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Review

Quantum Dots in Breast Cancer: Emerging Nanobiotechnological Tools for Targeted Therapy and Diagnosis

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Abstract- Breast cancer is the most common carcinoma in the recent era, and it is increasing day by day. There are various biomarkers for breast cancer, and the most important is human epidermal growth factor2 (HER2). Nanotechnology has advanced targeting systems for cancerous cells. Quantum dots (QDs) are nanoparticles which are used for bioimaging, biolabeling, and biosensing and synthesized by various techniques like top-down, bottom-up, and synthetic methods. This review delves into various types of QDs like semiconductors, carbon QDs, graphene QDs, and many more. Each type of QDs has specific advantages regarding breast cancer treatment by delivering drugs into cancerous tissue, targeted delivery, and minimizing systemic toxicity. However, there are some challenges with respect to stability, pharmacokinetics, specificity with respect to breast cancer therapy. Future research is required to develop biocompatible QDs which hold the potential for the enhancement of therapeutic efficacy and the reduction of side effects.

Keywords- Quantum Dots; Breast Cancer; Targeted therapy; Nanobiotechnology; Cancer Diagnostics

1. INTRODUCTION

Breast cancer is a malignant tumor that originates in the cells of the breast, most commonly in the ducts or lobules. It is one of the most prevalent cancers among women worldwide, though it can also affect men. Risk factors include age, genetic mutations (such as BRCA1 and BRCA2), family history, hormonal imbalances, lifestyle factors, and prolonged exposure to estrogen. Early stages often present as a painless lump, skin changes, or nipple discharge. Screening methods like mammography, ultrasound, and MRI enable early detection, significantly improving treatment outcomes. Treatment options vary depending on the stage and type and may include surgery, radiation therapy, chemotherapy, hormone therapy, and targeted biological agents. Advances in personalized medicine and molecular diagnostics have led to more effective, individualized treatments [1]. Globally, breast cancer accounts for approximately 685,000 deaths annually, making it the most common cause of cancer mortality among women. While survival rates exceed 90% in high-income countries due to early detection and advanced treatment, they drop to below 50% in low- and middle-income countries, where access to timely diagnosis and care is limited. This disparity highlights the urgent need for global health equity in breast cancer management [2,3]. Breast cancer research continuously faces many challenges in diagnostic and therapeutic fields, explored in the use of quantum dot (QD) technologies. Researchers are studying how to better target imaging and treatment approaches, to sharpen and improve the effectiveness of cancer therapies. Targets include visualizing of HER2 receptors, integration of peptide based QD nanomedicines for personalized drug delivery within specific cancers, as well as the simultaneous delivery of anti-cancer siRNAs and imaging agents for triple negative breast cancer (TNBC), that lack current specific treatment options. Most advances in semiconductor quantum dots have demonstrated their excellent fluorescence properties including durability against photobleaching as well as tunable emission wavelengths, which have made them increasingly appealing for use in more sensitive and specific detection than current imaging methods. Nevertheless, their cytotoxicity and unintended uptake into non-target tissues remain problems hindering extensive use [4]. Innovations like photothermal therapy and the creation of dual stimuli responsive nanoparticles specifically for treatment of HER2 positive breast cancer, have made researchers work towards improving drug delivery platforms. Carbon dots (CDs) have also attracted attention due to their capacity to improve natural imaging potential and clinically relevant targeted therapy delivery. Although still in very early stages of development, CDs already hold a great deal of promise in bioimaging, drug development, and photodynamic therapy, though, their long-term safety and social value are being rigorously examined. Another important research area is to understand the intracellular behavior as well as the molecular interactions of QDs [5]. Included are studies on QDs' internalization by cancer cells, the possibility of epigenetic and genotoxic changes resulting from QD exposure, their capacity to cause apoptosis, and their role in internalization and recycling of the folate receptors. In recent years, sophisticated biomedical imaging

platforms of QD-based nanotechnologies have been increasingly used to assess complex cancer cell behavior and tumor microenvironments in vitro and in vivo, providing useful information of tumor formation, progression, and metastasis [6].

Synthesis of novel nanomaterials and their associated cytotoxic effects also need to be a subject of research. To determine whether carbon and cadmium sulfide quantum dots (CsQDs) can be virally delivered to breast cancer cells and act as anti-cancer agents, based on the development of their toxicological profiles, investigations were also performed. Additionally, the use of quantum dot conjugates in photodynamic therapy is being developed as an approach to increase the efficacy of the therapy for breast tumors. With its quantum dots in the realm of diagnostics and biomarker discovery, quantum dots are being used to aid early mutation detection e.g. detection of BRCA1 gene alteration, and conducting quantitative evaluations of proteins that are related, like IGF1R, to cancer progression [7,8].

Table 1. Classification of quantum dots

Type of Quantum Dot	Material Composition	Examples	Key Features
Semiconductor Quantum Dots [12,13]	Made from elements of groups II–VI, III–V, or IV–VI	CdSe, CdTe, ZnS, InP	Strong fluorescence, size-tunable emission, widely used in imaging
Carbon Quantum Dots (CQDs) [14,15]	Carbon-based nanomaterials	Carbon dots, graphene quantum dots	High biocompatibility, low toxicity, versatile in bioimaging and drug delivery
Perovskite Quantum Dots [16]	Composed of metal halide perovskites	$CsPbBr_3$, $CH_3NH_3PbI_3$	Excellent light absorption, high quantum yield, sensitive to moisture
Graphene Quantum Dots (GQDs) [17,18]	Single or few-layered graphene structures	Graphene oxide-derived QDs	Good biocompatibility, stable fluorescence, promising for sensors and imaging
Silicon Quantum Dots [19,20]	Silicon nanoparticles	SiQDs	Environmentally friendly, photostable, suitable for biological applications
Metal Quantum Dots [21,22]	Made from noble or transition metals	Gold (Au), Silver (Ag) QDs	Surface plasmon resonance effects, useful in photothermal therapy
Polymer-based Quantum Dots [23]	Quantum dots embedded in or coated with polymers	Polymer-coated CdSe QDs	Improved stability and biocompatibility for drug delivery and imaging

Further, glycophenotype analysis and monitoring of biomarker co-localization point to how QDs can increase the accuracy and sensitivity of cancer diagnostics. The goal for continuous advancement of therapeutic solutions in breast cancer through quantum dot research continues. The development of advanced theranostic platforms is urgently needed to fulfil the large gap in the treatment of TNBC and to push the boundaries further in the development of effective targeted therapies. In addition, working to develop a better understanding of pathways of

detoxification for QDs and improved gene delivery systems and prevention strategies for breast cancer metastasis highlights the multiplicity of quantum dot technology to revolutionize breast cancer diagnosis and treatment [9,10].

Quantum dots (QDs) typically range in size from 2 to 10 nanometers, although their size can extend up to 100 nanometers depending on the type of surface coating applied. The emission of light from QDs spans various wavelengths, and this optical property is closely related to their particle size. This behavior, governed by quantum confinement effects, makes QDs highly advantageous for applications such as bioimaging and monitoring drug delivery processes. QDs can be classified based on their composition, which includes either single-element materials like silicon and germanium or compound semiconductors such as cadmium selenide (CdSe), cadmium telluride (CdTe), lead sulfide (PbS), lead selenide (PbSe), and carbon-based structures [11]. Among photoluminescent nanoparticles, the main categories include semiconductor quantum dots (SQDs), carbon dots (CDs), and others. A detailed overview of their classification is given in Table 1.

Semiconductor quantum dots are semiconducting materials known to be excellent photostable and photoperative. The fluorescence behavior of SQDs is strongly dependent on the size and the chemical components of their making. For example, the range of QD bandgap is ~2-3 nm which results in blue light emissions, whereas 5-6 nm brings narrower bandgap and blue to infrared emissions. Also, the elements forming the QD influence the bandgap energy, and bandgap energy generally decreases as the elements move across the periodic table from Group I to Group VI. Typically, such SQDs include an inorganic crystalline core (e.g., CdSe or CdTe), shielded by a zinc sulfide (ZnS) shell for boosting the quantum yield and reducing the propensity of oxidative damage to the core [24]. Further classifications of SQDs are made according to elemental composition. Good bioconjugation properties of Group I-VI QDs (e.g., copper, silver, and sulfur, selenium, or tellurium) can make them useful for targeted imaging [25]. Electrochemical immunosensing for cancer detection using group II-VI QDs (cadmium, zinc, with sulfur, selenium or tellurium) is also used [26]. Group III–V QDs (e.g. indium phosphide and gallium nitride) are known for their bright fluorescence as well as reduced toxicity, whereas Group IV–VI QDs (e.g. Lead sulfide and lead selenide) are size tunable as well sensitive to near infrared light [27]. Being able to penetrate deep tissue, emit infrared light, drug delivery and imaging applications make group IV QDs including carbon, silicon and germanium favored. However, despite their numerous advantages, there is a concern of the toxicity of these heavy metals in some QDs that has led to focusing on surface modification of these materials, or to research on safer carbon-based QDs [28].

Carbon-based nanoparticles under 10 nanometers in size are known as carbon dots (CDs), the terms carbon quantum dots (CQDs), polymer dots (PDs), and graphene quantum dots (GQDs) are used to categorize the three types of CDs. Quantum confinement effects are shown in CQDs that are low-molecular weight, photoluminescent nanoparticles. Their surface groups

are usually carboxyl, amine or hydroxyl groups that can be chemically conjugated with other molecules. Their biocompatibility can be increased by these functional groups, which in turn makes them great candidates for bioimaging and drug delivery. When CQDs receive photons, exciton (electron-hole pair) is created, which subsequently recombine and cause fluorescence [29,30]. Made from a few layers of graphene disks and covered with oxygen and hydrogen containing functional groups, these are known as graphene quantum dots (GQDs). The modifications improve their biocompatibility, biodegradability and stability. GQDs can be used for photodynamic as well as photothermal therapy since they emit light in the blue to green spectrum mostly. GQDs can react with light and produce reactive oxygen species (ROS) to selectively kill cancer cells, thus can be developed as cancer treatment [31].

