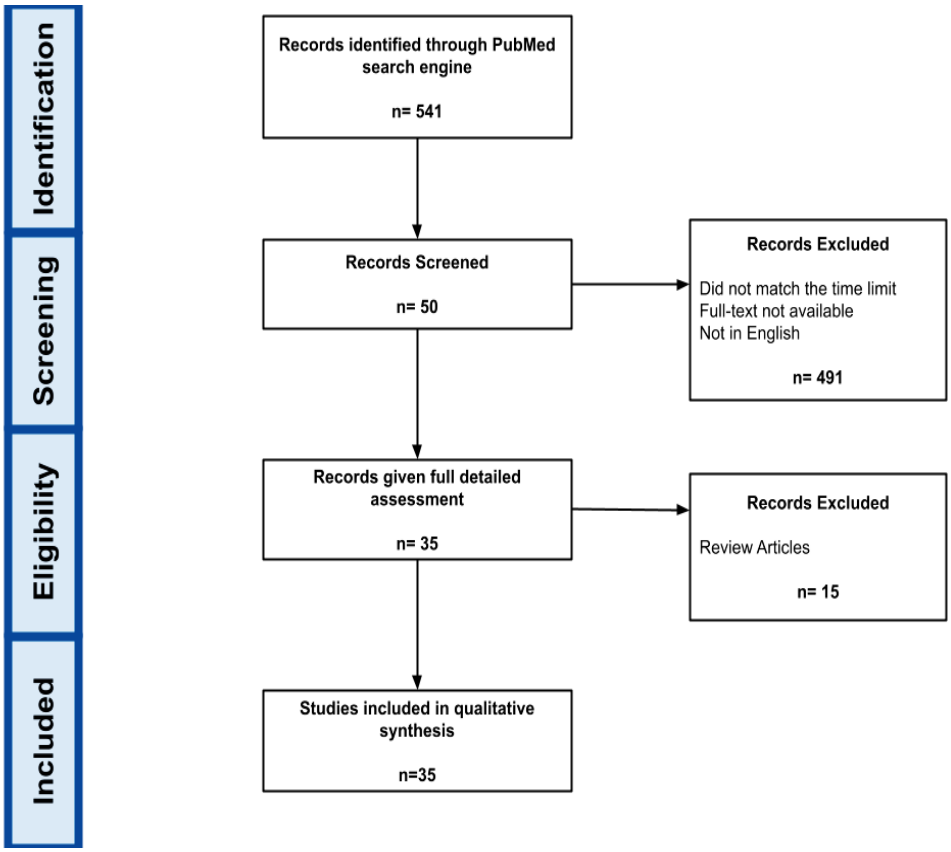

Figure 6: Flow diagram of selected studies

Breast Cancer Nanoparticles Combining Both Diagnosis and Treatment – The Imaging Aspect of Theranostics

Theranostics is the term used to describe the co-delivery of a radioactive or fluorescent compound along with a therapeutic compound to both image/diagnose and treat cancer simultaneously [81]. A study published in late 2022 sought to use cell membrane-coated polymeric nanoparticles containing a chemotherapeutic as well as imaging agents to bind to target tumor cells, release the chemotherapeutic agent, and visualize the target cells [16].

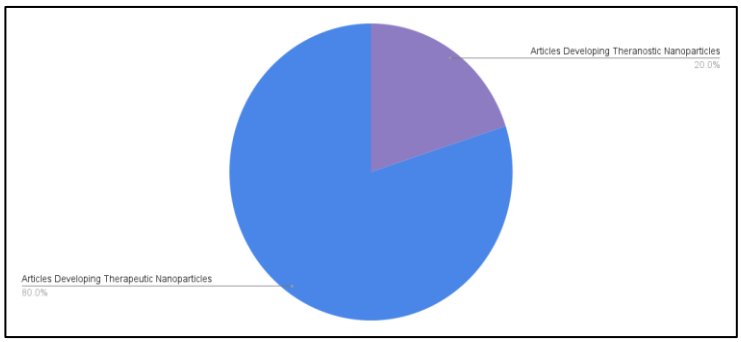

Figure 7: Distribution of nanoparticle engineering strategies in selected studies: 20% incorporating theranostic capabilities, 80% lacking theranostic functionality.

In terms of imaging, this study utilized red blood cell membrane-coated nanoparticles (RBC-NPs) and untreated cells as comparisons for the fluorescence capabilities of the new nanoparticle model they aimed to validate, namely the targeted theranostic human red blood cell-coated polymeric nanoparticles (TT-RBC-NPs) with fluorescein isothiocyanate (FITC) as the imaging agent [16]. The theranostic targeting was specifically directed toward the epithelial cell adhesion molecule (EpCAM), which is a well-known marker of EpCAM-positive MCF-7 breast cancer cells and is minimally expressed in normal human cells such as fibroblasts [16]. When the TT-RBC-NPs bind to EpCAM on tumor cells and are internalized, they subsequently fluoresce. The results demonstrated that TT-RBC-NPs successfully bind to MCF-7 cells and are taken up to a greater extent than RBC-NPs and untreated controls, as evidenced by increased fluorescence (Figure 8). Furthermore, the results validated that the FITC imaging agent can fluoresce when TT-RBC-NPs are internalized within tumor cells [16]. However, this study was a pilot study, as the nanoparticles were only tested in 2D and 3D in vitro models; therefore, further research, including in vivo mouse studies, is required before these findings can be applied to humans [16].

Mouse models were utilized in a study published in March 2024 that aimed to use the imaging component of a theranostic nanoparticle platform for image-guided monitoring of breast cancer metastasis [82]. This study engineered a breast cancer cell-derived nanovesicle encapsulating DOX as a chemotherapeutic, along with photothermally active emissive organic dyes and plasmonic gold nanoparticles, forming a platform abbreviated as AuNPs@BCMNVs-ICG NPs [82]. Multimodal imaging techniques, including whole-body near-infrared fluorescence (NIRF) scans and IVIS spectrum computed tomography scans, were used to detect tumors and their metastases [82]. This was achieved by injecting 7-week-old 4T1 breast cancer tumor-bearing female mice with 1.2×10^{11} nanoparticles/cm³ of AuNPs@BCMNVs-ICG NPs. The mice were then subjected to imaging at various pre-specified time points between 0.5 and 168 hours post-injection to measure radiodensity in the heart, liver, spleen, kidneys, and tumor [82]. The results showed that AuNPs@BCMNVs-ICG NPs were effective in imaging and visualizing nanoparticle accumulation within tumors and metastases across multiple organs at 0.5, 3, 6, 12, 24, 72, and 168-hour time points, with varying intensities depending on tumor load, which were validated through dissection findings (Figure 5) [82]. One limitation of this study is that it did not investigate metastasis in other common sites such as the lymph nodes, bones, lungs, and brain.

Human epidermal growth factor receptor-2 positive (HER2+) and triple-negative metastatic breast cancer (MBC) account for approximately 13% of incident breast cancer cases per year, and nearly 33% of metastatic breast cancer patients with these subtypes develop brain metastases [83]. In 2023, Lim et al. published a study focused on developing a nanoparticle platform to deliver DOX and imaging agents to brain metastases resulting from breast cancer83. They designed hyperbranched polymeric nanoparticles conjugated with fragments of a bispecific antibody targeting human epidermal growth factor receptor 3 (HER3), a receptor commonly overexpressed in breast cancer cells, particularly in HER2+ and MBC cases, to encapsulate DOX and a radioactive isotope for tumor and metastatic targeting [84]. The radioactive isotope used was zirconium-89 (^{89}Zr). PET and MRI imaging conducted at 24 hours demonstrated that nanoparticles with HER3 targeting, compared to non-HER3 hyperbranched polymers, successfully penetrated brain metastases, and that ^{89}Zr could be effectively visualized (Figure 6) [84]. Furthermore, there was a preferential difference in nanoparticle targeting based on metastatic presence, with tumor-associated brain regions showing 1.25% injected dose per gram (ID/g) of ^{89}Zr compared to 0.31% ID/g in unaffected brain regions [84].

Similarly, a study by Scialla et al. (2023) utilized iron oxide nanoparticles as the imaging agent within a wax-based nanovehicle containing both an imaging component and DOX for a triple-negative breast cancer (TNBC) tumor model85. Their results demonstrated that iron oxide nanoparticles were highly effective as a T2 contrast agent for MRI imaging, achieving a high transverse relaxivity (r2) value of 460–570 $mM^{-1}\cdot s^{-1}$85. This is significantly higher than previously approved agents such as Resovist and Feridex, which have r2 values of 61 $mM^{-1}\cdot s^{-1}$ and 41 $mM^{-1}\cdot s^{-1}$, respectively, indicating superior contrast enhancement capabilities [85].

A study published in 2022 by Whitaker et al. also developed a nanoparticle platform leveraging iron oxide for theranostic imaging [86]. Specifically, they designed a Janus nanoparticle (jNP) system incorporating ultrasmall superparamagnetic iron oxide nanoparticles (USPIONs), antibody targeting for either TNBC or pancreatic cancer (PDAC), a self-assembling zwitterionic microbubble, and a DNA capsule for the delivery of microRNA-126 [86]. The results demonstrated that the jNPs exhibited shorter T2 relaxivity and improved tumor contrast in MRI (Figure 6) compared to both a blank control and a previously validated polyethylene glycol (PEG)-based theranostic with the same contrast agent (PEG-USPION) [86]. However, as this study included both TNBC and PDAC models and all imaging results were derived from PDAC tumor models, it is difficult to draw direct conclusions for breast cancer applications [86].

