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Article

Advanced nanosystems for Breast Cancer therapy and diagnosis: A classification-based review

Nanosistemas avanzados para el tratamiento y diagnóstico del Cáncer de Mama: clasificación basada en una revisión

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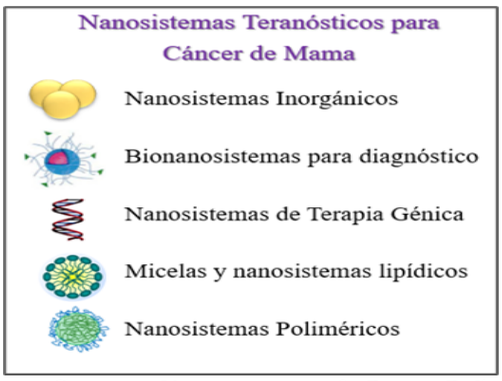
Abstract

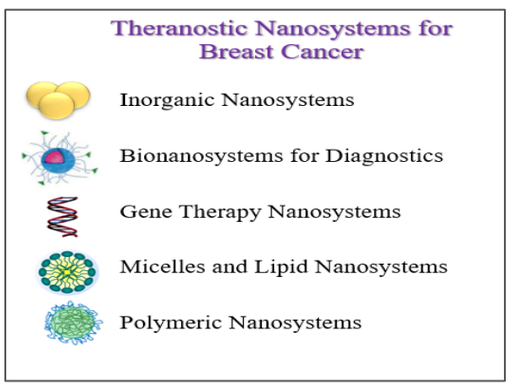
Breast cancer remains one of the leading causes of morbidity and mortality worldwide, particularly in aggressive subtypes such as triple-negative breast cancer [TNBC], for which conventional therapies exhibit limited selectivity, high systemic toxicity, and frequent drug resistance. In this context, nanotechnology has emerged as a pivotal strategy for the development of more effective, targeted, and precise diagnostic and therapeutic approaches. This review presents a comprehensive and up-to-date classification of advanced nanosystems applied to breast cancer diagnosis and treatment, encompassing organic, inorganic, hybrid, and biohybrid platforms. Polymeric and lipid nanoparticles, dendrimers, exosomes, carbon-based nanomaterials, MXenes, and multimodal theranostic systems are systematically analyzed. By correlating nanosystem composition, structural architecture, and therapeutic mechanisms, this classification provides a coherent conceptual framework to support the rational design of next-generation nanoplatforms aimed at precision medicine in breast cancer. Overall, this work highlights emerging trends toward multifunctional, stimulus-responsive, and integrated theranostic nanosystems with strong potential to overcome current clinical limitations, particularly in aggressive and treatment-resistant breast cancer subtypes.



Breast Cancer; Nanosystems of Drug Delivery; Theranosis

Resumen

El cáncer de mama continúa siendo una de las principales causas de morbilidad y mortalidad a nivel mundial, particularmente en subtipos agresivos como el cáncer de mama triple negativo [CMTN], para los cuales las terapias convencionales presentan baja selectividad, elevada toxicidad sistémica y frecuente resistencia farmacológica. En este contexto, la nanotecnología ha emergido como una estrategia clave para el desarrollo de enfoques diagnósticos y terapéuticos más eficaces, dirigidos y precisos. La presente revisión ofrece una clasificación integral y actualizada de nanosistemas avanzados aplicados al diagnóstico y tratamiento del cáncer de mama, que abarca plataformas orgánicas, inorgánicas, híbridas y biohíbridas. Se analizan de manera sistemática nanopartículas poliméricas y lipídicas, dendrímeros, exosomas, nanomateriales carbonosos, MXenes y plataformas teranósticas multimodales. Al correlacionar la composición de los nanosistemas, su arquitectura estructural y los mecanismos terapéuticos, esta clasificación proporciona un marco conceptual coherente para el diseño racional de nanoplataformas de nueva generación orientadas a la medicina de precisión en cáncer de mama. En conjunto, este trabajo destaca tendencias emergentes hacia nanosistemas multifuncionales, sensibles a estímulos e integrados, con alto potencial para superar las limitaciones clínicas actuales, especialmente en subtipos agresivos y resistentes al tratamiento.



Cáncer de Mama; Nanosistemas para la liberación de fármacos; Teranosis

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Introduction

Breast cancer remains the most frequently diagnosed malignancy in women and one of the leading causes of cancer-related mortality worldwide, with approximately 2.3 million new cases diagnosed annually. According to the most recent GLOBOCAN data, breast cancer accounted for 11.7% of all newly diagnosed cancer cases globally, surpassing other malignancies in incidence [Sung et al., 2021].

