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Nanomaterials for Breast Cancer

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Abstract: Breast cancer represents 16% of all malignant tumors diagnosed and is the leading cause of mortality in women worldwide. While significant advances in the diagnosis and treatment of breast cancer have been made over the years, the management of advanced stages of the disease and treatment-related adverse events continue to be a challenge. There is a need to develop tools for target-specific delivery of drugs to improve efficiency and decrease non-specific drug-induced toxicity. The field of nanotechnology has undergone a rapid revolution and nanostructures of carbon have produced some promising results in the treatment of breast cancer, at least in experimental settings. This chapter provides an overview of the emerging role of carbon nanomaterials for the treatment of breast cancer with emphasis on graphene, fullerenes, carbon nanotubes, nano diamonds, and carbon dots. The promises and challenges are also discussed.

Keywords: carbon nanostructures; graphene in breast cancer; fullerenes in breast cancer; nanodiamonds; nanomaterials for breast cancer

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INTRODUCTION

Breast cancer is the most common cancer type diagnosed in women and is the primary cause of mortality due to cancer in women around the world (1). According to GLOBOCAN 2018, more than 2.05 million new cases were diagnosed, and incidence is expected to increase by more than 46% by 2040 (2). The type and severity of breast cancer depends on the cell of origin. The breast is made up of three main parts: connective tissue, lobules, and ducts. Most breast cancers start in the lobes and the ducts (Figure 1). Based on its molecular subtypes, breast cancer can be categorized as luminal A, luminal B, human epidermal growth factor receptor 2 (HER2) type, and estrogen (ER)/progesterone receptor (PR)-positive (3). Among these categories, the ER/PR positive subtypes contribute approximately 70% of all reported cases (4). On the other hand, 20% of the reported cases are associated with triple-negative breast cancer (TNBC), a specific subtype of breast cancer that does not express estrogen receptor (ER), progesterone receptor (PR) or human epidermal growth factor receptor 2 (HER-2), making this class not sensitive to endocrine therapy or HER2 treatment (5). TNBC shows specific clinical features that include high invasiveness, high metastatic potential, proneness to relapse, and poor prognosis. Approximately 46% of TNBC patients will have distant metastasis at the time of diagnosis (6).

The list of drugs used in the clinic to treat breast cancer is extensive and includes tamoxifen, paclitaxel, doxorubicin, and epirubicin, among several others. The side effects caused by the direct application of these drugs include neutropenia, lymphedema, hair loss, nausea and vomiting, trouble thinking, pain, blood clots (deep vein thrombosis) and others. These effects also occur when therapy involves radiation, which is a cancer treatment that uses high doses of radiation to kill cancer cells and shrink tumors (7). Some open questions for investigation are: How to correct side effects? How to deliver drugs directly to the cancer cell? How to know if the drug is in the right place? Nanotechnology offers a possibility to address these questions. Now, we can design and manufacture various types of nanoparticles, including metallic or their oxides, as well as nanocomposites that

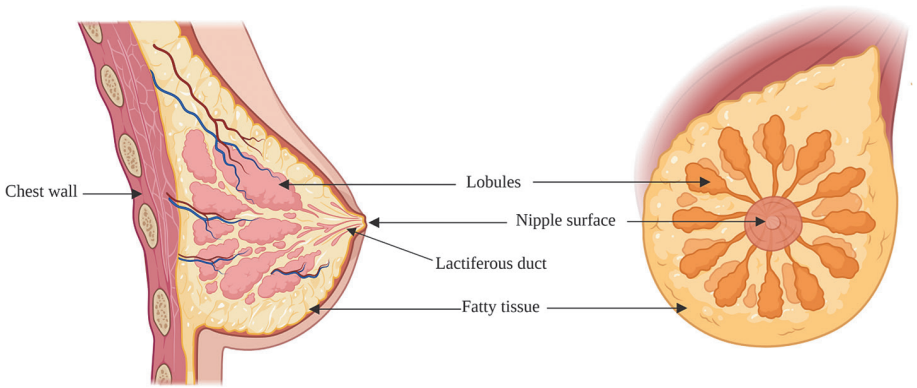

Figure 1. Breast anatomy. The main parts of the breast are indicated. This figure was created by using BioRender.com

can deliver drugs to a specific target place. In the case of cancer, part of its diagnosis and treatment has been done by using gold nanoparticles, silica nanoparticles coated with gold, nanopolymers that carry the drug and/or carbon nanostructures showing easy penetration into the cell due to their hydrophobicity (8). This chapter provides an overview of the emerging role of carbon nanomaterials for the treatment and diagnosis of breast cancer.