Another study published in 2024 by Pires et al. also utilized metal-based contrast agents within their nanoparticle formulation [87]. Their nanoparticle structure consisted of mesoporous silica (MCM-41), functionalized with amine groups, conjugated with the therapeutic agent diethylenetriamine pentaacetate (DTPA), and incorporated with a gadolinium cation (Gd^{3+}) for imaging, forming MCM-41-NH_2-DTPA-Gd^{3+} [87]. In vitro, relaxometry and phantom

studies were conducted to evaluate the effectiveness of Gd^{3+} as a contrast agent compared to previously validated agents before proceeding to in vivo experiments [87]. The in vivo results demonstrated a strong Gd^{3+} concentration-dependent signal effect (R^2 = 0.996). However, paired t-tests comparing voxel values obtained using Gd^{3+} and normalized voxel values from 2D regions of interest did not show statistically significant differences [87]. Nonetheless, the in vivo relaxometry study demonstrated statistically significant improvements, with Gd^{3+} showing a longitudinal relaxivity (r1) of 6.7 $s^{-1}\cdot mM^{-1}$ compared to 4.3 $s^{-1}\cdot mM^{-1}$ for the commercially used Magnevist (Gd-DTPA)87. Subsequent in vivo imaging confirmed significantly enhanced tumor contrast in T1-weighted MRI scans 15 minutes post-injection compared to pre-injection (Figure 8), supporting the potential superiority of Gd^{3+} [87]. The study acknowledged that further research is required to evaluate dosing, safety, and long-term effects of Gd^{3+} [87].

The final study employing a theranostic nanoparticle approach was published in 2022 by Kang et al., which aimed to treat TNBC using focused ultrasound ablation [88]. In this study, AS1411, a molecule known to inhibit the proliferation of cancer cells, was used to modify polyethylene glycol–poly(lactic-co-glycolic acid) (PEG-PLGA) nanoparticles to encapsulate perfluorohexane (PFH) and DOX, forming AS1411-DOX/PFH-PEG@PLGA, abbreviated as A-DPPs [88]. Focused ultrasound ablation induced a phase transition in PFH, enabling intratumoral imaging in vivo. The results demonstrated that A-DPPs exhibited higher gray values compared to saline and blank nanoparticle controls, indicating higher signal intensity and superior imaging performance (Figure 5) [88].

Enhancing Existing Breast Cancer Chemotherapies – Synergistic Nanoparticle Approaches

Seventeen of the thirty-five NPs created and reviewed in this literature review chose to synergistically enhance a variety of previously used chemotherapeutics, as they have already been clinically proven to have the capability to treat breast cancer and have been used for multiple years with validated safety.

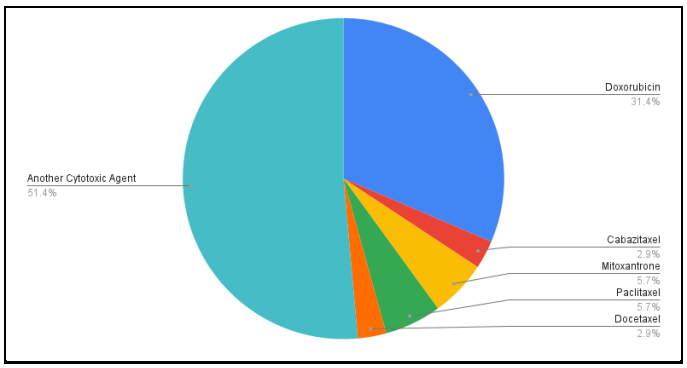

Figure 8: Use of chemotherapeutics and other cytotoxic agents in breast cancer nanoparticle targeting.

The most commonly used chemotherapeutic in the new NPs, appearing in eleven of the seventeen, was DOX [16,82,84,85,88-94]. The first NP is the theranostic TT-RBC-NP platform and was found to have the greatest cytotoxicity toward MCF-7 2D tumor cultures compared to free DOX and non-targeted RBC-NPs as shown in Figure 5 of Marshall et al. [16]. Furthermore, in 3D in vitro MCF-7 tumor spheroid models, TT-RBC-NP-treated cells displayed the lowest viability at 4, 24, and 48-hour time points, and they also exhibited the most cell death (red channel cells) at 4 and 24 hours (Figure 6) [16].

Another study investigated their NP platform to compare the effects on tumor volume and mouse survival of combination DOX, photothermal therapy, and photodynamic therapy, compared to no treatment and each therapy individually [82]. Findings indicated that the DOX synergistic therapy statistically significantly decreased tumor volume in mice bearing 4T1 breast cancer tumors, and after 6 weeks, the combination therapy group had the only surviving mice (Figure 6) [82].

In 2023, Yu et al. developed a photoacoustic imaging-guided NP with synergistic therapies, which demonstrated greater tumor inhibition than free DOX alone [94]. Their most effective NP platform was an all-in-one biodegradable polydopamine-coated UiO-66 framework nanomedicine (DUPM) with DOX and near-infrared light triggering (NIR) (DUPM-NIR), which was more efficacious at reducing the viability of 4T1 tumor cells as demonstrated in Figure 8G of Yu et al. [94].

A study published in 2023 by Lim et al. unsuccessfully developed an NP carrying DOX with greater efficacy in decreasing cell viability compared to free DOX (Figure 3) [84]. Similarly, another 2023 study using PEG-PLGA-DOX-NPs treated MDA-MB-231 breast cancer cells in vitro and assessed metabolic activity at 24, 48, and 72 hours [90]. Their results also showed that the designed DOX-NPs did not perform better at reducing metabolic activity, and thus tumor cell viability, compared to free DOX at all time points and concentrations. At 48 and 72 hours, the differences at all DOX concentrations were statistically significant (Figure 3) [90].

Furthermore, the AS1411-DOX/PFH-PEG@PLGA theranostic NP, although effective at visualizing tumors, was not as successful at reducing the viability of 4T1 tumor cells in vitro [88]. The NPs were only able to reduce viability to approximately 70%, whereas free DOX reduced viability to less than 20% as shown in Figure 2B of Kang et al. [88].

Another study published in 2024 created mesoporous silica nanoparticles (MSN) with polyethylene glycol (PEG) and trimethylammonium chloride (TA), MSN-PEG/TA 25, to encapsulate liposomal DOX (lipo-DOX) [92]. Results indicated that lipo-DOX incorporated into the MSN-PEG/TA 25 carrier outperformed lipo-DOX alone in increasing survival of 4T1 tumor-bearing mice when administered both intratumorally and intravenously [92]. However, this study did not compare the engineered NPs or liposomal DOX to free DOX, which is a major limitation in determining the efficacy of these additional manufacturing processes compared to validated DOX [92].

This limitation was also observed in a study that developed molecularly imprinted nanoparticles (nanoMIPs) with the alpha receptor epitope of estrogen (ERα) to encapsulate DOX [91]. Their in vitro 2D cytotoxicity assays demonstrated that both nanoplatforms containing DOX showed significant cytotoxicity to MCF-7 cells, with approximately 80% cell death after 72 hours [91]. However, the comparison groups included only nanoMIPs without DOX and lacked a free DOX control, which limits the ability to validate whether this platform is more efficacious than free DOX [91].

Many of these studies utilized DOX; however, only a few discussed potential side effects associated with its use. One study synthesized a modified peptide-targeted polyethylene glycol–acitretin conjugate (RPA) and a DOX-loaded RPA micelle (RPADm) [93]. In vivo results demonstrated that RPADm was highly effective at inhibiting

tumor growth of MCF-7 cells in mice compared to saline and free DOX; however, mice treated with DOX-loaded micelles showed increased body weight, suggesting a potential, yet uninvestigated, side effect [93].

Importantly, one study highlighted that DOX may contribute to TNBC metastasis through epithelial–mesenchymal transition (EMT) of cancer stem cells (CSCs) [89]. Free DOX-treated MDA-MB-231 and 4T1 cells exhibited increased expression of N-cadherin, Snail, Slug, and Vimentin, confirming that DOX promotes EMT in breast cancer cells (Figure 2E) [89]. Based on this, the researchers developed a combination NP incorporating DOX and dietary indole-3,3'-diindolylmethane (DIM) to target CSC-mediated EMT and breast cancer metastasis. This approach successfully reduced EMT markers and decreased cell viability in both breast cancer cell lines in vitro as shown in Figure 4 A and B of Shankar et al. [89].

A chemotherapeutic used in only one study was Cabazitaxel (CBZ), which binds to tubulin in microtubules during mitosis, thereby inhibiting cell division and tumor proliferation [95]. The authors had previously developed poly(2-ethylbutyl cyanoacrylate) NPs encapsulating CBZ (PEBCA-CBZ-NPs), which reduced M2 macrophages associated with tumor persistence [96]. In the current study, they compared two biodegradable poly(alkyl cyanoacrylate) (PACA) variants, PEBCA and PEHCA, loaded with CBZ to assess their effects on tumor cell viability [96]. In mice with patient-derived xenograft breast cancer models (HBCx39), both NP formulations reduced tumor volume more effectively than CBZ alone, with no statistically significant difference between the two NP formulations as shown in Figure 7 A of Valsalakumari et al. [96].

