Materials Advances

REVIEW

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Cite this: *Mater. Adv.*, 2025, **6**, 3017

A comprehensive review on the recent applications of nanozymes in breast cancer therapy and diagnosis

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Nanozymes have been developed as engineered nanomaterials that mimic the catalytic functions of natural enzymes. This review systematically evaluates the potential of nanozymes for detecting and treating breast cancer. The limitations of natural enzymes, which are associated with high cost, poor stability, and limited modifiability, are overcome by nanozymes through enhanced stability, lower expense, and tunable properties. Various nanozyme systems, including bimetallic catalysts, metal nanoclusters, MXene-based materials, metal–organic frameworks (MOFs), and carbon-based platforms, are examined. Advanced synthesis methods, such as hydrothermal, solvothermal, and biogenic approaches, are employed to produce nanozymes with well-defined structures and high catalytic activity. Therapeutic strategies are classified into catalytic therapy, sonodynamic therapy (ST), radiotherapy (RT), phototherapy, immunotherapy (IMT), and starvation therapy (ST), while diagnostic techniques are based on colorimetric, electrochemical, photothermal, and photoelectrochemical detection. The relationship between material composition and catalytic performance is analyzed, and challenges associated with drug resistance, tumor heterogeneity, and toxicity are addressed. It is demonstrated that nanozyme-based theranostic approaches are offered as promising alternatives to conventional treatments. Future clinical applications are expected to be improved by integrating these multifunctional platforms, and the need for safe, efficient, and cost-effective cancer treatment is emphasized. This study provides a clear basis for future clinical research.

Received 29th October 2024,
Accepted 24th March 2025

DOI: 10.1039/d4ma01089b

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1. Introduction

Nature's highly specialised catalysts, enzymes, drive all essential biochemical reactions in living organisms.[1] Due to their

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exceptional specificity and efficiency, they have been widely used in industries, medical diagnostics, and environmental remediation.[2,3] However, despite their utility, natural enzymes often face significant limitations—including high production costs, sensitivity to harsh conditions, and difficulties in storage and modification—that restrict their broader application.[4] To overcome these challenges, researchers have developed nanozymes, which are nanomaterials engineered to mimic the catalytic activities of natural enzymes while offering enhanced stability, lower cost, and greater tunability. As a result, nanozymes are increasingly being applied in diverse fields such as biosensing, imaging, therapeutics, and pollutant degradation, paving the way for more robust and versatile catalytic systems in biomedical and industrial contexts.[5,6]

Nanozymes have obtained significant attention in cancer treatment for their ability to target tumors' unique pathological features. Cancer is fundamentally characterised by uncontrolled cell proliferation, evasion of apoptosis, and a distinct microenvironment marked by hypoxia, acidity, and elevated levels of reactive oxygen species (ROS).[7] Nanozymes can be engineered to exploit these vulnerabilities by catalysing the localised production of cytotoxic species, such as hydroxyl radicals, which induce oxidative stress and trigger apoptosis in cancerous cells.[8] Moreover, their intrinsic multifunctionality enables nanozymes to serve as both therapeutic agents and diagnostic tools—facilitating real-time imaging and monitoring of treatment efficacy. This theranostic approach enhances targeted drug delivery, minimises systemic side effects, and complements conventional therapies, paving the way for more precise and effective cancer interventions.[9]

Capitalizing on these versatile catalytic functions in cancer therapy, researchers have extended nanozyme applications to target the unique microenvironment and treatment challenges of particular cancers such as breast cancer.[10,11] Breast cancer represents a diverse group of malignancies affecting the breast tissue and stands as one of the most prevalent cancers worldwide, especially among women.[12,13] Its heterogeneity is evident in the distinct molecular subtypes—such as hormone receptor-positive, HER2-positive, and triple-negative breast cancers (TNBC) —each with unique biological behaviors and treatment responses.[14,15] These differences influence prognosis and dictate the need for personalized therapeutic approaches. In recent years, innovative treatment strategies have emerged, including targeted therapies, immunotherapies, and advanced nanotechnology-based platforms. Among these, nanozyme-based interventions are showing promise by exploiting the unique tumor microenvironment (TME) of breast cancer. By harnessing the catalytic capabilities of nanozymes to generate ROS or enhance drug delivery, these systems offer a dual function—serving both as therapeutic agents and diagnostic tools—thereby paving the way for more precise and effective management of breast cancer.[16,17]

Building on these advances, a broad spectrum of nanozyme strategies has emerged to tackle breast cancer treatment and detection. Researchers have harnessed bimetallic nanozymes, metal nanoclusters, MXene-based constructs, MOF-based systems, and carbon-based platforms, each offering unique enzyme-like activities—such as peroxidase (POD)-like, oxidase (OXD)-like, catalase (CAT)-like, and Fenton-like reactions—to amplify ROS generation for effective tumor ablation.[18–20] These mechanisms enhance catalytic therapy *via* chemodynamic (CDT), photothermal (PTT), and photodynamic (PDT) modalities and extend to sonodynamic (SDT), radiotherapy-enhancing (RT), and starvation (ST) strategies that target tumor metabolism and microenvironment vulnerabilities.[21] In parallel, innovative detection approaches employing colorimetric, electrochemical, and photothermal sensors have been developed for sensitive and specific identification of breast cancer biomarkers—including HER2, MUC1, and miRNA-21—thereby integrating therapeutic and diagnostic (theranostic) functionalities.[22,23] This multifaceted nanozyme-based paradigm is set to revolutionize personalized breast cancer management by combining targeted treatment with real-time therapeutic efficacy monitoring.

This review is the first comprehensive work that bridges the gap between nanozyme-based detection and treatment strategies

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for breast cancer, offering an unparalleled synthesis of knowledge that spans the full spectrum of innovative catalytic nanotechnologies. By systematically analyzing diverse nanozyme platforms this article reveals how these multifaceted tools harness enzyme-like activities to not only ablate tumors through enhanced ROS generation and metabolic disruption but also to provide ultra-sensitive, real-time detection of key biomarkers such as HER2, MUC1, and miRNA-21. Readers will discover detailed discussions on the evolution of synthesis methodologies, structural designs, and multi-modal therapeutic approaches---ranging from catalytic, PTT, and SDT to advanced radiotherapy and starvation techniques—that address the complex challenges posed by the breast TME. Moreover, the review meticulously highlights all emerging trends in each application section, including innovations in material composition, synthesis precision, and integration of diagnostic and therapeutic functionalities, thereby mapping the transformative potential of nanozyme-based theranostics in personalized cancer care. Explore the subsequent sections, where every aspect of this cutting-edge field is examined in depth, setting the stage for future breakthroughs and redefining the paradigm of breast cancer management.

2. Types of nanozyme composites

2.1. Bimetal-based nanozymes

Bimetals are a group of nanozymes that contain two metal components at nanoscale size. This definition differs from bulk bimetallic alloys, such as bronze (containing copper and tin), due to their mechanical characteristics and corrosion resistance. Bimetals are structurally and characteristically different from monometallic systems because by combining two metals, electron density and metal–metal bond length are changed.[24] Monometallic nanozymes generally include noble metals such as Ag, Au, Pt, Pd, and Ru, which have a high price and toxicity for biological systems (except Au).[24] Bimetals generally cost less than monometals due to having a non-precious secondary metal.[25] In addition, the synergistic effect of materials in bimetals makes them provide better chemical and optical properties, greater stability, and less toxicity than monometallic nanozymes.[24,26] Chemical or biological processes generally prepare bimetals. Typical chemical methods include electrodeposition, hydrothermal growth, co-reduction method, galvanic replacement process, nanomaterials printing, and one-pot procedure. On the other hand, bioprocesses preparation includes using biological growth templates or reducing agents such as plant extracts, DNA, NADH, *etc.* In recent years, most of the studies on bimetal-based nanozymes were related to the composite of these systems, and there were fewer reports of the use of bimetals alone. Various structural evaluations have been performed for the synthesis of bimetal nanozymes. For example, the percentage of each metal in the bimetallic systems is a fundamental factor for the structure, morphology, and performance of the nanozyme.[27] A study presented a novel approach to breast cancer therapy using copper–palladium (Cu–Pd) bimetallic nanozymes, highlighting the synergy between the two metals in enhancing catalytic efficiency. Kinetically miscible Cu–Pd nanozymes were synthesized *via* a one-step coreduction method, ensuring homogeneous alloying and optimized Fenton-like activity. Through Density Functional Theory (DFT) calculations, it was revealed that the incorporation of Cu lowered the d-band center, promoting H_2O_2 adsorption and decomposition, thereby generating ROS more efficiently than monometallic Pd. This enhanced Fenton-like activity was demonstrated *in vitro* using 4T1 murine mammary cancer cells, where significant cytotoxicity was observed. The highest cytotoxicity was exhibited by Cu_3Pd nanozymes, with an IC_{50} of 59.55 μg mL^{-1}, significantly outperforming Pd nanozymes (IC_{50} = 95.82 μg mL^{-1}). These findings suggest that Cu–Pd nanozymes could be promising candidates for biocatalytic cancer therapy, leveraging bimetallic synergy for improved therapeutic effects.[18] Various morphologies have been reported for bimetals, including nanospheres,[28] nanosheets,[29] dumbbells,[30] dendritic,[31] nanotubes,[32] hollow nanoshells,[33] cage-like,[34] spinel-like,[35] nanorods,[36] *etc.* (Fig. 1). These structures are usually modified to achieve the best performance. In addition, pharmaceutical compounds such as doxorubicin and bimetals have been used for therapeutic purposes.[37] Overall, the unique structural and functional advantages of bimetallic nanozymes, including their tunable composition, enhanced catalytic properties, and reduced toxicity, make them highly promising for biomedical applications, particularly in breast cancer therapy.

2.2. Metal nanocluster-based nanozymes

Metal nanoclusters with less than 2 nm size contain several to tens of atoms, known as bridges between metal atoms and metal nanoparticles.[38] The small dimension of metal nanoclusters and discrete electronic structures has caused them to display different optical, electrical, and chemical properties than larger nanoparticles.[39] In addition, the unique structures of metal nanoclusters have caused properties such as chirality,[40] tunable fluorescence emission,[41] magnetism,[42] HOMO–LUMO transition,[43] promote photoluminescence,[44] and large Stokes shift.[39] The size of the nanocluster, the nature of the metal, and the type of stabilizer are three fundamental parameters in the properties of metal nanoclusters. One example illustrating this principle is using Au@PtOs nanoclusters in breast cancer therapy, as demonstrated in a recent study on multimodal exosome detection. By leveraging the unique catalytic SERS (surface-enhanced Raman scattering) and photothermal properties of these bimetallic nanoclusters, researchers developed a highly sensitive lateral flow assay (LFA) for identifying breast cancer-derived exosomes. The specific combination of gold (Au), platinum (Pt), and osmium (Os) within the nanocluster structure enhances both enzymatic activity and signal amplification, showcasing how metal composition directly influences performance. Experimental data highlight detection limits of 2.6×10^3, 4.1×10^1, and 4.6×10^2 exosomes per μL for colorimetric, SERS, and temperature modes, respectively—far surpassing conventional Au nanoparticle-based assays.[19] As expected, the size of the nanocluster has an essential effect on its catalytic properties. To prevent agglomeration and controlled growth of nanoclusters, various stabilizers such as surfactants,[45] sodium

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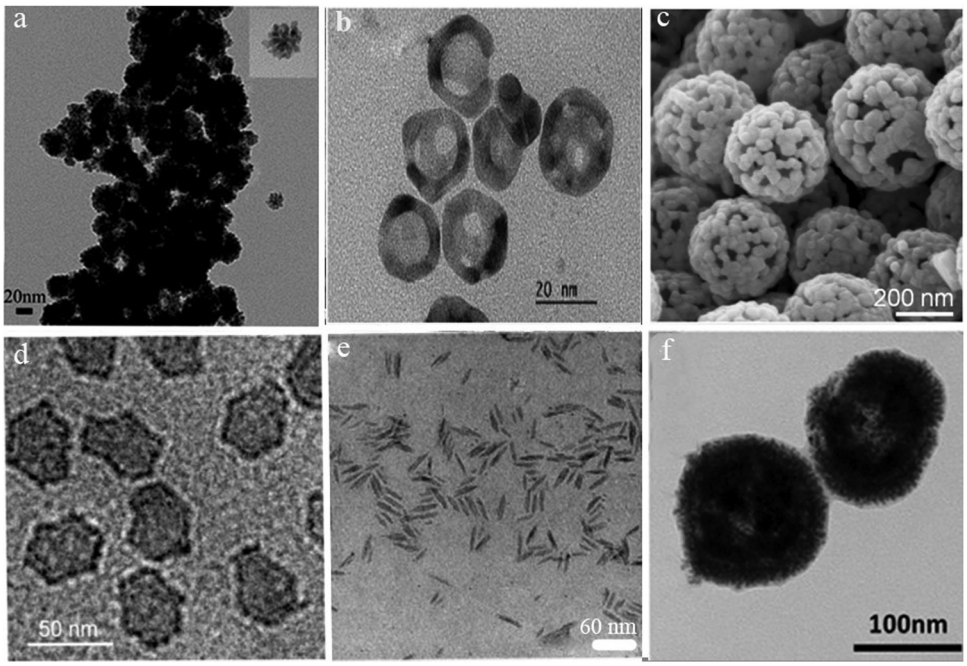

Fig. 1 TEM image of (a) $PdPt_3$ NPs[31] [reproduced from ref. 31 with permission from Elsevier, copyright 2022]. SEM images of (b) $Ag_{79}Au_{21}/GO$[33] [reproduced from ref. 33 with permission from American Chemical Society, copyright 2021], (c) $Cu_{1.5}Mn_{1.5}O_4$ CFNSs[28] [reproduced from ref. 28 with permission from Elsevier, copyright 2022]. TEM image of (d) Pd@Ir NSs[29] [reproduced from ref. 29 with permission from American Chemical Society, copyright 2022], and (e) FeCu–GO_x PNzyme[35] [reproduced from ref. 35 with permission from Elsevier, copyright 2022], (f) AgPd@BSA/DOX[37] [reproduced from ref. 37 with permission from Elsevier, copyright 2020]. In this series of images, you can observe different morphologies with varying metals that directly contribute to their catalytic capabilities.

citrate,[46] *etc.* are used. In addition to stability, these ligands can create essential properties in the structure. In a recent study, researchers utilized chia seed extract to stabilize nanoclusters during a sonochemical-assisted biogenic synthesis process. The extract was used as both a reducing and capping agent. The resulting nanoclusters were then tested for their efficacy against MCF7 cell lines (breast cancer cells) using the MTT assay. This nanozyme showed cytotoxic effects, indicating its potential as a treatment for breast cancer.[47] These findings underscore the crucial role of nanocluster size, metal composition, and stabilising agents in tailoring the physicochemical properties of metal nanoclusters, ultimately influencing their biomedical applications, including breast cancer diagnostics and therapy.