Numerous advantages are associated with the use of quantum dots in drug delivery systems. The first is their large surface area which allows them to attach multiple drug molecules (or targeting ligands or imaging agents). Second, some QDs such as CdSe/ZnS conjugated with captopril can cross the blood brain barrier (BBB) by transcytosis and carbon dots and GQDs can cross the BBB without modification. QDs also have the advantage of taking advantage of the enhanced permeability and retention (EPR) effect from their nanoscale size to acquire tumor sites with leaky vasculature. QDs surface modification with hydrophilic ligands or a semiconductor shell not only improves solubility, stability and optical properties, but is able to enter cells by endocytosis for increasing efficiency and length of intracellular delivery and activity [32].

Regarding cancer research, quantum dots were also shown to be applied as possible alternatives for early cancer detection, cancer imaging and targeted therapy. One of the examples is CdSe/ZnSe/ZnS QDs used for the detection of ovarian cancer and surface modified CdSe/CdS/ZnS QDs linked to transferrin and anti-claudin-4 antibodies for imaging of pancreatic cancer cells. Secondly, optical biosensors were also developed using cysteine conjugated CdSe/CdS QDs for skin cancer detection. Finally, in a nutshell, quantum dots have been proven to take a huge range of applications, mostly in bioimaging, detection of cancer and drug delivery [33,34]. Despite some of the toxicity and regulatory issues, problems with these compounds remain, however, as research continues on them, they are becoming safer and safer, and they are beginning to be valued as a useful tool for future medical applications.

2. APPROACHES OF QUANTUM DOTS FOR DRUG CONJUGATES

There are several sophisticated methods used to attach drugs to quantum dots (QDs), each offering distinct advantages. These techniques facilitate targeted drug delivery, sustained release, and enhanced therapeutic outcomes. The following outlines the primary strategies:

2.1. Covalent Bonding

The binding between drug molecules and QD can be covalently bonded, and it is a reliable and common way to bridge drug molecules and QD. This technique is used to effectively improve the therapeutic efficacy of a drug by allowing the controlled, targeted, and sustained release of the drug. Typically, QD's free amino or carboxyl groups are attached to corresponding groups on drugs or biomolecules. Various covalent bonding mechanisms are used based on carboxyl (-COOH) bearing QDs, which easily conjugate with free amino groups, hydroxyl groups on carbohydrates and several biomolecules, i.e. proteins, peptides, antibodies, etc [35]. One of the more common methods involves the use of EDC-NHS (N-hydroxy succinimide) chemistry, wherein EDC is a cross-linker that forms an amide bond between the QDs carboxyl group and the amine group of biomolecules. It is widely used for targeted drug delivery through receptor-mediated endocytosis or folate receptor-targeted drug delivery. Further, QDs bearing amine(-NH_2) groups are commonly conjugated by amine thiol group from other molecules using Sulpho-SMCC type reagents. Most commonly, these QDs are utilized in binding with peptides, proteins, receptors, and antibodies. In addition, the QDs can also form disulfide bonds with sulfur-containing compounds in order to solubilize hydrophobic QDs. Epoxide-containing QDs can finally be reacted with amine, thiol, and hydroxyl groups to yield stable secondary amine, thioether, or ether bonds. Overall, these are very suitable covalent conjugation methods for building advanced drug delivery systems and are present in a wide variety of possibilities [36,37].

2.2. Non-covalent bond

Non-covalent conjugations to quantum dots (QDs) are an attractive method for attaching drugs to QDs owing to flexibility and reversibility. By thus preserving the bioactivity and structural integrity of the drug, this approach maintains the possibility of the added drug to bind to the QD surface as is, making drugs to proceed further with their bioactivity and bioconjugation without change of chemical structure. For this method, the non-covalent interactions that are used for this system are electrostatic forces, hydrophobic interaction and van der Waals interaction which stabilize the drug on QD surface [38].

Supramolecular hybrid cyclodextrins (CDs) can be used to deliver doxorubicin (DOX) for cancer treatment as an example of non-covalent conjugation. In this work, DOX was bound to QDs through combination of electrostatic force and π–π stacking, both non-covalent forces. However, because it maintained DOX activity, this technique was useful. Unlike covalent bonding, that involves forming permanent chemical bonds between the drug and the carrier, non-covalent binding allows the drug to stay as it is, without any chemical changes. The preservation of DOX means that it maintains its desired biological function. Also, the non-covalent conjugation permitted pH sensitive drug release which released the drug in response to tumour acidic environment for localizing the drug at the location of the tumour [39,40].

2.3. Click Chemistry

The specific functional groups on both the drug and the QD surface make it possible to use the technique of click chemistry to attach the drug precisely and efficiently to the quantum dots (QDs). The creation of this method allows stable conjugates to be made without disturbing some other components. The commonly used reactions are copper catalyzed azide-alkyne cycloaddition (CuAAC) and strain promoted azide-alkyne cycloaddition (SPAAC) [41]. Its major benefit is that it is bio-orthogonal; the reactions can take place under physiological conditions (body's temperature and pH) without harming biological systems. This is how the drug doesn't get degraded so that it has maximum effect and at the same time delivery is precise. High adaptability of click chemistry can accommodate to a broad range of drug compounds and quantum dot surfaces, thus providing the flexibility of how drug can link to the QDs [42]. A just mentioned example of click chemistry in drug delivery is a study by Chen et al., where they linked the surface of zinc sulfide (CdSe/ZnS) QDs by connecting histone deacetylase inhibitors (HDACi) using the azide alkynyl cycloaddition method. Under mild conditions, the conjugation resulted in a hydrophilic nanohybrid, to avoid damage to the biological components. With this process, biological activity of HDACi and QDs was preserved. The nanohybrid showed high biological effect, which included the inhibition of growth of lung cancer cells and the increase of protein acetylation levels. This study demonstrates that click chemistry is a suitable method for conjugating drugs with QDs retaining biological functions and strengthened therapeutic potential [43].

2.4. Disulfide Linkage

Disulfide bonds are another useful method for conjugating drugs to quantum dots, offering the advantage of controlled drug release within the intracellular environment. These bonds help maintain the stability of drug molecules in oxidative environments and enable targeted delivery to specific sites, such as cancer cells [44]. In a study by Sangtani et al., they explored the use of disulfide, ester, and hydrazone linkages to conjugate doxorubicin (DOX) to QDs. Among these, disulfide linkages provided the highest stability and lowest toxicity, allowing for sustained drug release within endosomal compartments, making it an effective strategy for controlled drug delivery [45].

2.5. pH-Sensitive Linkage

pH-sensitive linkers represent an innovative approach for drug conjugation onto quantum dots, with the ability to release drugs specifically in the acidic environment of tumors. This technique enhances localized therapeutic effects while reducing systemic exposure, making it a promising strategy for cancer treatment. In a study by Bao et al., the use of a pH-sensitive linker was investigated in the conjugation of DOX to fluorescent carbon quantum dots (CQDs).

The linker was designed to be hydrophobic and reducible, with two terminal aldehyde groups that reacted to the lower pH found in tumor environments. This reaction triggered the controlled release of the drug, minimizing damage to surrounding healthy tissues [46]. At the same time, by making the drug pH sensitive, the study showed that it stayed stable inside the CQDs until it got to the tumor site where the drug could come out and degrade. It inhibited tumor growth much better than free drug formulations and was better than the system itself. This suggests that pH sensitive linkers have the capability to increase the specificity and efficacy of drug delivery systems [23].

3. QUANTUM DOTS IN BREAST CANCER

Modern nanotechnology at the forefront of quantum dots (QDs) with quantum mechanics meets materials science. Nanoscale semiconductors with sizes from 2 to 10 nanometers, for example, have specific optical and electronic properties which are different than of their bulk counterparts. Importantly, they can use their ability to control the interaction of light and electrons to help with tasks in many technological fields [47]. Cadmium-based QDs, and more specifically cadmium selenide (CdSe) QDs, have been extensively studied, and in this way, they have played an important role in the determination of quantum confinement effects. With these QDs, researchers have looked at simple single core structures as well as more complex core shell structures such as CdSe@ZnS as well as bioconjugated forms specially designed for specific applications. Similarly, cadmium sulfide (CdS) QDs are of interest due to their variety of electronic properties and have been developed from basic starting models to sophisticated, nanoengineered versions for biological applications [48]. Nevertheless, scientists developed safer alternatives because of potential toxic effects of cadmium. Indium-based QDs have emerged as a great potential candidate, due to their near infrared emissions that are extremely useful for biomedicine imaging applications. In addition, materials based on carbon atoms such as graphene quantum dots (GQDs) have become attractive due to their unique electronic properties and compatibility with a broad set of materials [49,50].

To the contrary, in recent years, specialized quantum dots with specific functionalities have been created. For example, zinc oxide QDs have been designed to tackle antibacterial use, and MXene QDs can enable next-generation technologies. One of the most remarkable features of QDs is their adaptability. When conjugated with antibodies, they serve as precise imaging agents capable of highlighting specific cellular activities. Moreover, surface modifications, such as attaching polyethylene glycol (PEG) molecules, have improved their biocompatibility and broadened their use in fields ranging from diagnostic imaging to therapeutic applications [51].