Two studies used Mitoxantrone (Mito), a chemotherapeutic that disrupts topoisomerase II activity, leading to DNA damage and cancer cell death [97]. One study utilized solid lipid nanoparticles (SLN) functionalized with distearoyl phosphatidylethanolamine–poly(ethylene glycol)–folic acid (DSPE-PEG-FA) to encapsulate Mito, resulting in greater reduction in MCF-7 cell viability compared to free Mito (Figure 4B) [97]. Another study encapsulated Mitoxantrone (MTO) within mesoporous organosilica drugs (MODs) and similarly demonstrated improved efficacy compared to free Mito (Figure 4) [98].

Taxanes, including Paclitaxel and Docetaxel, are another class of anti-breast cancer chemotherapeutics that function similarly to CBZ by stabilizing microtubules required for cell division [99]. In this review, two studies used Paclitaxel and one used Docetaxel. The study by Kharazmi and Attaran synthesized gold nanoparticles coated with polyethylene glycol and conjugated with Paclitaxel under different conditions to evaluate their effects on MCF-7 cells in vitro [100]. Their results showed that various concentrations of GNP-PEG-Paclitaxel reduced cell viability; however, the study lacked comparison to free Paclitaxel or other treatments, limiting its validity (Figure 10) [100].

In contrast, another study using Paclitaxel (PXL) included multiple control groups for their poly(propylene sulfide) nanoparticles (PPS-NPs), including PPS-NPs alone, NP-encapsulated PXL, PXL combined with anti-PD-1 immune checkpoint blockade, PXL alone, and saline [101]. Results from an estrogen receptor-positive breast cancer cell line (E0771) demonstrated that tumor volume decreased at 17 days post-treatment in NP-PXL groups compared to PXL alone. Additionally, the combination of NP-PXL with immune checkpoint blockade showed the greatest tumor reduction among all groups as demonstrated in Figure 2B-D of Manspeaker et al. [101].

Docetaxel (DTXL) was used in a study developing micro-combinatorial hydrogel particles (μCGP) to encapsulate the drug, and TNBC cell viability was assessed in vitro [102]. There was no statistically significant difference between the reduction in cell viability observed with DTXL-μCGPs, the comparator DTXL-SPN(), and free DTXL as shown in Figure 4D of Palange et al. [102].

Therapeutics Veering Away from Existing Chemotherapies

As seen in Figure 7, eighteen, or just over half, of the NPs created and reviewed in this literature review took a different approach to breast cancer treatment in their models, veering away from incorporating traditional chemotherapy and instead using a variety of agents to target different pathways, with the ultimate goal of BC suppression. This section will briefly explore why each of these nanomedicine systems did not incorporate traditional chemotherapeutics.

Firstly, Askar et al., in their 2023 paper exploring amygdalin-folic acid NPs, very simply explained their deviation from traditional chemotherapies as being due to the well-known systemic side effects on healthy somatic cells [120]. Additionally, two papers stated that their nanomedicine platforms for BC treatment were explored over traditional chemotherapy because the nanoscale design allows for improved tumor penetration and prolonged circulation in the bloodstream [103,118].

In a paper published by Li et al. in 2024 [111], their nanoparticle therapeutic was designed to induce BC cell cuproptosis and target immune checkpoint inhibition. The researchers explored more novel pathways of cell death, as BC cells and other cancer cells can often develop resistance to apoptotic and necrotic pathways, which are the primary mechanisms of action for traditional chemotherapies [111].

In contrast, a paper entitled Bispecific Aptamer-decorated and light-triggered nanoparticles targeting tumour and stromal cells in breast cancer-derived organoids: implications for precision phototherapies [105] acknowledged a limitation of traditional chemotherapies: although they exert systemic effects on highly proliferative somatic cells, they often fail to effectively target the entire tumour microenvironment (TME). Specifically, they do not adequately address the complex cross-talk between cancer and stromal cells, which supports tumour growth, progression, and chemoresistance [105]. Therefore, this nanomedicine design aimed to target both tumour cells and stromal components, effectively addressing the entire TME [105].

Another study designed a nanomedicine platform to leverage specific characteristics of the TME [115]. Huang et al. utilized a hypoxia-responsive dimeric prodrug, hQ-MMAE2, to exploit the naturally hypoxic core of BC tumours, a feature that traditional chemotherapeutics cannot specifically target [115]. Similarly, another study leveraged the weak acidity of the TME to activate the therapeutic agent within a magnetically modified nanoparticle specifically at the tumour core, which again is not achievable with traditional chemotherapies [112]. Likewise, Yang et al. designed their NP platform to respond to TME pH conditions to achieve highly specific BC tumour cell toxicity [107].

Another study acknowledged the harmful systemic side effects commonly associated with traditional chemotherapies and instead utilized gene silencing to specifically target cancer cells, as published by Abassi et al. in 2023 [117]. Their nanoplatform incorporated short interfering RNA (siRNA) particles to overcome the non-specific

cellular targeting of conventional chemotherapy [117]. Similarly, Combined Photosensitive Gene Therapy Effective Against Triple-Negative Breast Cancer in a Mouse Model by Hu et al. developed a nanomedicine approach using gene therapy combined with photodynamic therapy, again considering the systemic toxicity of traditional chemotherapies [104].

Additionally, Ragnhild et al., in their 2022 paper, highlighted the strong potential of DNA/RNA-based gene therapies for both TNBC and pancreatic cancer, while noting that no FDA-approved systemic delivery systems for tumour treatment were available at that time [86]. Their study explored the development of a Janus USPION Modular Platform (JUMP), which, consistent with the goal of targeted tumour delivery with minimal damage to surrounding somatic cells, did not include chemotherapy [86]. Furthermore, research by Ferreira-Goncalves et al. in 2022 discussed how current chemotherapies, radiation therapies, immunotherapies, and hormone therapies can have drastic impacts on patients' lives, negatively affecting self-esteem and causing toxicity to surrounding cells [106].

The paper published in 2024 by Glass et al. [119] aimed to develop a nanomedicine platform to address the high mortality associated with metastatic BC. The researchers recognized the limitations of traditional chemotherapies in preventing early-stage BC from progressing to metastasis, leading to the development of a nanomedicine incorporating bisphosphonates, an RALA (R-) peptide delivery system, and risedronate (R-RIS) [119]. However, their findings suggested that while R-RIS is beneficial in targeting pathways involved in metastasis, it would need to be combined with standard chemotherapies to more effectively treat primary tumour sites [119].

In contrast, research by Bonet-Aleta et al. utilized polydopamine nanoparticles (PDA NPs) alone to deplete intracellular labile copper pools in a TNBC model, a strategy previously combined with traditional chemotherapies [110]. Building on prior success with combination therapies, this study aimed to evaluate the standalone cytotoxic potential of PDA for improved cost-effectiveness and reduced systemic toxicity [110].

An aggressive and often metastatic form of BC, accounting for approximately 70% of cases, is hormone receptor (HR)-positive BC [121]. Fulvestrant, a common antagonist used in HR-positive BC treatment, blocks estrogen-mediated tumour growth but exhibits low cytotoxicity [121]. This limitation led to the development of a trimodal nanoparticle system by Zhi et al., which avoided traditional chemotherapeutics due to the better responsiveness of HR-positive cancers to hormone therapy [121].

Conversely, TNBC and HER-2 breast cancers are not responsive to hormone therapy, prompting research in 2023 utilizing algae-derived silver nanoparticles [113]. This study outlined five key reasons for exploring alternative cytotoxic agents over traditional chemotherapies: low specificity, rapid biodegradation, limited targeting ability, rapid drug clearance, and an increased risk of cancer recurrence [113].

Additionally, research by Scully et al. in 2023 explored overcoming issues of bioavailability, tumour delivery, and off-target toxicity commonly associated with chemotherapies by using a B-cell lymphoma 2 (BCL-2) inhibitor for TNBC [116]. Their nanoparticle platform encapsulated the inhibitor within poly(lactic-co-glycolic acid) and a phospholipid membrane derived from 4T1 murine mammary cancer cells, aiming to overcome chemoresistance associated with traditional therapies [116].

Lastly, a study by Pires et al. recognized the need for a chemotherapeutic agent within their NP design but selected a novel agent, MIH 2.4BI [87]. This compound has a unique structure that facilitates cellular penetration and acts as an intracellular antitumour agent, with charge distribution properties that enhance interactions with DNA and proteins [87].

Advancements with Light-Triggered and Photothermal Nanoparticulate Therapies Versus pH-Triggered Drug Delivery Systems to Specify Nanoparticles for Tumor Microenvironment Delivery

A unique characteristic of nanoparticles is their capability to be engineered to release therapeutics in a targeted, controlled manner, often with a prolonged release time to enhance therapeutic effects in patients. In this literature review, some studies explicitly designed their therapeutics to release upon two stimuli: a change in pH and a light-triggered event. This section will therefore explore the basis of platforms using these designs, the reasoning for this type of release, the success of the NP design, and the merits and challenges identified.