2.3. MXene-based nanozymes

MXenes is a group of two-dimensional (2D) materials that consist of transition metal carbides and/or nitrides with general formula $M_{n+1}X_nT_x$ (n = 1–4), where X is nitrogen and/or carbon (or boron), M includes early transition metal (like scandium, titanium, yttrium, zirconium, hafnium, vanadium, tantalum, chromium, niobium, molybdenum, tungsten, *etc.*), and Tx represents surface terminations groups (such as hydroxyl, oxygen, fluorine, *etc.*) change by altering the synthesis process.[48,49] MXenes as a new class of 2D materials was introduced by Barsoum and Gogotsi in 2011, and until now more than 30 types of MXenes have been synthesized.[50,51] According to the literature, MXenes are generally produced by etching a precursor material with the MAX phase.[49] In other words, MXenes are synthesized by removing the "A" layer (which generally includes elements of groups 13 and 14 of the periodic table such as aluminum, silicon and gallium) from a precursor material with the MAX phase.[48] For example, Ti_3C_2 MXenes are produced *via* the Ti_3AlC_2 precursor by selectively removing the aluminum layer with hydrofluoric acid.[50] In a recent study, Ti_3C_2 MXene nanosheets were utilized to capture and quantify circulating tumor cells (CTCs) for breast cancer diagnosis. The study employed Ti_3C_2@Au@Pt Nanozyme, which is synthesized by integrating Au and Pt nanoparticles onto 2D Ti_3C_2 MXene nanosheets. The Ti_3C_2@Au@Pt Nanozyme possessed photothermal properties and POD-like catalytic activity, which improved the detection mechanism's temperature signal.[52] In conclusion, MXenes, a rapidly expanding class of 2D materials, continue to gain significant attention due to their unique structure, versatile surface chemistry, and promising applications, as demonstrated by their recent use in biomedical fields such as cancer diagnosis.

2.4. MOF based nanozymes

MOFs are a group of porous materials that are created by coordination bonds of metal nodes and organic linkers.[53] Features like high porosity and surface area *via* arranged and uniform cavities, excellent crystallinity, extensive available active sites, and diversity of structure, morphologies, and raw materials have caused MOFs to be of interest in recent years.[54] MOFs are usually prepared *via* solvothermal, hydrothermal, ionothermal, mechanochemical, microwave-assisted,

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electrochemical, sonochemical, and layer-by-layer methods. MOFs typically belong to isoreticular MOFs, zeolitic imidazolate frameworks (ZIFs), porous coordination networks (PCNs), materials institute Lavoisier (MIL) MOFs, porous coordination polymers (PCPs), and University of Oslo (UiO) MOFs categories with rigid or flexible/dynamic structures.[55] Various applications have been reported for MOFs-based nanosystems, and enzymatic activity is one of their most important. According to the literatures, MOF-based nanozymes are divided into three general classes, which include pristine MOFs, MOF-based composites, and MOF-based derivatives.[56] MOF-based composites include components that improve the performance and stability of MOF nanozymes. In a study, a composite containing NH_2-MIL-88B, cholesterol oxidase, chondroitin sulfate, and doxorubicin was prepared for breast cancer therapy.[57] Cholesterol oxidase was covalently attached to NH_2-MIL-88B during the amidation reaction, and then doxorubicin was loaded into the MOF cavities. Subsequently, the composite was encapsulated by chondroitin sulfate. In this composite, NH_2-MIL-88B has POD-like activity and also acts as a carrier for drugs. In another study, a novel MOF-based nanozyme, MOF@Pt@MOF, was developed and utilized in an electrochemical biosensor for the ultrasensitive detection of exosomal miRNA-21, a crucial biomarker for breast cancer.[20] The structural design of this multi-layered nanozyme played a pivotal role in enhancing its catalytic efficiency and sensing capabilities. The core structure consisted of Pt NPs sandwiched between two layers of MIL-88 MOF, which not only stabilized the Pt NPs and prevented aggregation but also significantly improved catalytic activity through increased surface area (76.96 $m^2\ g^{-1}$) and micropore volume (0.2606 $cm^3\ g^{-1}$), as determined by BET surface area analysis. The high loading capacity for Pt NPs was confirmed by elemental analysis, showing a homogeneous dispersion with a Pt content of 0.2% within the MIL-88 framework. This unique architecture endowed the nanozyme with remarkable POD-like activity, demonstrated by a nearly two-fold increase in absorbance at 652 nm compared to MIL-88@Pt alone and four times higher than MIL-88, making it comparable to horseradish peroxidase (HRP) in catalytic efficiency. As a result, the biosensor demonstrated sensitivity and specificity in detecting exosomal miRNA-21 from breast cancer patients, achieving a detection limit as low as 0.29 femtomolar (fM) and successfully distinguishing miRNA-21 from single-base and double-base mismatches and non-complementary sequences.[20] This innovative platform offers a highly effective approach for early and accurate breast cancer diagnosis. Overall, MOFs' structural versatility and functional adaptability have enabled their development into highly efficient nanozymes, with applications ranging from drug delivery to biosensing, exemplified by MOF-based composites for breast cancer therapy.

2.5. Carbon-based nanozymes

Despite the impressive development of metal-based nanozymes, these compounds have disadvantages such as high price, agglomeration in the biological environment, low selectivity, possible toxicity, and low durability.[58,59] Carbon-based materials as an emerging group of nano-scale ingredients have received special attention in the past decades due to their high stability, remarkable electronic and optical effects, low toxicity, high chemical versatility, and high structural diversity.[60] Graphene, graphene oxide (GO), rGO, carbon nanotubes (CNTs), fullerenes, carbon nano onions (CNOs), carbon nanofibers (CNFs), carbon dots (CDs), carbon nanohorns (CNHs), carbon–nitride, nanoporous carbon, nano carbon black, and diamonds are the most well-known carbon-based materials.[61] The distinctive structural features of carbon materials caused enzyme-like functions in these structures. For example, CDs exhibit unique physicochemical properties, making them valuable components in composite nanomaterials for breast cancer treatment. The Mn-doped CDs (Mn-CDs) in the MnZ@Au nanosystem function as both a photosensitizer and a catalytic nanozyme, significantly enhancing PDT effectiveness. With a photothermal conversion efficiency of 56.1%, Mn-CDs efficiently absorb laser energy to generate heat, improving oxygen production through CAT-like activity. The MnZ@Au composite leverages the glucose oxidase (GO_x)-like activity of AuNPs to catalyze glucose oxidation, producing H_2O_2, which Mn-CDs then convert into oxygen to alleviate tumor hypoxia. This dual-enzyme catalytic reaction increases ROS levels and suppresses tumor glycolysis, as demonstrated by a 3-fold reduction in glucose uptake and a 2.4-fold decrease in lactate production under hypoxic conditions. The nanosystem's cascading catalytic activity and photothermal effects resulted in a 60.4% inhibition of breast tumor growth with MnZ@Au and laser irradiation, compared to only 32.3% inhibition with MnZ@Au alone. These synergistic interactions between CDs and other nanomaterials enhance PDT efficacy, demonstrating their potential as a multifunctional cancer therapy platform (Fig. 4(a) and (b)).[62] A recent study reports the development of a new catalytic nanographene oxide-based system that can enhance the effectiveness of PDT for treating breast cancer. The nanosystem consists of three key components –nGO as a carrier, Ce6 as a photosensitizer, and hemin as a CAT-like nanozyme. These components work together to effectively target and destroy cancer cells in a highly precise and controlled manner.[63] These findings highlight the potential of carbon-based nanomaterials, particularly carbon dots and nanographene oxide composites, as versatile and efficient platforms for enhancing PDT in breast cancer treatment through their enzymatic-like functions, oxygen-regulating capabilities, and synergistic interactions with other therapeutic agents.

3. Nanozymes in breast cancer treatment

3.1. Catalytic therapy

The enzymatic activity of nanozymes is a crucial aspect of their therapeutic potential, especially in treating breast cancer. This functionality often underlies specific therapeutic approaches, such as CDT, which utilizes nanozymes' ability to catalyze reactions that produce ROS.[64–66] CDT targets the TME by harnessing these catalytic processes, inducing localized oxidative stress to fight cancer cells. The capacity to tailor nanozymes

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for specific enzymatic functions has created new opportunities in breast cancer therapy, where this single factor can serve as an independent strategy or be incorporated into comprehensive treatment plans.

The development of nanozyme-based therapies for breast cancer has significantly evolved in recent years, driven by structural design and synthesis techniques advancements. Early nanozymes, such as boron oxynitride (BON), were synthesized through high-temperature pyrolysis, providing POD-like activity for generating ROS (Fig. 2(d)–(f)).[67] Over time, more sophisticated structures have emerged, incorporating multiple functionalities to enhance therapeutic effects. Hydrothermal and solvothermal methods have enabled the creation of advanced nanozymes, such as cerium oxide (CeO_2) nanoparticles and carbon-encapsulated magnetite nanodoughnuts (CEMNDs), which exhibit both POD-like and SOD-like activities (Fig. 2(a)–(c)).[68,69] This progression reflects a shift from single-function systems to multi-functional, synergistic designs that can address the complex needs of breast cancer therapy.

The mechanisms of action employed by these nanozymes center on their ability to catalyze critical reactions within the TME. A predominant approach involves POD-like activities, where nanozymes catalyze the decomposition of H_2O_2 into hydroxyl radicals, effectively inducing oxidative stress in cancer cells. Advanced nanozymes, such as 2D-CuPd nanosheets, combine OXD-like and POD-like activities to generate ROS, promoting apoptosis and cell cycle arrest in tamoxifen-resistant breast cancer cells.[72] Additionally, CDT, a subtype of catalytic therapy, has gained prominence for using Fenton and Fenton-like reactions to enhance ROS generation. Nanozymes like MoS_2-PEG and $Cu_{3-x}P$@HNTs leverage these reactions, catalyzing H_2O_2 in acidic environments to maximize localized oxidative damage while minimizing systemic side effects.[73,74]

The targeted specificity of nanozymes in this category is achieved by engineering them to interact with specific substrates and cell types. Typical targets include molecules abundant in the TME, such as H_2O_2, glutathione (GSH), and cholesterol.

