drugs and drug candidates

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Review

Breast Cancer Treatment: The Potential of Organic and Inorganic Nanocarriers in Targeted Drug Delivery

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Abstract: Breast cancer (BC) is the most prevalent form of malignancy among women on a global scale, ranking alongside lung cancer. Presently, conventional approaches to cancer treatment include surgical procedures followed by chemotherapy or radiotherapy. Nonetheless, the efficacy of these treatments in battling BC is often compromised due to the adverse effects they inflict on healthy tissues and organs. In recent times, a range of nanoparticles (NPs) has emerged, exhibiting the potential to specifically target malignant cells while sparing normal cells and organs from harm. This has paved the way for the development of nanoparticle-mediated targeted drug delivery systems, holding great promise as a technique for addressing BC. To increase the efficacy of this new method, several nanocarriers including inorganic NPs (such as magnetic NPs, silica NPs, etc.) and organic NPs (e.g., dendrimers, liposomes, micelles, and polymeric NPs) have been used. Herein, we discuss the mechanism of NP-targeted drug delivery and the recent advancement of therapeutic strategies of organic and inorganic nanocarriers for anticancer drug delivery in BC. We also discuss the future prospects and challenges of nanoparticle-based therapies for BC.

Keywords: breast cancer; inorganic nanoparticle; malignancy; nanoparticles; organic nanoparticle; targeted drug delivery

Citation: Alamelu, S.; Venkatesan, K.B.; Shagirtha, K.; Srinivasan, M.K.; Panneerselvam, C.; Aziz, A.T.; Ali Alshehri, M.; Seyed, M.A.; Pachaiappan, P. Breast Cancer Treatment: The Potential of Organic and Inorganic Nanocarriers in Targeted Drug Delivery. *Drugs Drug Candidates* **2024**, *3*, 813–837. https://doi.org/10.3390/ddc3040046

Academic Editors: Jean Jacques Vanden Eynde and Abdelwahab Omri

Received: 16 September 2024
Revised: 14 November 2024
Accepted: 21 November 2024
Published: 25 November 2024

1. Introduction

Cancer is a multifactorial cellular ailment characterized by the uncontrolled proliferation of cells and the ability to infiltrate surrounding tissues [1,2]. It attributes dysfunction in the mechanisms that regulate cell division and maintain balance within multicellular organisms. Breast cancer (BC) is a highly prevalent form of cancer. In 2018 alone, 2.1 million new cases and 630,000 mortalities were reported [3]. BC ranks as the most frequently identified cancer and holds the unfortunate distinction of being the leading cause of death among women.

Notably, in 2020, countries with a high or very high HDI (Human Development Index) exhibited a 55.9% incidence rate and a 12.8% mortality rate for female BC. In contrast, nations with a low or moderate HDI displayed incidence and mortality rates of 29.7% and 15.0%, respectively [4]. The prominent site of BC development is within the connecting lobules and the milk ducts responsible for milk production. An excess of progesterone

and estrogen receptors in BC cells initiates downstream signaling, subsequently activating genes that govern crucial functions like survival, angiogenesis, migration, proliferation, and other processes integral to tumor cells [5]. There are different types of breast cancer includes ductal, lobular, mucinous, inflammatory and mixed tumor (Figure 1) [6].

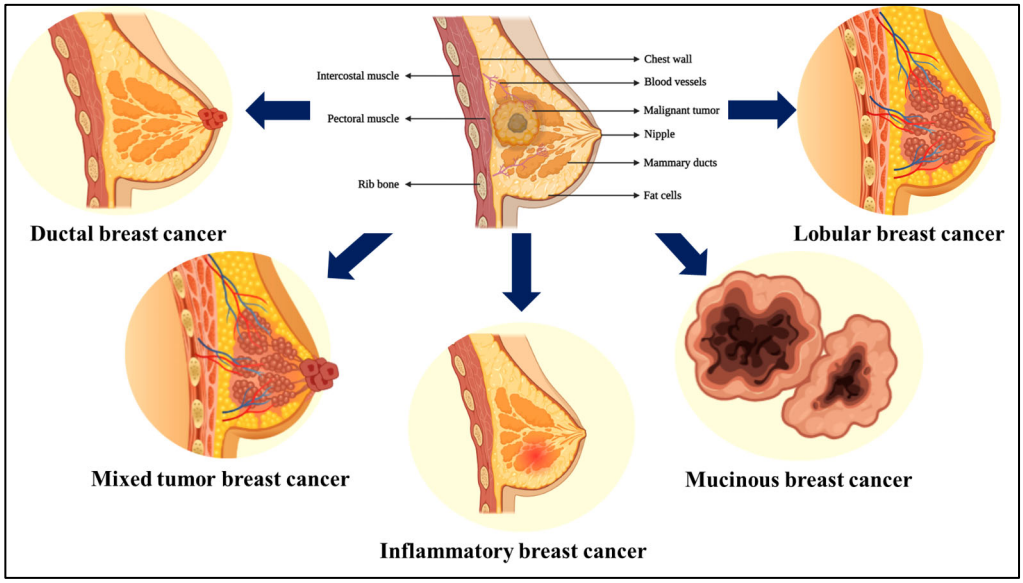

Figure 1. Types of breast cancer [6].

Neoadjuvant chemotherapy, surgical intervention for operable tumors, radiation therapy, adjuvant chemotherapy, and/or endocrine therapy constitute the array of approaches employed in BC treatment [7]. Among these, chemotherapy stands out as the most extensively employed modality in cancer treatment. Chemotherapeutic agents for BC encompass taxanes, anthracyclines, fluorouracil, plant alkaloids, topoisomerase inhibitors, platinum compounds, etc. [8]. Noteworthy examples include 5-fluorouracil, doxorubicin (DOX), gemcitabine, paclitaxel, cyclophosphamide, and cisplatin, among others [9–11]. Nevertheless, the systemic administration of chemotherapeutic agents often leads to significant overall toxicity due to their rapid circulation and wide distribution in the body. Unfortunately, BC patients commonly encounter unpredictable issues such as increased susceptibility to distant organ metastases, recurrences, and the emergence of chemoresistant tumors. The adverse effects associated with conventional cancer treatment methodologies is imperative to actively explore innovative and efficient alternatives [12].

There are many challenges that conventional delivery faces during BC therapy like (1) insufficient specificity for BC, (2) inefficient access of drugs to metastatic sites, (3) drug resistance at the cellular level, (4) drug resistance at the tumor microenvironment level, (5) difficulty in eradicating cancer stem cells, and (6) undesirable physicochemical characteristics of the drug. These challenges can be overcome by nanotechnology [13].

Ongoing research is dedicated to refining NPs to overcome the drawbacks associated with traditional methods. NPs have emerged as promising tools in BC treatment due to their targeted delivery capabilities and unique properties. These tiny particles, typically ranging from 1 to 100 nm in size, can be engineered to carry therapeutic agents directly to tumor cells while minimizing damage to normal cells. In nanoparticle-based drug delivery, NPs are functionalized with specific ligands or antibodies and loaded with anticancer drugs aiming to recognize receptors overexpressed on BC cells. This ensures the uptake and selective binding of NPs by tumor cells, promoting localized drug release and thereby mediating apoptosis [14] (Figure 2).

Nanoscale therapeutic agents for tumors can be categorized into inorganic and organic particles. Inorganic nanocarriers include CNTs (carbon nanotubes), metal and metal oxide NPs, silica NPs, QDs (quantum dots), organic materials encompass liposomes, dendrimers,

polymeric NPs, and other substances. The application of inorganic NPs in tumor treatment is attributed to their ease of production and their large surface area that allows for binding with different compounds [15]. Research indicates that modifying the surface properties of these NPs can enhance their targeted drug delivery potentiality, iin vivo durability, and biocompatibility [16]. Consequently, researchers are focused on investigating how surface modification of NPs can facilitate the targeted delivery of anticancer agents.

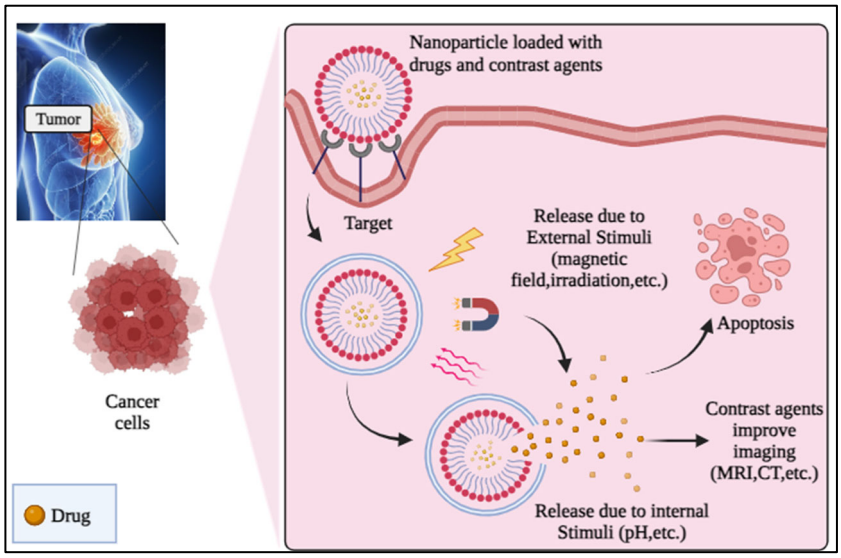

Figure 2. Mechanism of nanoparticles in the treatment of breast cancer.