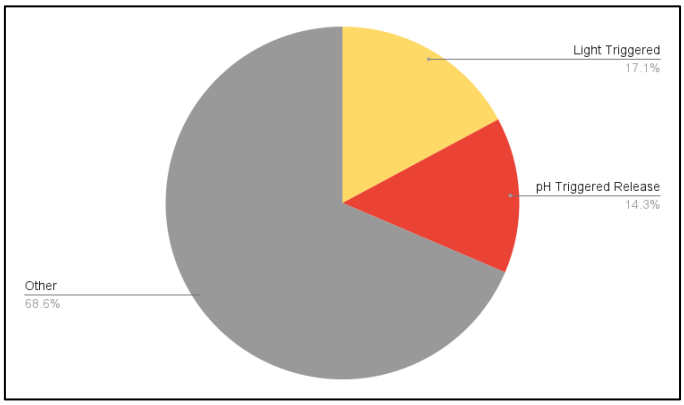

Figure 9: Triggered release mechanisms in reviewed studies: light, pH, or other methods.

Firstly, a paper published in 2023 by Mezghrani et al. built their NP platform on the concepts of photodynamic therapy (PDT) and photochemical internalization (PCI), which use light to induce disruption of cell membranes and are leveraged in cancer treatments for tumour cell death [103]. Specifically, two-photon excitation (TPE) is used to release porphyrin, the photosensitizer, from periodic mesoporous ionosilica nanoparticles (PMINPs), which also contain pro-apoptotic siRNA to induce cell death [103]. They found that their NP platforms, both PMINPs with PCI and siIAP/PMINPs, were able to reduce the viability of MDA-MB-231 BC cells compared to controls (Figure 4) [103]. The reduction in cell viability was attributed to disruption of the cell membrane via PCI, as well as the production of reactive oxygen species (ROS) from excitation [103]. siRNA also contributed by silencing genes required for tumour cell survival [103].

Hu et al., in a study published in 2024, also employed a photosensitizer with light triggering to disrupt the cell membrane and deliver a cytotoxic gene therapy [104]. Specifically, they developed positively charged amphiphilic triphenylphosphine-tocopheryl polyethylene glycol succinate (TPS) nanoparticles with a chloride e6 (Ce6) photosensitizer (TPS@Ce6) combined with microRNA-34a (miR-34a) to enhance PDT [104]. In vitro, all NP combinations with light (+L) performed best at reducing MDA-MB-231 cell viability,

and in vivo, the light-triggered NP treatment reduced tumour volume and N-cadherin expression, indicating reduced metastatic potential. However, the study did not address the lack of increased expression of pro-apoptotic caspase 3 (Figure 4) [104].

A previously discussed study incorporating DOX utilized a biodegradable polydopamine-coated UiO-66 nanomedicine (DUPM) combined with near-infrared (NIR) light triggering for synergistic effects [94]. They found that NIR exposure increased ROS generation from the NP, leading to depletion of 4T1 BC cells and enhanced PDT via redox reactions that depleted excessive glutathione in tumour cells [94].

Two studies utilized metal-based components for PDT nanoparticles. The first used gold-core/silica-shell nanoparticles to encapsulate water-soluble iridium (III) complexes as the photosensitizer (Iren-AuSiO2) [105]. These NPs were conjugated with targeting ligands, including EGFR-targeting (CL4), resequenced CL4 (Scr), and PDGFRβ stromal cell targeting (Gint4.T) [105]. Following injection and 254 nm light irradiation in BT-549+MSC and MDA-MB-231+MSC models, all NP combinations except Scr significantly reduced tumour cell viability through photodynamic mechanisms as demonstrated in Figure 5C–E of Camorani et al. [105].

The second study using gold nanoparticles (AuNPs), synthesized with rosmarinic acid, evaluated cytotoxicity at various ratios against L929, MDA-MB-231, MCF-7, and 4T1 cells as shown in Table 1 of Ferreira-Gonçalves et al. [106]. However, this study was preliminary, as viability assays were conducted without laser irradiation (Figure 12), thus lacking the PDT component [106].

In contrast, another study compared the cytotoxic effects of their NP platform with chemotherapy, PDT, photothermal therapy (PTT), and combinations thereof [82]. Their NP incorporated metastatic cell-derived nanovesicles with gold NPs, organic dye, DOX, and indocyanine green (a PTT agent). Results showed that combination therapy was most effective in reducing tumour volume and improving survival in 4T1 mice as demonstrated in Fig. 6D and E of Prasad et al. [82].

pH-controlled release of NP therapeutics relies on differences in pH between healthy tissues (pH 7.4), tumour tissue (pH 6.8), and endosomes (pH 4.5–6.8) [84]. One study developed a hyperbranched polymer (HBP) NP incorporating a HER3 bispecific antibody, DOX, and an acid-sensitive hydrazone linkage as shown in Abstract Figure of Lim et al. [84]. The NP successfully increased DOX release at lower pH levels (Figure 1); however, it did not demonstrate greater cytotoxicity than free DOX, indicating the need for further optimization [84].

Another study utilized pH differences to evaluate mitoxantrone (Mito) release from DSPE-PEG-FA nanoparticles [97]. At pH 5.0, representing tumour and endosomal conditions, Mito release reached 56% at 8 hours and 82% at 24 hours, compared to 12% and 32% at physiological pH 7.4 (Figure 2) [97]. Although slightly more effective at reducing BC cell viability, the mechanism underlying pH-dependent release was not clearly explained [97].

In contrast, Yang et al. clearly described their pH-responsive hybrid cell membrane (pH-HCM), composed of platelet membranes and pH-responsive vesicles, to facilitate release of iron–gallic acid coordination polymer nanodots (FeCNDs) (pH-HCM@FeCNDs) (Figure 1) [107]. They also incorporated PTT for comparison. In vitro results showed that FeCNDs with laser treatment slightly improved cell killing as shown in Figure 6A–C of Yang et al., while in vivo studies demonstrated that the combined pH-HCM@FeCNDs+laser treatment most effectively reduced tumour volume and weight (Figure 8) [107].

One study did not use pH to trigger drug release but instead investigated its effect on paclitaxel loading into nanoparticles [100]. Results showed greater loading efficiency at pH 4.1 compared to pH 6.7 and 11.1 (Figure 9), highlighting the need for further studies on pH-dependent drug release mechanisms [100].

Lastly, Scialla et al. explored a novel approach targeting tumour-associated macrophages (TAMs), particularly M2 macrophages, which support tumour persistence [85]. They developed lipid-core nanoparticles containing carnauba wax, iron oxide NPs, and DOX, with an outer mannose ligand targeting macrophages and an acid-sensitive PEG cap [85]. In vitro comparisons of acid-sensitive (AS_mLNVs-DOX), pH-insensitive (AI_mLNVs-DOX), and untreated cells showed increased uptake of acid-sensitive NPs by M2 macrophages under acidic conditions, mimicking the TME (Figure 4) [85]. Minimal uptake occurred at physiological pH, as the PEG cap remained intact without acid-triggered removal [85].

Metals and Elements in Nanoparticle Design – Focusing on Enhancing Therapeutic Potential

Metals are often used in therapeutics, particularly in cancer therapeutics, because they possess the ability to induce redox reactions and be “reactive” in ways that cause cellular damage, ultimately leading to tumour cell death [108]. Alternatively, metals can be used to encapsulate therapeutics due to their stability, strength, and relative biocompatibility. This section will explore the incorporation of metals into generated NPs, specifically iron, gold, silver, copper, and iridium.

Beginning with an interesting design incorporating iridium as a photosensitizer in a gold-core/silica-shell NP, a study by Camorani et al. in 2024 aimed to leverage energy transfer processes, with iridium acting as the donor and gold as the acceptor, to convert received energy into heat for tumour cell damage [105]. Although the study did not specifically investigate the interaction between the two metals, it evaluated extinction spectra over 28 days and concluded that the gold core provided excellent stability, with no significant variation over time (Figure 4) [105].

Another article used gold as an imaging agent when exposed to near-infrared (NIR) light, resulting in no direct effect on cell viability; however, the presence of gold (Au) in different formulations increased hemolysis, contrast value, radiant efficiency, and the photoacoustic signal-to-noise ratio during imaging [82]. In contrast, a study published in 2022 aimed to use gold as an NIR-responsive element for photothermal therapy (PTT) [106]. However, this study only evaluated the safety of AuNPs without NIR stimulation in vitro across various BC cell lines and in vivo in brine shrimp, leaving uncertainty regarding their effectiveness for tumour cell damage [106].

Cuproptosis and cuproplasia are newly identified forms of cell growth dependent on copper, which acts as a cofactor for enzymes required in cell proliferation. Two articles in this review targeted these pathways for BC cell death [109,110]. Firstly, Bonet-Aleta et al. developed polydopamine nanoparticles (PDA NPs) to disrupt copper-dependent pathways [110]. The PDA surface contains metal-chelating groups designed to deplete intracellular copper in MDA-

MB-231 TNBC and MCF-7 BC cells [110]. Their NP platform reduced cell viability in both cell lines (Figure 2a, Bonet-Aleta et al) and disrupted redox balance, leading to increased reactive oxygen species (ROS) production as shown in Figure 3a&b of Bonet-Aleta et al., ultimately causing cellular damage and death [110].