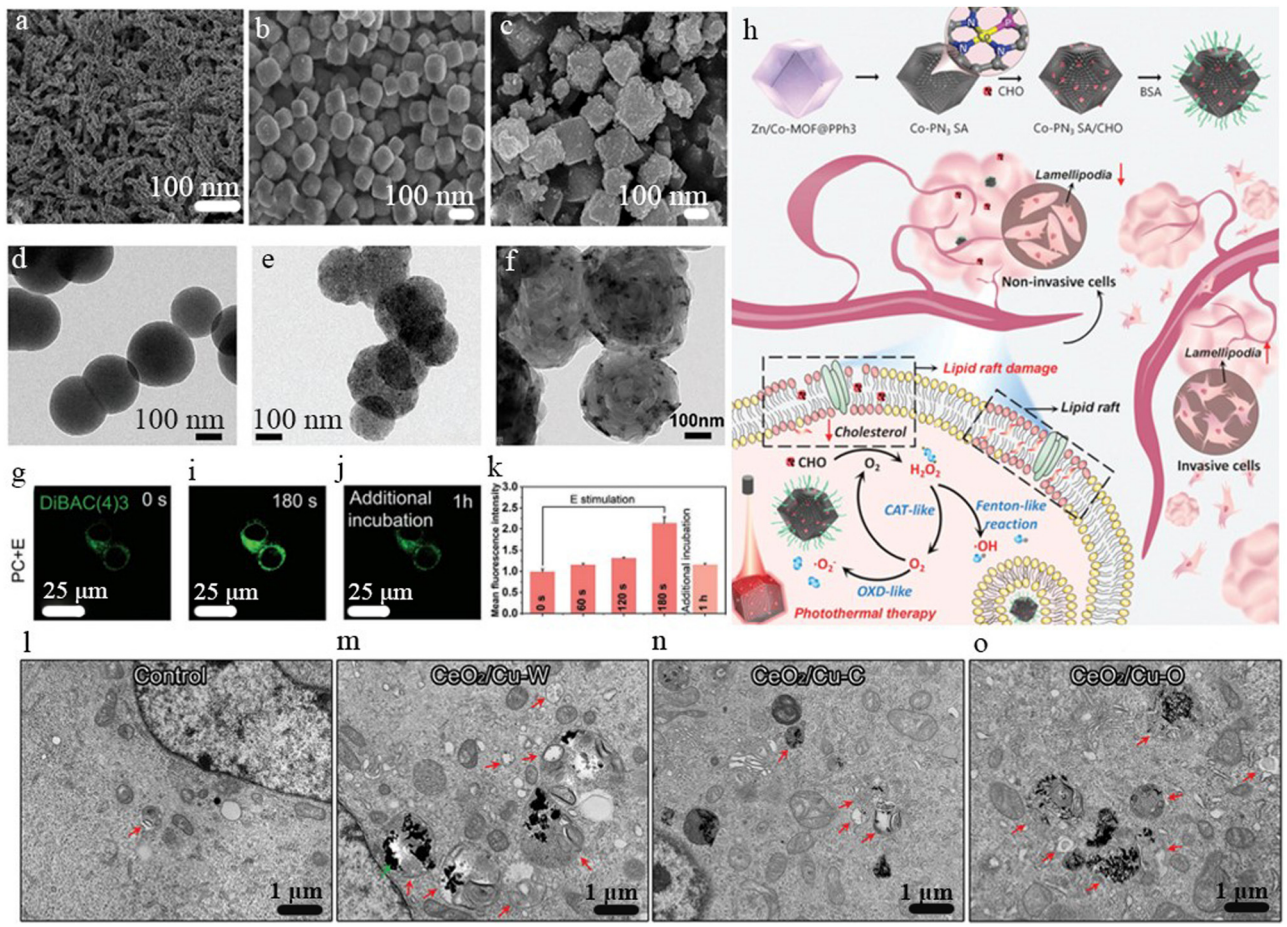

Fig. 2 (a)–(c) SEM images of CeO_2/Cu–W, CeO_2/Cu–C, and CeO_2–C are examples of various types of morphologies used for catalytic therapy[68] [reproduced from ref. 68 with permission from John Wiley and Sons, copyright 2023]. TEM images of BON (d), BON1000 (e), and BON1400 which demonstrate that physical treatment can alter the characteristics of the nanozyme (f)[67] [reproduced from ref. 67 with permission from John Wiley and Sons, copyright 2021]. (g)–(k) Fluorescence imaging, utilized for real-time monitoring, is extensively employed in cancer therapy and nanozyme technology[70] [reproduced from ref. 70 with permission from John Wiley and Sons, copyright 2022]. (h) Diagram illustrating the mechanism by which Co-PN_3 SA/CHO functions as a therapeutic agent. It depicts the catalytic therapy process and describes the synergistic effects of PTT[71] [reproduced from ref. 71 with permission from John Wiley and Sons, copyright 2023]. (l)–(o) TEM images are used to examine the ultrastructure[68] [reproduced from ref. 68 with permission from John Wiley and Sons, copyright 2023].

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For example, CEMNDs oxidize GSH, reducing its antioxidant protection in cancer cells, while Co–PN_3 SA/CHO nanozymes deplete cholesterol, disrupting cellular integrity (Fig. 2(h)).[69,71] These nanozymes have demonstrated efficacy in various breast cancer models, including murine 4T1 cells, human TNBC cells, and tamoxifen-resistant (MCF-7-TamR) lines, underscoring their adaptability to diverse cancer types.

In this category, nanozymes have also been integrated into various therapeutic strategies to enhance their clinical utility. Catalytic therapy remains the cornerstone, utilizing ROS production to target tumor cells selectively. CDT completes this by amplifying oxidative damage through Fenton-like reactions. Phototherapy, including PTT and PDT, has further augmented the therapeutic arsenal. Systems like CD47@CCM-Lap-CuS NPs combine PTT and CDT, achieving synergistic effects that improve therapeutic outcomes.[71] Additionally, immunotherapy applications, such as IR780@BSA@SPIO, demonstrate the potential of nanozymes to stimulate immune responses in traditionally resistant ''immune-cold'' breast cancers.[75]

Beyond therapy, nanozymes in this category are being explored for their diagnostic capabilities, offering dual roles in treatment and detection. As seen with aptamer-modified gold nanoparticles (pA-AuNPs), colorimetric detection methods enable sensitive visual diagnostics alongside therapeutic applications.[76] Photoelectrochemical systems, like MS-ICG@MnO_2, provide imaging-guided therapeutic capabilities, bridging the gap between diagnostics and treatment.[77] Self-powered electrosensitive detection devices, such as triboelectric nano-generators, integrate diagnostic and therapeutic functionalities into a single wearable system, representing a step forward in personalized cancer care (Fig. 2(g)–(k)).[70]

The collective progress in catalytic therapy by nanozyme has significantly impacted breast cancer treatment by addressing key challenges, including drug resistance, tumor heterogeneity, and systemic toxicity (Fig. 2(i)–(o)).[68] The ability of nanozymes to leverage the unique properties of the TME, such as acidic pH and elevated ROS levels, allows for precise, localized action with minimal off-target effects. Moreover, their integration into multi-modal therapies enhances the overall efficacy of treatment, leading to reduced tumor growth, suppression of metastasis, and improved survival rates. As the field progresses, nanozymes are poised to be increasingly central in breast cancer's precise and effective management. Table 1 provides a review of recent studies on the catalytic therapy of breast cancer using nanozymes.

3.2. Immunotherapy (IMT)

IMT is an advanced treatment that harnesses the immune system to fight diseases like cancer. Rather than directly attacking cancer cells, it enhances the body's natural defenses for more precise and lasting effects. This approach utilizes the immune system's ability to adapt and remember to create durable responses against diseases. Various methods are included, such as immune checkpoint inhibitors, adoptive cell transfer, cancer vaccines, and cytokine therapy, each targeting different immune functions. One promising innovation in this

Table 1 The catalytic therapy by nanozymes. It should be considered that this table represents the studies that catalytic therapy is regarded as the primary approach for breast cancer therapy

Nanozyme	Synthesis method	Activity	Substrate	Cell type	Therapeutic approach	Ref.
BON	High-temperature pyrolysis	POD-like	H_2O_2	4T1	Catalytic	67
CeO_2/Cu	Hydrothermal	SOD-like, POD-like	ROS	MDA-MB-231	Catalytic	68
pA-AuNPs	Co-precipitation	POD-like, OXD-like	Dopamine, glucose	MDA-MB-231	Catalytic	76
COF-CNT	Hydrothermal	POD-like	H_2O_2	4T1	Catalytic	70
2D-CuPd nanosheets	Co-precipitation	OXD-like, POD-like	H_2O_2	MCF-7-TamR	Catalytic	72
CD47@CCM-Lap-CuS NPs	Template sacrificial method	POD-like	TMB, H_2O_2	4T1	PTT, CDT	78
PEG-RLS/Fe@CDs	Solvothermal	POD-like	TMB, H_2O_2, methylene blue (MB)	4T1	CDT, PTT, photothermal detection	79
CEMNDs	Solvothermal	POD-like, GSH-OXD-like	H_2O_2, GSH	4T1	CDT, PTT	69
MS-ICG@MnO_2@PEG	Co-precipitation	POD-like, CAT-like	H_2O_2, GSH	4T1	CDT, PDT	77
$Cu_{3-x}P$@HNTs	Co-precipitation	POD-like	H_2O_2	4T1	CDT, PDT	74
MoS_2-PEG	Hydrothermal	POD-like	H_2O_2	4T1, GL261	Catalytic	73
Co–PN_3 SA/CHO	Solvothermal	OXD-like, CAT-like, Fenton-like	O_2, H_2O_2, cholesterol	4T1, Hepa 1–6	Catalytic, PTT	71
Supramolecular magnetonanohybrids	Co-precipitation	POD-like, CAT-like	ROS	TNBC	Catalytic, hyperthermia treatment, chemotherapy	80
IR780@BSA@SPIO	Self-assembly	POD-like	H_2O_2	4T1	CDT, PTT, MRI, fluorescence Imaging	75

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field is nanozymes. These agents help manage ROS, influence immune cell activity, and boost immune checkpoint therapies, representing a significant step forward by merging nanotechnology with immunology to address the challenges of cancer.[81,82]

The use of nanozymes in breast cancer IMT has evolved significantly, marked by advancements in structural complexity, synthesis methods, and therapeutic strategies. Early studies focused on relatively simple designs, such as the Zr–CeO nanozyme, synthesized *via* co-precipitation to scavenge ROS and improve oxygenation in TME. These nanozymes demonstrated SOD-like and CAT-like activities, enabling the conversion of superoxide anion and hydrogen peroxide into oxygen and water. By reducing ROS levels, they reprogrammed immunosuppressive cells, such as myeloid-derived suppressor cells (MDSCs) and tumor-associated macrophages (TAMs), enhancing the effectiveness of PD-1 blockade therapy. This foundational work laid the groundwork for more intricate and targeted designs.[83,84]

Building on these initial successes, subsequent research introduced structurally sophisticated nanozymes with dual or multifunctional catalytic capabilities. For instance, the trilobal PtNi structures of PPTNS nanozymes, synthesized through organic solution-heat injection, demonstrated enhanced ROS generation and magnetocaloric oscillation. These nanozymes activated the caspase-1-NLRP3 pathway, inducing pyroptosis---a form of programmed cell death critical for stimulating cytokine recruitment and anti-tumor immune responses. The transition from basic ROS scavenging to advanced ROS-driven cell death highlights the growing complexity of nanozyme mechanisms.[85]

The evolution of synthesis methods also contributed to increased functionality. As seen in CuCH-NCs, biomineralization techniques enabled the development of pH-sensitive, tumor-targeting nanozymes capable of catalyzing hydrogen peroxide into hydroxyl radicals. These structures, enclosed in albumin nanocages, combined hemodynamic and chemotherapy for TNBC, a challenging subtype of breast cancer. The specificity and efficacy of these designs underscored the importance of tailored synthesis methods in advancing nanozyme applications.[86]

A turning point in nanozyme development came with the integration of dual-modality therapies. For example, PFB nanozymes, designed for cold exposure (CE) therapy, combined glucose starvation with ROS generation. Their platelet membrane biomimetic coating ensured targeted delivery to cancer cells, while the CE treatment synergized with nanozyme activity to reduce intracellular glucose and ATP levels. This innovation enhanced ROS cytotoxicity and boosted immune responses, inhibiting tumor growth and metastasis. The ability to combine metabolic and immunotherapeutic mechanisms marked a significant advancement.[87]

Recent advancements, including the FeCu-DA and MDPH nanozymes, have refined therapeutic strategies by addressing tumor heterogeneity and cancer stem cells (CSCs). The FeCu-DA nanozyme, synthesized through pyrolysis, possesses dual-atom catalytic sites that enhance POD-like and CAT-like activities. Its ability to oxidize GSH and sustain hydroxyl radical generation made it particularly effective for inducing immunogenic cell death (ICD).[88] Similarly, MDPH nanozymes, designed to target CSCs, combined ferroptosis induction with immune checkpoint blockade, effectively suppressing tumor recurrence and metastasis. These advanced designs demonstrate how nanozymes can tackle complex challenges within the TME.[89]

The continuous evolution of nanozyme technology has significantly impacted breast cancer therapy by improving treatment precision, reducing off-target effects, and enhancing therapeutic outcomes. Innovations in biocompatibility, such as citrate coatings and platelet biomimicry, have reduced toxicity while ensuring effective delivery to tumor sites. By targeting key pathways like ROS regulation, metabolic disruption, and immune activation, nanozymes have achieved remarkable success in reshaping the TME and boosting the efficacy of immunotherapies.

In conclusion, the progression of nanozyme-based therapies reflects a concerted effort to address the multifaceted nature of breast cancer. These advancements have transformed the landscape of cancer immunotherapy from simple ROS scavenging to sophisticated dual-modality approaches. As research continues, integrating novel mechanisms and targeted delivery strategies promises even more significant potential for nanozymes in combating breast cancer and other challenging diseases. Table 2 presents a summary of recent studies on breast cancer treatment using nanozymes *via* IMT.