Despite significant advances in targeted therapies and personalized medicine, the clinical management of breast cancer continues to face substantial challenges, particularly in aggressive subtypes such as triple-negative breast cancer [TNBC]. This subtype is defined by the absence of estrogen, progesterone, and HER2 receptors and is characterized by pronounced molecular heterogeneity, highly invasive behavior, elevated rates of early recurrence, and limited responsiveness to conventional therapies. Consequently, TNBC is associated with an unfavorable prognosis and restricted therapeutic options compared with other breast cancer subtypes [Bianchini et al., 2016; Garrido-Castro et al., 2019].

Early diagnosis is a critical determinant of breast cancer survival and mortality reduction; however, conventional diagnostic strategies remain associated with significant limitations. Mammography, the standard screening modality, exhibits variable sensitivity [68–90%], which decreases markedly in younger women and in patients with high breast density, where false-negative rates may exceed 20% [Nelson et al., 2016]. Similarly, ultrasound and magnetic resonance imaging [MRI], although valuable as complementary tools, are associated with high false-positive rates, elevated costs, and limited accessibility, restricting their widespread use in population-based screening programs [Mann et al., 2019]. These diagnostic limitations contribute to delays in the detection of early-stage lesions and microtumors, particularly in biologically aggressive subtypes such as TNBC, which lacks specific molecular imaging biomarkers and is characterized by rapid tumor growth and short screening intervals [Bianchini et al., 2016]. Moreover, conventional imaging modalities display limited capacity to discriminate between malignant and benign tissues at the molecular level, hindering the early identification of oncogenic processes and accurate assessment of tumor heterogeneity.

As a result, a substantial proportion of breast cancer cases continue to be diagnosed at locally advanced stages, especially in low- and middle-income countries, where access to advanced diagnostic technologies remains restricted [Sung et al., 2021]. These shortcomings underscore the urgent need for innovative diagnostic strategies that are highly sensitive and specific, capable of detecting early molecular alterations and, simultaneously, integrating therapeutic functionalities, as exemplified by theranostic nanotechnology-based platforms.

From a therapeutic perspective, breast cancer management depends on clinical stage, molecular subtype, and patient condition, and typically involves surgery, radiotherapy, chemotherapy, hormone therapy, and targeted therapies, either alone or in combination. Surgery remains the cornerstone of treatment in early-stage disease, achieving local control rates exceeding 85–90% when combined with adjuvant radiotherapy. However, its efficacy declines significantly in locally advanced or metastatic disease, where effective systemic control is required [Waks & Winer, 2019].

Radiotherapy, widely employed as adjuvant or palliative treatment, has been shown to reduce local recurrence and improve overall survival, but is associated with adverse effects such as skin toxicity, cardiopulmonary damage, and tissue fibrosis, particularly in high-dose or prolonged treatment regimens [EBCTCG, 2011].

Systemic chemotherapy constitutes a central therapeutic strategy for locally advanced and metastatic breast cancer, as well as for aggressive subtypes such as TNBC. Although chemotherapy can improve disease-free and overall survival, its clinical use is constrained by systemic toxicity, limited tumor selectivity, and the development of drug resistance, which frequently result in relapse and severe adverse effects, including cardiotoxicity, myelosuppression, and neurotoxicity [O'Shaughnessy, 2005; Longley & Johnston, 2005].

Notably, chemotherapy remains the primary therapeutic option for TNBC due to the absence of well-defined molecular targets, despite the high rates of early relapse and poor prognosis associated with this subtype [Bianchini et al., 2016].

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While conventional therapies have substantially improved patient outcomes, critical limitations persist, highlighting the need for innovative strategies capable of integrating diagnosis, molecular targeting, and personalized therapy. Nanotechnology-based platforms offer the potential to overcome key limitations of traditional cancer therapies, including poor solubility of hydrophobic drugs, non-selective biodistribution, rapid systemic clearance, and dose-limiting toxicity. In addition, advanced nanosystems incorporate multifunctional features that enhance active targeting of tumor cells, optimize controlled drug release, and enable real-time diagnostic imaging, positioning nanoparticles as pivotal tools in the transition toward precision oncology. As highlighted by Mohajer et al. [2023], the field has rapidly evolved from monofunctional nanoparticles to sophisticated hybrid architectures capable of integrating chemotherapy, phototherapy, gene therapy, nanocatalytic therapy, and multimodal imaging within a single platform.