The second study developed a core-shell nanoscale polymer (NCP) NP incorporating copper (Cu II) and a triphenylphosphonium conjugate of 5-carboxy-8-hydroxyquinoline (TI) to induce cuproptosis [111]. The proposed mechanism involved TI functioning as an ionophore to transport Cu II into mitochondria, leading to downregulation of PD-L1 expression. Since PD-L1 suppresses immune responses, its downregulation promotes immune activation, along with the release of damage-associated molecular patterns (DAMPs) [111]. Results demonstrated that Cu/TI NPs reduced tumour weight and size in 4T1 models as shown in Figure 5 g & h and increased immune cell infiltration, restoring an anti-tumour inflammatory response in Figure 6 of Li et al. [111].

Five studies utilized iron in their NP formulations. The first targeted TNBC using iron oxide NPs combined with DOX [85]. Iron was incorporated in the form of superparamagnetic iron oxide nanoparticles (SPIONs), intended to enhance membrane affinity and improve therapeutic delivery [85]. The study found that their formulation improved DOX stability and targeting compared to free DOX and DOX-only nanovesicles. Additionally, incorporation into nanovesicles prevented SPION aggregation, which would otherwise hinder cellular uptake [85].

Another study utilized ultrasmall iron oxide nanoparticles (USPIONs) alongside DNA/RNA targeting systems and zwitterionic microbubbles to target TNBC, although USPIONs were primarily used for imaging, and no therapeutic results were reported [86].

Two studies incorporated iron as magnetite (Fe_3O_4). One study used Fe_3O_4 to generate magnetic mesoporous organosilica drug carriers (MODs) loaded with mitoxantrone (MTO), enhancing tumour targeting and therapeutic efficacy [98]. Their results showed improved reduction in cancer cell viability when magnetically modified as demonstrated in Figure 6D of Cubells et al. [98].

The second Fe_3O_4-based study incorporated phosphotungstate (PTA) to facilitate electron transfer between ferric and ferrous ions within the NP [112]. While the design effectively reduced cell viability, the study primarily focused on comparing the addition of serine and gluten. Silicon dioxide (SiO_2) was used to coat Fe_3O_4 particles for stabilization [112].

The final iron-based study utilized iron–gallic acid coordination polymer nanodots (FeCNDs) combined with a pH-responsive platelet-based hybrid membrane (pH-HCM) to form pH-HCM@FeCNDs [107]. Fluorescence results indicated increased intracellular ROS levels in 4T1 cells following treatment as shown in Figure 5 of Jalilian et al. Additionally, the photothermal properties of the iron-based platform were demonstrated through irradiation, which increased temperature to levels capable of inducing cell ablation [112].

Lastly, one study incorporated silver into its nanoparticle design, specifically developing green silver nanoparticles (AgNPs) coated with Noctiluca scintillans algae extract [113]. Gas chromatography analysis identified bioactive compounds such as n-hexadecanoic acid, beta-sitosterol, stigmasterol, and palmitic acid, all of which possess anticancer activity [113]. Cytotoxicity assays showed that algae-derived AgNPs reduced the viability of MDA-MB-231 BC cells compared to starch-coated controls, while having no significant effect on normal HaCat human keratinocyte cells (Figure 5) [113].

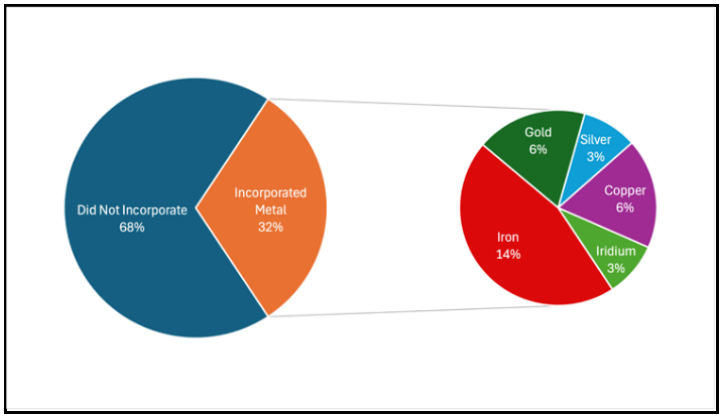

Figure 10: Inclusion of metallic elements in reviewed articles: proportion incorporating metals and the specific metals used.
Note: One study using iridium also included gold as a secondary metal.

Biocompatible Nanoparticle Coatings – Improving Stability, Tumor Targeting, and Reducing Adverse Hypersensitivity Side Effects

There is significant concern when introducing nanomedicine as a new therapeutic for cancers and other diseases, primarily due to the unknown long-term risks of introducing such particles into the body, as well as possible adverse reactions resulting from foreign particle rejection [114]. Of the thirty-five articles reviewed, nine specifically incorporated components to ensure their nanoparticles were biocompatible, aiming to reduce adverse reactions and increase treatment safety. Firstly, one study chose to utilize coatings from the most common cells in the body, erythrocytes, more commonly known as red blood cells (RBCs) [16]. The entire NP formulation in this study was referred to as TT-RBC-NPs, and assays were conducted to determine biocompatibility by assessing induced hemolysis when cells were exposed to NPs, Triton X-100 as the positive control, free DOX, and PBS [16]. The findings were extremely promising, as TT-RBC-NPs and RBC-NPs caused only approximately 5% hemolysis as shown in Figure 10 a & b of Marshall et al., whereas Triton X-100 resulted in approximately 85% hemolysis and free DOX resulted in 60% [16].

Alternatively, another study chose to coat their NPs with a white blood cell membrane, leveraging a neutrophil membrane-camouflaged platform to encapsulate their hypoxia-responsive dimeric prodrug hQ-MMAE2 (hQNM-PLGA) [115]. The neutrophil coating encouraged the NPs, similar to natural neutrophils, to migrate toward sites of inflammation, which tumours typically represent. Additionally, the NPs were able to disrupt the formation of neutrophil–circulating tumour cell (CTC) clusters, leading to reduced extravasation and metastasis of 4T1 cells (Figure 4) [115].

A study published in 2022 utilized platelet-derived particles to coat the nanoparticle membrane, which increased stability and enabled prolonged circulation in the bloodstream compared to non-coated counterparts, although no figures were presented to support this finding [107]. Interestingly, one study utilized a phospholipid membrane derived from 4T1 tumour cells themselves to coat the NPs [116]. This coating enabled greater interaction between NPs and TNBC cells, with increased uptake observed in 4T1 cells compared to non-targeted EpH4-Ev cells (Figure 3) [116].

In vivo, the 4T1 cell membrane coating increased nanoparticle accumulation in tumours in infected mice, as demonstrated by fluorescence and increased tumour mass in the presence of the coating (Figure 6) [116].

The remaining studies did not employ cell membrane coatings but instead used compounds believed to enhance stability and therapeutic delivery, based on prior use without significant adverse effects in the body. For example, Abbasi Dezfouli et al. utilized lipid-substituted polyethyleneimine (PEI) lipopolymers due to their known transfection efficiency, endosomal escape capability, and relative safety [117]. These non-viral vectors were optimized in this study as PEI-GA-Lau7 compared to previously validated PEI-LA, showing improved non-toxicity (40% vs. 10%), increased uptake of NPs into MDA-MB-231 cells, and enhanced gene silencing ability of the encapsulated siRNA [117]. However, the results were somewhat unclear and not easily presented in a way that demonstrated how PEI improved biocompatibility and safety compared to non-nanoparticle therapeutic delivery.

Similarly, another study claimed that the addition of polymers and silica to their NP improved biocompatibility; however, no assays were performed or results presented to support these claims [112]. In contrast, a study using micro-combinatorial hydrogel particles (μCGPs) tested the safety of the hydrogel platform itself and found that empty μCGPs were safe even at high concentrations (Figure 12) [102].

Another study utilizing light-triggered NPs assessed biocompatibility by first exposing 4T1 tumour cells to the NP without laser activation before evaluating its efficacy in reducing cell viability [94]. Their biodegradable polydopamine-coated UiO-66 framework nanomedicine (DUPM) was assessed alongside DOX@UiO-66 (DU) and other synthesis components, demonstrating that the NP was more biocompatible at all concentrations compared to free DOX (Figure 6) [94].

Lastly, one study developed a unique design using snake venom-loaded chitosan NPs targeting T-47D breast carcinoma cells [118]. Through an MTT assay, the researchers determined that chitosan NPs without venom did not reduce cell viability compared to venom-loaded NPs, which reduced viability to approximately 30% (Figure 7). Additionally, blank NPs induced significantly less hemolysis compared to venom-loaded NPs as shown in Figure 6A of Jimenez-Canale et al. [118].

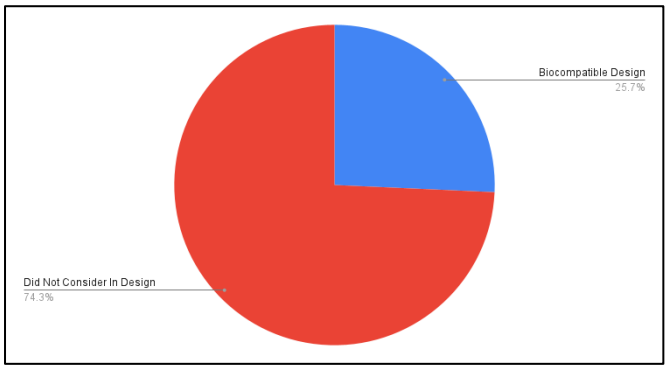

Figure 11: Distribution of studies incorporating biocompatible elements in nanoparticle coatings compared to those with no biocompatibility consideration.