The utilization of targeted drug delivery systems (DDS) employing NPs can achieve pharmacologically effective concentrations at lower doses compared to untargeted administration, thereby minimizing the required dosages. This approach, distinct from conventional chemotherapy, has the potential to significantly decrease side effects linked to toxicity and damage to tissues and normal cells. Hence, the development of innovative treatment methodologies, such as NP-based targeted DDS holds promise in mitigating these adverse effects [17].

In this review, we have provided an overview of the mode of mechanism and various NPs employed for the DDS of BC. Furthermore, this research sheds light on the potential risks and regulatory considerations concerning NPs.

2. Mode of NP-Based DDS

Utilizing NPs as a targeted delivery for chemotherapeutic drugs can effectively prevent systemic toxicity and toxicity to normal cells. This strategy involves both active and passive targeting methods [18]. Tumor blood supply channels exhibit distinct pathophysiological characteristics that enable NPs to accumulate predominantly within tumor cells. Tumor tissues, due to their increased metabolism rates, have greater demand for oxygen and nutrients. Consequently, new blood capillary systems form to provide these necessities, but they remain imperfectly developed, allowing the passage of particles of specific sizes [19].

2.1. Passive Targeting

Passive targeting exploits the inherent characteristics of the tumor microenvironment and the physical properties of nanoparticles to achieve selective accumulation in tumor tissues (Figure 3). When exposed to cancerous tissue, a drug is delivered passively, typically in an inactive form. Biological mechanisms like the ERS (Enhanced Retention System) or EPS (Enhanced Permeation System) are employed to localize NPs, ensuring their presence at particular tissues or specific disease sites. To prevent macrophage clearance, the nanoparticle size should be under 100 nm, and the surface should be hydrophilic to optimize

targeting efficiency and prolong circulation. Hydrophilic polymer coatings such as PEG (polyethylene glycol), poloxamers, poloxamines, polysaccharides, and block or branched amphiphilic copolymers can protect the NPs' hydrophilic surface from plasma protein adsorption [20,21]. Passive targeting can be further categorized into three subtypes: local medication application, tumor microenvironment, and leaky vasculature.

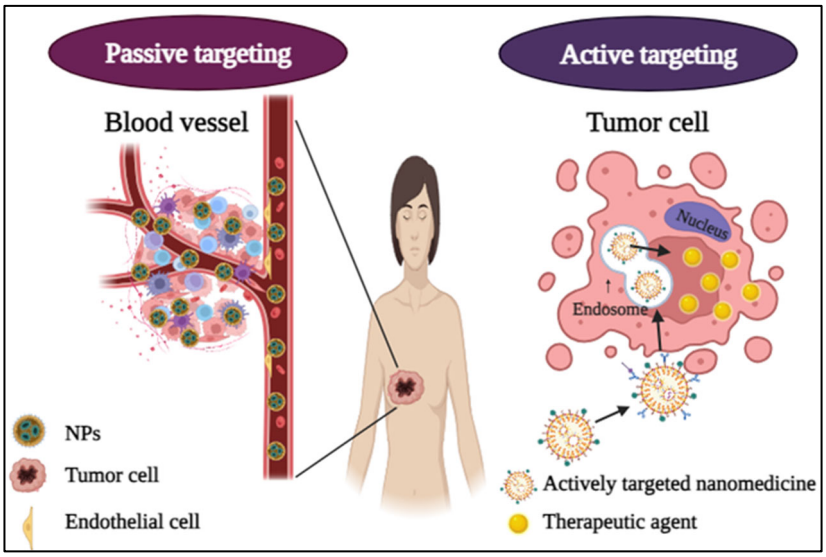

Figure 3. Schematic representation of passive and active targeting.

2.1.1. Vasculature with Leaks

The enhanced retention effect and permeability, first demonstrated by Maeda and Matsumura, leverages two key concepts: (1) polymeric NPs can enter cancer because the capillary endothelium in tumor tissue is more permeable to macromolecules than endothelium in healthy tissue, and (2) because cancer tumors lack lymphatic drainage, more medicine builds up inside the tumor tissue. The use of appropriate biodegradable polymers can increase drug concentration 10–100 times compared to freely circulating drugs [22].

2.1.2. Tumor Microenvironment

Passive drug targeting benefits from the tumor microenvironment. Chemotherapeutic agents in their active form are administered into the body and conjugated with tumor-specific materials. Once these polymer–drug conjugates reach their intended destination, the tumor environment triggers their conversion into an active form, known as tumor-activated prodrug therapy. Studies have demonstrated efficient cleavage of DOX by matrix metalloproteinase-2 (MMP-2) [23].

2.1.3. Local Drug Application

To avoid systemic toxicity and increase drug concentration at the tumor site, chemotherapy agents can be directly applied locally to the tumor site. For instance, the Mitomycin C–dextran combination administered intratumorally enhances anticancer agent concentration at the tumor site while decreasing systemic toxicity [24]. Prabha and Labhasetwar found prolonged and improved antiproliferative effects in a study employing the wild-type p53 gene for BC [25].

2.1.4. EPR

The EPR effect is a phenomenon where macromolecules and nanoparticles preferentially accumulate in tumor tissues due to their unique physiological characteristics. Tumors often possess abnormal blood vessels with larger fenestrations (gaps), which allow larger

particles to extravasate from the bloodstream into the tumor microenvironment. Additionally, tumors have a compromised lymphatic drainage system, which reduces the removal of particles, leading to prolonged retention of these agents in the tumor area. This phenomenon significantly improves the effectiveness of drug delivery systems by increasing local drug concentration while minimizing systemic exposure and side effects [26,27].

2.1.5. ERS

The ERS builds on the principles of the EPR effect. It refers to the design strategies employed to further improve the retention of nanoparticles in the tumor microenvironment. This can be achieved through various approaches, such as modifying the surface properties of nanoparticles (e.g., size, shape, and charge), using targeting ligands, or incorporating stimuli-responsive elements that activate the release of therapeutic agents in response to the tumor's unique microenvironment (e.g., pH, temperature, or specific enzymes) [28].

2.1.6. Retention of Nanoparticles in the Tumor Environment

Nanoparticles that utilize both EPR and ERS mechanisms can achieve higher therapeutic efficacy by ensuring that a greater proportion of the drug reaches the tumor site (Figure 4). For instance, by manipulating the size of nanoparticles to fall within the optimal range (typically 10 to 200 nm), they can effectively exploit the EPR effect. Additionally, surface modifications can enhance cellular uptake by tumor cells, and the incorporation of targeting ligands can direct nanoparticles specifically to cancer cells, further increasing their accumulation [29].

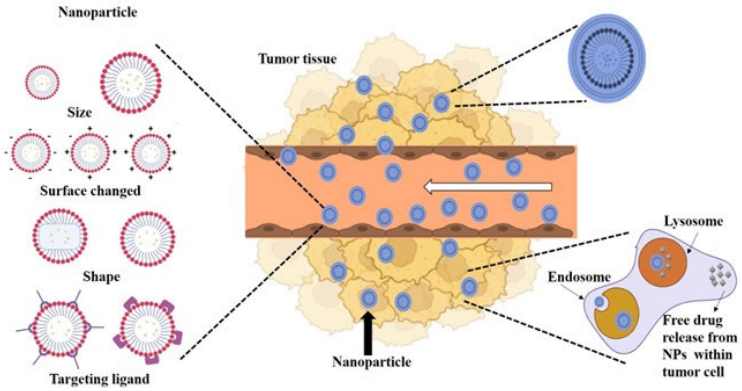

Figure 4. EPR and ERS effect of nanoparticles.

Moreover, the use of biodegradable and biocompatible materials in nanoparticle design enhances safety and minimizes toxicity, making them suitable for clinical applications. By integrating EPR and ERS strategies, advanced nanocarriers that improve drug solubility are developed, sensitive therapeutic agents are protected, and controlled release is enabled, ultimately leading to more effective cancer treatments with reduced side effects [30].

2.2. Active Targeting

Active targeting involves attaching drug-coated NPs to the desired target site (Figure 3). This approach enables drugs to accumulate more effectively in cancer tissue. Several methods can be employed to direct NPs toward cancer cells and ligand receptors, primarily relying on specific interactions such as lectin carbohydrates, antibodies, and antigens [31].

2.2.1. Directed Targeting—Carbohydrates

Lectin carbohydrates are a prime example of active pharmacological targets. Tumor cells have distinct carbohydrates on their surface compared to normal cells. Lectins, nonimmunological proteins, can attach to and recognize these glycoproteins on the cell surface. Certain carbohydrates can be used to create unique binding moieties for each cell,

facilitating lectin direct targeting. Targeting specific carbohydrates on tumors may have anticancer effects [32].

2.2.2. Receptor Targeting

This active targeting approach heavily relies on endocytosis. Ideally, drugs are conjugated to polymer carriers localized on the surface of the cell, entering the intracellular environment of the tumor after dissociation from the drug–polymer conjugate, thereby achieving an anticancer effect. This targeting system delivers three crucial molecules: (1) ligands or antibodies, (2) antigens or receptors, and (3) drug–polymer conjugates [33].

2.2.3. Antibody Targeting

Dhas et al. (2018) [31], disclosed the process by which mAb (monoclonal antibodies) guide NPs to solid cancer tissue in vivo. mAb fragments targeting HER-2 (human epidermal growth factor receptor 2) malignancy was conjugated with a liposomal-grafted polyethylene glycol chain, resulting in a prepared formulation. This formulation effectively targeted HER-2, resulting in increased cellular absorption of the drug and offering BC patients new drug delivery options [31].