The progress in QD based drug delivery systems speaks about their increasing contribution in nanomedicine. To improve safety and increase therapeutic effectiveness of these nanoparticles, we have designed modifications to how these nanoparticles interact with

biological systems. QDs are paired with biomolecules to assure that they arrive at the appropriate place, a giant step forward in medical technology that brings targeted drug delivery and co-delivery systems [52]. Quantum dots are a rapidly moving, important component of the growing world of nanotechnology. As the ability to tune them fine for specific applications, with deep quantum foundations, makes them useful drivers of science and industry innovation [53]. The mechanism of QDs is shown in Figure 1.

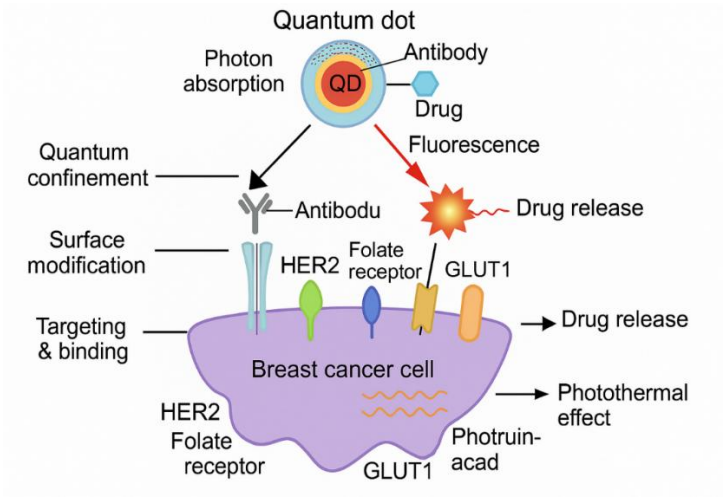

Figure 1. Mechanism of QDs in breast cancer

3.1. Semiconductor quantum dots

Due to their unique optical and electronic properties, semiconductor quantum dots (QDs) have become a current front nanomaterial with major promise for breast cancer diagnosis and treatment. Depending on elemental makeup, they are typically composed of elements from groups II-VI (e.g. CdSe, CdTe), III-V (e.g. InP) or IV-VI (e.g. PbS), and exhibit size & controllable photoluminescence, high quantum yield, and excellent photostability suitable for bioimaging and targeted therapeutic applications. In breast cancer diagnostics, QDs are frequently linked to specific biomarkers such as HER2, EGFR or Ki67 using monoclonal antibodies. It permits multiplexed labeling of cancer cells to permit simultaneous detection of multiple targets with minimal spectral overlap. When compared with conventional organic dyes, QDs have a broader absorption spectrum and a narrower emission spectrum, thus amplifying the sensing capability of imaging with multi colors [47,54].

In terms of therapy, QDs serve as nanocarriers for anticancer drugs like doxorubicin (DOX), 5-fluorouracil, or camptothecin. Selective drug delivery to tumor tissues is significantly improved by taking advantage of the biocompatibility of polymers and targeting ligands to modify surface of QDs to avoid off-target toxicity and improve therapeutic efficacy. This result provides the ability to program release of the drug payload from these conjugated QDs in response to specific stimuli, including the acidic tumor microenvironment, to achieve

controlled and localized treatment. Additionally, semiconductor QDs have been rolled into photothermal and photodynamic therapy systems, in which the great light absorption of semiconducting QDs in the near infrared range results in local generation of heat or reactive oxygen species capable of killing cancer cells upon light activation [55]. However, these advantages are limited by particular limitations, most notably the possibility of cytotoxicity of heavy metal based QDs, such as cadmium based QDs. Hence, ongoing efforts focus on reducing toxicity and increasing biocompatibility by modifying surface, developing less toxic, such as InP/ZnS QD, alternatives. Additionally, their pharmacokinetics, long term biodistribution and tissue clearance from the body needs to be studied thoroughly prior to any general application in clinical settings. However, semiconductor QDs greatly facilitate the realization of multifunctional nanodevices for the early detection, real-time imaging, and targeted therapy of breast cancer by combining diagnostics and treatment into an integrated approach called theranostics [56].

3.2. Graphene QDs in breast cancer

Recent advancements in GQDs have demonstrated substantial potential in breast cancer treatment (shown in Figure 2). In one study, GQDs were incorporated into hydrogels made from carboxymethyl cellulose (CMC) to deliver the anticancer drug doxorubicin (DOX). These hydrogel films exhibited pH-responsive behavior under acidic conditions (typical of tumor environments), the carboxyl groups became ionized, which increased electrostatic interactions with cancer cell membranes. This enhanced drug absorption and cellular internalization. Additionally, the inclusion of GQDs improved the hydrogel's heat resistance and structural stability [57].

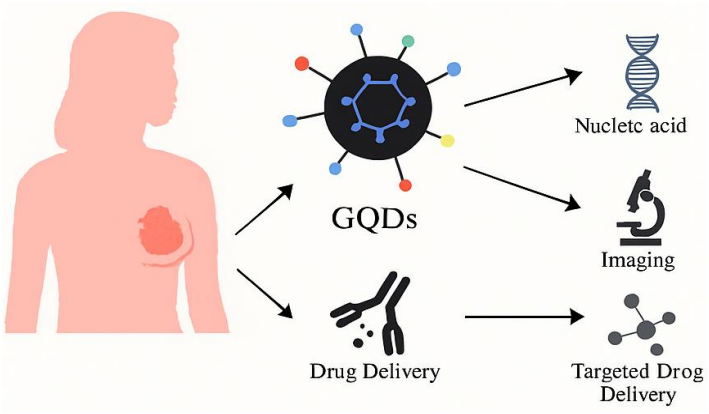

Figure 2. Application of GQDs in breast cancer

Another creative way entailed the combination of GQDs with titanate nanoflowers (TN), along with an anti-HER2 antibody for targeted DOX delivery. However, the large surface area available for drug loading was still provided by these flower-like nanostructures. By linking to

GQDs, they helped to enable fluorescence-based tracking of drug and enhanced drug uptake and cytotoxicity in HER2 positive breast cancer cells. A more potent targeted system was exhibited with its IC50 also being notably lower than that of free DOX [58]. Precision targeting was further proven by the fact that the antibody tagged GQDs were even more effective. In another study by Singh et al., methotrexate (MTX) loaded N doped GQDs with blue fluorescence were used. Consequently, sustained release of these nanoparticles resulted in more prolonged and efficient cell killing than free MTX. The safety profile was also confirmed, but good biocompatibility and low toxicity [58,59].

Table 2. Types of GQDs and their advantages as a carrier in breast cancer therapy

Type of GQD Carrier	Method of Preparation	Advantages in Breast Cancer Therapy
Pristine GQDs [64]	Top-down oxidation of graphite or GO	Excellent fluorescence, biocompatibility, and easy surface modification. Used in imaging and drug delivery.
Doped GQDs (e.g., N-GQDs, S-GQDs) [65,66]	Doping during bottom-up synthesis or post-treatment	Enhanced photoluminescence, better ROS generation, and increased drug loading capacity. Useful in photothermal/photodynamic therapy and gene delivery.
PEGylated GQDs [67,68]	Surface grafting with polyethylene glycol (PEG)	Improved solubility, circulation time, and reduced immune clearance. Promotes passive targeting via EPR effect.
Lipid-coated GQDs [69,70]	Encapsulation with a lipid bilayer	Enhances stability and allows encapsulation of both hydrophobic and hydrophilic drugs. Ideal for multifunctional drug delivery.
Polymer-functionalized GQDs [71]	Conjugation with biocompatible polymers	Allows controlled release, pH-responsiveness, and tumor-specific targeting. Often used for smart drug delivery systems.
Metallic GQD Hybrids (e.g., Au-GQD, Fe-GQD) [72,73]	Composite synthesis with metal nanoparticles	Enable dual imaging and therapy (theranostics), such as MRI and photothermal effects.
Targeted GQDs (e.g., with folic acid or antibodies) [74]	Bioconjugation with ligands	Specific targeting of breast cancer cells (e.g., HER2+ or folate receptor+). Enhances cellular uptake and minimizes off-target effects.

The second system was embedded GQDs and MB along with DOX in poly(lactic-co-glycolic acid) (PLGA) nanoparticles, coated with bovine serum albumin (BSA) as shown in Table 2. The combined nanoplatform exerted superior tumor killing effects as compared to traditional chemotherapy and photothermal therapy, when activated from NIR light [60]. The methylene blue released reactive oxygen species (ROS) upon laser irradiation, which then led to further damage of tumor cells. The treatment was very effective, but additional long-term studies on the toxicity and breakdown of the materials will be needed before these can be used in the clinic. Another study developed a drug delivery system based on polyaniline (PAN) and magnesium-aluminum layered double hydroxide (MgAl-LDH) composite mixed with DOX and N-doped GQDs. The drug release from this composite could be controlled and pH

dependent. Safe at very high doses, the unloaded nanocarrier was safe to healthy cells, the nanocarrier containing drug was very toxic but less so to cancer cells (MCF-7). But the evidence for its effectiveness has to be further tested in preclinical and clinical settings [61,62]. Importantly, glucosamine-functionalized GQD were then loaded with curcumin (CUR) in order to specifically target GLUT receptors, which are known to be overexpressed on many breast cancer cells. Non-targeted QDs were compared in cytotoxicity with these Gl-GQDs that released their drug payload in a pH-sensitive manner. The delivery was efficient, but the toxicity profile of glucosamine-linked GQDs needs further studies [63].