3.3. Sonodynamic therapy (SDT)

SDT has emerged as a promising non-invasive treatment modality for breast cancer, leveraging ultrasound and sonosensitizers to generate ROS that target tumor cells.[90] A critical enhancement to this therapy lies in developing nanozymes, which mimic natural enzyme activities and amplify the therapeutic efficacy of SDT. Over the years, these nanozymes have evolved in terms of structural complexity, synthesis methodologies, and functional diversity, each iteration contributing to more effective tumor targeting and suppression. This discussion explores the progression in

Table 2 The table below summarizes the various nanozymes utilized in IMT

Nanozyme	Synthesis method	Activity	Substrate	Cell type	Therapeutic approach	Ref.
Zr–CeO	Co-precipitation	SOD-like, CAT-like	ROS	MDSCs, TAMs	IMT	83
PPTNS	Organic solution-heat injection method	POD-like, CAT-like	H_2O_2, TMB	HUVECs	IMT, catalytic	85
CuCH-NCs	Biomineralization	POD-like	H_2O_2	TNBCs	IMT, catalytic	86
PFB	Adsorption-calcination strategy	POD-like	H_2O_2	4T1	IMT, catalytic, ST	87
MDPH	Co-precipitation	CAT-like	CSCs	4T1	IMT, catalytic	89
FeCu-DA	Pyrolysis	POD-like, CAT-like, GSH-OXD-like	H_2O_2, GSH	4T1	IMT, photothermal detection, catalytic	88

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nanozyme design and its implications for improving breast cancer therapy.

The structural evolution of nanozymes marks a notable trend, moving from simple cubic configurations to more intricate and multifunctional designs. Early systems like CaF_2 nanozymes, synthesized *via* direct precipitation, demonstrated POD-like activity, decomposing H_2O_2 to ROS in acidic tumor microenvironments (TME) (Fig. 3(f)–(h)).[91] These structures provided the foundation for SDT, offering minimal toxicity and straightforward synthesis. However, the field soon advanced to more sophisticated systems like $LaFeO_3$ (LFO) nanocrystals, which incorporate glucose oxidase (GO_x) to form cascade-reactive nanoreactors. These perovskite nanozymes, with multiple enzyme-mimicking properties, represented a leap forward, enhancing ROS production through the synergistic activation of oxidative stress pathways.[92] Further innovations, such as 2D $NiCoO_x$ nanosheets and magnetic hydrogel nanozymes (MHZ), integrated multifunctionality, including GSH depletion, hyperthermia generation, and catalysis.[93,94] These developments underscore a clear trend toward increasing structural complexity to address TME challenges.

The evolution of synthesis methods mirrors this growing complexity. While earlier nanozymes relied on direct precipitation for simplicity, more recent systems utilize advanced techniques like hydrothermal synthesis and hard-template fabrication. For instance, the hydrothermal method of producing PB + Ce6 hydrogel systems enabled precise control over Prussian blue nanoparticles' crystalline and catalytic properties.[97] Similarly, the hard-template approach to fabricating $NiCoO_x$ nanosheets created highly organized 2D structures with diverse enzyme-like activities.[93] These methodologies improved the catalytic efficiency of nanozymes and facilitated their integration into multimodal therapies. Ligand exchange processes in MHZ synthesis highlight the adaptability

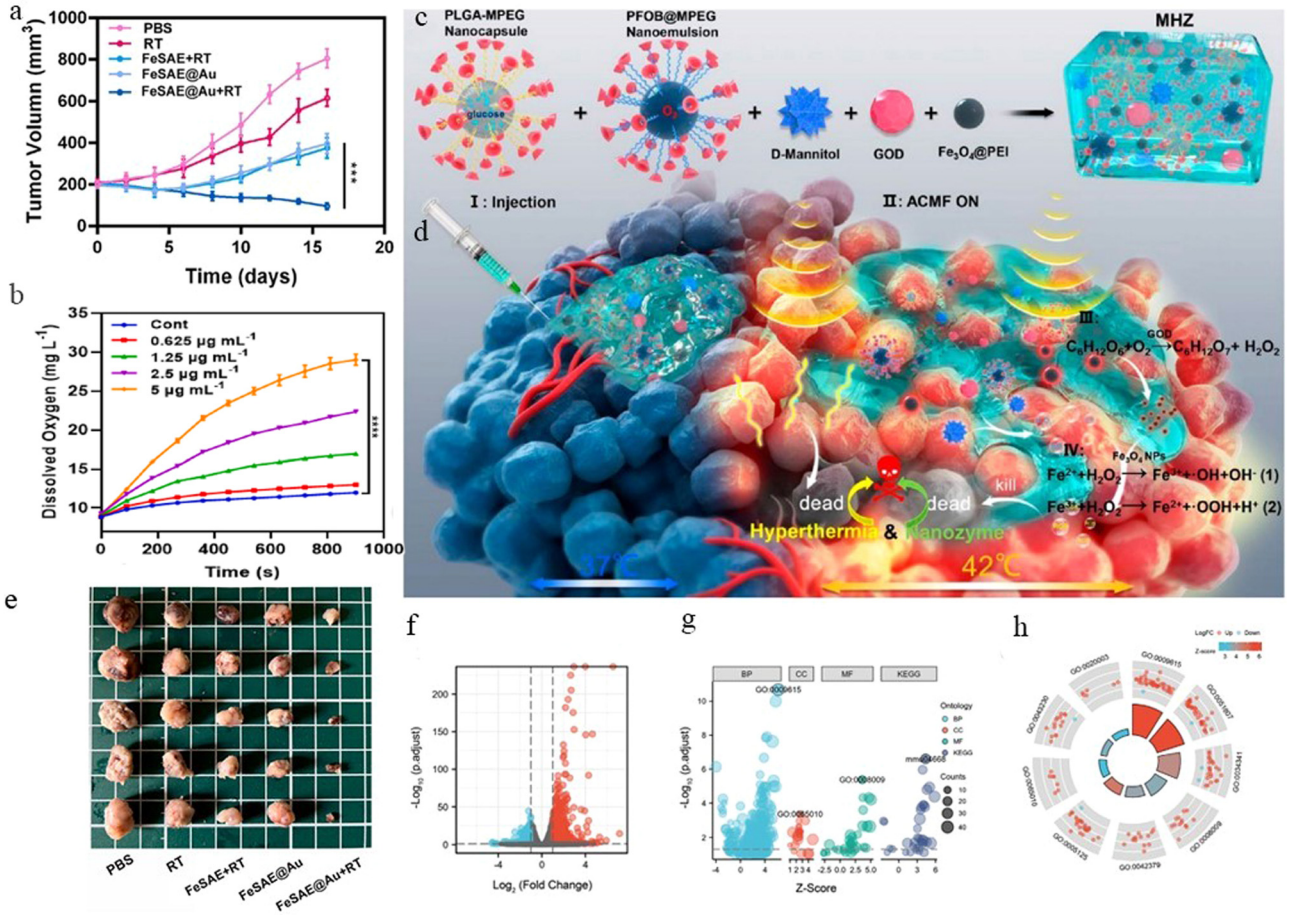

Fig. 3 (a) After the specified treatments, there were variations in the tumor volume of the mice. (n = 5), mean ± SD, which shows that using nanozyme diminished the tumor volume[95] [reproduced from ref. 95 with permission from Elsevier, copyright 2023]. (b) CAT-like propertie of P-RuCu: O_2 generation in a 1 mM H_2O_2 solution at various concentrations of P-RuCu at pH 6.5[96] [reproduced from ref. 96 with permission from Elsevier, copyright 2022]. (c) and (d) The illustration shows the structure and use of MHZ at a micro level, and it also shows the schematic mechanisms that are used in SDT. (c) Procedure for creating synthetic MHZ and its composition. (d) Scheme of the co-operative mechanism of MHZ on the generation of ROS and hyperthermia for cancer therapy[94] [reproduced from ref. 94 with permission from American Chemical Society, copyright 2019]. (e) Representative tumor image after different treatments[95] [reproduced from ref. 95 with permission from Elsevier, copyright 2023]. (f)–(h) Exploring therapeutic mechanisms on 4T1 cells through high-throughput transcriptome sequencing. (f) The volcano map reveals the US-triggered CaF_2 + H_2O_2 group's downregulated or upregulated genes compared to the control group. (g) Examination of genes with varying expression levels, (h) the circular chart for analyzing GO and KEGG[91] [reproduced from ref. 91 with permission from John Wiley and Sons, copyright 2022].

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of modern techniques in incorporating functional elements for combined hyperthermia and SDT applications.[94]

The functional diversity of nanozymes has also significantly expanded, moving beyond essential ROS generation to include multiple enzyme-mimicking activities. Nanozymes like CaF_2 primarily exhibit POD-like activity, catalyzing the breakdown of H_2O_2.[91] However, systems like LFO and $NiCoO_x$ feature additional OXD, CAT, and GPx-like activities, enabling them to address oxidative stress, deplete antioxidants like GSH, and alleviate hypoxia in tumor cells. The integration of these capabilities enhances tumor cell death pathways, such as pyroptosis and apoptosis, as seen in LFO nanozymes, which activate the ROS-TXNIP-NLRP3-GSDMD mechanism.[92] This multifunctionality has proven crucial in overcoming the complex defenses of TME, ensuring sustained ROS production and effective tumor suppression.

Another key development is the adaptation of substrates and therapeutic approaches. Most nanozymes target H_2O_2, leveraging its abundance in tumor tissues. However, modern systems have begun incorporating secondary substrates like glucose, as in MHZ, where glucose oxidase generates additional H_2O_2 to amplify ROS production.[94] This adaptability extends to therapeutic strategies, where the combination of SDT with complementary modalities has gained prominence. Early nanozyme in this category focused solely on SDT, while recent advancements incorporate hyperthermia and PTT. For instance, MHZ nanozymes combine magnetic heating and catalytic activity, while PB + Ce6 hydrogel systems merge PTT with SDT to maximize tumor ablation.[97] These synergistic approaches address tumor heterogeneity and improve treatment efficacy, as demonstrated by tumor inhibition rates of over 69% in 4T1 breast cancer models.

The impact of these innovations on breast cancer therapy is profound. *In vivo* studies reveal modern nanozymes achieve substantial tumor suppression with minimal side effects. For example, LFO@GO_x and $NiCoO_x$ systems reduce tumor viability to as low as 12.4–12.6% in 4T1 cells.[92] Furthermore, systems like MHZ and PB + Ce6 demonstrate better biocompatibility, ensuring that healthy tissues remain unaffected during treatment.[97] These advancements highlight the potential of nanozymes to overcome key challenges in cancer therapy, such as tumor resistance, hypoxia, and off-target toxicity. Integrating complexity, multifunctionality, and synergy, nanozymes offer a transformative approach to breast cancer treatment, leading to more effective, personalized therapies.

In conclusion, the continuous advancements in nanozyme design, synthesis, and application underscore their critical role in enhancing SDT for breast cancer. The trend toward more complex, multifunctional, and adaptive systems reflects a growing understanding of TME and the need for targeted multimodal therapies. As research progresses, integrating nanozymes with other emerging technologies promises to refine further and revolutionize cancer treatment strategies. The most recent studies in this field are summarized in Table 3.

3.4. Radiotherapy (RT)

Radiotherapy for breast cancer is a targeted treatment that uses high-energy radiation to destroy cancer cells, reduce the risk of recurrence, and preserve healthy surrounding tissue, often used after surgery to eliminate any remaining cancer cells.[98,99] Applying nanozymes in RT for breast cancer has undergone significant advancements, particularly in structural design, synthesis methods, enzymatic activity, substrate specificity, and therapeutic effectiveness. The structural evolution of nanozymes has progressed from simple metal nanoparticles to multi-functional, biomimetic platforms. Au–Ag@HA NPs represent one of the earlier nanozyme-based approaches for radiotherapy, incorporating hyaluronic acid (HA) for targeted accumulation in CD44-overexpressing breast cancer cells.[100] This targeted approach improved therapeutic precision and reduced off-target effects, enhancing radiotherapy efficiency. In contrast, FeSAE@Au represents a recent advancement featuring gold nanoparticles (AuNPs) anchored onto an iron single-atom enzyme (FeSAE) (Fig. 3(a), (c) and (d)).[95] This nanozyme exhibits dual enzyme-like activities, catalyzing glucose oxidation to generate H_2O_2 (GO_x-like), which is subsequently converted into $^{\bullet}OH$ (POD-like) to enhance RT-induced oxidative stress. The progression from Au–Ag@HA to FeSAE@Au highlights the increasing sophistication of nanozyme design, with more recent studies focusing on multifunctional catalytic mechanisms to amplify therapeutic efficacy.

Beyond structural complexity, the synthesis methods of nanozymes have also evolved, moving from simple co-precipitation techniques, as seen in RuCu NPs and BSA@CeO/Fe^{2+}, to multi-step functionalization approaches such as anchoring-pyrolysis (FeSAE@Au) and *in situ* polymerization (CuPy-Au@EM).[96,101,102] These modifications enabled precise control over particle size, surface functionalization, and enzymatic activity. For example, the one-pot solvothermal synthesis of P-RuCu facilitated high stability and biocompatibility by incorporating polyethylene glycol (PEG).[96] Similarly, the co-reduction method used in Au–Ag@HA NPs allowed for the simultaneous integration of multiple elements, enhancing their enzyme-mimetic activities and modulating ROS production.[100] Such advancements in synthesis have improved the efficiency of nanozymes in modulating TME and sensitizing cancer cells to radiation.