Nanoparticle Tumor Penetration and Receptor-Mediated Targeting – Overcoming Biological Barriers Through Tumor Marker Characterization

In attempts to limit off-target effects and accumulation in other tissues throughout the body, 40% (14) of the articles chose to incorporate some form of receptor targeting for the BC cells or cancerous cells in general. This was done to ensure that their NPs were directed toward cancerous areas while limiting cytotoxicity in normal body cells.

The first study utilized a novel cell-penetrating peptide called RALA (R-), which had been validated in previous in vitro and in vivo studies to deliver plasmid DNA, mRNA, and siRNAs, forming stable NPs with no observed side effects following repeated injections [119]. This study coupled RALA with risedronate (RIS) to form R-RIS, and in comparison to RIS without receptor targeting capability, R-RIS was able to accumulate more in the tumour site as well as common metastatic sites, as demonstrated by a larger mean fluorescence intensity (MFI) value (Figure 4) [119].

Another study that used cancer cell-derived vesicles also found that their NPs were able to accumulate in the tumour site and common metastatic sites as shown in Figure 5 c & d of Prasad et al., based on the idea that “like attracts like.” However, they did not compare their coated NPs to non-coated NPs to validate whether receptor targeting improved tumour localization [82]. Alternatively, a study using 4T1 cancer cell coating on their NPs did present results validating that normalized uptake of their NP was increased in 4T1 cells compared to non-targeted EpH4-EV breast epithelial cells as shown in Figure 3B–D of Scully et al. [116].

Another study utilized human red blood cells in their NP design and added targeted theranostic functionality (TT-RBC-NP versus RBC-NP), specifically CD326, which is a protein on the cell surface responsible for epithelial cell adhesion (EpCAM), commonly found in adenocarcinoma tumour cells but not often in normal cells [16]. They found that TT-RBC-NPs could effectively target EpCAM+ MCF-7 cells more than RBC-NPs, while only showing a slight increase in accumulation in EpCAM− fibroblast cells, as demonstrated by fluorescence intensity as shown in Figure 7b of Marshall et al. [16].

In contrast, another study using an exosome-coated (e-) platform to deliver their DIM and DOX combination mesoporous silica nanoparticles (DDMSNP) found that e-DDMSNP was most effective at reducing tumour volume; however, this was only compared to a no-treatment control and DOX alone as shown in Figure 7D–G of Sarkar et al. [89]. Although the authors claimed that exosome coating increased tumour accumulation, they did not provide evidence to support this, nor did they compare e-DDMSNP to DDMSNP alone, representing a major limitation [89].

Some forms of BC cells exhibit specific markers, as discussed in the introduction. Specifically, human epidermal growth receptor 3 (HER3) is overexpressed in many forms of breast cancer, and this knowledge was leveraged by Lim et al. in their NP design [84]. Their hyperbranched polymers (HBP) encapsulating DOX were functionalized with an HER3 bispecific antibody fragment for use against BT-474 (HER3+) and MDA-MB-231 (HER3−) cancer cells. They found that exposure to HER3+ BT-474 cells resulted in greater red fluorescence, indicating increased binding and cellular entry compared to HER3− MDA-MB-231 cells (Figure 2) [84].

Another study in 2023 by Palange et al. incorporated ligands for intracellular adhesion molecule 1 (ICAM1) and epidermal growth factor receptor (EGFR) into their NP platform [102]. They found that targeted DTXL-μCGP accumulated more than free DTXL and non-targeted DTXL in tumour and metastatic sites, as evidenced by increased absolute percentage of the injected dose (%ID) as shown in Figure 6D of Palange et al. [102].

Additionally, a pH-responsive nanoplatform designed with platelet coating retained the platelet ligand CD62p, which can bind to CD44 receptors commonly expressed on cancer stem cells and tumour cells [107]. Their results demonstrated that CD62p mediated uptake in 4T1 tumour cells, with its presence increasing nanoparticle uptake and subsequent therapeutic effect (Figure 15) [107].

A study in 2024 investigated the use of folate conjugates in their PEHCA and PEBCA endotoxin-free poly(alkyl cyanoacrylate) (PACA) NP variants to target cancer cells that often overexpress folate receptors [96]. Specifically, they used MCF-7 cells representing low functional folate receptor levels, T47D and MDA-MB-231 cells for high levels, and MDA-MB-468 cells for moderate expression [96]. They found that folate-functionalized PEHCA and PEBCA NPs did not show enhanced uptake in any BC cell line, even those with confirmed folate receptor overexpression as shown in Figure 3A of Valsalakumari et al., [96].

In contrast, another study investigating folate receptor-mediated delivery of mitoxantrone-loaded solid lipid nanoparticles performed imaging and flow cytometry analysis on MCF-7 cells exposed to mitoxantrone-loaded SLNs or folate-functionalized SLNs (SLN-FA) [97]. Confocal laser scanning microscopy (CLSM) results after 4 hours indicated improved accumulation of SLN-FA-Mito compared to SLN-Mito (Figure 6), and flow cytometry demonstrated increased mean fluorescence at all time points for SLN-FA compared to SLN alone (Figure 7) [97].

Similarly, a study using amygdalin-folic acid nanoparticles (Amy-F) targeted folate receptors on MCF-7 and MDA-MB-231 tumour cells, compared to MCF-10A epithelial cells [120]. UV-VIS-NIR spectrophotometry results after 24 hours showed increased uptake of Amy-F in MCF-7 and MDA-MB-231 cells, which are theorized to have high folate receptor expression, compared to lower uptake in MCF-10A cells with low receptor levels as shown in Figure 2e of Askar et al. [120].

The final study targeting folate receptors utilized fulvestrant (^{131}I-fulvestrant) combined with aminolevulinic acid (ALA) and perfluoropentane (PFP) to create ^{131}I-fulvestrant-ALA-PFP-FA-NPs [121]. This platform is based on the concept that ALA is a precursor to protoporphyrin IX (PpIX), a photosensitizer used in photodynamic therapy (PDT), which is a mitochondria-intensive process. Due to this, conversion often occurs in tumour sites because of their high mitochondrial content [121]. Through in vivo imaging and post-dissection quantification, tumour-bearing mice injected intravenously with the NP showed the highest accumulation in tumour tissue after 48 hours (Figure 7) [121].

The Dezfouli et al. study investigated the most effective receptor combination for their siRNA NP platform, incorporating gallic acid (GA) attached to either linoleic acid or lauric acid [117]. They found, through increased green fluorescence measurements, that PEI-GA-Lau7 NPs could target cells and deliver siRNA more efficiently than PEI-LA in MDA-MB-231 BC cells [117].

Lastly, a mesoporous organosilica drug (MOD) platform with mitoxantrone (MTO) was magnetically modified with Fe_3O_4. This magnetic modification was proposed to enable passive targeting and preferential accumulation in cancer cells; however, no experimental results were presented to validate this claim [98].

Immune Cell Interactions – Evaluating the Role of Nanoparticles in Depleting or Leveraging Immune Cells in the Context of Breast Cancer

In line with investigating the biocompatibility of nanoparticles, there is still a significant amount unknown about the effects nanoparticles have on immune cells, both in terms of off-target effects and the potential for reactivation of immune cells to re-establish an inflammatory response to the tumour. Of the thirty-five articles reviewed, 20% [7] incorporated some aspect of immune cell evaluation into their study.

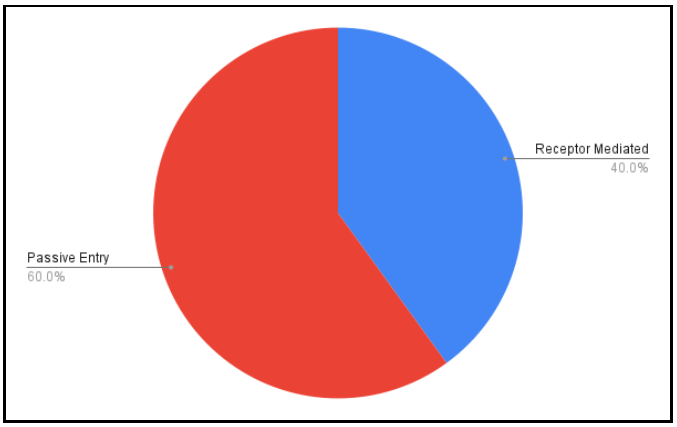

Figure 12: Distribution of nanoparticle targeting approaches in reviewed studies: receptor-mediated uptake versus passive accumulation.

The first paper investigating immune cells utilized the coating of an immune cell (neutrophils) in their NP design and examined the effect on neutrophils in vivo after treatment [115]. Specifically, their NM-PLGA NP treatment serves as a competitive inhibitor for neutrophils in vivo, preventing them from binding to 4T1 cells (Figure 4) and thereby inhibiting the formation of neutrophil–circulating tumour cell (CTC) clusters, which are often associated with high metastasis and poor prognosis [115].