3.3. Carbon QDs

In the investigation of quantum dots (QDs) for breast cancer treatment, researchers developed carbon quantum dots (CQDs) conjugated with the pyrimidine analogue 5-fluorouracil (5-FU). These 5-FU-loaded CQDs demonstrated low toxicity towards healthy cells while exerting a dose-dependent cytotoxic effect on MCF-7 breast cancer cells. Importantly, the conjugation enhanced the drug's efficacy without significantly affecting normal tissues [75]. Figure 3 illustrates the varied uses of carbon quantum dots (CQDs) for breast cancer therapy, encompassing approaches like light-activated treatment, hindering tumor growth, delivering drugs, and imaging through fluorescence, thereby demonstrating the wide-ranging utility of CQDs in combating this disease. Another study made curcumin loaded chitosan based CQDs with Fe_2O_3 nanoparticles. Moreover, it demonstrated efficient drug tracking by using the fluorescence of CQDs due to pH-sensitive drug release as well as strong anticancer activity of the MCF-7 cells [76]. A more stable and further antineoplastic benefit resulted from the addition of Fe_2O_3. Despite this, the biocompatibility and toxicity profile of this system still needs to be further evaluated in vivo [49]. In a similar manner, camptothecin (CPT) was delivered with carbon quantum dots doped with dysprosium (Dy-CQDs). When these nanocarriers were loaded with different doses of doxorubicin, the released drug remained sustained and pH responsive for up to 100 hours and displayed an optimal cytotoxicity depending on the drug dose. Additionally, since Dy-CQDs are superparamagnetic, they may have future applications in magnetic resonance imaging (MRI) and targeted cancer therapy. These findings still need to be validated in vivo [77].

The other innovation involved the development of transferrin (Tf)-conjugated and DOX-loaded CQDs aimed at targeting breast cancer cells. They also loaded more doxorubicin (DOX) into the acidic tumour microenvironment, where transferrin receptors were overexpressed. Fluorescent imaging showed high uptake to MCF-7 cancer cells, and they exhibited twice the cytotoxicity of free DOX, making them potential agents for targeted breast cancer therapy [78, 79]. The synthesized nitrogen doped CQDs functional with quinic acid and loaded with gemcitabine (Gem) were finally loaded. The system gave both imaging and therapeutic capabilities as a multifunctional system [80]. The nanocarriers themselves emitted bright blue

fluorescence for tumour specific imaging as well as selectively targeted angiogenic factors overexpressed in MCF-7 cells. The release of drugs was mainly triggered by acid environments and spared the healthy tissues. The first portion confirmed the superiority of this gemgem, gaining greater than 10-fold higher permeation relative to free gemcitabine in cells and showed superior tumor targeting and therapeutic performance by both cytotoxicity tests and in vivo imaging [81].

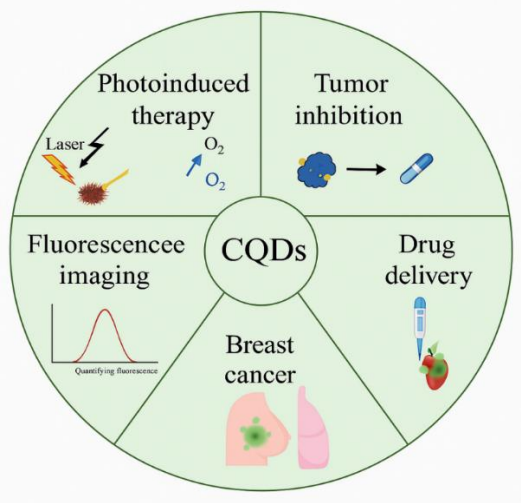

Figure 3. Applications of carbon QDs in breast cancer treatment

3.4. Perovskite Quantum Dots in Breast Cancer

Lead halide perovskite quantum dots (QDs, particularly $CsPbX_3$ (X = Cl, Br, I) based structure have been attracting increasing interest in biomedical applications due to their good photoluminescence quantum yield and tunable emission wavelengths coupled with narrow emission spectra. These QDs are investigated for high-resolution imaging as well as potential delivery of therapeutic agents in the context of breast cancer. Real-time imaging of cancer cells with improved signal to noise ratio is possible due to their sharp and bright fluorescence. For instance, the use of $CsPbBr_3$ QDs for imaging HER2 positive breast cancer cells was demonstrated because such QDs can be conjugated to specific antibodies. However, the instability of perovskite QDs in aqueous environments and the presence of toxic lead content present challenges. Although the work done so far has already led to real, applicable in vivo imaging tools, further research is ongoing to develop encapsulation techniques and lead-free alternatives such as tin based perovskite QDs that may offer safer options for in vivo imaging [82,83].

3.5. Metallic Quantum Dots in Breast Cancer

Gold (Au) and silver (Ag) nanoclusters are metallic QDs which possess unique optical and electronic properties associated with the localized surface plasmon resonance. Specifically,

these nanostructures are very useful for imaging and photothermal therapy in breast cancer. Tumor targeting QDs functionalized with gold have been used for dual imaging and heat generation based on near infrared light exposure exploiting fluorescence and heat generation properties. This is exemplified by gold QDs conjugated to trastuzumab that can target HER2 receptors on breast cancer cells, thus resulting in a photoablation of tumor tissues using increased photothermal ablation. However, less explored properties of silver QDs include antimicrobial and potential anticancer activities. In most cases, metallic QDs are biocompatible, and especially if properly surface modified, they offer a stable platform for multifunctional diagnostic and therapeutic systems [84,85].

3.6. Silicon Quantum Dots in Breast Cancer

Nontoxic, biodegradable Silicon QDs represent an alternative to the traditional heavy-metal based QDs. They are photoluminescent and amenable to surface functionalization and therefore are suitable candidates for biomedical imaging due to their long fluorescence lifetimes. In breast cancer, silicon QDs are developed as fluorescence-based detection for biomarkers including estrogen receptors and HER2. Safe interaction with cellular environments is allowed because of their inherent biocompatibility, and no long-term toxicity is caused by their degradation into nontoxic byproducts (orthosilicic acid). A specific example is the silicon QDs encapsulated in polymeric nanoparticles that delivered and follow anticancer agents which are effective to target MCF-7 breast cancer cells and enhance cell tracking. It can also be integrated into biosensors for real time progression of tumor and efficacy of drugs [86,87].

4. STANDARD DIAGNOSTIC AND THERAPEUTIC STRATEGIES OF BREAST CANCER

4.1. Diagnostic methods of breast cancer

4.1.1. Mammography and Digital Breast Tomosynthesis

Breast cancer screening for the past decades has relied on mammography – low dose X ray imaging. Many non-palpable cancers are found in organized mammography programs and such screening programs reduce breast cancer mortality by about 30% among screened women. Successful analog to digital transition occurred over last century as mammography improved image quality and workflow. Digital breast tomosynthesis (DBT or “3D mammography” is introduced to overcome the problem of tissue, overlap (especially in dense breasts). Multiple low dose projections of the compressed breast are acquired over an arc and computer reconstruction [88]. In the massive studies, large and blinded, this technique has been shown to modestly increase cancer detection and reduce false positives compared with standard 2D mammography. In the Oslo Tomosynthesis Screening Trial, for example, an increase from 6.1 to 8.0 cancers per 1000 exams was reported along with a reduction in false positive rate from

10.3% to 8.5% [89]. Just as in the Danish "STORM" trial, DBT showed a 17% reduced number of recalls and increased detection. In multiple studies, these confirmations have been made. DBT, however, has its limitations: it exposes the patient to a higher radiation dose than 2D mammography, although the latter still finds controversy in its ability to depict submicroscopic calcifications. In addition, tomosynthesis still has trouble in extremely dense breasts, where cancers can be obscured by fibroglandular tissue. To summarize, mammography (especially with tomosynthesis) is still the first-line imaging screening despite proven efficacy and because it has lower sensitivity in dense breasts and delivers many false positives (and resultant biopsies) [90,91].

4.1.2. Breast Ultrasonography

Breast Ultrasonography is widely used as a supplement to mammography. It produces real-time images of breast tissue without ionizing radiation. High-frequency transducers can distinguish solid from cystic lesions, measure blood flow, and guide needle biopsies. This modality is particularly valuable in younger women and those with dense breasts, where mammography sensitivity is limited. Breast ultrasound can detect some cancers occult on mammography, and it is effective in characterizing palpable masses and architectural distortion. However, ultrasound has notable limitations [92]. First, its specificity is relatively low: benign findings (fibroadenomas, fibrocystic change) often have sonographic features overlapping malignancy, leading to a high false-positive rate. In practice, many lesions seen on ultrasound require biopsy to exclude cancer. Second, ultrasound is operator-dependent image quality and interpretation vary with the sonographer's or radiologist's skill and experience. Third, ultrasound cannot reliably image microcalcifications (tiny calcium deposits) that may herald ductal carcinoma in situ, whereas mammography excels at detecting calcifications. Finally, while ultrasound is helpful in dense breasts, it still has lower sensitivity than MRI in extremely dense or high-risk cases. For these reasons, ultrasound is not used as a primary screening tool for average-risk women, but rather as a problem-solving modality or an adjunct in selected populations [93, 94].