In parallel, nanocarrier-based formulations of bioactive compounds, including lipid nanoparticles and polymeric micelles, have demonstrated improved stability, bioavailability, and therapeutic potency of molecules such as curcumin, which inherently exhibits poor bioavailability. These formulations have shown significant synergistic effects in breast cancer cell lines, including MCF-7, MDA-MB-231, and SK-BR-3 [Zhu et al., 2024]. Furthermore, the development of stimulus-responsive platforms—activated by light, ultrasound, pH, or redox conditions—has enabled spatially and temporally controlled therapies, minimizing damage to healthy tissues while enhancing therapeutic precision.

Advances in gene therapy, particularly siRNA-based approaches, have positioned biopolymers and engineered exosomes as high-impact candidates for silencing key oncogenes, reversing drug resistance, and modulating tumor survival pathways, with robust effects demonstrated in solid tumors, including breast cancer [Subhan & Torchilin, 2023].

Concurrently, inorganic nanomaterials such as metal oxides, quantum dots, and two-dimensional nanomaterials [MXenes] have expanded therapeutic possibilities by integrating imaging modalities with photothermal therapy [PTT], photodynamic therapy [PDT], and nanocatalytic strategies based on reactive oxygen species generation.

More recently, advanced theranostic platforms capable of combining phototherapy, chemotherapy, nitric oxide release, ferroptosis induction, and immunogenic cell death [ICD] activation have emerged. Notably, ASNP-type nanosystems have demonstrated tumor microenvironment reprogramming and highly promising systemic antitumor effects in TNBC models [Zhao et al., 2025]. Similarly, biohybrid nanosystems—such as polydopamine nanoparticles loaded into mesenchymal stem cells—have exhibited enhanced tumor infiltration and superior therapeutic efficacy compared with conventional nanoparticulate platforms [Ferreira et al., 2021]. In addition, acoustically responsive systems, including perfluorohexane nanodroplets, enable ultrasound-guided tumor visualization and site-specific drug release following acoustic activation [Baghbani et al., 2017].

Collectively, these advances reflect a clear shift toward the development of highly integrated, intelligent nanosystems tailored to precision medicine. Nevertheless, there remains a critical need for a functional and comparative classification framework that systematically organizes nanosystems according to their composition, structural architecture, therapeutic mechanisms, and degree of diagnostic integration. Accordingly, the present work proposes a systematic reclassification of nanosystems applied to breast cancer treatment, grounded in recent evidence and a multidimensional analysis encompassing organic, inorganic, hybrid, biohybrid, and fully theranostic platforms. This classification aims to provide a conceptual framework for future nanotherapeutic development and a methodological reference for researchers seeking to design next-generation platforms capable of addressing the persistent clinical challenges associated with breast cancer.

Methodology

Study design

A comprehensive bibliographic review of nanosystems applied to the diagnosis and treatment of breast cancer was conducted, integrating experimental studies performed in vitro and in vivo, as well as specialized review articles.

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Search strategy

The literature search was carried out using the following databases: PubMed, Scopus, Web of Science, ACS Publications, ScienceDirect, and MDPI. The search terms included combinations of the following keywords: breast cancer, nanoparticles, nanosystems, nanomedicine, theranostics, and photothermal therapy.

Inclusion criteria

Articles published between 2017 and 2025. Studies focused on breast cancer or closely related experimental models.

Reports describing nanoparticles characterized in terms of composition, architecture, or therapeutic mechanism.

Studies evaluating therapeutic efficacy, diagnostic performance, or theranostic functionality.

Exclusion criteria

Studies lacking experimental data or adequate nanosystem characterization.

Articles not related to breast cancer.

Review articles without relevant technical or methodological information.

Data extraction and analysis process

a] Information was extracted regarding nanosystem type, particle size, zeta potential, encapsulation efficiency [EE%], therapeutic mechanism, imaging modality, route of administration, cellular or animal models, and key outcomes.

b] Nanosystems were classified into four main categories: organic, inorganic, hybrid, and biohybrid platforms.

c] A comparative analysis was performed to identify emerging trends, functional complexity, and levels of integration between diagnostic and therapeutic capabilities.

Finally, the extracted data were consolidated into a global classification table aimed at supporting the rational design of nanotherapeutic platforms for breast cancer.

