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RESEARCH ARTICLE

Theranostical Approach as a Therapeutic Resource For Breast Cancer: A Systematic Review

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Abstract

According to the World Health Organization, breast cancer is the second type of cancer that most affects Brazilian women and the second cause of death for women in the world.It was estimated that in 2020 and 2021 there would be 66 thousands of new cases of breast cancer in Brazil. An alternative to solve these problems is the theranostic approach, as it can identify the presence of new cancer cells and act efficiently in the elimination of neoplastic cells through nanoparticles (NP) that induce oxidative stress and cell apoptosis, thus reducing the possibility of recurrence of breast cancer. This article is a systematic review based on articles published between 2015 and August 2021, in the following databases: PubMed, SciELO (Scientific Electronic Library Online), ScienceDirect, SEER (Surveillance, Epidemiology and Results Program), in addition to epidemiological bulletins were used, also health libraries of the Ministry of Health and National Cancer Institute, World Health Organization, using as inclusion criteria: year of publication, descriptors, journal, title, objectives and results, articles that didn't meet any criterion were excluded. Nanoparticles are versatile materials, as they allow the manipulation of both shape and size, in addition to enabling the inclusion of specific ligands on their surface capable of interacting with breast cancer tumor cells, they can be drug carriers, photosensitive, sensors and contrast that help in imaging diagnosis. The theranostic approach has evolved to become a promising strategy in personalized medicine, being able to act as a tool to optimize dosage levels for each patient, either to evaluate the result of an early-stage therapy, which allows appropriate and individualized changes in therapeutic protocols of each patient.

Keywords: Theranostic, Nanoparticles, Breast Cancer, Nanomedicine

1 | INTRODUCTION

According to the National Cancer Institute (INCA), carcinoma is already considered a public health problem worldwide and is among the top four positions responsible for premature deaths, before the age of 70 years. According to the World Health Organization, for every 5 people in the world, one will develop some type of cancer during their lifetime, in the last 20 years cases have practically doubled from 10 million in 2000 to 19.3 million in 2020 (WHO, 2021). Breast cancer is considered the second type of cancer that affects Brazilian women and the second cause of death for women in the world. It was estimated that in 2020 and 2021 there would be 66 thousandsof new cases of breast cancer in Brazil per year (INCA, 2020).

According to Migowoski (2018), the Ministry of Health's guidelines for breast cancer detection are divided into two domains: screening and early diagnosis. Screening practices are through self-examination and clinical assessment in asymptomatic patients, while early detection methods fall within the procedures used in patients with signs that suggest breast cancer, such as clinical examination followed by mammography.

Bilateral mammography is recommended for women aged 50 to 69 years, every two years, however there is an increase of cases in women of younger ages. Case studies of patients treated at INCA shows that when early diagnosed, the survival of patients with breast cancer highly increases, however, there is a great enlargement in advanced stages cases in women over 35 years old, revealing a failure in the present tracking (PERES, 2015).

Above the new cases, there is still concern about recurrence cases. Around 6% of breast cancers have metastatic feature diagnosis and a survival rate of 21% in the first five years. These rates tend to be high due to deficiencies in the process of diagnosing the disease (PERES, 2015). Using prognostic factors to assess the clinical course of breast cancer, which covers the risk of recurrence, progression and death, it's observed that when inserting adjuvant systemic therapies, a large increase is obtained in patient survival (ALMEIDA, 2020).

In addition to the aforementioned factors, the disease intervention approaches still needs to be contemplated. Currently, the main approach is through chemotherapy, where little therapeutic effect has been observed in the treated models, besides a substantial systemic toxicity (BHANUMATHI et al., 2018), another approach is a surgery to remove tumors and tissues from adjacent areas, however, this isn't a possibility in all cases, as these therapies often lead to a relapse of cancer, subjecting them to repeat treatment, which increases meaningfully the SUS's expensesrelated to cancer, from diagnosis to treatment and follow-up (OLIVEIRA, 2021).

To overcome these problems, studies about theuse of nanostructures that accumulate quickly and selectively in targets of interest have become one of the focuses of health engineering in the last decade, also improving diagnostic images, it can be as a treatment for cancer (KANDASAMY&KUMAR, 2020). This article aims to describe theranostic methods as a revolutionary option in the diagnosis and treatment of cancer and to address the nanoparticles (NP) that have greater therapeutic efficacy in breast cancer.