4.1.3. Breast Magnetic Resonance Imaging (MRI)

The sensitivity of all imaging tests is highest with breast MRI. MRI is performed using strong magnets and gadolinium contrast, giving high resolution images that accentuate tumor angiogenesis, and tissue contrast. Studies have had many proving that MRI can detect cancers that are invisible even on serumograpy and ultrasound especially in women with dense breasts or women at high risk of developing cancer. For the example of MRI, pooled analyses have been performed and report sensitivities of 90–97%, well above the 60–80% sensitivity typically observed by mammography or ultrasound. MRI is especially suitable for the identification of multifocal or multicentric disease and for discrimination between scar tissue and tumor. Its use in the clinical setting is indicated for breast screening high risk women (e.g mutation carriers

of the BRCA), for further evaluation of other imaging not conclusive and to stage a known cancer [95, 96]. The great drawback of MRI is the cost and the resource intensity that comes with it. MRI is an expensive and time-consuming test that is not as available as other tests. In addition, it has a relatively high false positive rate (additional biopsies due to enhancement) as enhancement can occur in benign proliferative conditions. Thus, MRI for patients is reserved except for those with very high pretest probability (where the benefit outweighs the false positives) or indeterminate imaging findings. In addition, MRI not only does not have the limitation of breast density (it does not depend on the amount of fibroglandular tissue in the breasts) but also is a substantially more effective detection modality than ultrasound (i.e. it finds substantially more additional cancers per 1000 screened women and will probably reduce the number of additional cancers found as much as 3–4 times more than ultrasound alone). The result from this data suggests that MRI is the most powerful modality for lesion detection and lesion characterization, however, practical limitations (cost, ease of use, no contrast required) hinder its widespread use [96, 97].

4.1.4. Molecular Biomarkers in Breast Cancer

At the same time, many have focused on searching for molecular biomarkers of breast cancer using parallel to the imaging. Up to now, no approved biomarker based on blood is available for primary diagnosis or screening. However, only a few markers have been cleared by the Food and Drug Administration (FDA) for specific uses; serum CA 15-3 and CA 27-29 (both MUC1 glycoprotein fragments) are cleared for monitoring therapy response or recurrence in known breast cancer, and the markers for HER2/neu and circulating tumor cells are used in the stages and prediction. None of these would serve for early diagnosis [98, 99]. However, numerous candidate protein markers, autoantibodies, microRNAs and metabolites have been proposed, but none has achieved the level of sensitivity and specificity to merit clinical use. Standard biomarkers in tissue include hormone receptors (ER and PR) and HER2 that are assessed using immunohistochemistry or in situ hybridisation. They are not screening tools but they are necessary for choosing the right therapy when a cancer comes up [100, 101].

4.1.5. Genomic and Liquid Biopsy Tools

Prognostic tools have entered practice as genomic and transcriptomic assays. These so-called Oncotype Dx, Mammaprint and Prosigna tests analyze panels of genes in the tumor tissue to predict recurrence risk, and direct chemotherapy decisions. However, they have improved personalized therapy, but don’t help with initial diagnosis. We continue to have great interest in liquid biopsies (circulating tumor DNA, cell free methylated DNA or circulating tumor cells), which hold great promise for noninvasive monitoring but have not yet realized proven clinical sensitivity for routine screening or early detection. Finally, in summary, here, even though the use of such advanced technologies in breast cancer diagnosis (specifically ELISA immunoassays, PCR and next generation sequencing, mass spectrometry, etc), we still

have not been able to arrive at any validated biomarkers for breast cancer diagnosis, and this is a very big gap which needs to be bridged in the current diagnostic methods [102, 103].

4.1.6. Histopathological Diagnosis

Histopathological examination (examining tissue) is necessary to definitively diagnose breast cancer. Current standards strongly favor the utilization of a percutaneous needle biopsy as the first diagnostic step for suspicious lesions. A core needle biopsy (14 gauge or vacuum assisted) is performed under imaging guidance (ultrasound, stereotactic Xray or MRI) with local anesthesia. It consists of a minimally invasive procedure that provides cores of tissue sufficient for microscopic diagnosis and biomarkers (ER/PR/HER2, Ki 67). Importantly, core biopsies preoperatively have the advantage of avoiding immediate open surgery in the benign cases, allowing simultaneous planning of surgery and axillary management, and lessening a cosmetic consequence by using smaller incisions. In fact, professional guidelines and quality measures require an attempt at needle biopsy to avoid unnecessary surgical biopsies [104, 105].

4.1.7. Fine-needle aspiration (FNA) cytology and Core-needle biopsy

Fine-needle aspiration cytology which uses a thin needle to withdraw cells has been largely supplanted by core biopsy for primary diagnosis of most breast masses. FNA has lower sensitivity and specificity, a high rate of non-diagnostic or indeterminate results, and cannot distinguish in situ from invasive cancer. It remains useful in limited situations (e.g. simple cysts, evaluation of known metastases). Core-needle biopsy provides architectural context and enough tissue for molecular tests, making it far more informative. As noted above, core biopsy can occasionally “underestimate” disease; small invasive foci or adjacent ductal carcinoma in situ may be missed, and histologic grading may be downgraded in small samples. Nonetheless, when biopsies are properly targeted and adequate, core histology is highly accurate for diagnosis. Surgical (excisional) biopsy is reserved for cases where needle biopsy fails to resolve the diagnosis or sampling is technically impossible [106, 107].

4.1.8. Tumor Heterogeneity and Diagnostic Uncertainty

The tumor is heterogenous, which is a persistent challenge in breast cancer diagnosis. Breast cancers can be composed of many subclones with different genetics and phenotypes. This means that one biopsy sample from a tumor may not accurately reflect the entire ‘genomic landscape’ of that tumor. We have seen studies of cases that show discordance between core biopsy and whole resection specimens for key biomarkers (e.g. ER, PR, HER2). In practice this would mean that the status of the receptor or grade assigned on a small biopsy might be altered by reviewing additional tissue, which could affect treatment decisions. Also, for multifocal tumors or cancers with skip lesions, one sample may not be sufficiently characterized of these tumors. Some effects of these factors contribute to lead to false negative biopsies or underestimation of aggressiveness. The sampling limitations are also present when

tumors are small or are impossible to reach despite advanced imaging guidance: sampling can still fail, or there can be inadequate sampling. In essence, the high intratumoral heterogeneity together with sampling limitations can result in interpretive errors and diagnostic uncertainty, which may explain the indications for repeat biopsy or multiple modality correlation in equivocal cases [108-110].

4.1.9. Clinical and Economic Implications

Clinical and Economic Considerations with none of the modalities have passed without cost or side effects. Though beneficial at the population level, mammography has also had several recalls and benign biopsies. In fact, false positive mammograms, and over diagnosed cancers (cancers which would never have become clinically meaningful) are estimated to poison health systems by the figure of tens of billions of dollars per year. Tomosynthesis barely improves accuracy but takes more radiation per exam. Breast ultrasound is inexpensive and widely used but its low specificity yields a lot of additional biopsies for benign conditions (e.g. using it as an adjunct to screening would lead to many more than we would get from supplemental computer mammography) and recent analysis has questioned the incremental cancer yield over that of supplemental computer mammography and its cost effectiveness. However, when the screening population is dense and high risk, MRI will find more cancers (at a high cost) and is generally considered cost effective only in subsets of very dense women (e.g., BRCA mutation carriers). In general, the presence of intense imaging workup leads to increased patient anxiety and HC cost owing to the additional tests. Finally, although advanced biomarker and genomic tests and new imaging technologies that are under development are expensive and not yet considered part of normal practice, this may vary from country to country [92,111].

The current diagnostic modalities (figure 4) are quite strong and have many limitations. Although mammography (with tomosynthesis) is ‘the workhorse’ of screening, it suffers in dense breasts and yields a high false positive rate. Ultrasound and MRI complement one another and while simple, add complexity if dependent on interpretation or (expensive) additional forms of interpretation or operator dependence. Definitive diagnosis requires tissue biopsy which is invasive and prone to sampling error. But there are some biomarkers that have been promising but not accurate enough for early detection yet. A number of these shortcomings indicate a need for more sensitive or specific molecular tests, advanced imaging (contrast, enhanced techniques, elastography), and integrated analytic tools (computer aided detection, AI, radiogenomics) for earlier and better characterization of breast cancer. The field can only hope to further reduce breast cancer mortality, minimizing harm, costs, only by combination of modalities and technological development.

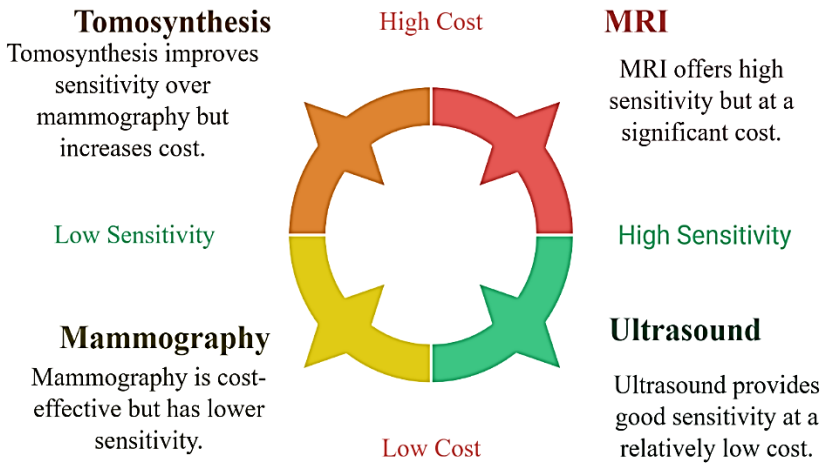

Figure 4. Breast cancer diagnostic modalities

4.2. Standard therapies in breast cancer

Triple-negative breast cancer (TNBC) patients need to receive chemotherapy as an additional treatment method. Patients with TNBC receive two or three-drug anthracycline-based treatment which is used before surgery during the neoadjuvant phase and after surgery in the adjuvant phase. Although chemotherapy comes with established acute and chronic side effects researchers continue to recognize its importance for disease control and stopping relapses. Patients receive TNBC treatment through different chemotherapy protocols using anthracyclines (e.g., doxorubicin, epirubicin) and taxanes (e.g., paclitaxel) as well as antimetabolites (e.g., capecitabine, gemcitabine) and vinca alkaloids (e.g., vinorelbine) as part of their treatment options. The treatment approach using immunotherapies delivered effective results for patients with HER2-positive and TNBC subtype tumors which contains high densities of tumor-infiltrating lymphocytes and elevated levels of programmed death-ligand 1 (PD-L1) molecules [112,113].