CARBON NANOSTRUCTURES

Since the discovery of fullerene C_{60} (9), carbon-derived nanostructures have become one of the most prominent research areas, and most of these studies have focused on C_{60} and carbon nanotubes. Their ability to present in different allotropic forms has led to a great diversity of nanostructures with fascinating geometries and properties (10). This includes nanostructures such as fullerenes, graphenes, carbon nanotubes, nanodiamonds, and nano-onions, all of which are allotropes of carbon (Figure 2). *Fullerenes* are carbon molecules that can take different geometric shapes such as sphere, ellipsoid, tube, or ring. *Graphene* is a structure with atoms arranged in a regular hexagonal pattern. *Carbon nanotubes* are cylindrical structures that can be single-walled or multi-walled. *Nanodiamonds* are nanostructures that have the crystalline phase of diamond. And finally, *nano-onions* have a multilayer graphene structure. In principle, all of these nano compounds can undergo modifications in their structure through acid attacks mainly, which allows the generation of carboxyl or hydroxyl radicals that facilitate their functionalization with different molecules through different types of bonds.

The properties of nanostructures are characterized using various techniques including X-ray photoelectron spectroscopy (XPS used to determine the type of bonds), X-ray diffraction (XRD to determine crystallinity), TEM and SEM (to determine size and agglomeration level), and FT-IR and RAMAN (to find functional groups). The functionalization of a carbon nanostructure involves several synthesis steps. It must include a recognition entity such as a monoclonal antibody or another molecule that recognizes a site expressing a signal to which it can bind to (Figure 3), a molecule that can be detected by a specific wavelength, and finally, the specific drug for the type of cancer (e.g., breast cancer). Recent studies indicate that early detection and targeted therapy can help decrease deaths due to breast cancer, representing a way in which carbon nanostructures can be applied (11). Next, we cite carbon nanostructures and their uses against breast cancer.

Figure 2. Carbon nanostructures. Examples of carbon nanostructures and their differences. This figure was created by using BioRender.com

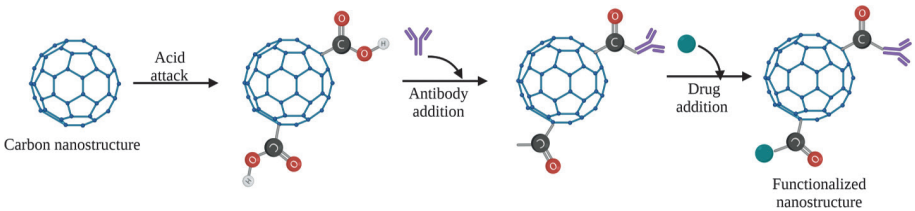

Figure 3. Functionalization of carbon nanostructures. Example of the functionalization of carbon nanostructure adding an antibody and a drug. First, carbon nanostructure suffers an acid attack to carboxylate the structure, after that, antibodies are added in some carboxile groups to recognize the target cells, and finally, the drug is added to functionalize the nanostructure. This figure was created by using BioRender.com

Graphene in breast cancer

A bioactive multifunctional CePO4/CS/GO scaffold—formed by the combination of graphene oxide (GO) nanoparticles, $CePO_4$ nanobars and bioactive chitosan (CS)—shows characteristics of photothermal therapy in killing tumors, generating macrophage polarization, promoting blood vessels formation, and induction of bone formation. This scaffold may become a promising platform for the treatment of breast cancer bone metastases by destroying residual bone tumor cells after photothermal therapy and subsequent healing of the bone defects (12). Similarly, graphene oxide (GO) nanocomposites, loaded with superparamagnetic iron oxide nanoparticles spliced with polyethylene glycol (PEG) and grafted with methotrexate and stimulus-sensitive linkers (GO-SPION-MTX), have been developed for photothermal and chemotherapy of breast cancer. GO-SPION-MTX nanocomposites are internalized by folate receptor-positive cancer cells and induce high cytotoxicity when exposed to near infrared (NIR) lasers (13). Table 1 summarizes some of the key studies on the use of graphene in breast cancer.