Results

Box 1

Table 1

Classification of nanosystems for the treatment and diagnosis of breast cancer

Main Class	Subclass / Example	Material / Structure	Diagnostic – Therapeutic Function	Key Mechanism [s]	Breast Cancer Applications	Reference[s]
Organic – Biodegradable Polymers	Polymeric NPs [PLGA]	Biodegradable polyesters and copolymers	Primarily targeted chemotherapy; can incorporate photo/sono-responsive agents	Controlled release, EPR effect, antibody or peptide conjugation	Paclitaxel and doxorubicin delivery	Liu et al., 2018
Organic – Dendrimers	PAMAM, PPI, QD- or metal-conjugated dendrimers	Highly branched, multifunctional architectures	Chemotherapy + PDT/PTT; fluorescent imaging in some designs	High density of terminal groups; co-delivery of drugs and photosensitizers	PAMAM-based systems with DOX or photosensitizers tested in MCF-7, MDA-MB-231, 4T1	Kim, 2007; Saw et al., 2022; Zhang et al., 2021; Zhou et al., 2023
Organic – Advanced Liposomes	RGD-Lip-CUR, HER2-immunoliposomes, Zn-loaded liposomes	Phospholipid bilayer encapsulating hydrophilic or lipophilic drugs	Targeted chemotherapy; combination of CUR with conventional drugs; imaging potential	Apoptosis induction, ROS generation, RGD/HER2 targeting, MDR overcoming	Treatment of MCF-7, SK-BR-3, HER2+ tumors	Harini et al., 2019; Jamshidifar et al., 2021; Mahmoudi et al., 2021
Organic – SLNs / NLCs / Nanoemulsions	CUR-SLNs, epirubicin+CUR SLNs, CUR or thymoquinone nanoemulsions	Solid or mixed lipid matrices; stabilized oil droplets	Chemotherapy with improved stability and sustained release	Mitochondrial apoptosis; synergistic drug effects; reduced systemic toxicity	MCF-7, MDA-MB-231, SK-BR-3	Zhu et al., 2024
Organic – Polymeric Nanogels & Micelles	TPP-PEG-PE–CUR micelles; chondroitin-CUR nanogels	Hydrophobic core / hydrophilic shell; mitochondrial or CD44 targeting	Advanced chemotherapy; combination therapy	Enhanced uptake, lysosomal escape, mitochondrial targeting	CD44+ BC models, MCF-7, TNBC	Soleymani et al., 2021; Yin-Hua et al., 2020
Organic – Biopolymers for siRNA	Chitosan, HA, alginate, collagen NPs; siRNA exosomes	Polysaccharide-based or biohybrid systems	Gene therapy [siRNA]; some co-deliver drugs	Silencing of STAT3, PIK3CA, survivin, EGFR; MDR reversal	MCF-7, MDA-MB-231, 4T1, orthotopic models	Inoue et al., 2012; Silva et al., 2022; Zhang et al., 2022
Organic – Exosomes / Exosome-Mimics	siSurvivin, siPIK3CA, siCD44 exosomes; EMs	Natural or mimetic vesicles with lipid membrane	Biohybrid vectors for siRNA and drugs; imaging ligands	Down-regulation of oncogenes; enhanced apoptosis	ER+, TNBC, HER2+ models	Yang et al., 2016
Bio-Based – Functionalized CNCs	CNCs/FA-CS-FITC	Rod-like cellulose nanocrystals coated with chitosan derivative	Targeted bioimaging; future theranostic platform	High affinity to folate receptor; 5× higher uptake	MDA-MB-231 [FR+]	Pinto et al., 2021
Inorganic – Metals & Oxides	SPIONs, AuNPs, Re-clusters, ferrites	Metallic or metal-oxide cores	MRI, CT, PAI + chemotherapy / PTT / PDT	Hyperthermia, ROS generation, stimulus-responsive release	Targeted BC imaging and therapy	Jamshidifar et al., 2021; Meng et al., 2009
Inorganic – Carbon-Based	GO, CNTs, CQDs/GQDs	2D graphene sheets, nanotubes, quantum dots	Theranostics: imaging + PTT/PDT + chemotherapy	NIR absorption, photothermal conversion, ROS	GO-DOX, CNT-CUR, CQDs in MCF-7	Ali et al., 2022; Badea et al., 2020; Ji et al., 2012
Inorganic – MXenes	$Ti_3C_2T_x$	Functionalized 2D nanosheets	High-efficiency PTT; drug delivery potential	High photothermal conversion; protein inhibition	BC PTT models; CD44/HER2 targeting potential	Liao et al., 2023
Inorganic – Mesoporous Silica	MSNs-DOX+CUR; MSNs-MTX+siRNA	Porous silica core, functionalized surface	Drug + gene co-delivery; imaging when doped	Synergistic therapy; MDR reduction	MCF-7, MDA-MB-231	Hanafi-Bojd et al., 2016; Hao et al., 2015

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The analyzed studies reveal a broad and rapidly evolving landscape of nanosystems developed for breast cancer diagnosis and therapy. Based on compositional features, structural architecture, and functional integration, the reviewed nanosystems were classified into organic, inorganic, hybrid, and biohybrid platforms. Table 1 summarizes the main nanosystem classes, representative examples, diagnostic and therapeutic functions, key mechanisms, and reported applications in breast cancer models.