Research in immune-oncology and targeted therapy progresses yet the methods face barriers due to their elevated costs and major adverse effects. New therapeutic approaches have not overcome the resistance development that diminishes the effectiveness of current BC treatments [35,114]. Cancer cells face therapeutic pressure initially but tend to develop mechanisms that allow their survival resulting in disease progression towards more severe malignancies. Drug resistance develops from three major biological phenomena: drug efflux systems become elevated while detoxification enzymes become activated and anti-apoptotic pathways grow more effective. ABC transports including P-glycoprotein and multidrug resistance protein-1 are specific resistances together with breast cancer resistance protein (BCRP/ABCG2) that was first identified in drug-resistant breast cancer cells [115,116].

The establishment of therapeutic resistance depends heavily on breast cancer stem cells (BCSCs). The mechanism of asymmetric division enables BCSCs to create various tumor cell

types which leads to drug resistance and return of the disease. Sustained therapeutic stress becomes manageable by BCSCs through their primitive developmental state and powerful DNA repair systems which support survival and multiplication. BCSCs exist within specific niches where hypoxic and elevated reactive oxygen species conditions protect them from treatment effects including radiotherapy [117]. Dormant BCSCs stay in a quiescent G0/G1 phase that allows them to escape proliferative cell treatments until proper growth conditions trigger their activation. High activity of aldehyde dehydrogenase-1 (ALDH1) which indicates stem cell properties supports cancer cell resistance through early differentiation and improved survival levels. The drug efflux mechanism driven by ATP-binding transporters makes BCSCs share a similar drug-resistance feature with bulk tumor cells because it lowers drug concentration in cells below therapeutic levels. The Wnt/β-catenin together with NF-κB and Notch and Hedgehog and TGF-β and Hippo pathways receive activation in BCSCs which ultimately enhances drug resistance. Resistance toward breast cancer stem cells occurs when treating the disease with anthracyclines, aromatase inhibitors, estrogen receptor antagonists, anti-HER2 monoclonal antibodies and taxanes like paclitaxel which are commonly prescribed in breast cancer treatment [118,119].

Table 3. Quantum Dots products with their important parameters

QD Product	Properties	Target Biomarker	Cell Lines Used	Application Type	Outcome of Study	Critical Assessment
QD-Ab Conjugates (Anti-HER2, EGFR, mTOR)[120, 121]	Multicolor emission, High photostability, Water-soluble coating	HER2, EGFR, mTOR	Various breast cancer lines	Multiplexed cell labeling	Successful multiplexed labeling of membrane and nuclear biomarkers; quantitative fluorescence analysis possible	Pros: Simultaneous detection of multiple markers; stable signals; high sensitivity. Cons: Requires precise conjugation methods; potential cytotoxicity if QDs are not well-coated.
Near-Infrared (NIR)-emitting QDs conjugated with anti-HER2 antibody[122, 123]	NIR emission (deep tissue imaging), Biocompatible at 60 µg/mL, Stable	HER2	SK-BR-3 (HER2+), MCF7 (HER2-)	Targeted imaging, Toxicity testing	Effective targeting of HER2 receptors; low in vitro toxicity after 1 and 24 h exposure	Pros: Better tissue penetration due to NIR light; highly specific targeting. Cons: Production of NIR QDs is expensive; risk of long-term in vivo toxicity remains.
QD-IHC for Ki67 detection[47, 124]	High brightness, Reduced photobleaching, Improved quantification	Ki67 (proliferation marker)	108 HER2+ non-luminal breast cancer tissues	Immunohistochemistry, Prognostic marker detection	Higher inter-observer agreement (κ = 0.874); Strong correlation with conventional IHC (r = 0.993); Ki67 >30% associated with shorter disease-free survival	Pros: Better reproducibility and accuracy vs. traditional IHC; excellent prognostic value. Cons: Requires specialized imaging equipment; higher cost compared to conventional IHC.
QD-Aptamer conjugates for ATP detection[125, 126]	High specificity for target molecules, Multiplexed detection possible	ATP (not directly cancer marker but cellular energy indicator)	HepG2, SK-BR-3, MCF7	Molecular sensing, Biosensing	Specific and sensitive ATP detection using aptamer-conjugated QDs; NIR QDs tested for biocompatibility	Pros: Specific detection; customizable targeting. Cons: Limited direct application to tumor tissue diagnosis; aptamer stability needs to be controlled.

Various quantum dot (QD)-based formulations utilized in cancer diagnostics, particularly for breast cancer as summarize in Table 3. QD-antibody conjugates targeting biomarkers such as HER2, EGFR, and mTOR have demonstrated successful multiplexed imaging with high sensitivity and photostability, though they require precise conjugation to minimize cytotoxicity. Near-infrared (NIR) emitting QDs conjugated to anti-HER2 antibodies have shown effective tissue penetration and low in vitro toxicity, making them suitable for targeted imaging applications. QD-enhanced immunohistochemistry (QD-IHC) for Ki67 detection has improved diagnostic accuracy and prognostic evaluation by offering better reproducibility and stronger correlation with clinical outcomes compared to conventional IHC. Furthermore, QD-aptamer systems have enabled specific ATP detection, showcasing potential in biosensing applications, although their direct applicability in tumor tissue diagnostics remains limited due to aptamer stability concerns.

5. CHALLENGES OF QUANTUM DOTS

5.1. Toxicity Concerns

Numerous research groups face a vital concern regarding QD utilization primarily for in vivo use because of potential cytotoxicity. The biological system carries the risk of allowing heavy-metal-based traditional QDs (made from cadmium and lead) to free toxic ions. Heavy metal releases through these ions cause two main harm factors including oxidative stress effects and inflammation damage alongside cellular functional disruption. Research on QD safety shows that zinc sulfide shells or biocompatible molecules including polyethylene glycol (PEG), cysteine, and gelatin, help minimize risks, but experts still need more information about long-term safety aspects. Scientists work to establish safer quantum dot alternatives because carbon-based QDs, together with graphene QDs (GQDs) and silicon QDs demonstrate lower toxicity properties. Research must explore breast tissue interactions and total body effects of nanomaterials through advanced studies to understand their prolonged potential impacts [127,128].

5.2. Stability and Pharmacokinetic Limitations

QDs face problems operating within the complex biological environment because they need stable functioning and structural integrity. The degradation as well as nonspecific interactions between QDs and serum proteins in biological fluid will weaken fluorescence properties and affect targeting delivery and circulation duration. The unstable condition affects QD performance in imaging functions along with drug transportation abilities. Research directions today emphasize improving QD stability through biological surface treatments combined with biocompatible protective shelling techniques to enhance their body residency time and pharmacological activities [129,130].

5.3. Targeting Specificity

QDs must undergo highly selective ligand–QD linkage processes to enable them deliver treatment selectively to breast cancer cells that express the HER2 marker. The chemistry at QD surfaces produces secondary binding with various unintended molecules that reduces their capacity to specifically target their objective. The attachment procedures can unintentionally modify QD fluorometry and electronic characteristics leading to reduced performance in combined diagnostic therapy applications. A new advanced conjugation system is necessary to maintain quantum dot optical characteristics during binding operations with cancer-specific receptors such as HER2 [130,131].

5.4. Limited Clinical Translation

The extensive experimental research along with promising preclinical findings have failed to result in widespread clinical adoption of QDs. QD application received limited clinical trial registration during late 2024 because only several trials were started worldwide although some studies were later withdrawn. A restricted scope of clinical implementation reveals the substantial difference between laboratory-based progress and practical healthcare deployment. The lack of clinical progress in QDs stands as an obstacle because of regulatory requirements about toxins and manufacturing variability and continued effects monitoring. To enable the clinical application of QDs for breast cancer treatment it is essential to conduct comprehensive research as well as implement improved regulatory systems [130,132].

6. APPLICATIONS FOR QUANTUM DOTS

Quantum dots serve multiple purposes in medical applications including bio diagnostics, bioimaging, photodynamic therapy and targeted drug delivery. Targeted binding becomes possible when QDs receive receptor-specific ligand attachment. Folate molecules serve as receptor-specific targeting agents when attached to the QD surface. Folate–QD conjugates showed detectable presence in mouse lymphoma models after their incubation phase. The fluorescence intensity of these QDs enhanced specifically at locations showing high levels of folate receptors because of their specific binding properties to receptor-rich areas. Folate receptors overexpression in cancer cells enables their detection to identify malignancies because elevated folate receptor levels are specific to cancer cells [133,134].

QDs deliver enhanced photostability which extends imaging time beyond what conventional fluorescent dyes can achieve because dyes have stronger susceptibility to photobleaching. The detection capabilities of cadmium-based QDs stood for multiple days following intraocular injection through vivo imaging assessments. When researchers delivered QDs through subcutaneous injection into mice they detected most of the fluorescent signals in brain tissue. The maximum fluorescent signal occurred three days after the injection and lasted

until one week post-injection. The high-resolution imaging method identified the exact subcellular positions of these conjugates with precision. QDs showed the ability to enter different cell types thus establishing a new method for in-vivo neuroimaging studies. The application of QDs proves efficient in monitoring living cells and their detection operations [135,136].