3. Drug Delivery NPs

Developing methods to selectively target and eliminate cancerous cells while minimizing harm to normal cells is a major challenge in cancer treatment. Nanocarriers benefit from their strong circulation, allowing them to traverse biological barriers. Additionally, they mitigate the toxicity and adverse effects linked to traditional treatments while enhancing access to pharmaceuticals within cells. Despite the benefits of combination therapy, hurdles remain, such as dissimilar physicochemical properties of drugs, uneven drug uptake by cancer cells, and the interplay of synergistic effects reliant on drug concentrations [34].

Various strategies for drug delivery via nanosystems include:

1. Dual-nano delivery (both drugs carried by separate nanocarriers)
2. Simultaneous co-delivery (both drugs simultaneously conveyed by nanocarriers)
3. Hybrid delivery (one drug administered freely, the other via nanocarriers)

Drug delivery systems can encompass active, passive, or combined targeting mechanisms, including the effect of EPR [35]. Active targeting involves affixing targeting molecules to drug carriers [36], while passive targeting exploits tumor-specific characteristics like pH and temperature. Both avenues facilitate drug delivery to tumor sites.

Drug delivery NPs exist in various forms, materials, and sizes, each with distinct drug loading capacity, stability, release kinetics, and cellular targeting [37]. Refining the targeted delivery potential of these NPs can involve various techniques. While this publication focuses on the combinational administration of NPs, we recommend external sources for comprehensive insights into targeted therapies [38–40].

4. Inorganic Nanocarrier

Inorganic nanocarriers encompass a range of materials such as carbon nanotubes (CNTs), fullerenes, magnetic NPs, graphene, and NPs composed of silver, gold, quantum dots, and silica. These nanocarriers exhibit various advantageous traits, including biocompatibility, the capability to accumulate within cells discreetly, controlled release of therapeutic substances, targeted drug delivery to specific cells, and evading recognition by P-gp (P-glycoprotein) [41].

4.1. Carbon-Based Nanoparticles

CNTs are distinct structural variants of fullerenes, featuring cylindrical walls formed from graphene sheets that have undergone specific rolling angles. The elongated, hollow structures can be categorized into SWNTs (single-walled nanotubes) or MWNTs (multiwalled nanotubes) based on the presence of one or more layers of graphene sheets. These CNTs, currently in developmental stages, showcase remarkable attributes such as exceptional

thermal conductivity, optical properties, and electrical characteristics [42]. Moreover, they have evolved into versatile tools for DDS, particularly in the realm of tumor targeting [43].

CNTs possess unique qualities that make them proficient optical absorbers in the near-NIR (infrared radiation) spectrum, a region where biological systems exhibit high transparency. This is attributed to their adaptable surface properties and distinctive thermal characteristics [44]. The term "nanophotothermolysis" encapsulates the process of employing laser irradiation and biofunctionalized CNTs to eradicate tumor cells [45].

Xiao et al. (2009), observed two distinct visual traits in SWNTs. They elaborated on how the nanotubes could be employed to selectively and photothermally eliminate tumors by detecting significant Raman signals and NIR absorption within tumor cells [46]. The in vitro experiments involving HER2 expressing SK-BR-3 cells and HER2-negative MCF-7 cells have the dual ability of a composite to both identify and selectively eliminate tumor cells upon conjugation with HER2 IgY. Another parallel study by Neves et al. (2013), echoed similar findings [47]. Tait and Gibson (1992) [48], achieved targeted treatment of BC by coupling SWNTs with annexin V (AV) to facilitate photothermal therapy using a 980 nm laser. AV is known for its binding affinity to anionic phospholipids on the tumor cell surface and endothelial cells lining tumor vasculature, which played a crucial role in this approach [48].

While CNTs offer promising potential for drug delivery, challenges arise due to their preformed supramolecular nanotube structure, posing difficulties in drug loading. Loading patterns typically involve either direct loading onto the surface or filling the interior through capillarity-driven mechanisms. Loading efficacy, however, remains limited to around 5% (w/w) of the total nanotube weight [49]. Nonetheless, hydrophobic drugs with smaller profiles can directly bind to coating polymers on prefunctionalized CNTs, substantially enhancing loading capacity. For instance, one study exhibited a 400% (w/w) increase in DOX's loading capacity through a coating-polymer strategy [50]. Conversely, drugs with bulkier structures present challenges in attaching additional ligands due to surface space constraints, impacting the multifunctionality of drug delivery systems [51]. To address this, Shao et al. (2013), pioneered a solution involving the coupling of PTX (paclitaxel) with lipid docosanol molecules. This lipid chain was then connected to CNT surfaces through hydrophobic interactions, and folic acid was incorporated to enhance cell penetration and treatment effectiveness both in vivo and in vitro [52]. CNTs hold significant promise as effective carriers for drug delivery, although their preparation is intricate. Challenges also arise from issues related to solubility, biodegradability, and diverse drug-loading methods [53].

Ramadan et al. (2023) [54] demonstrated that chitosan-coated magnetite graphene oxide (CS-Fe_3O_4-GO) effectively enhances the drug-loading and controlled release of carboplatin for BC treatment. The nanocomposite showed high drug-loading efficiency and pH-responsive release behavior, with superior cumulative release at acidic (pH 5.0) and physiological (pH 7.4) conditions. In vitro cytotoxicity tests confirmed that CARB-CS-Fe_3O_4-GO exhibited better anticancer performance than free carboplatin against MCF-7 and Hep-G2 cell lines. This study highlights CS-Fe_3O_4-GO as a promising nanocarrier for the selective and sustained delivery of carboplatin [54]. The encapsulation and carboplatin loading capacities were enhanced using PEGylated multiwall carbon nanotubes (MWCNTs). Notably, the release of carboplatin from PEGylated MWCNTs at pH 6.8 demonstrated a pH-dependent drug activity. This characteristic positions them as a promising carrier for chemotherapy drugs that encounter high resistance, exhibit significant side effects, or have limited oral bioavailability [55].

Gooneh-Farahani et al. (2021) [56] successfully synthesized pH-sensitive BSA-stabilized graphene/chitosan nanocomposites for enhanced drug delivery in tumor environments. The optimal 2 wt% BSG nanocomposite achieved a controlled release of 84% DOX over 28 days, demonstrating a reduced burst release compared to pure chitosan nanoparticles. Release kinetics analysis indicated that the addition of BSG altered the drug release mechanism, allowing for a more uniform release profile within the first 24 h. Metabolic

activity assays confirmed the effectiveness of the DOX release in inhibiting SKBR-3 breast cancer cell spheroids, validating the nanocomposite's potential in targeted cancer therapy (Figure 5) [56].

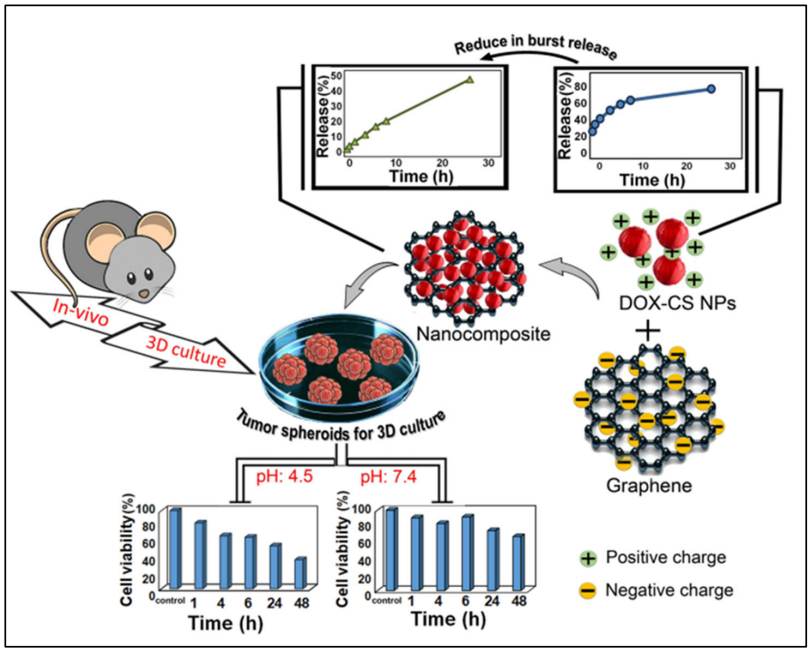

Figure 5. Schematic illustration of the fabrication process for BSG/chitosan nanocomposites, along with a comparison of release profiles between chitosan nanoparticles and an analysis of 3D culture systems. Reproduced with permission from ref. [56]. Copyright 2021 Elsevier.

4.2. Metallic NPs

Metallic nanoparticles (MNPs) can also be categorized as inorganic NPs. Over the last decade, significant research attention has been directed toward these inorganic NPs due to their valuable medicinal and imaging attributes. These NPs typically share a common structure characterized by an organic surface layer covering a core, dictating their electrical, magnetic, and optical characteristics. Notably, gold NPs and QDs stand out as the frequently utilized types of MNPs in the context of BC treatment.

Gold NPs

Gold nanoparticles (AuNPs) have gained significant attention in recent years due to their versatile applications achieved through size [57], shape [58], and surface modifications [59]. The most common method for producing AuNPs involves citrate-mediated reduction of Au^{3+} in aqueous solutions. The AuNPs possess well-defined properties, minimal cytotoxicity [60–64], and find widespread use in DDS. By coating their surfaces with organic compounds, the AuNPs can be targeted toward biomarkers and specific receptors. Disulfides and thiolates are commonly employed for surface functionalization due to their strong attraction to Au surfaces. Therapeutic agents can bind to AuNPs either noncovalently or covalently, allowing controlled drug release at desired sites [65]. Figure 6 is a schematic representation of the potential pH-triggered release of DOX from AuNPs through a pH-sensitive hydrazine linkage.