NP interaction with macrophages was investigated in another study, which compared RBC-NPs and TT-RBC-NPs to non-coated bare PLGA NPs, and found statistically significantly lower macrophage uptake as shown in Supplementary Figure 3 of Marshall et al. [16]. Additionally, their models demonstrated macrophage uptake levels comparable to PEG-NPs, which are considered the gold standard, further supporting that their NPs can target tumour cells while evading the immune system [16].

In contrast, another study targeted M2 macrophages, rather than undifferentiated M0 macrophages, to reduce their tumour microenvironment-associated anti-inflammatory effects [85].

Looking at another immune cell type, an NP design by Li et al. was developed to activate the immune system and reinitiate an antitumor immune response [111]. Specifically, their NPs containing Cu/TI function by inducing mitochondrial oxidative damage in cancer cells, leading to the release of damage-associated molecular patterns

(DAMPs). This process promotes the maturation of dendritic cells (DCs) and increases the proportion of mature DCs to support an antitumor response (Figure 4) [111].

One limitation of this study is that it did not further investigate whether increased mature DC levels would enhance the activity of macrophages, B cells, or T cells [111]. In contrast, an NP was designed by Manspeaker, O'Melia, and Thomas to target lymph nodes and stem-like CD8+ (cytotoxic) T cells [101]. Their NP, carrying paclitaxel, was able to increase the proliferation of cytotoxic T cells and augment the number of tumour-infiltrating T cells responsible for killing BC tumour cells (Figure 2) [101].

A related study using amygdalin-folic acid NPs (Amy-F) on MCF-7 and MDA-MB-231 cells evaluated a wide range of cytokine and chemokine signaling expressions from tumour cells, which in turn influence immune response activation or suppression [120]. Amy-F reduced MAPK and p38 expression in both cell lines, which are typically associated with cell survival (Figure 4), while also downregulating CD4 and CD80 expression [120]. Furthermore, NKG2D expression, which is commonly present on activated natural killer (NK) cells and T cells, was increased in both BC cell lines (Figure 5) [120].

The study was comprehensive and further investigated the downregulation of the anti-inflammatory molecule TGF-β, inhibition of IFN-γ, subsequent VEGF-induced angiogenesis, and, interestingly, reduction of pro-inflammatory IL-2 and IL-6 levels (Figure 6) [120]. However, these findings were limited to cytokine and chemokine expression, and although inferences could be made about immune cell activity, no direct assays were conducted on immune cells themselves.

In comparison, a study considered a gold standard within this literature review for immune cell investigation evaluated both immune cell characterization and cytokine expression [96]. Their PEBCA NP platform, selected over PEHCA, and loaded with cabazitaxel, slightly reduced the percentage of neutrophils, significantly reduced the number of dendritic cells and intermediate monocytes (iMO), and increased the percentage of macrophages (Mϕ) (Figure 8) [96].Further investigation into long-term effects on inflammatory monocytes revealed increased levels of TNF-α and IFN-γ in the tumour site, along with decreased intracellular levels of the anti-inflammatory cytokine IL-10 (Figure 9) [96].

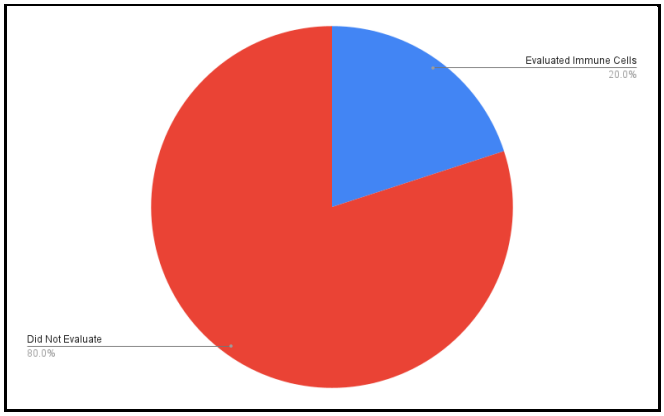

Figure 13: Categorization of reviewed articles based on evaluation of immune cell responses following nanoparticle introduction.

In Vitro, In Vivo, or Spheroid Breast Cancer Cell Models – Evaluating the Methods by Which Nanoparticles Were Tested

A very apparent limitation in many research studies is the model used to test therapeutics, as traditional 2D models often cannot replicate the complex tumour microenvironment (TME) or the therapeutic effects on aggregated tumour cells, compared to a single layer of 2D cells evenly exposed to treatment. 3D models, often referred to as spheroids or organoids, attempt to replicate the in vivo TME and tumour exposure to therapeutics within an in vitro system; however, many in vivo interactions are still not captured. In the context of testing potential therapeutics and investigating the TME, mice are considered the gold standard for in vivo research, with results often translatable to humans. Among the literature reviewed, 31.4% (11) of studies conducted only in vitro 2D experiments, 8.6% (3) conducted both in vitro 2D and 3D experiments, and 60% (21) conducted research using both in vitro 2D models and in vivo mouse models.

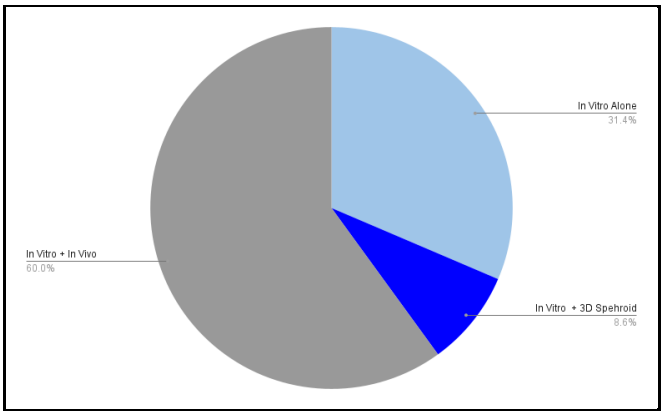

Figure 14: Experimental models used in reviewed studies to test nanoparticle platforms: in vitro 2D only; in vitro 2D with 3D models; combined in vitro and in vivo (mouse) studies; and in vivo (mouse) studies only.

The papers that tested their NP therapeutics using only 2D in vitro models often stated that the research was conducted as a preliminary or pilot study to justify the NP platform design and to support grant applications for further research [87,90,97,98,100,103,106,112,117,118,120]. Three studies expanded their in vitro models by incorporating 3D systems, although they did not include in vivo components [16,91,105]. The study by Marshall et al. [16] utilized a 3D spheroid model that had been previously optimized and validated using MCF-7 cells as shown in Abstract Figure of Zhang et al. [122]. In comparing three methods microwell liquid overlay, the hanging-drop/agar method, and spheroid embedding in collagen they determined that the optimized hanging-drop/agarose method was most effective and used it in the reviewed study [122].

In contrast, another study developed a more complex 3D scaffold using thermal-induced phase separation to synthesize 3D porous polyurethane (PU)-based scaffolds coated with collagen I [91]. MCF-7 cells were then seeded onto $5 \times 5 \times 5$ mm³ scaffolds at a density of 0.5×10^6 cells per scaffold and cultured for five weeks before being exposed to various treatments, depending on the experimental design [91]. Lastly, the study by Camorani et al. [105] employed a different approach to 3D model development by co-culturing 2×10^3 cancer cells with 8×10^3 mesenchymal stem cells in 24 ultra-low attachment plates with 2% Matrigel Basement Membrane Matrix Growth Factor

Reduced (MBMMGFR) from Corning Incorporated. This study also generated patient-derived cancer organoids using BC cell samples from three patients by transferring cells into working media with collagenase type II, shaking for 16 hours, and filtering through 100 µm and 40 µm strainers to isolate organoids from single cells [105]. The organoid suspension was then centrifuged, plated in ultra-low attachment plates, centrifuged again after 24 hours, resuspended in media containing MBMMGFR, and 35 µL droplets were solidified in 24-well plates for 20 minutes before adding media and allowing organoids to grow and be passaged every 2–3 weeks [105].

Although these studies used different approaches to developing 3D models, as no standardized method currently exists, incorporating a 3D component remains essential for mimicking the TME in the absence of in vivo models. For the remaining studies, research evaluating the effects of NP platforms on tumours and cells was conducted both in vitro using 2D tumour cell cultures and in vivo in mice using specific BC cell lines, particularly when receptor-targeting designs required receptor-positive models. Briefly, 71.4% (15) of studies utilized one BC cell line, 19% (4) utilized two, and 9.5% (2) utilized three or more cell lines in their experiments (Figure 15).

The BC cell lines used included 4T1 (30%, 9), MCF-7 (16.7%, 5), MDA-MB-231 (36.7%, 11), MDA-MB-468 (6.7%, 2), BT-474 (3.3%, 1), T-47D (3.3%, 1), and E0771 (3.3%, 1). Among the female mouse models used, the most common was BALB/c mice (45.5%, 10), followed by SCID mice (18.2%, 4) and nude mice (22.7%, 5). Alternatively, C57BL/6 mice were used in 9.1% (2) of studies, and one study used rat models without explanation, which will not be further discussed (Table 1). All mice used were female, typically ranging from 5–10 weeks of age, with varying weights; some studies reported weight data, while others did not. Additionally, it appears that BALB/c mice are commonly validated for BC tumour cell in vivo studies. However, studies using nude or C57BL/6 mice did not justify their selection, which may be due to availability or institutional preferences.