Table 3 The table below summarizes the various nanozymes utilized in SDT

Nanozyme	Synthesis method	Activity	Substrate	Cell type	Therapeutic approach	Ref.
CaF_2	Direct precipitation	POD-like	H_2O_2	4T1, H22	SDT, catalytic	91
LFO	Hydrothermal	OXD-like, POD-like, GPx-like, CAT-like	ROS, H_2O_2, GSH, O_2	4T1	SDT, catalytic	92
2D $NiCoO_x$	Hard template	OXD-like, POD-like, GPx-like, CAT-like	H_2O_2, GSH, O_2	Mouse 4T1	SDT, catalytic	93
MHZ	Ligand exchange	POD-like	H_2O_2, glucose	Mouse 4T1	SDT, hyperthermia	94
PB + Ce6@Hy	Hydrothermal	CAT-like	H_2O_2	4T1	SDT, PTT	97

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The mechanism of action of nanozymes has evolved from single-enzyme mimics to multi-enzyme catalytic systems, significantly enhancing their therapeutic effects. Initially, nanozymes exhibited POD-like activity, as seen in FeSAE@Au, where glucose oxidation led to H_2O_2 accumulation, further catalyzed to generate $^{\bullet}OH$, inducing oxidative damage to cancer cells.[95] More recently, multi-functional nanozymes, such as P-RuCu, have combined POD-like and CAT-like activities, enabling dual functionalities to enhance radiation-induced DNA damage (Fig. 3(b)).[96] Similarly, BSA@CeO/Fe^{2+} exhibited a combination of CAT-like, SOD-like, and Fenton-like reactions, sequentially converting O_2^- into H_2O_2 and then into highly toxic $^{\bullet}OH$ radicals. This cascade reaction mechanism intensified oxidative stress within tumors, overcoming radioresistance and increasing therapeutic efficacy.[101]

Substrate specificity has also expanded to optimize nanozyme-based RT. Early designs focused on simple oxidation reactions utilizing glucose and H_2O_2 (GO_x), whereas recent nanozymes interact with more complex substrates, including GSH and tumor cell-derived exosomes. For example, CuPy-Au@EM, which mimicked tumor-derived exosomes, leveraged POD, GO_x, and GSH oxidase (GSH-OXD) activities to generate ROS and disrupt redox homeostasis in cancer cells.[102] This approach enhanced radiosensitization by depleting intracellular GSH, weakening the tumor's antioxidant defense mechanisms. Additionally, nanozymes such as $SnFe_2O_4$ incorporated GSH-OXD activity to exploit TME vulnerabilities further, reducing radioresistance by amplifying oxidative stress.[103]

The efficacy of nanozyme-based RT has been validated in preclinical models, particularly in murine breast cancer models using the 4T1 cell line, known for its aggressive and metastatic nature. Studies have demonstrated significant tumor suppression and improved survival outcomes. For instance, FeSAE@Au combined with RT resulted in a 4.5-fold reduction in tumor weight compared to PBS-treated controls.[95] Similarly, BSA@CeO/Fe^{2+} achieved a tumor suppression rate of 83.07% in 4T1-bearing mice, demonstrating potent radiosensitization effects.[101] These results highlight the effectiveness of nanozymes in enhancing radiation-induced cytotoxicity while minimizing damage to normal tissues. Furthermore, nanozymes such as CuP-based hydrogel and $SnFe_2O_4$ have introduced additional functionalities, including PTT, further enhancing therapeutic outcomes by inducing apoptosis and mitochondrial disruption.[103,104]

A key advantage of nanozyme-based RT is its ability to overcome significant limitations of conventional radiotherapy, such as tumor hypoxia, radioresistance, and systemic toxicity. By generating oxygen within the TME, nanozymes like P-RuCu and $SnFe_2O_4$ have alleviated hypoxia-induced resistance, leading to increased radiation efficacy. Additionally, the integration of high-*Z* elements such as gold (Au), ruthenium (Ru), and platinum (Pt) has enhanced X-ray energy deposition, amplifying radiation effects at lower doses. Moreover, hydrogel-based delivery systems, such as CuP-based hydrogel and $SnFe_2O_4$, have enabled localized and sustained nanozyme release, minimizing systemic toxicity and improving biocompatibility. These advancements have significantly improved the therapeutic window of RT while reducing side effects.[96,103]

In conclusion, the field of nanozyme-based RT for breast cancer has evolved into a sophisticated and highly effective therapeutic approach. Advancements in structural complexity, synthesis methodologies, enzymatic activity, and targeted delivery have significantly enhanced treatment precision and efficacy. Integrating multi-modal therapies, such as PTT, has further improved tumor eradication, making nanozymes a promising platform for future clinical applications. Research efforts should focus on optimizing nanozyme formulations for clinical translation, addressing biocompatibility concerns, long-term stability, and regulatory approval to ensure their successful implementation in breast cancer therapy. The most recent studies in this field are summarized in Table 4.

3.5. Phototherapy

Nanozymes have emerged as a transformative tool in breast cancer therapy, particularly in enhancing phototherapy through enzyme-mimicking catalytic activity. Over the years, their structural complexity has evolved significantly, transitioning from simple metal-based nanoparticles with POD-like activity to highly engineered hybrid nanostructures incorporating MOFs, core–shell architectures, and bimetallic systems. This progression has improved catalytic efficiency, targeted drug delivery, and enhanced phototherapeutic outcomes. A notable example of this advancement is the MnZ@Au nanozyme, which integrates Mn-doped carbon dots, ZIF-8, and Au nanoparticles. This system exhibits dual glucose oxidase (GO_x)-like and CAT-like activities, enhancing oxygen production and ROS generation to overcome

Table 4 Nanozymes utilized in radiotherapy applications

Nanozyme	Synthesis method	Activity	Substrate	Cell type	Therapeutic approach	Ref.
FeSAE@Au	Anchoring-pyrolysis	POD-like, GO_x-like	Glucose, H_2O_2, TMB	4T1	RT, catalytic, colorimetric detection	95
RuCu NPs	Co-precipitation	POD-like, CAT-like	H_2O_2, TMB	MDA-MB-231	RT, catalytic, colorimetric detection	96
Au–Ag@HA NPs	Co-reduction	POD-like, CAT-like	H_2O_2	4T1	RT, catalytic	100
SFO	Hydrothermal	GSH-OXD-like, CAT-like	GSH, H_2O_2	4T1	RT, catalytic, PTT	103
CuPy-Au@EM	*In situ* nucleation and chemical deposition	GO_x-like, GPx-like, POD-like	Glucose, GSH, H_2O_2	4T1	RT, catalytic, colorimetric detection	102
BSA@CeO/Fe^{2+}	Co-precipitation	CAT-like, SOD-like, POD-like	H_2O_2, O^{2-}	4T1	RT, catalytic	101
CuP-based hydrogel	*In situ* chemical oxidative polymerization	POD-like, GSH-OXD-like	GSH, H_2O_2	4T1	RT, catalytic, PTT	104
Pt@Alg	Co-precipitation	POD-like	ROS	4T1	RT	105

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tumor hypoxia. As a result, tumor growth inhibition reached 60.4% when combined with laser irradiation, significantly outperforming treatment without phototherapy.[62]

The increasing complexity of nanozymes has been closely linked to advancements in synthesis techniques. Initially, simple wet-chemical methods dominated the field, but recent studies have employed more precise strategies such as co-precipitation, hydrothermal, solvothermal, and thermal decomposition methods. For instance, hydrothermal synthesis was used in MoS_2–bPEI–$CeFe_2O_4$ nanoflowers, yielding high photothermal conversion efficiency and Fenton-like catalytic activity, leading to 80% tumor cell destruction.[106] Similarly, thermal decomposition facilitated the development of Ag_2S@Fe_2C nanozymes, ensuring monodispersity and enhanced tumor-homing functionality.[107] These methodological refinements have significantly improved nanozyme stability, biocompatibility, and catalytic performance, making them more suitable for clinical applications.

Beyond synthesis improvements, nanozymes in this category have evolved from single-function catalytic agents to multi-enzyme mimetic platforms, incorporating POD, CAT-like, glucose oxidase, and SOD-like activities. While early nanozymes primarily mimicked POD-like behavior to catalyze H_2O_2 decomposition into $^{\bullet}OH$, recent designs have expanded their enzymatic repertoire to address tumor hypoxia and oxidative stress regulation. For example, the Sm-TCPP-Pt/TPP nanozyme has CAT-like activity, improving PDT efficacy and leveraging mitochondria-targeting ligands to enhance ROS accumulation precisely where it is most effective.[108] This shift towards multi-functionality has directly translated into increased tumor apoptosis rates and reduced drug resistance, as demonstrated in PdRu-RCE@PCM, which incorporated both POD- and CAT-like functionalities, enhancing photothermal conversion and ROS-driven cytotoxicity.[109]

In parallel with enzymatic improvements, the variety of substrates utilized by these nanozymes has expanded, broadening their potential applications in breast cancer therapy. Hydrogen peroxide remains the primary substrate, as seen in Sm-TCPP-Pt/TPP, which leveraged H_2O_2 decomposition to alleviate hypoxia.[108] However, recent developments have explored alternative substrates, such as glucose in MnZ@Au, which utilized GO_x-like activity to disrupt cancer cell metabolism while simultaneously generating ROS.[62] Additionally, some nanozymes, such as PPy@BSA–MnO_2, have been designed to target intracellular GSH, further amplifying oxidative stress and enhancing CDT.[110] The strategic diversification of substrates has played a crucial role in improving nanozyme selectivity and the ability to manipulate the TME to enhance therapeutic efficacy.

These advancements have been particularly beneficial in treating TNBC, an aggressive subtype with limited treatment options. Most studies in this collection focused on TNBC models, particularly 4T1 and MDA-MB-231 cell lines, due to their high metastatic potential and resistance to conventional treatments.[111] Research utilizing HM/D-I-BL nanozymes demonstrated effective tumor oxygenation and enhanced PDT performance, achieving a remarkable 93.5% tumor inhibition rate in 4T1 tumor-bearing mice.[112] Similarly, MoS_2–bPEI–$CeFe_2O_4$ nanoflowers exhibited potent CDT and photothermal synergy, making them effective in MDA-MB-231 cells.[106] Some nanozymes, such as PdRu-RCE@PCM, have even been tested across multiple cancer models, including HeLa and A549 cells, confirming their broad-spectrum applicability.[109] These findings suggest that nanozymes can be tailored to different breast cancer subtypes, paving the way for more personalized treatment strategies.

One of the most promising trends in nanozyme-based phototherapy has been the integration of multiple treatment modalities, such as PTT, PDT, CDT, and chemotherapy. Several studies highlight the enhanced efficacy of these synergistic approaches (Fig. 4(f) and (g)).[113–115] For instance, HMPB@Lip leveraged iron redox reactions alongside photothermal conversion, leading to a 92.2% tumor inhibition rate (Fig. 4(c)–(e)).[116] Likewise, I/C@M used MnO_2-mediated oxygenation to amplify ROS-dependent cytotoxicity, resulting in 86.3% tumor cell death (Fig. 4(h)).[114] Furthermore, as demonstrated in PNC nanozymes, photothermal catalytic therapy achieved 45.06% photothermal conversion efficiency, further improving tumor destruction.[117] By combining multiple mechanisms, these advanced nanozyme systems have led to higher treatment efficacy, minimized side effects, and enhanced tumor selectivity.

As research continues to refine phototherapy by nanozyme technology, the focus has shifted toward clinical applicability. The structural evolution, advanced synthesis methodologies, multi-enzyme activity, expanded substrate interactions, and hybrid therapeutic strategies collectively represent a significant step toward real-world cancer treatment solutions. Moving forward, key areas of development include personalized nanozyme formulations for specific breast cancer subtypes, hypoxia-responsive and tumor-targeted nanozymes, and the enhancement of biocompatibility for safer human application. Given their capacity for precision-targeted, minimally invasive, and highly effective therapy, nanozymes hold immense promise in revolutionizing breast cancer treatment by phototherapy. If these advancements can be translated into clinical settings, nanozyme-based phototherapy could represent a new frontier in oncology, offering hope for patients with aggressive and treatment-resistant breast cancers. Table 5 summarizes the latest studies in this field.