Organic nanosystems

Organic nanosystems constitute the most extensively explored category, particularly biodegradable polymer-based nanoparticles such as PLGA systems. These platforms are primarily employed for targeted chemotherapy delivery and can be further functionalized to incorporate photo- or sono-responsive agents. Their therapeutic performance is mainly attributed to controlled drug release, enhanced permeability and retention [EPR] effects, and the possibility of surface conjugation with antibodies or targeting peptides, enabling effective delivery of chemotherapeutic agents such as paclitaxel and doxorubicin [Liu et al., 2018]. Dendrimer-based nanosystems, including PAMAM and PPI dendrimers, represent a structurally sophisticated class characterized by highly branched architectures and a high density of functional terminal groups. These systems have been widely investigated as carriers for combined chemotherapy and photodynamic or photothermal therapy, as well as for fluorescence imaging when conjugated with quantum dots or metallic components. PAMAM-based platforms loaded with doxorubicin or photosensitizers have demonstrated enhanced cytotoxicity in breast cancer cell lines such as MCF-7, MDA-MB-231, and 4T1, highlighting their versatility for multifunctional applications [Kim, 2007; Saw et al., 2022; Zhang et al., 2021; Zhou et al., 2023].

Advanced lipid-based nanosystems, including RGD-modified liposomes, HER2-targeted immunoliposomes, and zinc-ion-loaded liposomes, exhibit improved tumor selectivity and therapeutic efficacy. These platforms enable targeted chemotherapy and combination strategies involving curcumin and conventional anticancer drugs, promoting apoptosis, reactive oxygen species [ROS] generation, and reversal of multidrug resistance through ligand-mediated targeting [Harini et al., 2019; Jamshidifar et al., 2021; Mahmoudi et al., 2021].

Solid lipid nanoparticles [SLNs], nanostructured lipid carriers [NLCs], and nanoemulsions have also been extensively investigated to enhance the stability, bioavailability, and sustained release of bioactive compounds such as curcumin and thymoquinone. These systems induce mitochondrial apoptosis and synergistic anticancer effects while reducing systemic toxicity, demonstrating significant antiproliferative activity in MCF-7, MDA-MB-231, and SK-BR-3 breast cancer models [Zhu et al., 2024].

Polymeric nanogels and micelles further expand the functional scope of organic nanosystems by enabling mitochondrial or CD44-mediated targeting. Formulations such as TPP-PEG-PE curcumin micelles and chondroitin-based nanogels exhibit enhanced cellular uptake, lysosomal escape, and increased apoptotic activity in TNBC and CD44-positive breast cancer models [Soleymani et al., 2021; Yin-Hua et al., 2020].

Gene delivery and bio-derived nanosystems

Biopolymer-based nanosystems designed for siRNA delivery, including chitosan, hyaluronic acid, alginate, collagen nanoparticles, and engineered exosomes, represent a highly specialized class within organic and biohybrid platforms.

These systems enable efficient silencing of oncogenes such as *STAT3*, *PIK3CA*, *survivin*, and *EGFR*, leading to inhibition of proliferation, metastasis, and reversal of multidrug resistance in *in vitro* and *in vivo* breast cancer models [Inoue et al., 2012; Silva et al., 2022; Zhang et al., 2022].

Natural and exosome-mimetic vesicles provide additional advantages, including intrinsic biocompatibility, reduced immunogenicity, and enhanced cellular targeting. Exosome-based delivery of siRNA targeting *BCL-2*, *PIK3CA*, or *CD44* has demonstrated significant apoptotic induction and improved therapeutic responses in ER-positive and TNBC models, as well as enhanced sensitivity to doxorubicin treatment [Yang et al., 2016].

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Bio-based nanosystems derived from cellulose nanocrystals [CNCs], particularly when functionalized with chitosan derivatives, folic acid, and fluorescent markers, have emerged as promising diagnostic platforms. These rod-like nanostructures exhibit high affinity toward folate receptor–positive TNBC cells, such as MDA-MB-231, achieving up to five-fold higher cellular internalization while maintaining low cytotoxicity, thereby offering strong potential for future theranostic applications [Pinto et al., 2021].