Stimulus-sensitive polyelectrolyte nanoparticles have been developed for the chemo-photothermal destruction of breast cancer cells. This novel system, called layer by layer (LBL) Lipo-graph, is composed of alternating layers of graphene oxide (GO) and poly (L-lysine) conjugated to graphene oxide (GO-PLL) deposited on cationic liposomes that encapsulate doxorubicin. Toxicity tests showed that LBL Lipo-graph can effectively kill MD-MB-231 cells after NIR irradiation. The presence of GO-PLL in the outer layer of LBL Lipo-graph can increase cell uptake and can also increase drug accumulation within cells (23). In a study reported in 2021 (24), graphene oxide nanoparticles (HA-GO-Met) loaded with metformin grafted with hyaluronic acid (HA) exhibited anticancer efficacy at much lower doses compared to metformin alone. HA-GO-Met nanoparticles induced apoptosis and inhibited cell migration of triple negative breast cancer cells by targeting the miR-10b/PTEN axis through NFκB-p65. Treatment with HA-GO-Met nanoparticles reduced tumor burden and abolished tumor-borne toxicity in peripheral organs, exhibiting anticancer efficacy in TNBC cells both in vivo and in vitro as well.

Complexes that include photoluminescent graphene quantum dots with glucosamine as a targeting agent, and with curcumin as an anticancer agent, have been proven to inhibit cells of the MCF-7 breast cancer line, a result that sounds

TABLE 1 **Graphene in breast cancer. Some of the main studies in that used graphene in breast cancer are listed**

Nanostructure	Cell line / Experimental model	Parameters and outcome	Reference
Graphene oxide functionalized with curcumin	MDA-MB-231 and SKBR3 cell lines	Slight cytotoxic effects (15–25% cell destruction) at 100 μg/mL	(14)
Gold nanoparticles-modified graphene oxide	Electrochemical methods	The electrochemical signal enhancement achieved via gold nanoparticles and graphene oxide system allowed for sensitive detection of the breast cancer biomarker ERBB2 and the control marker CD24.	(15)
Graphene quantum dot (GQD)-based nanocarrier labeled with Herceptin (monoclonal antibody trastuzumab) (HER) and β-cyclodextrin (β-CD) conjugated with Doxorubicin	Cellular cancer cells BT-474 and MCF-7 and BT-474	The combination of HER and DOX promoted the anticancer activity of DL-GQD.	(16)
POxylated graphene oxide conjugated with DOX and D-α-Tocopherol succinate (TOS) drug combination	Cancer cells MCF-7	A stronger therapeutic effect than that attained using the free drug combination.	(17)
Graphene-Nanoparticle-Based Self-Healing Hydrogel	Cancer cells 3T3	Enhanced cell killing efficiency with synergistic chemo-photothermal therapy.	(18)
Graphene-Coated Optical Fiber SPR Biosensor	Technique of the attenuated total reflection (ATR) method to detect deoxyribonucleic acid (DNA) hybridization along with individual point mutations in BRCA1 and BRCA2 genes.	The proposed hybrid SPR biosensor enhanced sensitivity to detect mutations	(19)
Graphene oxide (GO) and graphene quantum dots (GQDs) with curcumin (Cur)	MCF-7 and MDA-MB-468	The 1:1, 1:3, and 1:5 ratios of the complexes (GO:Cur or GQDs:Cur) enforced cell death ~60, ~80, and ~95% at 100 μg/mL after 48 h of treatment.	(20)
CePO4/CS/GO scaffold	Cancer cells MC3T3-E1, RAW264.7, MDA-MB-231 and hBMSCs	CePO4/CS/GO scaffold kills residual bone tumor cells after photothermal therapy and subsequent bone defect healing, for therapy of breast cancer bone metastases.	(12)
Graphene oxide (GO)/cobalt ferrite nanoparticles	Cancer cells MCF-7 and BALB/c mice	The cell viability decreased to 30% and the tumor cytoskeleton was ruined specially by the nanoparticle concentration of 0.002 gr/ml at the frequency of 250 and 350 kHz.	(21)
GO-based nanocomposites with EDTA	Cancer cells MCF-7	Increase of apoptosis percentage in 30.12%	(22)

promising due to the observed behavior pH-sensitive, sustained release for nano-assembly (25). Graphitic carbon nitride (g-C3N4) Quantum Dots synthesized through the usual calcination method served as nanoplatforms for dual two-photon excited photodynamic therapy (TPE-PDT) and two-photon imaging (TPI) (26). In a recent review, it has been discussed that the combination of carbon nanomaterials, including carbon nanotubes, fullerenes, graphene and nanodiamonds, in combination with nuclear medicine isotopes, can be useful for the diagnosis of various types of cancer including breast cancer (27). In contrast, in a study aimed at following the targeting of doxorubicin conjugated with gold-doped mesoporous silica nanoparticles and graphene quantum dots, it was observed that cell viability was lower when doxorubicin alone was used. (28).