3.6. Starvation therapy (ST)

ST is an innovative cancer treatment strategy that exploits the unique metabolic dependencies of tumor cells by depleting essential nutrients, primarily glucose and oxygen, to induce cancer cell death.[123] Unlike traditional therapies such as chemotherapy and radiation, which directly target tumor cells but often lead to systemic toxicity, ST leverages enzymatic catalysis to disrupt TME, selectively starving cancer cells while sparing healthy tissues.[124] The fundamental principle of ST is based on the fact that cancer cells exhibit a high metabolic rate and an increased reliance on glycolysis (the Warburg effect), making them particularly susceptible to glucose deprivation and oxidative stress. Using nanozymes such as glucose oxidase (GO_x) and catalase CAT-like nanozymes, ST catalyzes glucose oxidation into gluconic acid and H_2O_2, creating a nutrient-deficient and oxidative environment that triggers apoptosis, ferroptosis, and necrosis. Beyond its direct cytotoxic effects, ST has been integrated into multimodal treatment approaches,

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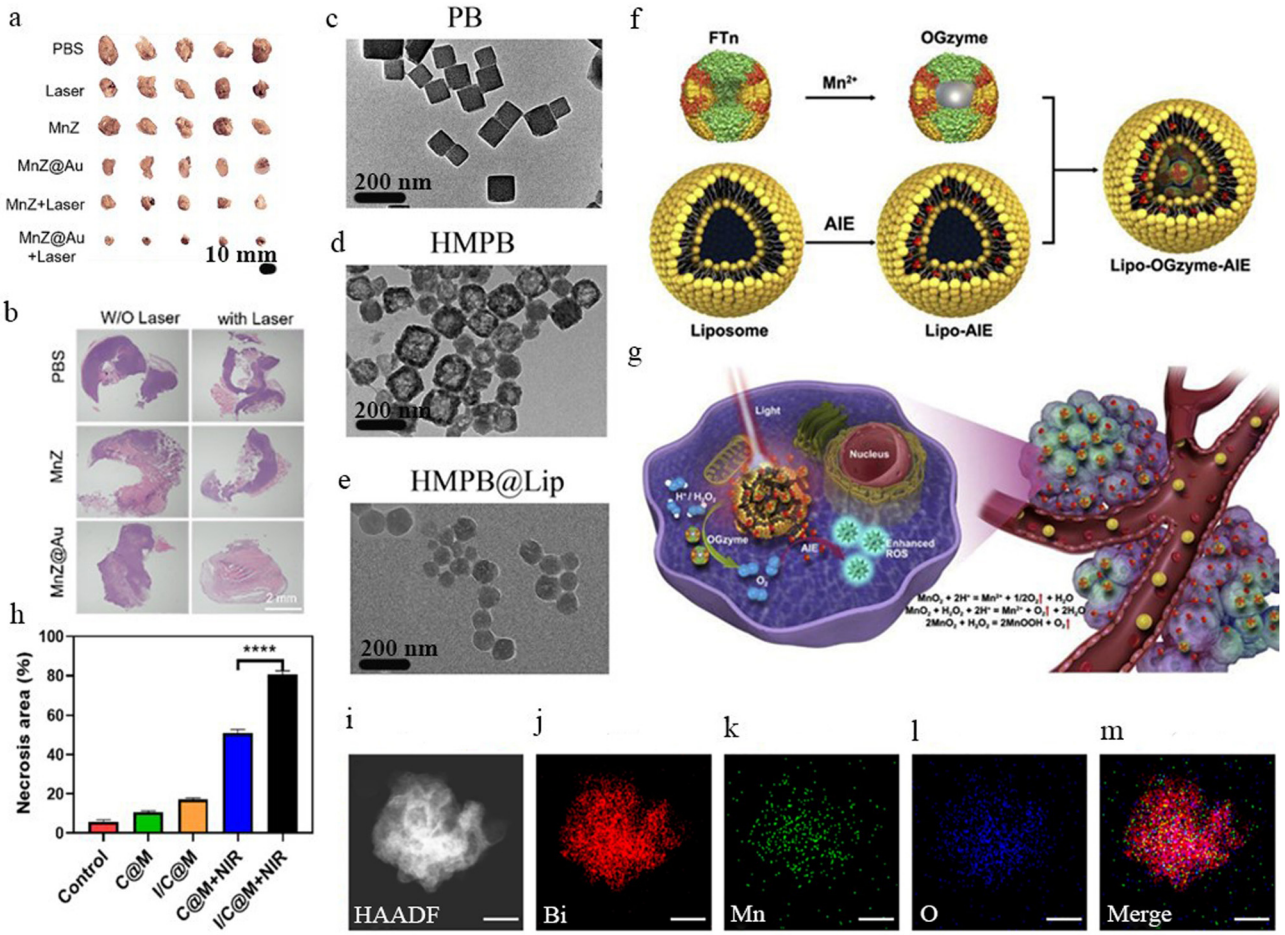

Fig. 4 (a) Images of the tumors that have been dissected after undergoing treatments for 14 days. This image shows how nanozyme is effective. (b) The tumor sections were examined using hematoxylin and eosin staining for histological studies after a 14-day treatment. The dashed white lines indicate the presence of necrotic areas[62] [reproduced from ref. 62 with permission from American Chemical Society, copyright 2023]. (c)–(e) TEM images of solid PB NCs, HMPB@Lip, and HMPB NCs[116] [reproduced from ref. 116 with permission from Elsevier, copyright 2021]. (f) and (g) The diagram illustrates how nanoparticles are prepared and the nanozymes trigger cascade reactions. (f) Structures of the Lipo-OGzyme-AIE and OGzymes and. (g) The nanoparticles in tumors are thought to act by being encapsulated into liposomes, which allows for efficient tumor uptake of the OGzymes. Afterward, the OGzymes are believed to penetrate hypoxic tumor tissues and normoxic tumor areas. The OGzymes are thought to possess CAT-like activity, which enables them to generate oxygen intratumorally through a catalytic reaction that responds to TME, particularly in hypoxic conditions[115] [reproduced from ref. 115 with permission from Elsevier, copyright 2020]. (h) Quantitative assessment of the necrotic area[114] [reproduced from ref. 114 with permission from American Chemical Society, copyright 2023]. (i)–(m) HADDF-STEM and elemental mapping of BDS@MnOx. Scale bars = 100 nm[118] [reproduced from ref. 118 with permission from American Chemical Society, copyright 2023].

including CDT, PTT, and IMT, amplifying its effectiveness against resistant and aggressive tumors.[125] The clinical potential of ST is especially promising for treating solid tumors like breast cancer and TNBC, where conventional therapies often fail due to hypoxia and metabolic adaptability. With advancements in nanozyme technology and targeted delivery systems, ST is evolving into a powerful, minimally invasive cancer treatment that enhances tumor selectivity and reduces side effects, offering a new paradigm in oncological treatment strategies.[126]

The advancement of nanozyme-based ST in breast cancer has led to increasingly complex nanoplatforms with improved catalytic mechanisms and therapeutic efficacy. Initially, simple enzyme-mimicking nanoparticles were used to catalyze glucose oxidation, depriving tumor cells of nutrients. Over time, these systems evolved into multifunctional architectures incorporating synergistic treatments such as PTT, CDT, and IMT.[127] Structural innovations, such as hierarchical core–shell architectures in Fe_3O_4@ZIF-8/GO_x@MnO_2, have enhanced catalytic efficiency, stability, and TME responsiveness.[127] Additionally, advances in synthesis techniques, including thermal decomposition and wet-chemical methods, have enabled precise control over nanozyme properties, ensuring better biocompatibility and therapeutic effectiveness.[128,129]

A key development in nanozyme therapy has been integrating multiple catalytic activities to enhance tumor starvation and oxidative stress-induced apoptosis. While early nanozymes relied on GO_x-like activity to deplete glucose and generate hydrogen peroxide,[128] newer designs incorporate POD-like, OXD-like, and glutathione-oxidase (GSH-OXD)-like functions (Fig. 4(i)–(m)).[118,129] These advanced nanozymes, such as Fe_2O_3/Au hybrids and BDS-GO_x@MnO_x, exploit metabolic vulnerabilities in cancer cells by generating ROS and disrupting antioxidant defenses. Furthermore,

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Table 5 The list of nanozymes utilized for phototherapy

Nanozyme	Synthesis method	Activity	Substrate	Cell type	Therapeutic approach	Ref.
MnZ@Au	Ion exchange and *in situ* reduction	GO_x-like, CAT-like	Glucose, H_2O_2	4T1, MCF-7	PDT, photoacoustic (PA) imaging	62
Sm-TCPP-Pt/TPP	Solvothermal	CAT-like	H_2O_2	MCF-7	PDT, catalytic	108
nGO-hemin-Ce6	Co-encapsulation	CAT-like	H_2O_2	MCF-7	PDT, catalytic	63
Ce6@HMPB NPs	Chemical etching	CAT-like	H_2O_2	4T1	PTT, PDT, catalytic	113
OGzyme	Biomimetic synthesis	CAT-like	H_2O_2	4T1	PDT, catalytic	115
PtCo@Gem-HA-PEG	Co-precipitation	CAT-like, POD-like	H_2O_2	4T1	PDT, catalytic	119
PdRu-RCE@PCM	Co-precipitation and thermal decomposition	POD-like, CAT-like	H_2O_2	4T1, A549, HeLa, 3T3	PTT, PDT, catalytic	109
Plasmonic Au NBP@Cu_2O	Co-precipitation	POD-like	H_2O_2	4T1	PTT, Catalytic	120
Ag_2S@Fe_2C-DSPE-PEG-iRGD	Thermal decomposition	POD-like	ROS	4T1	PTT, catalytic, MRI, fluorescence imaging	107
FeS-Dox@bLf NZs	Wet-chemical synthesis	POD-like	H_2O_2	4T1	PDT, catalytic	121
MoS_2–bPEI–$CeFe_2O_4$ NFs	Hydrothermal	POD-like	H_2O_2, TMB	MDA-MB-231	PTT, catalytic, colorimetric detection	106
PNC	Thermal decomposition	POD-like	H_2O_2	4T1	PTT, catalytic	117
HMPB	Hydrothermal	POD-like	Unsaturated lipids	4T1	PTT, catalytic	116
PPy@BSA–MnO_2	Chemical oxidation polymerization	GSH-OXD-like, POD-like	GSH, H_2O_2	4T1 murine	PTT, catalytic, MRI	110
HM/D-I-BL	Co-precipitation, hydrothermal	GSH-OXD-like, POD-like	GSH, H_2O_2	Mouse 4T1	PDT, PTT, catalytic, MRI	112
Fe–N–C SAzyme	Co-precipitation	POD-like	H_2O_2	TNBC	PTT, catalytic	111
I/C@M	Co-precipitation	GSH-OXD-like, POD-like, CAT-like	GSH, H_2O_2	4T1, MDA-MB-231	PDT, PTT, catalytic	114
AFH	Co-precipitation	GSH-OXD-like	GSH	4T1	PTT, catalytic	122

targeting specific tumor substrates, such as H_2O_2 and GSH, has expanded the effectiveness of nanozyme therapy beyond simple starvation, ensuring multi-pathway tumor destruction. The superior performance of these platforms has been demonstrated in aggressive breast cancer subtypes like TNBC, where nanozymes have achieved substantial tumor reduction compared to conventional therapies.[126]

The integration of combination therapies has further amplified the impact of nanozyme-based ST. These platforms have achieved superior tumor suppression and immune activation by merging catalytic reactions with PTT, CDT, and IMT.[127] For instance, Fe_2O_3/Au hybrid nanozymes leverage mild PTT and ferroptosis induction, while Fe_3O_4@ZIF-8/GO_x@MnO_2 promotes macrophage polarization and immune modulation.[127,129] These strategies enhance systemic anti-cancer immunity, as evidenced by increased M1 macrophage activation and reduced regulatory T cells (Tregs). Tumor inhibition data confirm the superior efficacy of nanozyme therapy, with platforms like BP@Au@MnO_2-PEG achieving a 64.4% reduction in cancer cell viability. Moving forward, research will likely focus on tumor-targeted, biodegradable nanozymes with enhanced immune system activation, ensuring long-term suppression and minimal side effects.[127] Nanozyme-based ST is thus emerging as a highly efficient, minimally invasive approach to overcoming aggressive breast cancer. The latest research in this field is summarized in Table 6.

4. Nanozymes in breast cancer detection

4.1. Colorimetric detection

Colorimetric detection, a foundational technique in analytical chemistry, utilizes color changes to detect and quantify analytes, with its roots traced back to the 19th-century Beer–Lambert law relating absorbance to concentration. This method spans direct detection, where the analyte produces a color, to indirect methods, involving reactions with chromogenic agents, and ranges from visual assessments to sophisticated spectrophotometric instrumentation.[130,131]

Building on this foundation, recent advancements in nanozyme development have expanded the applications of colorimetric methods, particularly in the realm of breast cancer detection;[132] The development of nanozymes for breast cancer detection through colorimetric methods has seen remarkable progress, marked by innovations in material composition, catalytic mechanisms, target specificity, and clinical applications.[133] These advancements are pushing the boundaries of cancer diagnostics and laying the groundwork for sustainable and accessible healthcare technologies.

The synthesis methods for nanozymes demonstrate a trend toward eco-friendliness and precision. Liquid-phase exfoliation and ultrasonication are frequently employed to produce nanoscale materials with enhanced catalytic properties, as seen in FeOCl nanosheets.[134] Hydrothermal synthesis, used for blood-derived nanoparticles (BDNPs) and cauliflower-derived carbon dots (CFCDs), emphasizes sustainability by utilizing natural precursors.[135,136] Acid oxidation and rolling circle amplification, as applied in graphene quantum dot nanozymes (TMB-GQDzymes), highlight advanced functionalization techniques for hybrid systems.[137] Additionally, chemical co-precipitation with subsequent surface modification (e.g., Fe_3O_4@MnO_2) underscores integrating multi-functional capabilities (Fig. 5(f)–(i)).[137] These approaches prioritize simplicity, biocompatibility, and adaptability for clinical translation.