Researchers have explored combining reduced graphene oxide (rGO) with AuNPs to deliver covalently bound drugs to BC cells [66]. In a study, the anticancer medication MTX (Mitoxantrone) was covalently bonded to MPA (3-mercaptopropionic acid), creating MTX-terminated thiol compounds that were utilized to functionalize AuNPs. These functionalized AuNPs were incorporated into an rGO dispersion to form a nanocomposite. The hydrodynamic size of AuNPs increased upon thiol MTX (SMTX) functionalization, confirming the modification. When compared to SMTX-AuNPs, drug release from the

AuNPs/rGO nanocomposite was less affected, presumably because of the graphene oxide sheets' lower stacking barrier or the progressive hydrolysis of the amide link.

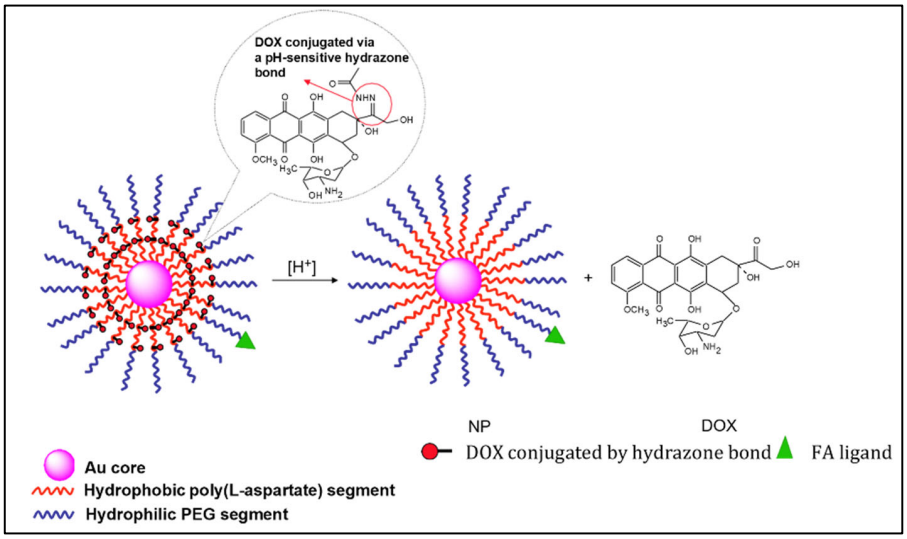

Figure 6. Schematic representation of the Au-Poly(L-aspartate-DOX)-b-PEG-OH/*FA NP and its pH-triggered drug release. (*FA—folic acid). Reproduced with permission from ref. [60]. Copyright 2009 Elsevier.

In vitro studies using MCF-7 BC cells have leveraged the higher transferrin receptor expression on cancer cell membranes for targeted therapy by conjugating transferrin to AuNPs [67]. Inhibition of vascular endothelial growth factor receptor (VEGFR-2)/epidermal growth factor receptor (EGFR) is critical for BC metastasis and hyperplasia. Quercetin-loaded AuNPs were shown to hinder epithelial–mesenchymal transition, a driver of BC malignancy, in both MDA-MB-231 and MCF-7 cells. Levels of protein expression related to BC progression were modulated by this DDS. Additionally, functionalizing AuNPs with different molecules or ligands enhanced their stability and capacity to regulate protein expression or induce cancer cell death.

AuNPs were employed to enhance the effectiveness of radiotherapy against BC cells in a different study, using benign MCF-10A cells and MCF-7 cancerous cells. Functionalized AuNPs coated with cysteamine and thioglucose improved radiation efficiency in cancer cell eradication [68]. DOX-loaded AuNPs demonstrated the ability to overcome MDR (multidrug resistance) in MCF-7/ADR (Adriamycin) tumor cells [69]. Despite their advantages in drug carrier research, including facile imaging via techniques like transmission electron microscopy (TEM) and controlled functionalization, a limitation of AuNPs is their limited biodegradability within biological systems due to their inherent stability.

Thipe et al. (2024) [70], developed and characterized gold nanoparticles encapsulated with *Ginkgo biloba* phytochemicals (GB-AuNPs) to treat BC. These nanoparticles demonstrated strong anticancer effects against MDAMB-231 cells, enhanced antitumor cytokines (IL-12, TNF-α, IFN-γ), and suppressed protumor cytokines (IL-6, IL-10). GB-AuNPs exhibited better safety and efficacy than cisplatin, highlighting the potential of green synthesized nanoparticles (Nano-Ayurvedic medicine) as an innovative cancer treatment [70].

4.3. Quantum Dots

Effective imaging of tumor cells is crucial for monitoring disease progression and evaluating the effectiveness of treatments. QDs play a significant role in this regard due to their exceptional optical properties that enable long-term tumor imaging [71,72]. QDs are nanoscale semiconductor crystals, typically ranging in size from 2 to 10 nm. These NPs consist of a central metal core that emits a narrow spectrum of light, varying from visible to infrared (IR) based on its size. The outer shell can be composed of doped metals or semiconductor layers, tailored for specific applications. By attaching ligands

and peptides to their surface, QDs can be directed toward specific cancer targets. Notably surpassing other NPs, QDs excel in in vivo cellular imaging due to their tunable optical properties, substantial surface-to-volume ratio, resistance to fading, and high brightness. However, a drawback of QDs is their inherent hydrophobicity, necessitating polymer coatings or multilayer ligand shells to impart water solubility [73]. Polyethylene glycol (PEG) conjugation mitigates potential toxic deposition and enables improved surface functionality [74–76].

QDs facilitate multiplexed imaging, outperforming conventional techniques such as western blot and immunofluorescence, by providing simultaneous biomarker data collection [77]. For instance, in a review involving BT-474 and MCF-7 cell lines expressing distinct levels of mammalian target of rapamycin (mTOR), progesterone receptor (PR), estrogen receptor (ER), EGFR, and HER2 biomarkers, QDs emitting at various wavelengths were employed. Conjugating these QDs with primary antibodies targeting the protein biomarkers allowed simultaneous quantitative and multicolor biomarker detection [78]. Another study by Sun et al. (2018) [79] introduced water-soluble CuInS2/ZnS QDs as imaging agents to detect BC cells. These QDs were linked to an anti-Ki-67 mAb, which recognizes a nuclear-related protein linked to cell cycling. By coating initially hydrophobic QDs with octadecylamine and encapsulating them within an amphiphilic polymer, they maintained the optical properties of the QDs. In vitro studies on MDA-MB-231 BC cells showed no significant toxicity, although minor changes in cell shape and viability were observed [79]. Srinivasan et al. (2024) reported that pH-sensitive CVC-ZnO QDs prevents the DMBA-induced mammary cancer by modulating antioxidant status, lipid peroxidation levels, and detoxification enzymes activities [80]. Similarly, pH-sensitive CVC-ZnO QDs activates the apoptosis in MDA-MB-231 cells by regulating antiapoptotic and proapoptotic genes [81]. The study demonstrated that CVC-ZnO QDs exhibit pH-responsive behavior, releasing carvacrol specifically in the acidic tumor microenvironment. This targeted release enhances anticancer effects against MDA-MB-231 breast cancer cells while minimizing toxicity to normal cells. The nanoformulation regulated apoptosis through markers like Bcl2, Bax, caspase-3, and caspase-9. These findings highlight the potential of CVC-ZnO QDs as an effective, tumor-targeted drug delivery system (Figure 7).

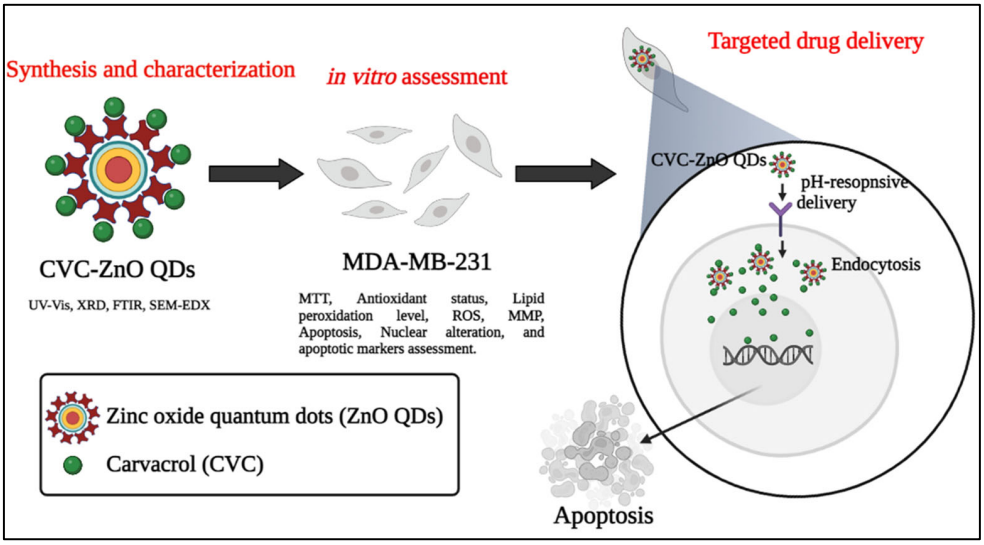

Figure 7. Schematic representation of pH-sensitive CVC-ZnO QDs on metastasis triple-negative breast cancer cell line MDA-MB-231 [76].