Inorganic and hybrid nanosystems

Inorganic nanosystems, including metallic nanoparticles, metal oxides, and carbon-based nanomaterials, play a critical role in advanced diagnostic and therapeutic strategies. Superparamagnetic iron oxide nanoparticles [SPIONs], gold nanoparticles, rhenium clusters, and ferrite-based systems have been widely applied in magnetic resonance imaging [MRI], computed tomography [CT], and photoacoustic imaging, as well as in photothermal and photodynamic therapies. These platforms leverage hyperthermia, ROS generation, and stimulus-responsive drug release to achieve enhanced antitumor efficacy [Jamshidifar et al., 2021; Meng et al., 2009].

Carbon-based nanomaterials, including graphene oxide [GO], carbon nanotubes [CNTs], and quantum dots [QDs], function as highly efficient theranostic platforms due to their strong near-infrared absorption, photothermal conversion efficiency, and capacity for pH- or enzyme-responsive drug release. GO-based systems loaded with doxorubicin or hyaluronic acid–functionalized platforms targeting CD44 have demonstrated potent antiproliferative effects in breast cancer models, while CNT–curcumin conjugates exhibit enhanced photothermal and cytotoxic activity [Ali et al., 2022; Badea et al., 2020; Ji et al., 2012; Koh et al., 2019].

Two-dimensional MXenes, such as $Ti_3C_2T_x$ nanosheets, represent an emerging class of inorganic nanomaterials with exceptional photothermal efficiency and favorable drug-loading capacity. These materials have demonstrated strong potential for photothermal therapy and hybrid platform integration, particularly when functionalized with targeting ligands relevant to breast cancer biomarkers [Liao et al., 2023].

Mesoporous silica nanoparticles [MSNs] further bridge organic and inorganic strategies by enabling co-delivery of chemotherapeutic agents and siRNA. Functionalized MSNs loaded with combinations such as doxorubicin–curcumin or methotrexate–siRNA exhibit controlled release, enhanced apoptosis, and effective suppression of multidrug resistance in MCF-7 and MDA-MB-231 models [Hanafi-Bojd et al., 2016; Hao et al., 2015].

Discussion

The integrated analysis of the reviewed literature demonstrates that nanosystem development for breast cancer management has undergone a marked transition from monofunctional drug delivery platforms to highly hierarchical, multifunctional, and genuinely theranostic architectures, in which diagnosis, therapy, and tumor microenvironment modulation converge within a single nanoengineered system. This evolution reflects a broader paradigm shift in nanomedicine, where modern nanoplatforms are no longer conceived solely as passive carriers but as active, stimuli-responsive systems capable of dynamic interaction with biological environments [Mohajer et al., 2023].

Among organic nanosystems, biodegradable polymers such as PLGA, PLA, HPMA, and PEA continue to form the structural backbone of numerous formulations due to their excellent biocompatibility, tunable physicochemical properties, and surface functionalization versatility. These characteristics enable efficient encapsulation of both hydrophilic and hydrophobic agents and facilitate molecular targeting strategies, which are particularly relevant for aggressive subtypes such as TNBC that lack well-defined therapeutic targets [Liu et al., 2018].

Moreover, the encapsulation of bioactive compounds such as curcumin into lipid-based systems—including RGD-modified liposomes, anti-HER2 immunoliposomes, solid lipid nanoparticles, and hyaluronic acid–functionalized micelles—results in pronounced improvements in cellular uptake, apoptotic induction, and circumvention of multidrug resistance mechanisms in breast cancer cell lines such as MCF-7, MDA-MB-231, and SK-BR-3 [Harini et al., 2019; Jamshidifar et al., 2021; Mahmoudi et al., 2021].

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These findings position lipidic and micellar nanosystems as intermediate yet highly adaptable platforms within the functional classification, with increasing potential for theranostic integration.

A higher level of technological complexity is observed in nanosystems designed for gene therapy applications, particularly those employing siRNA delivery. Biopolymers such as chitosan, hyaluronic acid, alginate, and collagen, as well as natural and engineered exosomes, have demonstrated remarkable efficiency in silencing key oncogenic drivers, including *STAT3*, *PIK3CA*, *survivin*, *EGFR*, and *CD44*. These systems not only suppress tumor proliferation and metastatic potential but also restore chemosensitivity through the reversal of multidrug resistance pathways [Hanafi-Bojd et al., 2016; Hao et al., 2015]. Exosome-based platforms offer distinctive advantages over synthetic nanocarriers, including intrinsic biocompatibility, reduced immunogenicity, prolonged circulation time, and inherent cellular targeting capacity, making them particularly attractive for precision gene therapy in breast cancer [Yang et al., 2016].