Fullerenes in breast cancer

Molecular coupling studies have shown that letrozole, a drug commonly used for the treatment of breast cancer, has greater biological activity and improvement when forming a self-assembly with sheets of graphene and fullerenes compared to the single molecule (29). Studies indicate that targeted hyperthermia has a high potential to become a cancer treatment modality, although it must be precisely controlled to avoid damaging adjacent healthy tissues. The use of an array consisting of emitters of quantum dots arranged in a buckyball shape demonstrated that it is possible to control super-radiance using an external electric field, which indicates that the use of a series of super-radiant pulses can improve breast cancer hyperthermia by minimizing damage to adjacent healthy tissues (30). Table 2 presents some of the most recent studies of fullerenes used for the diagnosis and treatment of breast cancer.

TABLE 2 **Fullerenes in breast cancer**

Nanostructure	Cell line / Experimental model	Parameters and outcome	Reference
Fullerene-Docetaxel conjugate	Cancer cells MCF-7 and MDA-MB23	Enhanced the bioavailability of docetaxel by 4.2 times and decreased the drug clearance by 50%.	(31)
Glycine-tethered C60-fullerenes conjugated with *N*-desmethyl tamoxifen	Cancer cells MCF-7	Availability of tamoxifen in a biological system for prolonged duration.	(32)
Fullerene-Doxorubicin conjugate	Biophysical methods	Release of DOX from fullerene at different pHs. At pH 5.25, all DOX had been released and 43 % at pH 7.5.	(33)
Fullerene C_{60}	DMBA-induced breast cancer in rats	Fullerene C_{60} decreases MDA level, increases GSH level and Catalase activity and thus it protects breast tissue against cancer.	(34)

Carbon nanotubes

Breast cancer causes metabolic disturbances and thus, volatile metabolites in the breath of patients can be used to diagnose the disease. Yang et al., developed an electronic nose composed of carbon nanotube sensors resulting in 86% sensitivity and 97% specificity, while the area under the receiver operating curve was 0.99. These electronic nose breath tests can be applied intraoperatively to discriminate breast cancer and/or identify molecular subtypes, helping medical staff choose the best treatment decision (35).

Oxidized graphene nanoribbons, decorated with folic acid and loaded with a selective estrogen receptor modulator (tamoxifen citrate), were prepared from multi-walled carbon nanotubes, the results showed a drug loading efficiency of 56%, concentration and time-dependent apoptosis, and a preferential cellular internalization, which might represent a promising platform for the efficient and selective delivery of tamoxifen to breast cancer cells (36).

Similarly, Adabi et al. designed and developed an electrochemical immunosensor, based on an electrospun carbon nanofiber mat, for the detection of Her-2. The sensor was modified with Au nanoparticles, cysteamine molecules, carbon nanotubes, and specific antibodies. The results indicated that the designed immunosensor has a high potential for the determination of Her-2 given its non-invasive, precise, and fast analysis (37).

Dopamine and mucin-1 functionalized electroactive carbon nanotubes have also been synthesized as signal generating probes for the construction of electrochemical immunosensors for the early diagnosis of breast cancer. The developed immunosensor permitted the detection of MUC-1 in the linear range of 0.05-940 U/mL, with a detection limit of 0.01 U/mL (38). Table 3 shows some of the most recent studies of carbon nanotubes used for the diagnosis and treatment of breast cancer.