4.4. Mesoporous Silica NPs

Mesoporous silica nanoparticles (MSNPs) have garnered significant attention in the realm of DDS and imaging due to their distinct attributes. These NPs possess a noteworthy combination of features, including a substantial surface area, pore volume, tunable pore

sizes, and a highly modifiable surface [82–87]. Their adaptable properties make them an attractive alternative among inorganic nanomaterials.

MSNPs exhibit remarkable potential with unique characteristics that enable them to serve as effective carriers for biodegradable substances like genes and proteins. This capability stems from their ability to accommodate a substantial and controlled payload of drugs while ensuring controlled release only upon reaching the intended target site. A notable instance involves the use of green fluorescent MSNPs as drug carriers in a DDS. This system employed an anti-HER2/neu monoclonal antibody, achieving specific targeting of BC cells [88]. The MSNPs were initially loaded with a green fluorescent dye, facilitated by a PEG spacer to enable imaging.

The efficacy of MSNPs' targeting capacity was validated using both HER2-negative (MCF-7 BC cells and NIH3T3 murine fibroblast cells) and HER2-overexpressing (BT474 BC cells) cells. Notably, green fluorescence was prominently observed in BT474 cells. The study revealed that a minimal amount of Trastuzumab was nonspecifically bound to all three cell types when combined with MSNs. Intriguingly, certain MSNs demonstrated the ability to image within the cytosol after escaping endosomal vesicles in the intracellular environment.

Hu et al. (2022) [89], developed PhMSON@Dox-HA, a nanocarrier composed of polydopamine and tetrasulfide-doped hollow mesoporous silica nanospheres loaded with DOX and coated with hyaluronic acid to prevent drug leakage. This nanocarrier targets tumors due to HA modification and releases drugs in tumor cells' cytoplasm through GSH-triggered decomposition. Additionally, polydopamine enables photothermal therapy under 808 nm laser irradiation, achieving effective tumor elimination through synergistic chemo-photothermal therapy (Figure 8) [89].

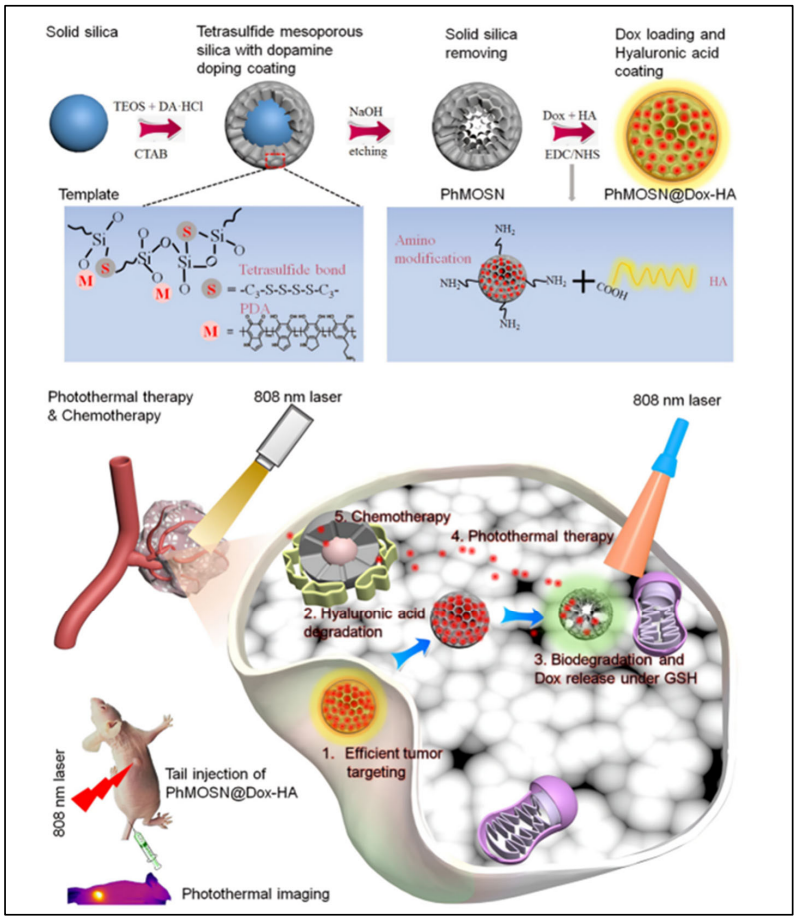

Figure 8. Graphical representation of the applications of mesoporous silica nanoparticles doped with tetrasulfide and polydopamine, loaded with DOX, for synergistic antitumor chemo-photothermal therapy. Reproduced with permission from ref. [89]. Copyright 2021 Elsevier.

Another notable application of MSNP-based DDS for delivering siRNA (small interfering RNA) to MDR (multidrug-resistant) BC cells in nude mice, is to overcome DOX resistance [90]. The chosen siRNA targeted the P-glycoprotein (Pgp) drug exporter and was screened using the MDR/MCF-7 cell line. To stabilize and protect the Pgp and DOX siRNA system, MSNs were functionalized with polyethylene imine (PEI) and PEG copolymers. This strategy led to reduced reticuloendothelial aggregation, substantial Pgp knockdown, intracellular DOX-induced apoptosis, increased retention and permeability at tumor sites, and synergistic suppression of tumor growth in xenografts. The approach also enabled the administration of lower DOX doses, potentially mitigating DOX-associated cardiovascular damage. Additionally, when compared to separate therapies, the combination DDS had greater pharmacological activity.

In terms of biocompatibility and toxicity, studies on MSNPs inspire more impact than metal-based NPs, which are hazardous heavy metals detrimental to human health. Additionally, the capacity of the porous NPs to concurrently deliver a cocktail of medications to a target area, coupled with the abundance of silica as a material, offers promising advantages. However, a notable limitation of MSNPs is their limited tumor penetration capability [91]. Consequently, substantial surface modifications are imperative to facilitate the in vivo application. Table 1 summarizes the inorganic nanoparticles, methods, targets, and key findings in breast cancer treatment and imaging.

Table 1. Summary of inorganic nanoparticles, targets, and key findings in breast cancer treatment and imaging.

Nanoparticles	Method	Cell Line/Animal Model	Target Receptor/Molecule	Key Findings (Imaging/Treatment)	Ref.
SWNTs	Photothermal therapy (Raman signals, NIR absorption)	SK-BR-3 (HER2-positive) and MCF-7 cells (HER2-negative)	HER2	Selective photothermal elimination of HER2-expressing cells. Demonstrated specificity through conjugation with HER2 IgY.	[46]
	Photothermal therapy	SK-BR-3 and MCF-7 cells	-	Reinforced the selectivity of CNTs for tumor cells upon functionalization.	[47]
	PTX + lipid docosanol + folic acid	MCF-7 cells Female athymic nude mice	HER2	Enhanced cell penetration and treatment effectiveness with folic acid targeting.	[52]
AuNPs	Transferrin-conjugated AuNPs targeting transferrin receptors on cancer cells	MCF-7 cells	-	Enhanced targeted therapy through receptor-mediated uptake.	[67]
	Quercetin-loaded AuNPs modulating VEGFR-2/EGFR expression	MCF-7 and MDA-MB-231 cells	EGFR, VEGFR2	Inhibited epithelial–mesenchymal transition (EMT) and reduced protein expression linked to BC progression, enhancing anticancer potential.	[68]
	Cysteamine- and thioglucose-functionalized AuNPs improving radiotherapy efficiency	MCF-7 and MCF-10A cells	-	Improved radiation efficiency, selectively targeting cancerous cells while sparing benign cells.	[68]
	DOX-loaded AuNPs overcoming MDR (multidrug resistance)	MCF-7/ADR (Adriamycin-resistant Breast cells)	EGFR	DOX-loaded AuNPs demonstrated the ability to overcome drug resistance mechanisms, restoring treatment efficacy.	[69]
	rGO-AuNP nanocomposite functionalized with MTX-terminated thiol compounds	MCF-7 cells	EGFR, VEGFR2	Stable drug delivery platform with reduced stacking barriers; sustained drug release and enhanced efficacy due to progressive hydrolysis of the amide link.	[66]