Through QD-based methods researchers can undertake external visualization along with internal visualization of cells. Cell-mediated delivery systems along with surface alteration techniques optimize how imaging functions and cells absorb these methods. Scientific researchers have proven their ability to trace Quantum Dots inside human breast cancer cells. Scientists used QD-based anti-HER2 antibodies to detect nanoparticles as they moved through tumor blood vessels of mice in a particular study. Some QD conjugates received direct live monitoring that illustrated their activities from vascular flow to tissue escape to area navigation until they bound with HER2 receptors for cellular invasion. The implemented imaging methods give scientists profound understanding of how biomolecules move and how subcellular processes operate [137,138]. Science has utilized QDs to track metastatic cancer cells inside living organisms. Specific types of QDs received infusions with tumor-targeting antibodies before their entry into the body where they promoted targeted accumulation within tumor cells. Using QD-labeled tumor cells researchers conducted effective tracking experiments with multiphoton microscopy after the animals received these cells. The experimental methods achieved effective multicolor monitoring of biological processes inside living organisms [138].

The quantum dot technology serves as an important tool for conducting multiplex analysis of cancer cells while detecting biomarkers. According to Fatima et al. QD antibodies using anti-HER2 EGFR mTOR achieved cell line labeling within a single hour incubation period. Researchers used five QD types to place cancer biomarkers specifically on cellular membranes or cell nuclei. The study performed quantitative measurements by evaluating QD fluorescence intensity permitting the simultaneous detection of multiple biomarkers [54]. The combination of Förster Resonance Energy Transfer (FRET) with QDs requires efficient water-based biomolecule conjugation methods to perform biomolecular studies. The diagnostic method known as immunohistochemistry (IHC) has operated as a standard tool in cancer diagnosis throughout many decades yet remains restricted by its quantitative imprecision as well as its inability to undertake multicolor molecular profiling which leads to inconsistent assessment among observers [139]. Quantum Dots present better options for multiplexed fluorescent labeling because they demonstrate superior photostability as well as simultaneous excitation capabilities and separated emission spectra. The optical features of QDs combined with their ability to attach many biomolecules classify them as an optimal choice for modern biosensing applications and bioimaging procedures. Recent research has demonstrated the success of QD-aptamer conjugates as detectors for a specific molecule named adenosine triphosphate (ATP) [140].

Yao et al. investigated the toxicity effects of NIR-emitting QD-based molecules with HER2-specific monoclonal antibodies on three breast cancer cell types including HepG2 and HER2-positive SK-BR-3 and HER2-negative MCF7. At a concentration of 60 μg/mL these bioconjugates showed biocompatibility after one as well as twenty-four hours of exposure while efficiently targeting HER2 receptors [122]. Omidian et al. have used QD-based immunohistochemistry (QD-IHC) to detect Ki67 in breast cancer tissues through their research. Research data showed QD-IHC achieved strong agreement with regular IHC ($r = 0.993$) and enhanced inter-rater consistency ($\kappa = 0.874$) when scoring Ki67 at a 30% threshold in 108 samples of This turned out to be very important for diagnosing HER2-positive breast cancer. The patients with high Ki67 expression showed reduced disease-free survival outcomes specifically among those without lymph node involvement. Study findings supported QD-IHC as an improved method for Ki67 analysis thus strengthening its role as an individual risk marker for HER2-positive breast tumors [141].

Table 4. QDs used in breast cancer applications, with their limitations

Challenges	**Recommended Future Improvement**	**Potential Benefit**
Toxicity of heavy metal-based QDs (e.g., cadmium)[28, 47]	Develop and optimize heavy metal-free QDs (e.g., carbon QDs, silicon QDs, graphene QDs)	Safer for in vivo human applications; reduced regulatory barriers
Limited tissue penetration with visible QDs[142, 143]	Use and enhance NIR-II (1000–1700 nm range) emitting QDs	Deeper tissue imaging, clearer tumor localization in live tissues
Inefficient targeting due to nonspecific binding[125, 144]	Improve surface functionalization with highly specific antibodies, aptamers, or peptides	Increased targeting precision; lower background signals
Batch-to-batch variability in QD synthesis[125, 144]	Standardize QD production protocols under GMP (Good Manufacturing Practices)	Reliable, reproducible QDs for clinical trials and diagnostics
High cost of QD production and conjugation[125, 144]	Develop cost-effective, scalable production methods (e.g., green synthesis)	Make QD-based diagnostics affordable and accessible
Photobleaching over long periods (though much less than dyes)[145, 146]	Engineering of ultrastable QDs with protective shells (e.g., thick ZnS or SiO2 shells)	Enable long-term imaging sessions without loss of signal
Complex imaging system requirements (QD-IHC vs. conventional IHC)[147, 148]	Design user-friendly QD-imaging platforms compatible with standard pathology labs	Easier adoption of QD-based techniques in hospitals and clinics
Multiplexing still limited to 5–6 colors[149]	Innovate multi-spectral imaging techniques that can decode more than 10–15 colors simultaneously	More comprehensive tumor profiling in a single assay

Various quantum dots (QDs) are employed in breast cancer research, highlighting their applications in imaging, targeted drug delivery, and biosensing. Despite their high photostability and tunable emission properties, many QDs face limitations such as cytotoxicity due to heavy metal content, challenges in biocompatibility, and potential long-term toxicity. Surface modification and encapsulation techniques have been explored to address these

concerns, but clinical translation remains limited. Table 4 emphasizes the trade-off between diagnostic sensitivity and biological safety. Thus, further research is needed to develop safer and more efficient QDs for clinical breast cancer management.

6.1. Electrochemical aspect of QDs in diagnosis of breast cancer

Electrochemical biosensors and especially biosensors incorporating nanomaterials, like quantum discounts (QDs) are also becoming a volatile breast cancer diagnostic tool. The world market of electrochemical biosensors is expected to achieve USD 24 million, and the estimated compound annual growth rate (CAGR) is 9.7%. Their application in clinical point-of-care (POC) testing is growing by leaps and bounds, and it is estimated that eventually the market will be worth USD 33 billion. Electrochemical biosensors based on QDs are characterized by high sensitivity and specificity due to the special optoelectronic properties of QDs that depend on both factors, primarily the size-tunable fluorescence of QDs, high surface-to-volume ratio, and the good electron transfer ability. Such properties can be used to accurately identify breast cancer biomarkers, such as circulating tumor cells (CTCs), genomic, and proteins (such as HER2, CA 15-3, and BRCA1/2) [150]. Notably, QDs enhance the enhancement of signals on the electrochemical sensory bracket, leading to the drastic reduction of the detection limit and consequent ability to diagnose the disease by use of early-stage recognition. However, the future possibility of electrochemical glucose-sensing using QDs and nanotechnology is tremendous and hence seems to be a great potential to transform the idea of low cost, highly sensitive disposable biosensors at a larger related clinical use. Moreover, the flexibility of QD-based electrochemical biosensors may further expand them to other fields such as infectious disease surveillance and biowarfare agent identification where their use opens a new horizon both in their design and in clinical application.

At the International Cancer Institute, biomarkers are described as measurable molecules that are present in the tissues, blood or other body fluids, and reflect physiological processes, whether normal or abnormal such as cancer [47, 53]. Biomarkers in the context of breast cancer are usually released or created by tumor cells and any strange change in concentration can be an indication of malignant activity. Biomarkers of breast cancer have diagnostic and clinical relevance due to a high level of specificity and sensitivity, which allows detecting early-stage disease, monitoring its progression, determining the effectiveness of treatment, and predicting its outcome. They are essential devices in cancer that are used to differentiate between benign and malignant diseases as well as to personalize treatment approaches. Two broad types of biomarkers of breast cancer include proteomic and genetic. Proteomic markers of breast cancer comprise RS/DJ-1, HSP60, HSP90, mucin-1 (MUC1) and carbo hydrate antigens as CA 15-3 and CA 27-29, which are excessively expressed in the breast cancer tissue and are applied to monitor the disease. Genetic biomarkers include BRCA1, BRCA2 tumor suppressor genes, whose mutations have been found to be strongly linked to hereditary breast and ovarian cancer

and p53 that controls the cell cycle and apoptosis, and also microRNAs (miRNAs),which work after transcribing the genes to regulate them and are being increasingly perceived as useful molecular markers. The estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) are some of the vital biomarkers that have been used in clinic practice. These receptors are regularly tested in terms of cancer classification and planning its treatment. ER is an estrogen bindable nuclear receptor that modulates gene expression associated with cell proliferation. It means that it is likely to respond well to such hormone treatment as tamoxifen, and the ER-positive tumors are usually less aggressive and slow [151].