Expanding on these synthesis strategies, nanozyme development has diversified significantly in terms of structural design

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Table 6 The list of nanozymes utilized for ST

Nanozyme	Synthesis method	Activity	Substrate	Cell type	Therapeutic approach	Ref.
BP@Au@MnO_2-PEG	*In situ* reduction	CAT-like, GO_x	H_2O_2, glucose	4T1	ST, catalytic, PDT, PTT	127
IrRu-GO_x@PEG	Thermal decomposition	CAT-like, GO_x, POD-like	H_2O_2, glucose	4T1, U87	ST, catalytic	128
Fe_2O_3/Au hybrid	Thermal decomposition	GO_x, POD-like	H_2O_2, glucose	TNBC	ST, catalytic, PTT	126
BDS-GO_x@MnO_x	Wet-chemical synthesis	GO_x, GSH-OXD-like	Glucose, GSH	4T1	ST, CDT	118
Fe_3O_4@ZIF-8/GO_x@MnO_2	Solvothermal	OXD-like, CAT-like, GO_x	H_2O_2, glucose	4T1	ST, catalytic, PTT	129

and material composition. The field now incorporates many nanostructures, ranging from simple metallic oxides to more complex hybrid and carbon-based materials. For instance, BDNPs synthesized from hemoglobin showcase a sustainable and biocompatible approach to material sourcing.[135] Similarly, graphene quantum dots (GQDs) and CFCDs are emerging as promising carbon-based materials due to their strong surface chemistry, electron conductivity, and environmental friendliness.[136,137] Hybrid structures, such as manganese dioxide-modified magnetite nanoparticles (Fe_3O_4@MnO_2), integrate multiple functionalities, enabling simultaneous magnetic separation and catalytic activity.

These structural advancements facilitate the customization of nanozymes to meet specific diagnostic needs, such as enhancing stability, sensitivity, and selectivity under complex biological conditions. This adaptability makes nanozymes versatile tools in addressing the diverse challenges of cancer detection.

Complementing these advancements in structural design, the catalytic mechanisms employed by nanozymes have expanded beyond traditional POD-like activity. For instance, FeOCl nanosheets and BDNPs use H_2O_2 to generate ROS, whereas Fe_3O_4@MnO_2 nanozymes utilize molecular oxygen, allowing catalytic reactions without relying on H_2O_2.[134,135,139] Furthermore, CFCDs improve enzymatic efficiency through competitive activation, which differs from traditional Michaelis–Menten kinetics by enhancing substrate binding affinity.[136] Hybrid systems like TMB-GQDzymes integrate catalytic oxidation with photothermal effects, introducing dual-modality detection capabilities.[137]

Complementing these advancements in structural design and catalytic mechanisms, nanozymes have demonstrated exceptional sensitivity in detecting clinically relevant biomarkers, which are crucial for early breast cancer diagnosis. For instance, FeOCl nanosheets achieve detection limits as low as

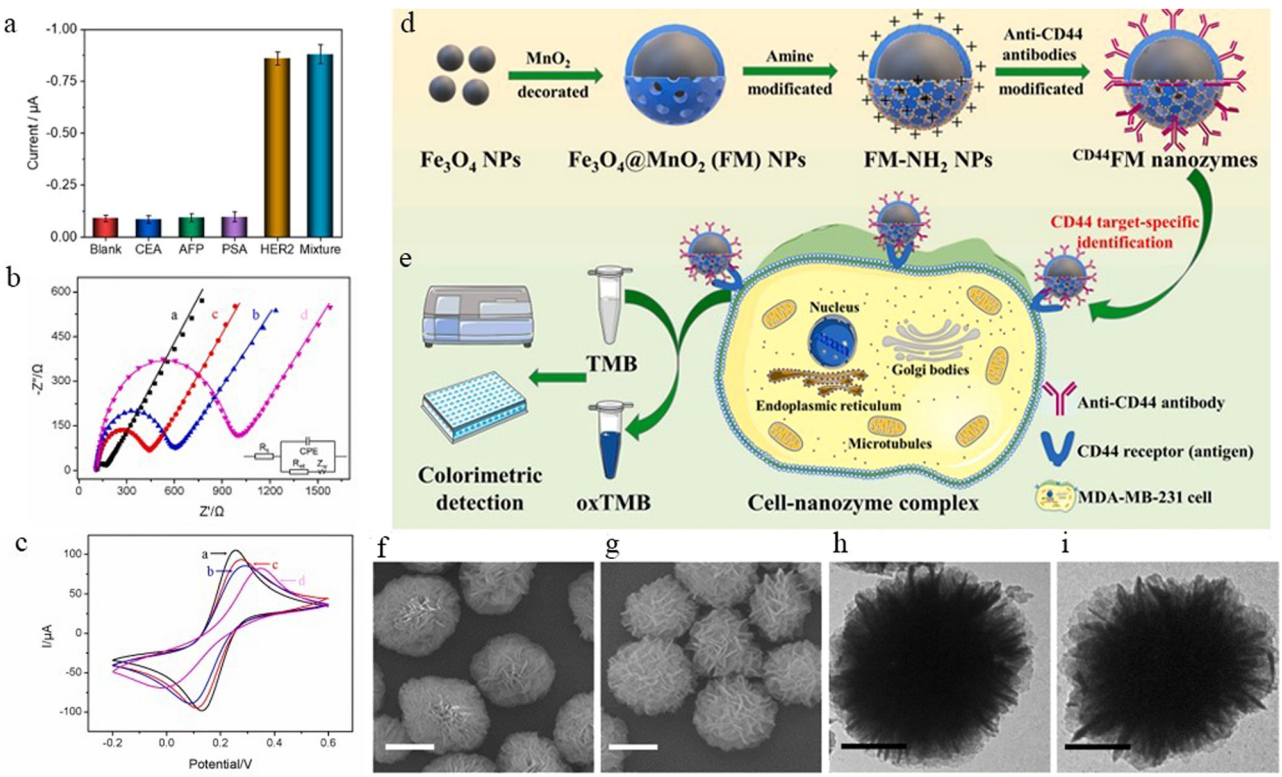

Fig. 5 (a) The selectivity of the electrochemical immunoassay[138] [reproduced from ref. 138 with permission from Elsevier, copyright 2023]. (b) and (c) Graphs of electrochemical impedance spectra show Nyquist plots (b) and cyclic voltammograms (c) of bare GCE[22] [reproduced from ref. 22 with permission from Elsevier, copyright 2023]. (d) and (e) Fe_3O_4@MnO_2NPs grafted with anti-CD44 mAbs[139] reproduced from [ref. 139 with permission from Elsevier, copyright 2023]. (f) and (g) SEM images and (h) and (i) TEM images of DFs and TMB-GQDzymes@DFs with 1 μm and 500 nm scale bars, respectively[137] reproduced from [ref. 137 with permission from Elsevier, copyright 2023].

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~2.23–2.76 μM for biothiols such as glutathione (GSH) and cysteine (Cys). Tumor-derived exosomes, biomarkers critical for early cancer diagnosis, are targeted using dual-aptamer recognition strategies with LOD of 1027 particles per μL.[134] Similarly, CFCD-enhanced assays reduce the detection threshold for alkaline phosphatase (ALP), a breast cancer marker, from 0.1 U mL^{-1} to 0.01 U mL^{-1}, while Fe_3O_4@MnO_2 nanozymes achieve cellular detection limits as low as 186 MDA-MB-231 cells.[136]

Leveraging the exceptional sensitivity and precision of nanozyme-based colorimetric diagnostics, integrating multimodal detection systems is a significant trend in the field. Nanozymes like TMB-GQDzymes exemplify hybrid platforms that combine colorimetric detection with photothermal effects under near-infrared (NIR) laser irradiation.[137] This dual-mode approach enhances diagnostic reliability by providing orthogonal validation of results. Similarly, Fe_3O_4@MnO_2 nanozymes enable magnetic separation of cancer cells from biological fluids, followed by colorimetric detection, showcasing their utility in handling complex sample matrices (Fig. 5(d) and (e)).[139]

The incorporation of hybrid systems reflects a shift toward strong diagnostic platforms that can operate in diverse clinical and research settings. These versatile systems improve the reliability of cancer diagnostics and broaden the scope of nanozyme applications to include multi-disease detection and real-time monitoring.

Alongside these advancements, the increasing focus on eco-friendly materials and scalable synthesis methods highlights the commitment to developing sustainable, cost-effective solutions that improve the accessibility and global impact of nanozyme technologies. Using eco-friendly materials and scalable synthesis methods is another emerging trend in nanozyme research. For example, BDNPs derived from hemoglobin and CFCDs synthesized from cauliflower leverage natural, renewable resources, aligning with green chemistry principles. Scalable methods such as hydrothermal synthesis further reduce production costs, making these materials viable for widespread use.[135,136]

While sustainability and scalability drive the global adoption of nanozyme technologies, ongoing research must address critical challenges in specificity, biocompatibility, and integration with cutting-edge diagnostic platforms to unlock their full potential. Despite these advancements, challenges remain in achieving absolute specificity and eliminating background interference. Strategies such as dual-aptamer designs and selective surface functionalization have shown promise but require further optimization. Future research should also focus on improving the biocompatibility of nanozymes to minimize cytotoxicity and immune responses *in vivo*. Additionally, integrating nanozyme-based platforms with wearable devices and multiplexed systems could revolutionize cancer diagnostics by enabling real-time and multi-biomarker detection.

Building on efforts to overcome existing challenges, the transformative potential of nanozymes in cancer detection—particularly in breast cancer—becomes apparent through their structural versatility and innovative applications in diagnostics. Nanozymes are emerging as a powerful tool for detecting breast cancer using colorimetric methods. Their structural diversity, multifunctional catalytic mechanisms, and clinical applicability indicate a field poised for significant impact. By addressing current challenges and focusing on sustainable, scalable designs, nanozyme research has the potential to redefine the landscape of cancer diagnostics, making early detection more accessible, reliable, and cost-effective. The ongoing convergence of nanotechnology, materials science, and clinical medicine will propel this promising field to new heights.

4.2. Electrosensitive detection

Electrochemical detection is an advanced analytical technique for biomedical research that integrates biological recognition elements, such as enzymes, antibodies, or DNA, with electrochemical transducers to detect specific analytes.[140] This method leverages the electrochemical signals generated during biochemical interactions, such as enzymatic redox reactions or antigen–antibody binding, to achieve high sensitivity and specificity.[140,141]

Nanozyme-based electrochemical detection methods have emerged as powerful tools for biomarker identification, offering exceptional sensitivity, LOD, and dynamic applicability in disease diagnosis, particularly cancer. These systems leverage the catalytic properties of nanozymes to catalyse key reactions like the decomposition of H_2O_2 into measurable electrochemical signals.[142]

Innovations in nanozyme synthesis have paralleled these advancements in detection, optimizing their catalytic performance for specific applications. Synthesis methods have evolved to create defect-rich, high-surface-area nanozymes tailored for specific applications. Hydrothermal and sol–gel methods are prevalent, as seen in FeMn-NC and FeNC nanozymes, where controlled doping with metals like Fe, Mn, or Cu optimizes catalytic performance (Fig. 5(a)).[23,138] As in Mn_3O_4/Pd@Pt nanostructures and DNA-functionalized nanozymes, self-assembly techniques enable precise structural configurations, enhancing active site exposure and stability (Fig. 5(b) and (c)).[22,143,144] Bioconjugation strategies, such as incorporating Cu^{2+} ions into BSA nanoparticles, exemplify efforts to enhance reactivity through surface functionalisation.[145] Hybrid nanozymes, integrating multi-functional materials like MOFs and metallic nanoparticles, are becoming increasingly sophisticated. For instance, the MOF@Pt@MOF structure provides a synergistic catalytic framework combining conductivity, porosity, and enzyme-like activity.[20]

These advancements in nanozyme synthesis have directly influenced detection mechanisms, where innovative catalytic and signal amplification strategies are driving improvements in sensitivity, stability, and specificity. The detection mechanisms often center on POD-like activity, where nanozymes catalyse H_2O_2 decomposition, triggering substrate oxidation (*e.g.*, TMB, dopamine) and producing detectable signals. This enzymatic mimicry, augmented by nanostructural engineering, enhances signal intensity and stability.[146,147] Advanced systems incorporate signal amplification strategies, such as DNAzyme walker cleavage cycles and CRISPR/Cas12a-mediated amplification, significantly boosting detection thresholds.[144,148] Tetrahedral DNA nanostructures and aptamer-functionalized interfaces enable selective target recognition, particularly for biomarkers

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like HER2 and MUC1, ensuring high specificity.[143] As seen in binanozyme cytosensors, magnetic separation techniques enhance detection by seamlessly isolating CTCs under a magnetic field, combining enrichment and electrochemical analysis.[149]

Integrating these advanced detection mechanisms has enabled nanozyme systems to achieve remarkable sensitivity and specificity, with detection limits at fM levels and dynamic adaptability for clinical applications. The miRNA-21 ratiometric biosensor achieved a LOD of 0.16 fM, while HER2 and MUC1 biosensors exhibited LODs of 4.5 pg mL^{-1} and 0.085 pg mL^{-1}, respectively.[22,146] These ultra-sensitive detection capabilities are crucial for early diagnosis and monitoring of low-abundance biomarkers in complex biological samples. The dynamic detection ranges, spanning from fM to nM concentrations, highlight the adaptability of these systems across varying analyte levels, ensuring their reliability for clinical applications.