Table 1. *Cont.*

Nanoparticles	Method	Cell Line/Animal Model	Target Receptor/Molecule	Key Findings (Imaging/Treatment)	Ref.
AuNPs	pH-sensitive DOX release using Au-Poly(L-aspartate-DOX)-b-PEG-OH/FA NPs	4T1 cells Mouse mammary carcinoma cells	EGFR, VEGFR2	pH-triggered drug release system providing targeted delivery at acidic tumor environments, improving controlled drug release and therapeutic potential.	[65]
	Ginkgo biloba phytochemicals (GB-AuNPs)	MDA-MB-231 cells	IL-12, TNF-α, IFN-γ (enhanced); IL-6, IL-10 (suppressed)	GB-AuNPs demonstrated strong anticancer effects, superior safety, and efficacy compared to cisplatin, promoting Nano-Ayurvedic medicine for cancer treatment.	[70]
QDs	QDs conjugated with antibodies for biomarkers: mTOR, PR, ER, EGFR, and HER2	BT-474 and MCF-7 cell lines	-	Enabled simultaneous, multiplexed detection of biomarkers using QDs emitting at different wavelengths, improving imaging beyond traditional techniques.	[78]
	CuInS2/ZnS QDs conjugated with anti-Ki-67 mAb; QDs encapsulated with amphiphilic polymer	MDA-MB-231 cells		Demonstrated in vitro imaging without significant toxicity, though minor changes in cell shape and viability were observed. Maintained QD optical properties post-encapsulation.	[79]
	pH-sensitive CVC-ZnO QDs	DMBA-induced mammary cancer (Female Sprague Dawley rats) MDA-MB-231 cells	Apoptotic genes	CVC-ZnO QDs prevented mammary cancer progression by regulating antioxidant and detoxification pathways. Induced apoptosis in MDA-MB-231 cells by modulating apoptotic gene expression, showing potential as an anticancer agent.	[80] [81]
Silica NPs	Anti-HER2/neu monoclonal antibody targeting using green fluorescent MSNPs with PEG spacer for drug delivery and imaging.	MCF-7, NIH3T3, and BT474 cell lines	-	Specific targeting of HER2-overexpressing BT474 cells with minimal nonspecific binding to other cells. Green fluorescence observed predominantly in BT474 cells. Intracellular MSNPs escaped endosomal vesicles for cytosolic imaging.	[88]
	PhMSON@Dox-HA	4T1 cells 4T1 tumor-bearing mice	-	GSH-triggered drug release, photothermal therapy under 808 nm laser, effective tumor elimination through synergistic chemo-photothermal therapy.	[89]
	MSNP-based DDS delivering siRNA targeting P-glycoprotein (Pgp) to overcome DOX resistance. MSNPs functionalized with PEI and PEG for stabilization.	MDR/MCF-7 (Multidrug-resistant BC cells) Nude mice (xenografts)	-	Substantial Pgp knockdown and intracellular DOX-induced apoptosis. Synergistic tumor growth suppression in xenografts. Increased drug retention and permeability at tumor sites. Lower DOX doses used, reducing cardiovascular damage risk.	[90]

5. Organic Nanocarriers

Organic carriers, primarily composed of carbon and hydrogen-based NPs, commonly ensnare or attach drugs within the matrix. These NPs possess excellent biocompatibility and an enhanced capacity for loading drugs [92]. Liposomes, dendrimers, micelles, and polymeric NPs are examples of these organic nanocarriers.

5.1. Dendrimers

Dendrimers have a core molecule and a 3D arrangement resembling a tree. These dendritic structures can expand through synthesis by adding branches, a process often

denoted as "Generations", characterized by tiers between successive branching points [93]. Alternatively, expansion can occur by polymerizing the central molecule. Dendrimers possess adaptable solubility traits, enabling modifications, facile control over the size and molecular mass, and the ability to link with various ligands [94]. Leveraging these attributes, they can serve as effective targeting agents.

Moreover, dendrimers find utility in the binding encapsulation and both hydrophobic and hydrophilic medications. This functionality arises from the attachment of functional groups to their branches. Beyond covalent linkage, drugs can be housed within hydrophobic microcavities within the dendritic branching crevices or absorbed onto dendrimer surfaces via ionic interactions [95]. However, the assertion of dendrimer-mediated drug loading must have been exaggerated due to the intricate, highly branched cage-like structure.

Targeted inhibition of CXCR4 using LFC131-functionalized dendrimers carrying DOX (LFC131-DOX-D4) effectively suppressed the migration of breast cancer cells, reducing metastasis. These dendrimers enhanced cytotoxicity in CXCR4-expressing BT-549-Luc and T47D cells compared to nontargeted formulations. The results highlight the potential of LFC131-DOX-D4 for selective BC treatment by inhibiting CXCR4-mediated metastasis. This approach offers a promising strategy for reducing cancer spread and improving therapeutic outcomes [96].

Aleanizy et al. (2020) [97] successfully developed trastuzumab (TZ)-grafted dendrimers loaded with neratinib for targeted treatment of HER2-positive BC. The TZ-conjugated dendrimers demonstrated enhanced cellular uptake and higher antiproliferative activity against SKBR-3 cells compared to plain neratinib or neratinib-loaded dendrimers. The sustained drug release profile further supports their potential in reducing resistance and improving therapeutic outcomes. These findings suggest TZ-grafted dendrimers as promising carriers for targeted BC therapy [97].

5.2. Liposomes

These entities consist of multilayer and monolayer liposomes, which are spherical structures made up of layers of amphiphilic lipids. The central aqueous compartment of the multilayer system can encapsulate both water-insoluble and water-soluble pharmaceuticals, protecting against external factors [98]. Liposomes, acting as dendrimers, can function as targeted carriers by attaching ligands or antibodies. They exhibit an advantage in treating conditions that impact immune system phagocytes due to their tendency to accumulate in these cells [99]. The issue of premature degradation and clearance of intact liposomes by the RES (reticuloendothelial system) phagocytic cells can be resolved by coating them with an inert polymer and biocompatible material.

Deng et al. (2013) [100] introduced Layer-by-Layer NPs, designed for constructing a highly stable layer containing a high concentration of siRNA on a nanoscale core. This novel category of drug delivery platforms holds significant potential for clinical application. Given their authorization as drug carriers, exemplified by Doxil (Dox liposomal) for treating BC, as well as their prolonged circulation and controlled drug release profiles, phospholipid liposomes were selected for loading DOX. For siRNA loading, PEI and Poly-L-arginine (PLA) coatings were individually applied to the nanoparticle surfaces. PLA was favored due to its biodegradability, unlike PEI. To enhance in vivo stability through CD44-mediated interactions with the HA (hyaluronic acid)-terminal layer, an additional layer of HA was applied to the nanoparticle surface for active targeting. Notably, the study demonstrated reduced toxicity by reducing the use of polycationic compounds. The delivery system also addressed the challenge of siRNA release after the endosomal escape by utilizing biodegradable components, resulting in siRNA being a control released. Furthermore, concurrent delivery of DOX and siRNA led to greater tumor regression, and in some cases, complete regression, compared to DOX-only therapy [100].

Guo et al. (2014) [101] developed distinct liposomes, each with a specific role, composed of a combination of three substances: 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine-N-dodecanoyl (N-dod-PE), 1,2-Dioleoyl-3-dimethylammonium-propane (DODAP), and

1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC). Within the acidic endosomal environment, DODAP-incorporated liposomes became more positively charged, leading to fusion with the endosomal membrane and subsequent release of encapsulated siRNA into the cytoplasm. N-dod-PE was utilized as an anchor for attaching either nonspecific immunoglobulin G or an anti-C-X-C chemokine receptor type 4 (CXCR4) antibody (aCXCR4), allowing precise targeting of liposomes to metastatic breast cancer (MBC) cells overexpressing CXCR4, thus inhibiting cancer metastasis by approximately 90%. This approach proved significantly more effective than simply blocking individual drug pathways [101].

To tackle the challenge of treatment and targeting strategies for multidrug-resistant (MDR) cancer, Liao et al. (2015), developed AS1411-functionalized liposomes loaded with DOX and ammonium bicarbonate, a bubble-generating agent, specifically to target DOX-resistant breast cancer cells (MCF-7/ADR) (Figure 9). Molecular dynamics simulations revealed that the interaction between nontargeted liposomes and nucleolin receptors was unfavorable, while the G-quadruplex structure of the AS1411-nucleolin complex showed a spontaneous and highly stable interaction, indicated by significant negative binding energy. In vivo studies using nude mice bearing MCF-7/ADR tumors demonstrated that AS1411-functionalized liposomes achieved higher cellular concentrations of DOX in tumor tissues compared to free DOX or PEGylated liposomes. This targeted approach significantly inhibited tumor growth and minimized systemic side effects, such as cardiotoxicity [97].

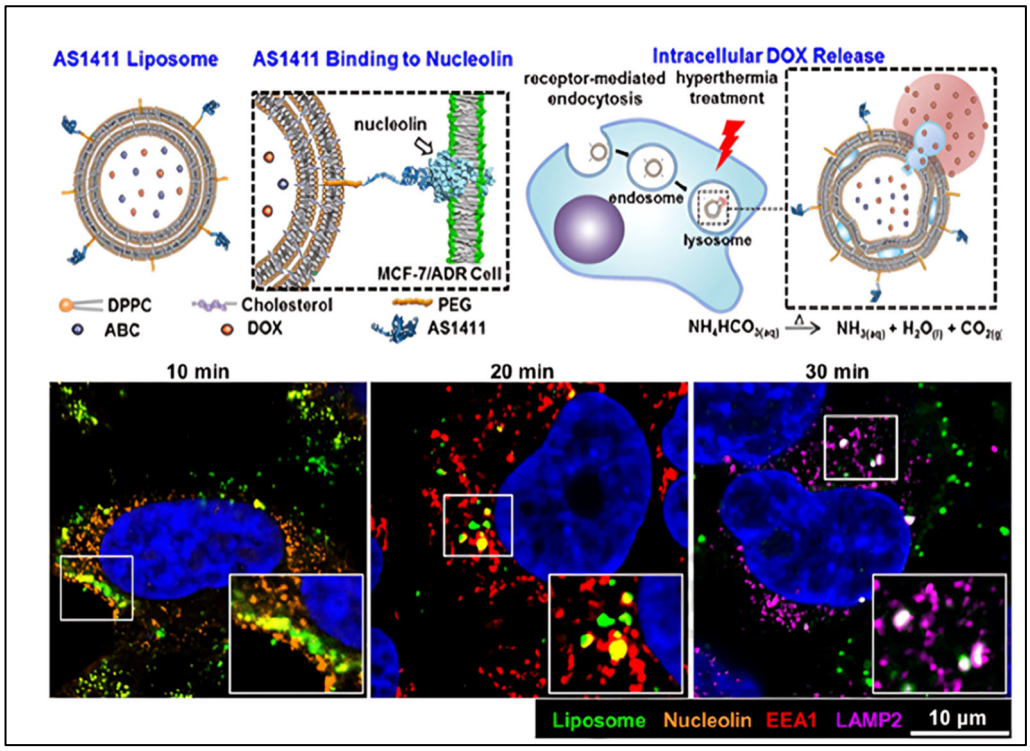

Figure 9. An illustration of nucleolin-targeted liposomal delivery in breast cancer. This schematic depicts the structure of an AS1411-functionalized liposome that binds to nucleolin on the cell membrane. This binding triggers receptor-mediated endocytosis, leading to the accumulation of DOX inside the cell. The release of DOX is initiated by the generation of CO_2 bubbles, resulting from the thermal reduction of encapsulated ammonium bicarbonate. Reproduced with permission from ref. [102]. Copyright 2015 Elsevier.