Bio-based nanosystems derived from cellulose nanocrystals [CNCs] further expand the theranostic landscape by combining structural rigidity, surface modifiability, and biological affinity. When functionalized with chitosan derivatives, folic acid, and fluorescent probes, CNC-based platforms exhibit markedly enhanced internalization—up to five-fold higher—in folate receptor–positive TNBC cells such as MDA-MB-231, while maintaining low cytotoxicity and favorable colloidal stability [Pinto et al., 2021]. These attributes underscore their potential as next-generation bio-derived theranostic scaffolds.

Inorganic nanomaterials represent a complementary yet indispensable component of advanced breast cancer nanotherapy, particularly in applications requiring imaging integration and externally triggered therapies. Metallic nanoparticles [Au, Fe, Re], metal oxides [SPIONs, ferrites], and carbon-based nanomaterials [GO, CNTs, QDs] enable seamless coupling of diagnostic imaging modalities—including MRI, CT, fluorescence, and photoacoustic imaging—with photothermal therapy [PTT], photodynamic therapy [PDT], and nanocatalytic approaches based on reactive oxygen species generation [Jamshidifar et al., 2021; Meng et al., 2009].

Notably, graphene-based platforms and CNT conjugates demonstrate exceptional near-infrared absorption and photothermal conversion efficiencies, translating into potent antitumor activity and spatially controlled therapeutic effects in breast cancer models [Ali et al., 2022; Badea et al., 2020].

Emerging two-dimensional nanomaterials such as MXenes [e.g., $Ti_3C_2T_x$] further extend the functional horizon of inorganic nanosystems. Their large surface area, high photothermal efficiency, and capacity for drug loading and surface modification position them as promising second-generation platforms for PTT-based therapies and hybrid nanostructure development, particularly in the context of highly invasive breast tumors [Liao et al., 2023].

At the highest level of functional integration, fully hybrid and biohybrid theranostic platforms have demonstrated unprecedented therapeutic complexity and efficacy. Systems such as ASNP nanoparticles integrate photothermal therapy, nitric oxide release, ferroptosis induction, and immunogenic cell death activation within a single architecture, resulting in effective tumor microenvironment reprogramming and systemic antitumor immune responses in TNBC models [Zhao et al., 2025].

Similarly, polydopamine-based nanosystems loaded into mesenchymal stem cells act as biohybrid vectors with enhanced tumor homing and deep tissue penetration, achieving synergistic chemo-photothermal effects in three-dimensional tumor models [Ferreira et al., 2021].

Acoustic-responsive nanodroplets, such as perfluorohexane-based systems, further illustrate the potential of externally triggered nanotherapies by enabling real-time ultrasound imaging and site-specific drug release upon acoustic activation, achieving significantly increased intratumoral drug accumulation [Baghbani et al., 2017].

Collectively, these findings reveal a clear and consistent trend toward the development of intelligent, multifunctional nanosystems designed to address the biological complexity and heterogeneity of breast cancer, particularly in aggressive and treatment-resistant subtypes such as TNBC.

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The proposed classification framework highlights the progressive integration of therapeutic modalities, diagnostic capabilities, and biological targeting strategies, providing a structured foundation for the rational design of next-generation nanoplatforms. Ultimately, this integrative approach underscores the transformative potential of advanced nanosystems in overcoming longstanding clinical limitations and advancing precision oncology in breast cancer.

Conclusions

Conventional breast cancer therapies, while having significantly improved overall survival, continue to present critical limitations related to systemic toxicity, insufficient tumor specificity, and the development of therapeutic resistance, particularly in aggressive subtypes such as triple-negative breast cancer [TNBC]. In this context, advanced nanosystems represent a highly promising alternative to overcome these challenges through molecular targeting, controlled drug release, and multimodal therapeutic strategies.

The global classification proposed in this review provides a systematic organization of nanosystems applied to breast cancer into organic, inorganic, hybrid, and biohybrid platforms, integrating key parameters such as composition, structural architecture, therapeutic mechanisms, and diagnostic functionality. This framework reveals a clear evolutionary trajectory from monofunctional nanocarriers toward highly integrated, stimulus-responsive, and genuinely theranostic systems capable of combining chemotherapy, gene therapy, phototherapy, sonodynamic therapy, ferroptosis induction, and immunogenic tumor cell death within a single nanoplatform.

Notably, biohybrid and multimodal nanosystems demonstrate exceptional potential to enhance tumor accumulation, modulate the tumor immune microenvironment, and improve therapeutic efficacy, particularly in preclinical TNBC models.