Nanodiamonds

Nanodiamonds are one of the most promising carbon nanostructures in biomedicine due to their unique properties: they are biocompatible, have low toxicity, are mechanically and chemically stable, show stable photoluminescence, and have a multifunctional and easily modifiable surface, among others (46). Hyperthermia is one of the methods to attack malignant tumors (47). Therefore, a group of researchers synthesized nanodiamonds using high pressure and temperature, doped them with boron and tested them on MCF7 cells. These nanostructures were proven to be more efficient than nanodiamonds obtained by detonation due to their significant capacity to absorb infrared light, which hold promise for their use in hyperthermia and thermoablation of tumors. (48). In other studies, drugs such as melittin, the main component of bee venom, have been tested. When administered alone, melittin's toxic effects on cancer cells were lower than when administered using a carbon nanostructure (49). Polyglycerol-coated nanodiamonds-conjugated doxorubicin were pH-sensitive to hydrazone bonding. When the complex was compared to DOX in free form, the complex induced endoplasmic reticulum stress without substantial DNA damage, while DOX caused massive damage in DNA, as well as stress in endoplasmic reticulum (50). Table 4 summarizes some of the latest reports on the use of NDs in the treatment and diagnosis of breast cancer.

TABLE 3 Carbon nanotubes in breast cancer

Nanostructure	Cell line / Experimental model	Parameters and outcome	Reference
SWCNTs and MWCNTs	Cancer cells MC4L2 and mice	CNTs decreased the tumor volume. BCL2 gene was down-regulated, and BAX and Caspase-3 were up-regulated in the treated groups with CNTs.	(39)
Cisplatin Loaded Multiwalled Carbon Nanotubes	Cancer cells MDA-MB-231	Significant decrease of caspase-3 and p53 expression after 48 h, accompanied by a down-regulation of NF-κB in cells exposed to MWCNT-COOH-CDDP	(40)
Hyaluronic acid (HA)-modified amino single-walled carbon nanotubes (NH2-SWCNTs) conjugated with Doxorubicin (DOX)	Cancer cells MDA-MB-231	Inhibiting proliferation and inducing apoptosis of cells.	(41)
Glycopolymer decorated multiwalled carbon nanotubes conjugated with Doxorubicin (DOX)	Cancer cells MCF-7 and MDA-MB-231	The glycopolymers improve transportation of Dox into the cells, causing boosted effects of the chemotherapeutic drug.	(42)
MWCNTs) functionalized using Hyaluronic acid (HA) and α-Tocopheryl succinate (α-TOS) and loaded with Doxorubicin (Dox) (α-TOS-HA-MWCNTs/Dox conjugate)	Cancer cells MDA-MB-231	Growth inhibition effect and high total apoptotic ratio in the MDA-MB-231 cells treated using α-TOS-HA-MWCNTs/Dox as compared to other formulations	(43)
Novel-formulated platinum nanoparticles (Pt-NPs) supported on polybenzimidazole (PBI)-functionalized MWCNT (MWCNT/PBI/Pt-NPs)	Cancer stem cells (CSCs)	Decrease in the proliferation rate of CSCs but not bone marrow mesenchymal stem cells	(44)
Carbon nanotubes (CNT)-loaded ginsenosides Rb3	Cancer cells MDA-MB-231 and BT-549	Rb3 suppresses the PD-1/PD-L1 pathway in triple-negative breast cancer	(45)

TABLE 4 Nanodiamonds in breast cancer

Nanostructure	Cell line / Experimental model	Parameters and outcome	Reference
Nanodiamond-based layer-by-layer nanohybrids	TNBC cells and xenograft TNBC tumors	Delivery of miR-34a remarkably suppressed cell proliferation, migration and induced the apoptosis of TNBC cells *in vitro* and inhibited tumor growth *in vivo via* down-regulating *Fra-1* expression	(51)
Paclitaxel- and cetuximab-conjugated nanodiamond nanocomposite	Cancer cells MDA-MB-231, MCF-7 and BT474	Enhanced mitotic catastrophe and apoptosis by targeting EGFR of TNBC cells	(52)
NDs conjugated with immunoglobulin G (IgG–gFND)	Breast cancer/natural killer/monocyte co-culture system and breast cancer mouse model.	*In vitro* studies demonstrated the targeted immune cell uptake of IgG–gFND, resulting in significant immune cell activation and no compromise in immune cell viability. IgG–gFND remained at the tumor site following intratumoral injection compared to uFND which migrated to the liver and kidneys	(53)
NDs functionalized with benzoquinone	Cancer cells MDA-MB-231 and MCF-7	Induction of cell death	(54)

Carbon dots

Carbon dots (CDs) are an emerging subset of nanomaterials, defined by characteristic sizes of <10 nm. CDs possess a carbon core that is functionalized by various groups at the surface (55). These materials possess physicochemical properties, such as photo-induced electron transfer and photoluminescence, high biocompatibility, and low toxicity, making them potential materials for biosensing, drug delivery and bioimaging, making them useful for the diagnosis and treatment of breast cancer (56).