2 | MATERIALS AND METHODS:

This study is a systematic review under the PRISMA recommendations, developed from March to September of 2021. The following databases were used: PubMed, SciELO (Scientific Electronic Library Online), ScienceDirect, SEER (Surveillance, Epidemiology and Results Program), In addition, epidemiological bulletins were used and health libraries from the Ministry of Health and National Cancer Institute, World Health Organization as well, where the following descriptors were used: Breast

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Carcinoma in situ, Breast ductal Carcinoma, Recurrence Breast Cancer, Nanomedicine, Nanomedicine, Nanoparticles and cancer image, Nanomaterials, Breast Cancer and Theranostic. To obtain relevant articles, the following inclusion criteria were used: year of publication between 2015 and August 2021, descriptors used, publication journal, title, objectives and main results, articles that did not meet these criteria, such as: approach only the genetic aspects of breast cancer or not directly related to NP as a theranostic approach were disqualified.

3 | RESULTS AND DISCUSSION:

For this review, a total of 248 articles were found, of which only 23 were related to the topic, however only 11 associated the NP with the theranostic approach for breast cancer, as shown in table 1. The articles that didn't fit the topic were excluded corresponding to 225.

The need to mitigate side effects and increase drug specificity was essentialfor the development of a new delivery system known as Smart Drug Delivery Systems (SDDSs) this system uses smart nanocarriers such as liposomes, dendrimers, superparamagnetic iron oxide NP, NP de meso-porous silica, carbon nanotubes, gold NP and quantum dots (HOSSEN, 2019).

Each NP has characteristics that specializes its theranostic applicability, from the delivery of drugs in a more efficient and less toxic way to their use as imaging agents. In table 1, it is possible to observe that even being part of the same group of NP, whether metallic or organic, they have differences between them, allowing their use in multiple approaches.

Tan et al. (2020) report that AuNPs functionalized with folic acid conjugated to chitosan, there was an improvement in the efficacy of drug therapy against breast cancer cells. Other authors, as Sharma et al. (2015), report the wide use of gold NP in as a supply of drug, where it is encapsulated or adsorbed on the polymeric mesh, promoting low toxicity and great capacity to associate with drugs or molecules by adsorption or by chemical linkage, however, in their article,the authors don't directly relate them to breast cancer.

Within the metallic NP´s, evidence from Lopes and Torres (2019), with silver NPs conjugated with folic acid and beverage in its interior, decreased more than 80% in the cell viability of breast cancer cells. When combined with albumin, they were able to reduce up to 70% of breast cancer cells.

Another metal NP´s used is zinc, in a study by Vafaei et al. (2020) demonstrated promising cytotoxicity against breast cancer cells compared to non-tumor cells and a potential effect of triggering apoptosis in treated cells in relation to cells not treated. Furthermore, Sharma et al. (2015) report that zinc NP´s can be used successfully in cancer therapy, because of their excellent tumor activityand having agreat relaxivity for MR.

Although iron NP´s not been used for breast cancer treatment, these NP´s have been extensively studied as new contrast agents for MRI (Nuclear Magnetic Resonance), due to their biocompatible characteristics and lower toxicity compared to gadolinium, since the iron is found naturally in the body, they're excellent for real-time monitoring of tumors and easily coated with various polymers, thus may work in different applications (TÓTARO et al, 2017; RICARDO, 2019).

In addition to metallic NP´s, quantum dot NP´s or quantum dots (QDs) are still used in the theranostic approach. These NP´s have optical, fluorescent and electronic properties. Some authors explored the possible applications by functionalizing these particles with biocompatible polymeric materials or with antibodies, acting in the delivery of drugs in intracellular environment through EPR or active targeting, combining their fluorescent characteristics with drug delivery, so it is possible to obtain a theranostic system capable of diagnosing and treating (KULKARNI et al, 2019; RESHMA; MOHANAN, 2018).

Kulkarni et al. (2019) report studies for breast cancer using QDs with addition of a fluorescent probe with selective receptor for VEGF. In 12h, the probe was bound to the receptor and, therefore, the tumor was detected in mice through imaging.

Other NP´s used for breast cancer are carbon-based and graphene, according to Cheng et al. (2019),

TABLE 1: NPs and their characteristics indicated by their respective authors and theranostic applicability