Building on their ultra-sensitive detection capabilities, integrating hybrid materials in nanozyme design has further enhanced performance, leveraging properties like conductivity, catalytic synergy, and multi-functionality. The integration of hybrid materials marks a significant trend in nanozyme design. Carbon-based nanozymes like FeNC and rGO/MoS_2 are favored for their electrical conductivity and modifiable surfaces, while dual-metal nanozymes such as FeMn-NC and CH–Cu@J-Cu_2O capitalize on synergistic effects for enhanced catalysis. Multifunctional hybrids like MOF@Pt@MOF and TCPP-Fe@HMUiO@Au-ABEI incorporate additional features such as signal amplification and structural flexibility, achieving superior performance compared to single-component systems.[20,144,147,149]

The growing focus on genetic biomarkers, particularly miRNA detection, reflects the ongoing evolution of nanozyme-based systems, with hybrid materials and advanced techniques paving the way for more versatile and clinically applicable diagnostic tools. A notable focus on miRNA detection underscores the shift toward genetic biomarkers, with miRNA-21 and miRNA-155 prime targets for breast and cervical cancer diagnostics. Techniques combining nanomotors, DNAzyme amplification, and electrochemiluminescence (ECL) offer promising real-time and multiplexed analysis opportunities.[150] As the field advances, emphasis on hybrid materials, miniaturized detection systems, and integration with portable devices could further expand the clinical and point-of-care applications of nanozyme-based sensors.

Interdisciplinary innovations driving enzyme-based electrochemical detection forward highlighted. These innovations merge nanotechnology, materials science, and biomedical engineering to tackle critical challenges in diagnostics. The versatility and sensitivity of these systems hold significant promise for future developments in healthcare and disease management.

4.3. Photothermal and photoelectrochemical detection

Photothermal detection represents a transformative approach in cancer diagnostics, utilizing the photothermal properties of nanomaterials to achieve high sensitivity and specificity. By converting absorbed near-infrared (NIR) light into heat, these nanomaterials generate temperature changes that correlate with the concentration of specific biomarkers.[151] This technique is particularly effective for early and non-invasive detection of breast cancer biomarkers, such as CTCs, MUC1, and miRNAs. Integrating nanozymes, which possess both enzymatic and photothermal properties, further amplifies thermal signals and enhances the accuracy of target-specific reactions. With the additional benefits of portability and compatibility with imaging-guided systems, photothermal detection is a solution for real-time clinical applications.

Recent studies have significantly advanced the synthesis of nanozymes, incorporating innovative materials and catalytic properties to enhance their functionality. For instance, heterostructured Ag_3PO_4/Ag/TiO_2 nanorod arrays, PtCo@Prussian Blue nanozymes, and IrWOx nanoparticles have been synthesized using tailored methods to improve photothermal and enzymatic activities.[148,152,153] These nanozymes facilitate versatile detection mechanisms, such as bifunctional photoelectrochemical sensing, DNAzyme walker processes, and ROS scavenging, enhancing sensitivity and specificity. Combining photothermal properties with catalytic activity, as seen in Ti_3C_2@Au@Pt nanozymes, amplifies thermal signals under NIR exposure, enabling highly sensitive detection of biomarkers like CTCs and miR-155.[52] These approaches demonstrate the versatility and efficacy of nanozyme-enabled technologies in both diagnostics and therapy.

Targeting critical breast cancer biomarkers, including MUC1, CEA, and miR-155, underscores the diagnostic precision of nanozyme-based platforms. Detection limits have reached remarkable sensitivity, with values as low as 0.1 ng mL^{-1} for CEA and consistent reproducibility across assays. Additionally, integrating photothermal and imaging-guided systems addresses the dual goals of diagnosis and treatment, especially in advanced cancer stages like metastasis. Emerging trends highlight using multi-functional materials, biocompatibility enhancements, and imaging modalities to ensure clinical relevance. As the field evolves, addressing scalability and cost will be critical to translating these technologies from the lab to broader clinical applications, paving the way for improved outcomes in breast cancer management. Table 7 presents an overview of the nanozymes used in breast cancer detection.

5. Future prospects

The future of nanozyme technology in breast cancer theranostics is poised for transformative advancements that will redefine both diagnostic and therapeutic paradigms. One of the most promising directions involves the rational design of nanozymes with precisely tailored catalytic activities. Future research should focus on atomic-scale synthesis methods—such as atomic layer deposition, self-assembly, and controlled pyrolysis—to fine-tune electronic properties and active sites. These approaches, combined with advanced computational modeling and DFT, will enable researchers to predict and optimize the structure–function relationships of nanozymes. This level of precision is essential for developing catalysts that can selectively generate ROS in the TME, thus maximizing cancer cell ablation while minimizing damage to surrounding healthy tissues.

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Table 7 Overview of nanozymes employed in breast cancer detection

Nanozymes	Mechanism	Type of sensor	Target	LOD	Ref.
FeOCl nanosheets	POD-like	Colorimetric	GSH and Cys	2.23 μM and 2.76 μM	134
TMB-GQDzymes	POD-like	Colorimetric/photothermal dual-mode biosensor	MCF-7 cell-derived exosomes	1027 particles per μL, 2170 particles per μL	137
CFCDs	Phosphatase	Colorimetric	Alkaline phosphatase (ALP)	0.01 U mL^{-1}	136
^{CD44}FM nanozymes	OXD-like	Colorimetric	TNBC, MDA-MB-231 cells	186 cells	139
BDNP-100	POD-like	Colorimetric	H_2O_2 and glucose	40 μM	135
MNPs	POD-like	Colorimetric	Melanoma CTCs	13 cells per mL	154
Au@PtOs	POD-like	Colorimetric, SERS (surface-enhanced Raman scattering), photothermal mode	Breast cancer exosomes	2.6×10^3 exosomes per μL, 4.1×10^1 exosomes per μL, 4.6×10^2 exosomes per μL	19
FeMn-NCetch/SAC	POD-like	Electrochemical and photothermal	HER2	3.9 pg, 7.5 pg mL^{-1}	23
FeMn-NCedge	POD-like	Electrochemical immunoassay	HER2	5.4 pg mL^{-1}	138
CuS@Pt-SA	POD-like	Electrosensitive	miRNA-21	0.16 fM	22
Mn_3O_4/Pd@Pt/HRP nanoprobe	POD-like	Electrosensitive	HER2	0.08 ng mL^{-1}	143
rGO/MoS_2	POD-like	Electrosensitive	CTCs	6 cells mL^{-1}	149
CuO nanozyme	POD-like	Electrosensitive	CTCs	27 cells mL^{-1}	155
FeNC	POD-like, GO_x	Electrosensitive	HER2	4.5 pg mL^{-1}	146
MOF@Pt@MOF	POD-like	Electrosensitive	Exosomal miRNA-21	0.29 fM	20
CH–Cu@J-Cu_2O	CAT-like, POD-like	Electrosensitive	MUC1	0.085 pg·mL^{-1}	147
PtCo@rGO	POD-like	Electrochemiluminescence (ECL) cytosensor	MCF-7	1 cells mL^{-1}	156
sponge-like Au@Ru	POD-like	Electrochemical immunosensor	HER2	0.15 pg mL^{-1}	157
TCPP-Fe@HMUiO@Au-ABEI	POD-like	ECL detection	exomiR-155	273.20 aM	144
TiO_2@Ag	POD-like	ECL detection	miRNA-155	0.45 fM	150
Ag_3PO_4/Ag/TiO_2	POD-like, alkaline phosphatase	Photothermal and photoelectrochemical detection	MUC1, CEA	0.430 ng mL^{-1}, 0.058 ng mL^{-1}	152
PB	POD-like	Photoelectrochemical detection	miR-155	1.2 fM	148
$IrWO_x$-PEG	CAT-like	Photothermal and photoelectrochemical detection	Metastatic breast cancer cells	—	153
SPIO@NC	POD-like, CAT-like	Dual-modality imaging	TNBC cells	—	158

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Another critical avenue is the exploration and integration of hybrid nanostructures. By merging carbon-based materials' robust, biocompatible characteristics (*e.g.*, graphene, carbon dots) with metal nanoparticles' or MOFs' high catalytic efficiency, researchers can create multifunctional systems that overcome current limitations. For instance, such hybrid nanozymes could harness carbonaceous materials' superior conductivity and chemical stability alongside metallic components' tailored enzyme-mimetic activities. This synergy is expected to yield platforms that perform highly efficient catalysis and offer enhanced optical, magnetic, and electrical properties, paving the way for real-time imaging and precise therapeutic interventions.

In addition to structural innovations, significant progress is anticipated in targeted delivery and controlled activation. The future development of smart nanozymes will involve surface modifications that grant immune resistance and active targeting capabilities. Techniques like PEG conjugation, cell membrane cloaking, and aptamer functionalization will be instrumental in extending circulation time, reducing off-target toxicity, and ensuring that these catalysts home in on specific tumor markers or pH gradients characteristic of the TME. Next-generation nanozymes can be activated "on demand," providing precise temporal and spatial control over therapeutic action by responding to endogenous stimuli such as hypoxia, oxidative stress, or enzymatic cues.

Furthermore, integrating nanozymes with state-of-the-art imaging modalities is critical to realizing accurate theranostic systems. Incorporating functionalities for magnetic resonance imaging (MRI), positron emission tomography (PET), or near-infrared (NIR) fluorescence into nanozyme platforms will allow clinicians to monitor drug distribution, assess treatment efficacy, and dynamically adjust therapeutic regimens in real time. Such multifunctional platforms can simultaneously deliver therapy and provide diagnostic feedback, enhancing personalized treatment strategies for various breast cancer subtypes.

Scaling up production without compromising nanozyme quality is another challenge for future research. Developing green, cost-effective, reproducible synthesis methods is vital for clinical translation. Emphasis on eco-friendly precursors and scalable processes—such as liquid-phase exfoliation or hydrothermal synthesis using natural templates—will facilitate the manufacture of nanozymes that meet rigorous safety and performance standards. In parallel, comprehensive studies addressing pharmacokinetics, biodistribution, and long-term biocompatibility in relevant animal models must be undertaken to build a robust preclinical foundation.

Moreover, converging nanozyme research with emerging fields like artificial intelligence and machine learning is anticipated to accelerate discovery and optimization. Data-driven approaches can analyze vast experimental datasets to identify trends and predict the behavior of new nanozyme compositions. Such insights will streamline the development process and enable real-time customization of nanozyme properties to suit individual patient profiles, thus moving closer to genuinely personalized cancer therapy.

Lastly, the future of nanozyme-based breast cancer therapy will likely benefit from combinatorial treatment strategies. Integrating nanozymes with established modalities—such as chemotherapy, radiotherapy, immunotherapy, and phototherapy—can exploit synergistic mechanisms to overcome drug resistance and tumor heterogeneity. By concurrently disrupting metabolic pathways, inducing oxidative stress, and modulating immune responses, these multimodal platforms promise to enhance overall therapeutic efficacy and patient outcomes.

In summary, its interdisciplinary approach will define the next generation of nanozyme research—merging advanced material science, precision engineering, computational modeling, and clinical insights. With ongoing innovations focused on enhancing catalytic efficiency, targeting specificity, and multifunctionality, nanozymes are set to become a cornerstone in the future landscape of breast cancer theranostics, offering a highly precise, adaptable, and scalable solution for improved patient care.

6. Conclusion

Research on nanozymes targeted at breast cancer applications has yielded transformative insights into their catalytic, diagnostic, and therapeutic capabilities. Nanozymes have been engineered into diverse formulations—such as bimetallic, metal nanocluster, MXene-based, MOF-based, and carbon-based systems—that enable precise modulation of the tumor microenvironment. Their unique enzyme-mimicking properties allow them to catalyze reactions that generate ROS, triggering apoptosis, disrupting metabolic processes, and overcoming drug resistance in cancer cells. Integrating nanozymes into multimodal treatment strategies, including catalytic therapy, immunotherapy, sonodynamic therapy, radiotherapy, phototherapy, and starvation therapy, creates robust theranostic platforms that combine targeted treatment with real-time monitoring of therapeutic outcomes.

The accumulated evidence demonstrates that nanozymes are effective in tumor ablation through enhanced ROS production and early diagnosis by detecting breast cancer biomarkers with high sensitivity. This dual functionality promises to revolutionize personalized cancer care by providing precise therapy and diagnostic capabilities. However, several challenges remain. Future research must optimize biocompatibility and minimize systemic toxicity while ensuring long-term stability and reproducibility of nanozyme formulations. Addressing issues of scalability, tumor heterogeneity, and targeted delivery is crucial for advancing clinical translation. Furthermore, comprehensive regulatory and safety evaluations will be essential to integrate nanozyme technology into standard treatment protocols. Overcoming these bottlenecks will pave the way for nanozymes to become a cornerstone in next-generation breast cancer management, offering more effective, minimally invasive, and personalized therapeutic solutions.

Overall, continued interdisciplinary collaboration and innovative nanomaterial engineering are imperative to fully realize the clinical potential of nanozyme-based therapies effectively.

Author contributions

Amir Kashtiaray: conceptualization, writing – review & editing, investigation, writing – original draft. Mahdi Karimi: writing –

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review & editing, investigation, writing – original draft. Mostafa Ghafori-Gorab: writing – review & editing. Ali Maleki: supervision, project administration.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The authors would like to express their gratitude for the partial support from the Research Council of the Iran University of Science and Technology (IUST) during their research project.

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