However, significant challenges remain for clinical translation, including long-term biosafety assessment, large-scale manufacturing, batch-to-batch reproducibility, and regulatory harmonization.

Overall, this review establishes a robust conceptual framework for the rational design of next-generation nanosystems aimed at precision medicine in breast cancer and provides a critical foundation for future research focused on clinical validation and translational development of advanced nanotherapeutic strategies.

Declarations

Conflict of interest

The authors declare no conflict of interest. They have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

Author Contributions

Beatriz Martínez-Pérez contributed to the conception of the study, definition of the methodology, and critical review of the literature. Minerva Mata Rocha and Jorge Fernández Retana contributed to the literature review and to the development and validation of the results table.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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Use of Artificial Intelligence

The authors used ChatGPT solely as a supporting tool for language editing and final text revision. All scientific content, analysis, and intellectual decisions were made by the authors.

Abbreviations

A

- **ASNP** – Aza-BODIPY/S-Nitrosothiol Nanoparticles
- **AuNPs** – Gold Nanoparticles

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B
- **BC** – Breast Cancer
- **BCL-2** – B-cell Lymphoma 2

C
- **CD44** – Cluster of Differentiation 44
- **CD44+** – CD44-positive
- **CNCs** – Cellulose Nanocrystals
- **CNTs** – Carbon Nanotubes
- **CQDs** – Carbon Quantum Dots
- **CT** – Computed Tomography
- **CUR** – Curcumin

D
- **DOX** – Doxorubicina
- **DNAzyme** – DNA Enzyme
- **DSPE-PEG** – Phospholipid polyethylene glycol side [surface modifier]

E
- **EE [%]** – Encapsulation Efficiency
- **EGFR** – Epidermal Growth Factor Receptor
- **ER / ER+** – Estrogen Receptor Positive
- **EM / EMs** – Exosome Mimics
- **EPR** – Enhanced Permeability and Retention Effect

F
- **FA** – Folic Acid
- **FITC** – Fluorescein Isothiocyanate
- **FR** – Folate Receptor

G
- **GO / rGO** – Graphene Oxide / Reduced Graphene Oxide
- **GQDs** – Graphene Quantum Dots

H
- **HA** – Hyaluronic Acid
- **HER2** – Human Epidermal Growth Factor Receptor 2
- **HPMA** – N-(2-hydroxypropyl)methacrylamide

I
- **ICD** – Immunogenic Cell Death

M
- **MCF-7 / MDA-MB-231 / MDA-MB-468 / SK-BR-3 / 4T1** – Breast cancer cell lines
- **MDR** – Multidrug Resistance
- **MRI –** Magnetic Resonance Imaginig
- **MSC** – Mesenchymal Stem Cells
- **MSN / MSNs** – Mesoporous Silica Nanoparticles
- **MTX** – Methotrexate
- **MXenes** – Two-dimensional metal carbide/nitride materials

N
- **NIR** – Near-Infrared
- **NLC** – Nanostructured Lipid Carrier
- **NP / NPs** – Nanoparticle[s]
- **NO** – Nitric Oxide
- **NS** – Nanosponge

O
- **OCT** – Optical Coherence Tomography

P
- **PAI** – Photoacoustic Imaging
- **PAMAM** – Poly[amidoamine] Dendrimer
- **PDT** – Photodynamic Therapy
- **PEA** – Poly(ester amide)
- **PEG** – Polyethylene Glycol
- **PIK3CA** – Phosphatidylinositol-4,5-
- bisphosphate 3-kinase catalytic subunit
- alpha
- **P-gp** – P-glycoprotein
- **PFH** – Perfluorohexane
- **PLGA** – Poly[lactic-co-glycolic acid]
- **PTT** – Photothermal Therapy

Q
- **QDs** – Quantum Dots

R
- **RGD** – Arginine–Glycine–Aspartic Acid peptide
- **ROS** – Reactive Oxygen Species

S
- **siRNA** – Small Interfering RNA
- **SK-BR-3** – Human HER2-positive Breast Cancer Cell Line
- **SLN** – Solid Lipid Nanoparticle
- **SPIONs** – Superparamagnetic Iron Oxide Nanoparticles
- **STAT3** – Signal Transducer and Activator of Transcription 3

T
- **TA** – Targeting Agent
- **$Ti_3C_2T_x$** – Titanium Carbide MXene
- **TNBC** – Triple-Negative Breast Cancer
- **TPP** – Triphenylphosphonium

Z

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- **Zn – Zinc**

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