For the treatment of breast cancer, CDs were synthesized and functionalized with doxorubicin (CDs-DOX), finding that, compared to free doxorubicin, the CDs-DOX complex had a higher cellular uptake and better anti-tumor efficacy on MCF-7 cells (57). Recently, the development of N-hydroxyphthalimide-derived carbon dots doped with gadolinium, Fe3+ and Mn2+ was reported. Normal and cancerous cell lines were treated with doped carbon dots, and cell viability was measured, obtaining that Mn2+ doped Carbon Dots (Mn-CDs-NHF) presented antitumor properties,

without affecting the cell viability of normal cells, and reduce the volume of primary mammary tumors while allowing magnetic resonance imaging. Suggesting that they can be used as theranostic agents in preclinical models (58).

The use of biomarkers for the diagnosis of breast cancer is of great significance, among them is microRNA-21, whose expression is increased and is a biomarker for early-stage breast cancer detection. Recently, a 3D hydrogel based on carbon dots and chitosan was fabricated for sensitive quantification of micRNA-21 in MCF-7 cancer cells. The DNA hydrogel bioassay strategy revealed a great stability and a superb sensitivity for microRNA-21, with a suitable linear range (0.1–125 fM) and a detection limit (0.03 fM). Thus, it is suggested that nanocomposite hydrogels can be used for multicolor imaging of MCF-7 cancer cells (59).

Carbon dots have a tissue penetration that varies according to their luminescence and are ideal for imaging. However, their drawback is that they degrade in the body before reaching the target cells. Xu et al. (60) recently reported a study combining carbon dots with mesoporous organosilica nanocapsules (MON-CDs) and found that after 1 h of incubation in breast cancer cells, the nanoparticles were found close to the cell membrane and after 2 h the nanoparticles were mainly distributed in the cytoplasm, suggesting that MON-CDs possess near-infrared luminescence and have good imaging capabilities in confocal microscopy and photoacoustic imaging. In another study, a novel dual-element sensor array based on two CDs was constructed. Interestingly, the sensor array distinguished cancer patients (liver and breast cancers) from healthy people and discriminated and quantified amyloidogenic proteins with high accuracy demonstrating its potential for rapid cancer detection on a large scale (61). All these studies indicate that CDs have potential use in the treatment and diagnosis of breast cancer.

FUTURE PERSPECTIVES

The most recent advances in the use of carbon nanostructures as vehicles to deliver drugs specifically to cancerous tumors, offers the possibility to minimize damage to healthy cells or reduce the side effects that affect the patient, can be a very useful tool for this purpose. We have learned to generate modifications on the surface of such nanostructures, generating groups capable of binding with drugs, especially those that can inhibit the growth and spread of cancer cells and with molecules capable of recognizing such cells, specific antibodies and compounds such as lactate, among others. It is worth noting that antibiotic such as tamoxifen can recognize estrogen receptors and therefore, can act as a recognition molecule. Thus, the combination of a nanostructure with an antibiotic or anticancer drug with a specific molecule that recognizes only the cancer cells, and a quantum dot that emits a fluorescent signal under a certain wavelength may enable early diagnosis of breast cancer. These examples show how carbon nanostructures can be useful for the diagnosis and treatment of breast cancer during the early stage of the disease even if there are just a few malignant cells. However, additional studies using different breast cancer cell lines must be carried out to evaluate the toxicity of the nanostructure alone and the complexes that are formed with it to guarantee patient safety.

CONCLUSION

These examples show how carbon nanostructures can be useful for the diagnosis and treatment of breast cancer during the early stage of the disease, even when stage one is incipient with the presence of just a few malignant cells, thus representing their promising use by physicians in the clinic. However, additional studies at the laboratory level using different breast cancer cell lines must be carried out to evaluate the toxicity of both the nanostructure alone and the complexes that are formed with it in order to guarantee patient safety.

Conflict of Interest: The authors declare no potential conflicts of interest with respect to research, authorship and/or publication of this manuscript.

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