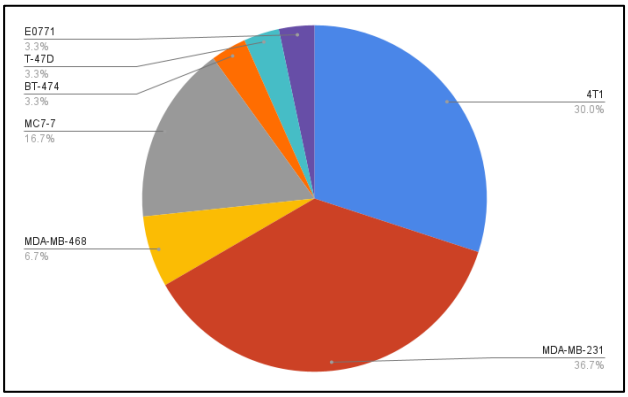

Figure 15: Breast cancer cell lines utilized in reviewed literature which conducted both in vitro and in vivo research *Some studies utilized more than one cell line for experiments to compare (Figure 16)*

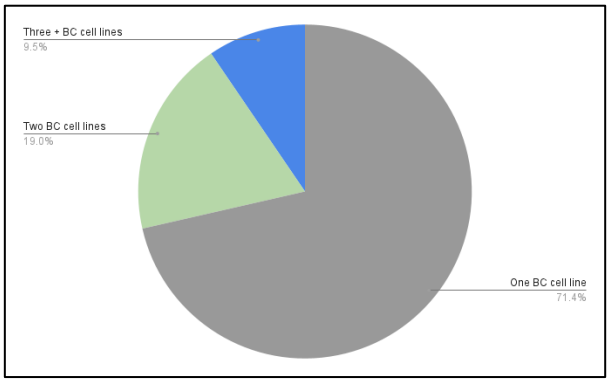

Figure 16: Depiction of the distribution of proportions of quantity of breast cancer cell lines used in literature reviewed

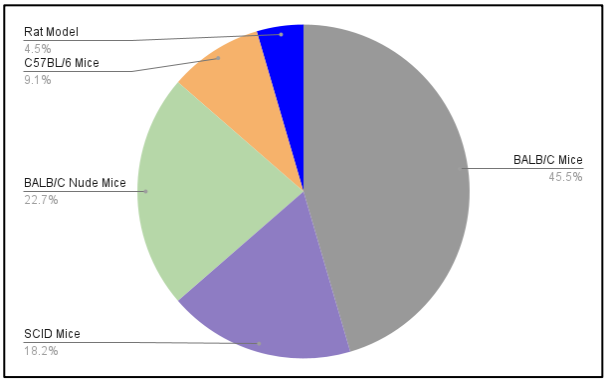

Figure 17: Proportion of in vivo studies using different animal models. *Note: One study used both BalB/C mice and SCID mice for experiments*

Table 1: Information for studies which conducted both in vitro and in vivo research, including paper title, reference number, in vivo model and tumour cell line/s used.

Ref #	In Vivo Model	Breast Cancer cell line/s used
111	BALB/C mice	4T1
82	BALB/C mice	4T1
119	BALB/C mice and BALB/C SCID mice	MDA-MB-231 and MCF-7
89	BALB/C mice	MDA-MB-231 and 4T1
84	BALB/C SCID mice	BT-474 and MDA-MB-231
85	C57BL/6 mice	MDA-MB-231
96	BALB/C Nude mice	MDA-MB-231, MDA-MB-468, MCF-7 and T-47D
121	BALB/C Nude mice	MCF-7
115	BALB/C mice	4T1
92	BALB/C mice	4T1
93	BALB/C Nude mice	MCF-7
110	BALB/C Nude mice	MDA-MB-231, MDA-MB-468, and MCF-7
104	BALB/C Nude mice	MDA-MB-231
88	BALB/C mice	4T1
102	BALB/C SCID mice	MDA-MB-231
86	Rat model	MDA-MB-231
101	C57BL/6 mice	E0771
113	BALB/C SCID mice	MDA-MB-231
116	BALB/C mice	4T1
107	BALB/C mice	4T1
94	BALB/C mice	4T1 and MDA-MB-231

Discussion

This review contributes to existing knowledge by compiling various approaches to tackling the use of nanoparticles to treat breast cancer, presenting study results with noted limitations, and comparing methods with similar objectives. Twenty percent of the articles reviewed chose to incorporate the concept of theranostics into their nanoparticle models, which is a growing area of research aimed at co-delivering an imaging agent and a therapeutic compound to both image/diagnose and treat cancer simultaneously [81]. However, many of the papers presented in this section were pilot studies, with extensive research still needed to validate nanoparticle efficacy and safety, particularly in the context of human use and long-term systemic effects that NPs may pose [16,82–88].

We then investigated how nearly half of the NP formulations chose to encapsulate an approved chemotherapy, among other components, within their engineered structures to reduce BC cell viability [16,82,84,85,88–102]. The limitations of the papers in this section primarily involved validating whether these costly and time-consuming engineered NPs should continue in development rather than using free chemotherapeutic agents. Many studies presented results where NPs did not reduce cell viability to a greater extent than free chemotherapy, or where the decrease was not statistically significant [16,82,84,85,88–102].

Additionally, 17.1% and 14.3% of papers incorporated novel light-triggered and pH-triggered therapeutic release mechanisms, respectively [82,84,85,94,97,100,103–107]. From these studies, it becomes clear that a combination targeted approach may be most beneficial. The ability to selectively release therapeutics in the tumour microenvironment (TME) pH environment may reduce off-target effects, while photodynamic therapy (PDT) demonstrates strong potential for enhanced tumour cell death. However, as it is unsafe to apply near-infrared radiation (NIR) to the entire body, PDT may not be suitable for metastatic cancer. Similarly, in cases where metastasis occurs near the stomach, pH-triggered release may be affected by the naturally low gastric pH.

Furthermore, 32% of the reviewed articles incorporated metallic elements into their NP design, either as imaging agents, cytotoxic agents, or structural components. A major limitation of these approaches is that many rely on redox reactions and the generation of reactive oxygen species (ROS), raising safety concerns regarding toxicity [82,85,86,98,105–107,109–113]. Many of the metals used, such as gold [82,105,106], silver [113], and iridium [105], are not naturally present in the body, potentially introducing unknown side effects. Although iron [85,86,98,107,112] is naturally occurring, excessive accumulation may lead to heart, liver, and other organ damage, emphasizing the importance of investigating off-target effects when incorporating metallic elements into NP platforms for BC treatment.

To address safety concerns, nine studies investigated the biocompatibility and cytotoxicity of their NP platforms independently. Overall, studies that evaluated the effects of NPs on tumour versus normal cells addressed a major concern regarding the novelty of nanotechnology and its potential systemic effects [16,94,102,107,112,115–118]. However, it is strongly recommended that all thirty-five studies particularly those involving in vivo research should include biocompatibility assessments or incorporate specific design elements to enhance safety and minimize off-target effects.

Similarly, fourteen studies incorporated receptor-targeting strategies into their NP design to improve tumour specificity. These strategies significantly enhanced accumulation in tumour and metastatic sites, reducing off-target effects and improving therapeutic efficacy [16,82,84,89,96–98,102,107,116,117,119–121]. Receptor-functionalized NPs, including HER3 antibodies, folate ligands, and cell membrane coatings, demonstrated increased uptake in cancer cells compared to non-targeted cells. However, some studies lacked appropriate controls or comparative analysis, limiting the strength of

their conclusions, particularly for translation to in vivo models and clinical applications.

Furthermore, seven studies evaluated either systemic immune effects of NP treatments or their ability to re-establish immune responses within the tumour [16,85,96,101,111,115,120]. While many studies investigated signaling pathways and gene expression, few directly assessed changes in immune cell populations. Additionally, some studies reported unexpected gene expression patterns or inconclusive findings that were not adequately explained.

Lastly, the reviewed literature examined the experimental models used to evaluate NP therapeutics, including 2D in vitro, combined 2D and 3D in vitro, and in vitro followed by in vivo (mouse) studies (Table 1). It can be concluded that incorporating an in vivo model, or at minimum a 3D in vitro model, is essential for accurately evaluating NP efficacy. Studies relying solely on 2D models cannot replicate the complexity of the TME and may produce results that differ significantly from those observed in vivo.

Conclusion

To conclude, nanomedicine is a vast and rapidly evolving field with significant potential for the treatment of various diseases, including breast cancer, the most commonly diagnosed cancer in Canadian women. To date, approximately eighty nanomedicines have been approved for clinical use across multiple diseases; however, only ten to fifteen have been approved for breast cancer treatment. Additionally, several nanomedicines have been withdrawn from the market due to systemic toxicity and limited understanding of long-term effects. This literature review analyzed thirty-five recent studies, published between January 2022 and January 2025, exploring nanoparticle-based therapies for breast cancer. Despite promising advancements in nanoparticle design and targeting strategies, further research is required to validate long-term safety, optimize therapeutic efficacy, and provide comprehensive evidence for regulatory approval. Finally, with sustained interdisciplinary collaboration, these nanoparticle platforms and future innovations hold strong potential to transition into effective clinical therapies for the treatment of breast cancer.

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