Hu et al. (2023) [103] developed an intelligent, MMP-2-responsive liposome delivery system (NLG919@Lip-pep1) that co-delivers AUNP-12 and NLG919 to target both T cells and tumor cells. This system disrupts the PD-1 signaling pathway, restores T cell activity, and alleviates the immunosuppressive microenvironment at tumor sites. Leveraging the EPR effect and MMP-2 overexpression, it achieves precise drug release at invasive tumor

margins. Their approach enhances combination immunotherapy with high efficiency and low toxicity, offering a promising strategy for treating MBC by reactivating the body's antitumor immune response [103].

Massadeh et al. (2020) [104] developed PEGylated polymer–lipid hybrid nanoparticles (PLNPs) for the delivery of anastrozole (ANS) to improve its therapeutic performance. The optimized nanoparticles exhibited a uniform size distribution (193.6 ± 2.9 to 218.2 ± 1.9 nm), low zeta potential, and spherical morphology. Differential scanning calorimetry confirmed effective ANS incorporation within the polymeric matrices. The system achieved high entrapment efficiency (~80%) and showed sustained drug release. Flow cytometry results demonstrated that the ANS-PLNPs induced apoptosis in estrogen-positive MCF-7 breast cancer cells. Overall, the PEGylated nanoparticles proved to be a promising, stable, and effective drug delivery system for cancer therapy [104].

5.3. Micelles

Polymeric micelles are formed by randomly or block arranged amphiphilic copolymers, undergoing self-assembly in aqueous settings. Distinguished from liposomes by their hydrophobic core and hydrophilic shell, micelles provide a platform for loading multiple drugs simultaneously. These structures offer finer control over drug release, enhanced stability compared to liposomes, and narrower size distribution [105]. With inherent adaptability, polymeric micelles are favored for DDS. Drugs can be loaded onto micelles through chemical or physical means depending on the preparation technique [106].

A well-received biocompatible and biodegradable polymer is granted FDA (Food and Drug Administration) poly (D, L-lactide-co-glycolide) approval [107,108]. When combined with a hydrophilic polymer in diblock copolymers like poly (lactide-co-glycolide) (PLGA)/PEG, this hydrophobic block copolymer is commonly employed to co-encapsulate or conjugate various combinations of anticancer drugs, boosting loading efficiency. An amphiphilic copolymer named "methoxy poly (lactide-co-glycolide)-poly (ethylene glycol)" was harnessed to fabricate micellar NPs for combined drug delivery. These nanomicellar carriers stood out for their simple production process and effective loading of hydrophilic DOX and hydrophobic paclitaxel. Administering both drugs within one nanoparticle led to superior inhibition of tumor cell growth compared to individual treatments, displaying synergistic effects [109].

Hydrophobic PLGA copolymer and hydrophilic PEI were melded by Wang et al. (2016), to generate nano-micelles. Here, PLGA constituted the core for physically loading hydrophobic DOX, while anionic miRNAs were linked to cationic PEI. These nanomicelles were surface-coated with HA to target the CD44 receptor and acquire a negative charge, reducing cytotoxicity. The system's improved intracellular accumulation of DOX and Micro-RNA (miRNA) suggested a synergistic impact on cancer cell death [110].

Zhai et al. (2017) [111], development of amphiphilic diblock copolymers rich in diselenide were crafted to encapsulate two synergistically beneficial anticancer drugs. Camptothecin and DOX aided in the creation of core-cross linking micelles using visible light-induced dynamic diselenide bond exchange within the hydrophobic core. Core-cross linking methods were employed to enhance the stability of drug-loaded polymeric NPs, reducing drug leakage under prolonging blood circulation and physiological conditions. This approach significantly accelerated the release of camptothecin and DOX in the tumor's redox microenvironment. In vivo experiments confirmed the nanocarriers potent tumor-suppressive effects, achieved with low dosages of the combined drugs [111].

5.4. Polymeric NPs

Polymeric NPs employ several methods for loading drugs, including dissolution, submicron colloidal systems, trapping, adsorption, binding, and encapsulation [112]. These approaches fall into two categories based on nanoparticle preparation: nanocapsules and nanospheres. Nanocapsules form vesicle systems where pharmaceuticals reside within oily or aqueous environments, surrounded by a polymer membrane. Nanospheres are

polymeric matrices with medication distributed throughout all particle spaces [113]. These systems can be tailored for targeted delivery to tissues and tumor cells, but achieving consistent synthesis conditions is a challenge in designing polymeric NPs [114].

The submicron size of polymeric NPs enables enhanced cell adsorption and drug accumulation within tumor tissues during the initial and sustained pharmaceutical release phases, using biodegradable materials [112]. Furthermore, these NPs can modify the pharmacokinetic and pharmacodynamic traits of bioactive compounds, offering an avenue to overcome the drawbacks of conventional DDS [115].

Numerous polymeric NPs have been employed in anticancer drug delivery and therapy, including an approach by Chiang et al. (2014), involving a two-step, double-emulsion procedure for pH-sensitive nanocapsules [116]. Another example is Zhu et al. (2014), who created PLGA NPs for the simultaneous delivery of vitamin E and docetaxel (DTX) [117]. These NPs, ranging in size from 100 to 120 nm and encapsulation efficiency (EE) from 85 to 95%, were more effective than free DTX in vitro analysis (Figure 10). Addressing triple-negative BC, Su et al. (2015), developed NP-IPS NPs combining indocyanine green, PTX, and surviving siRNA for gene therapy, photothermal therapy, and chemotherapy [118].

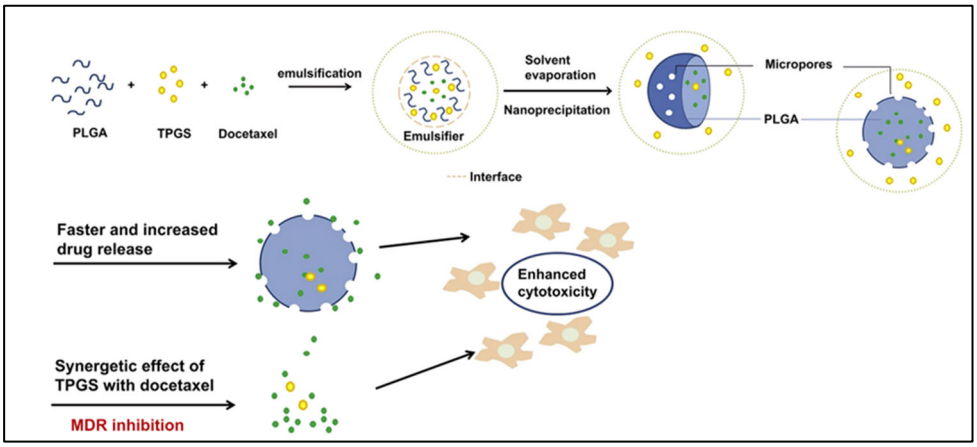

Figure 10. Schematic graph of TPGS functions as a pore former and promotes antitumor activity of DTX-loaded NPs [117].

Chitosan, a natural biopolymer with low toxicity, biodegradability, and biocompatibility, is favored for tissue engineering and drug delivery. Esfandiarpour-Boroujeni et al. (2017) and Olov et al. (2018), created chitosan-based polymeric NPs through self-assembly, targeting folate receptors in BC cells. These NPs demonstrated a high loading capacity for hydrophilic and hydrophobic medicines [119,120]. Biomarker identification and accurate diagnosis lead to effective treatment decisions, where targeted drug delivery systems play a vital role. NPs can be tailored for effective targeting through passive and active strategies [107–109]. Surface ligands interact with target receptors for active targeting, enhancing drug absorption. Various receptors such as proteins, polysaccharides, ligands, peptides, and aptamers have been explored for this purpose.

Moammeri et al., 2022 developed folic acid–PEGylated niosomal nanocarriers for the codelivery of cisplatin (CIS) and epirubicin (EPI) to treat BC. The nanocarriers showed excellent drug encapsulation efficiency, stability over two months, and sustained drug release at physiological pH. Cellular assays confirmed enhanced apoptosis and reduced cancer cell migration compared to free drugs. FA-PEGylated niosomes (FPNCE) increased the expression of pro-apoptotic genes (Bax, Caspase-3/9) and reduced anti-apoptotic (Bcl2) and metastatic markers (MMP-2/9). In vivo studies on BALB/c mice further validated the reduction in tumor invasion and mitosis index. This strategy demonstrates promising potential for safer, targeted BC treatment with reduced toxicity [121]. Table 2 summarizes the organic nanoparticles, methods, targets, and key findings in breast cancer treatment and imaging.