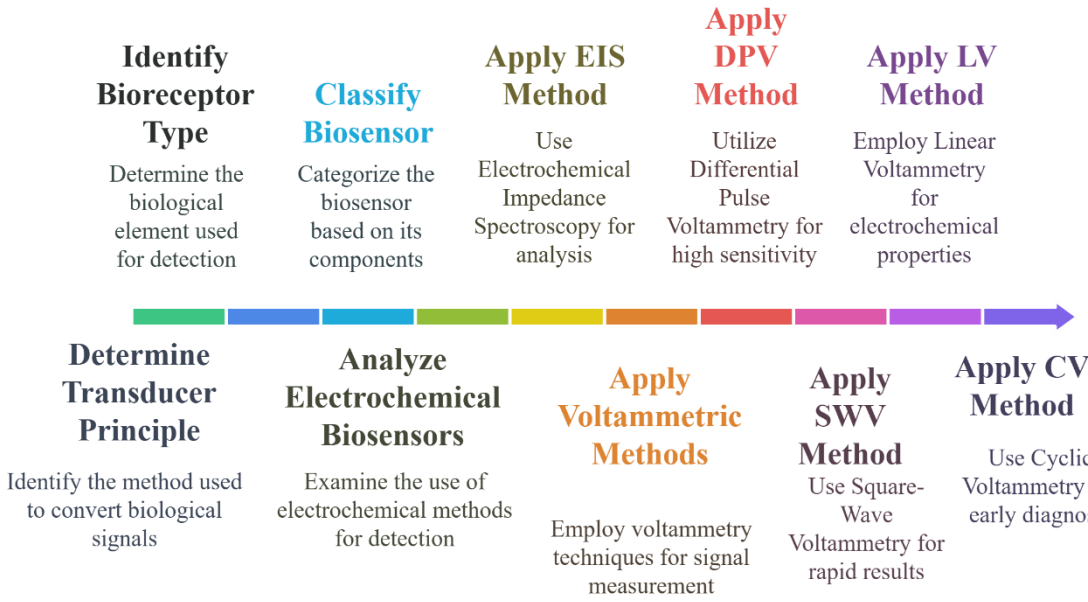

Figure 5. Classification and analysis of biosensors

The presence of PR which frequently accompanies ER itself is an indicator of the active estrogen signaling. PR levels tend to be high in the context of ER positivity, which is related to better outcomes, but it may be necessary to perform additional testing because of the discrepancies between PR and ER status. HER2 receptor that plays a role in growth and division of cells is overexpressed in 15-20% of breast cancer and is associated with aggressive tumours. Chemical positives of HER2 tend to react well to targeted sterilization treatments like trastuzumab which is good news. Triple-negative breast cancer (TNBC), which comprises 15-20 percent of all cases, is a specific subtype of breast cancer in which ER, PR and HER2 are not expressed. TNBC is characterized as a disease with an aggressive clinical course, poor prognosis, and a narrow therapeutic window and chemotherapy is its major treatment method. Newer research includes exploring new targets of TNBC which includes the vascular endothelial growth factor (VEGF) which helps in encouraging angiogenesis of tumors, and the

androgen receptor (AR). High VEGF is related to higher metastatic potential. Besides these classical biomarkers, recent implications have drifted towards circulating tumor cells (CTCs), circulating nucleic acids, and new protein markers [58]. CA 15-3 antigen specifically is employed in the monitoring of breast cancer and not in early detection. In healthy patients, the level of CA 15-3 is usually below 30 U/mL, but higher rates (mostly over 100 U/mL) can suggest the advanced status of the disease, the reoccurrence of the disease, or the metastases. An increase of CA 15-3 is seen in about 30 50 percent of patients with breast cancer when this disease is active. Additionally, the BRCA 1 and BRCA 2 genes are mutated and thus have been the most known family related markers since they are closely linked to familial breast cancer affliction. They lead to genomic instability and uncontrolled cell division in their loss of functions and as such they play a relevant part in early diagnosis, risk evaluation, and prevention efforts [152,153].

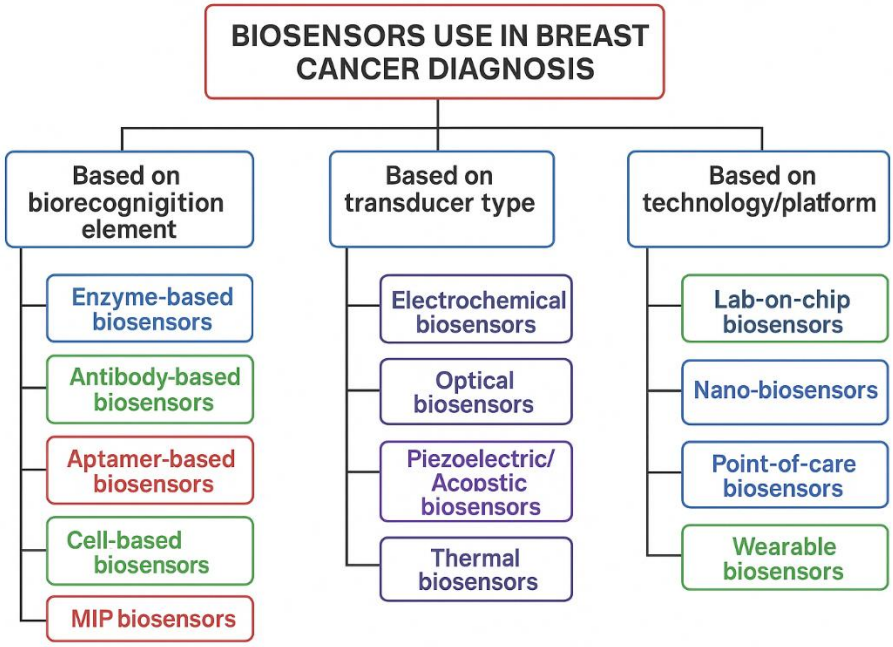

Figure 6. Classification of Biosensors used in BC diagnosis

Figure 5 presents a systematic workflow for analyzing electrochemical biosensors, starting from identifying the bioreceptor type and transducer principle to applying specific electrochemical methods such as EIS, DPV, LV, SWV, and CV for precise detection and characterization of biological signals (Figure 5). This stepwise approach ensures high sensitivity and specificity in diagnostics. Figure 6 categorizes biosensors based on biorecognition element (e.g., enzyme-, antibody-, aptamer-, cell-based, and MIP biosensors), transducer type (electrochemical, optical, piezoelectric/acoustic, thermal), and technology/platform (lab-on-chip, nano-, point-of-care, and wearable biosensors) (Figure 6). Together, these classifications highlight the diversity of biosensor designs tailored for effective

breast cancer screening, enabling clinicians to select appropriate diagnostic platforms based on application needs [154].

6.2. Future perspective of Quantum dots in breast cancer

Quantum dots (QDs) hold significant promise for the future of breast cancer diagnosis and therapy due to their exceptional optical properties, including high brightness, resistance to photobleaching, and tunable emission spectra. In the coming years, QDs are expected to play a pivotal role in the development of multiplexed imaging systems that can detect multiple tumor markers simultaneously with high sensitivity and spatial resolution. This would allow for earlier and more accurate detection of breast cancer subtypes, even at the molecular level, potentially improving personalized treatment planning. Additionally, advancements in QD-based biosensors may lead to minimally invasive diagnostic methods such as liquid biopsies, offering real-time monitoring of tumor progression and therapeutic response [47]. On the therapeutic front, the integration of QDs with nanocarriers and targeting ligands offers a platform for image-guided drug delivery and theranostics. Researchers are working on engineering biocompatible and biodegradable QDs to overcome toxicity concerns that currently limit clinical applications. Moreover, hybrid QDs incorporating organic coatings or natural polymers may enhance safety profiles and enable targeted therapy with controlled drug release, especially for aggressive or drug-resistant breast cancer types. Future directions also include QDs' potential in photodynamic therapy (PDT) and photothermal therapy (PTT), where they could be used both to locate and eradicate cancer cells selectively [129,141]. With continued interdisciplinary research and regulatory advancements, QDs could revolutionize both diagnosis and treatment strategies in breast oncology.

The biomedicine field increasingly uses Quantum dots (QDs) as versatile nanomaterials because of their strong optical properties and photostable nature along with their multi-functionality. These nanomaterials generate strong and adjustable fluorescence signals which enable their use in nucleic acid detection and cancer cell imaging and targeted pharmaceutical transport systems. Scientists have established multiple chemical methods which enable attaching antibodies to QD surfaces thus improving tumor cell recognition specificity and efficiency. High priority issues associated with traditional QD cores based on heavy metals (such as cadmium) include their potential toxicity to cells and difficulties managing particle aggregation and both small particle size and broad pharmacokinetic variability. Multiple QD variations have been studied for breast cancer uses because they exhibit different functional and structural features. Strong luminescence properties of CdSe/ZnS QDs (among other cadmium-based QDs) make them the most explored nanocrystals yet researchers develop non-toxic alternatives to address their toxicity concerns. The biocompatible properties and functionalization features of Carbon QDs (CQDs) and graphene QDs (GQDs) make them appropriate for biosensing applications as well as bioimaging functions. The properties of

silicon QDs encompass both excellent safety features and easy biodegradability capability. Indium phosphide (InP) QDs represent current advancements in nanotechnology by offering safe alternatives to cadmium-based QDs which maintain optical efficiency capabilities. The development of safer QDs remains a primary research objective because recent investigations seek biocompatible and easily degradable semiconductor nanocrystals. Researchers optimize surface engineering methods to achieve three vital goals which include stability enhancement combined with reduced nonspecific interactions and improved drug conjugation efficiencies. Sustained research on QD formulations targets the development of safe delivery approaches which retain optical properties at high levels. The clinical application of QDs in breast cancer diagnostic procedures requires resolving toxicological and delivery problems to achieve successful integration.

7. CONCLUSION

Quantum dots (QDs) represent a transformative class of nanomaterials in breast cancer research due to their high quantum yield, tunable fluorescence, and multiplexing capability. Advanced QDs such as InP, carbon, silicon, and graphene-based variants are now being engineered to overcome the limitations of cadmium-containing cores, particularly cytotoxicity and instability. Surface functionalization strategies, including ligand exchange and polymeric coatings, have significantly enhanced their biocompatibility, pharmacokinetics, and target specificity. The integration of QDs into multimodal platforms enables real-time tumor imaging, biosensing, and targeted drug delivery with precision. As QD technology advances, clinical translation hinges on addressing toxicity, optimizing biodistribution, and scaling reproducible synthesis. With continued progress in nanomaterial science, QDs hold strong potential for precise, non-invasive diagnosis and personalized therapy in breast oncology.

Declarations of interest

The authors declare no conflict of interest in this reported work.

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