Table 2. Summary of organic nanoparticles, targets, and key findings in breast cancer treatment and imaging.

Nanoparticles	Target/Method	Cell Line/Animal Model	Target Receptor/Molecule	Key Findings (Imaging/Treatment)	Ref.
Dendrimers	LFC131-functionalized dendrimers carrying DOX (LFC131-DOX-D4)	BT-549-Luc and T47D	CXCR4	Enhanced cytotoxicity in CXCR4-expressing cells, reduced migration and metastasis compared to nontargeted formulations. Promising for selective inhibition of breast cancer metastasis.	[91]
	LFC131-functionalized dendrimers carrying DOX (LFC131-DOX-D4)	SKBR-3 (HER2-positive breast cancer cells)	HER2	Enhanced cellular uptake and antiproliferative activity compared to plain neratinib. Sustained drug release supports reduction of resistance and improved outcomes.	[92]
Liposomes	Layer-by-layer nanoparticles (NPs) with siRNA and DOX loaded in phospholipid liposomes; coatings with PEI and Poly-L-arginine (PLA)	TNBC xenograft model using MDA-MB-468 cells	HER2	Developed highly stable siRNA delivery system using biodegradable PLA. HA layer for CD44-mediated active targeting. Concurrent delivery of DOX and siRNA showed greater tumor regression than DOX alone.	[95]
	Liposomes composed of N-dod-PE, DODAP, and DOPC; targeting CXCR4 in MBC cells	MDA-MB-231 and MDA-MB-468	HER2	DODAP liposomes enhanced positive charge in acidic endosomal environment, facilitating siRNA release. Specific targeting of CXCR4 overexpressing MBC cells resulted in approximately 90% inhibition of cancer metastasis.	[96]
	AS1411-functionalized liposomes with DOX and ammonium bicarbonate	MCF-7/ADR cells (DOX-resistant breast cancer)/Nude mice	Nucleolin receptor	Stable interaction between AS1411 and nucleolin receptor (G-quadruplex complex); higher DOX concentration in tumors; reduced cardiotoxicity; significant tumor inhibition compared to free DOX or PEGylated liposomes.	[97]
	NLG919@Lip-pep1	MMP-2-responsive liposome (NLG919@Lip-pep1) delivering AUNP-12 and NLG919	PD-1 receptor	Restored T-cell activity; disrupted PD-1 signaling; improved immune response; enhanced drug release at invasive tumor margins through EPR effect and MMP-2 targeting; low toxicity with high therapeutic efficiency for metastatic breast cancer.	[98]
	PEGylated polymer-lipid hybrid nanoparticles (PLNPs) loaded with anastrozole (ANS)	MCF-7 cells	Estrogen receptor	High entrapment efficiency (~80%); sustained drug release; effective apoptosis induction in MCF-7 cells; nanoparticles exhibited stable morphology with low zeta potential, providing a promising drug delivery system for breast cancer therapy.	[99]
Micelles	Nano-micelles with PLGA core and PEI	MCF-7 and MDA-MB-231	HER2	PLGA loaded hydrophobic DOX, while cationic PEI linked to anionic miRNAs. HA surface coating targeted CD44, enhancing intracellular drug accumulation and cancer cell death.	[105]
	Amphiphilic diblock copolymers encapsulating	MCF-7 and EMT-6 Femal Balb/c mice	HER2	Core-cross linking micelles enhanced stability, reduced drug leakage, and accelerated drug uptake.	[106]
Polymeric NPs	PLGA NPs for co-delivery of Vitamin E and Docetaxel (DTX)	MCF-7/ADR cells Female nude mice	HER2	NPs (100–120 nm) achieved encapsulation efficiency (EE) of 85–95%, more effective than free DTX in vitro.	[112]
	NP-IPS NPs combining indocyanine green, paclitaxel (PTX), and survivin siRNA	MDA-MB-231 Nude mice **(xenografts)**	HER2, TNBC	Multimodal approach using gene therapy, photothermal therapy, and chemotherapy for enhanced treatment efficacy.	[113]

Table 2. *Cont.*

Nanoparticles	Target/Method	Cell Line/Animal Model	Target Receptor/Molecule	Key Findings (Imaging/Treatment)	Ref.
Polymeric NPs	Chitosan-based polymeric NPs through self-assembly	MCF-7	-	High loading capacity for both hydrophilic and hydrophobic drugs, targeting folate receptors for improved delivery.	[114,115]
	FA-PEGylated niosomal nanocarriers (FPNCE) delivering cisplatin (CIS) and epirubicin (EPI)	SKBR3 and 4T1 cells BALB/c mice	Bcl2, Bax, Caspase-3/9, MMP-2/9	Enhanced apoptosis compared to free drugs. Increased pro-apoptotic (Bax, Caspase-3/9) expression. Decreased anti-apoptotic (Bcl2) and metastatic markers (MMP-2/9). In vivo results showed reduced tumor invasion and mitotic index, supporting reduced toxicity and improved drug targeting.	[116]

6. Challenges and Future Direction

Regulatory considerations for NPs involve evaluating their safety, efficacy, and quality for use in drug delivery systems. Presently, preclinical and clinical testing requirements for NP-based DDS are similar to those for small molecule drugs. Preclinical assessments involve animal tests to determine nanomedicine safety and efficacy. Subsequent clinical trials evaluate nanoparticle safety and efficacy in human subjects through three phases. Despite recent approvals of NP-based therapies, the absence of clear guidelines for characterization and production hinders their clinical potential. Some of the approved and under clinical trials NP-DDS for BC treatment are represented in Table 3.

Table 3. Some of approved and under clinical trials nanoparticulated drug delivery systems for breast cancer treatment.

Delivery System	Composition	Market Name	Active Molecule	Approval (Year)	Ref.
Liposome	HSPC/CHOL/DSPE-PEG	Doxil®/Caelyx®	Dox hydrochloride	1995	[122]
Liposome	EPC/CHOL	Myocet®	Dox	2001	[123]
Protein drug conjugate	MCC-DM1	Kadcyla®	Ado-Trastuzumab Emtansine	2013	[124]
Polymeric micelle	mPEG-PLA	Genexol-PM®	Paclitaxel	2007	[125]
Polymeric nanoparticle	Albumin	Abraxane	Paclitaxel	2005	[126]
Mesoporous silica nanoparticles	Antibody siRNA	T-NP	Trastuzumab	Under clinical trial	[127]
Polymeric nanoparticle	Nanoparticle-bound albumin	Pazenir	Paclitaxel	2019	[128]
Liposome	PEGylated liposomal/CKD602	S-CKD602	Topoisomerase I inhibitor	Phase I	[129]

Abbreviations: HSPC: hydrogenated soyphosphatidylcholine, DSPE-PEG: N-(carbonyl methoxy poly ethylene glycol 2000)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine, PEG-PLA: monomethoxypoly(ethyleneglycol)-block-poly(D,L-lactide), DM1: maytansine derivative, EPC: egg phosphatidylcholine. T-NP: Trastuzumab loaded MSNP-PEI-PEG (mesoporous silica nanoparticles-polyethylenimine and polyethyleneglycol), S-CKD602: STEALTH liposomal formulation of CKD-602.

Developing NPs for clinical use presents regulatory challenges. As these particles often carry drug and targeting molecules on their surfaces, new methods and tests are needed to assess their performance and physical properties. Nanotherapeutics can interact with plasma proteins and immune cells, necessitating consideration of biocompatibility and immunotoxicity during evaluations. Complex diseases like cancer benefit from nanomedicines, but patient heterogeneity requires robust clinical trial protocols to prevent unforeseen adverse effects post-approval.

Efforts to establish regulatory frameworks have been made by US, European, and Japanese regulators and industries through the ICH (International Conference on Har-

monization). Regulatory agencies, such as the EMA (European Medicines Agency) and the US FDA (Food and Drug Administration), have formed working groups to address nanomedicine challenges. The FDA has issued guidance documents on nanotechnology applications in regulated products and encourages manufacturers to engage with them early in product development. Patenting nanoparticle-based drug formulations faces challenges due to the term "nano" having multiple definitions, leading to uncertainty. Nanotechnology patent landscape mapping is difficult due to varying terminologies describing similar nanostructures. For instance, multiwalled carbon tubes are referred to as "nanofibers", "fibrils", and "nanotubes".

7. Conclusions

Treatment for BC has a lot of challenges. Traditional treatments like chemotherapy have drawbacks such as side effects and resistance. NPs offer a promising solution. They deliver drugs precisely, improving efficacy and reducing side effects. NPs can carry multiple drugs and target tumor cells specifically, enhancing treatment results. Despite their potential, NPs face obstacles to becoming standard treatments, like regulation and clinical testing. Regulatory agencies are working on guidelines for safe and effective nanomedicines. Nanomedicine has the potential to transform cancer treatment. NPs can improve targeted drug delivery and combination therapies, offering more effective and personalized treatment with fewer side effects. Challenges remain, but the benefits for patients and healthcare are immense, bringing hope for better cancer treatments.

Author Contributions: Conceptualization, S.A. and K.B.V.; writing—review and editing, S.A. and K.B.V.; writing—original draft preparation, S.A. and K.B.V.; investigation, K.S., M.K.S., A.T.A. and M.A.A.; formal analysis, K.S., M.K.S., M.A.A., M.A.S. and S.A.; resources, S.A. and P.P.; supervision, P.P. and C.P. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this review. Data sharing is not applicable to this article.

Conflicts of Interest: The authors declare no conflicts of interest.

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