NPs	Author/Year	Feature	Therapeutic Applicability
liposome	PALAZZOLO 2018	Ability to deliver hydrophilic and hydrophobic molecules, increase permeability, biodistribution and targeting specificity, more efficient labeling and an improvement in radiolabel retention.	Abraxane^{TM} albumin-bound paclitaxel formulation, first of its kind approved by the FDA. It has reduced treatment volume, antitumor activity.
	LAMICHHANE, et.al., 2018.		It reports four drugs in clinical trials in phases I and III.
Silver	LI, Yanan et al. 2018	Photothermal converters, imaging probes,drug carriers for theranos c applicability, induce cell cytotoxicity with ROS release, malleability, flexibility, high electrical and thermal conduc vity, cataly c ac vity.	Toxicity to breast cancer cells. Potential in drug delivery. Bright fluorescent red allows for detection and localization of drugs within cells.
	LOPES, et al., 2019		Silver NPs loaded with folic acid and booze caused an over 80% decrease in breast cancer cells.
Quantum Dots	RESHMAe MOHANAN. 2019	Semiconductor nanocrystals, optical, fluorescent and electronic properties, biocompatible, ease of entering the cell through EPR, due to its fluorescence it is possible to carry out diagnosis and treatment.	When compared to other imaging techniques such as PET, MRI, etc., fluorescence imaging uses less dangerous non-ionizing radiation. Deep tissue imaging can be achieved using quantum dots, adjusting their size and composition, luminescent emission wavelengths.
	KULKARNI, et al., 2019.		Quantum dots charged with silver sulfide, after 24h fluoresced in tumors.
dendrime	DING, et al., 2020.	Polarity and water solubility, biocompatibility, pharmacokinetics, biodistribution and retention with specificity in malignant tissues, more efficient in detecting tumors than FDG.	The PAMAM dendrimer containing the radionuclide Ga 68 with a macrocyclic chelating complex NOTA (1,4,7-triazacyclononane-1,4, 7-triacetic acid) in the extremities, offers excellent results in different types of tumors including those that could not be detected by 2-fluorodeoxyglucose (FDG) the standard agent for PET.
Gold	TAN, et al., 2020.	Optical properties, low toxicity, ability to associate with drugs or molecules by adsorption and chemical bonding, high stability, high light to heat conversion efficiency, strong light absorption and emission, and biocompatibility.	Combining AuNPs with liposomes has the potential to kill cancer cells through photothermal therapy.
Zinc	VAFAEI, et al.,	Low toxicity for healthy cells, low cost, polar and hygroscopic.	Promising cytotoxicity against breast cancer cells compared to non-tumor cells.
Carbon	TADE e PATIL. 2020	Thermal conductivity, lower toxicity, biocompatibility and multifunctionality.	Administration of IR780 / GQDs-FA in one group of mice and pure IR780 in another group. After 24h, an intensity of NIR fluorescence was noted in the tumor region
graphene	CHEN G, et al.,2020	Photothermal agent considering its high NIR absorbance and satisfactory therapy.	PEGylated nano-GO (nGO-PEG) in mice after intravenous injection high passive accumulation due to tumor RPE was observed. Nano-GO reduction (nRGO) with significantly increased NIR optical absorption can be used as a highly efficient PTT agent against cancer

Source: Authors themselves.

graphene NP´s can be used as a photothermal agent considering their high NIR absorbance and with a satisfactory therapeutic. Furthermore, recent studies report the use of carbon nanoparticles with graphene sheets in different theranostic strategies, such as MRI (magnetic resonance) and CT (computed tomography).

NP´saren't restrictedly metallics, there is another group, organic NP´s with structural characteristics divergent from each other and assume the following conformations: liposomes, dendrimers, nanoemulsions, nanospheres, polymeric nanocapsules and drug-polymer conjugate. Among these NP´s, liposomes are the first nanocarriers approved by regulatory agencies for the transport of various chemotherapeutic agents, the first liposomal formulation approved on the market was Doxil® for the treatment of AIDS-related Kaposi's sarcoma, other liposomes used for treatment of cancer are also available, as DaunoXome® (VIEIRA; GAMARRA, 2016).

According to Lamichhane et al., (2018) the use of liposomal formulationsis showing more efficient labeling and an improvement in radiolabel retention, its quantification by PET and SPECT a non-invasive analysis over time.Like liposomes, dendrimers can also be applied in the field of PET and SPECT bioimaging, such as the PAMAM dendrimer containing the radionuclide Ga 68 with a macrocyclic chelating complex NOTA (1,4,7-triazacyclononane-1,4, 7-triacetic acid) on the extremities after self-assembly into stable micelles, which effectively accumulate in tumors, offers excellent results in different types of tumors including those that couldn't be detected by 2-fluorodeoxyglucose (FDG) the standard agent for PET (DING, 2020). Been a nanoparticle that may be designed for a specific application demand, it has high solubility, expected biocompatibility, pharmacokinetics, bioavailability, biodistribution and retention with specificity in malignant tissues (SHUKLA, 2016; CASTRO, 2018).

4 | CONCLUSION:

The theranostic approach progressed to become a promising strategy in personalized medicine, as it has the ability to provide unique features and methodological novelty in aiding and monitoring, individualized assessment, besides real-time treatment follow-up. The imaging agent may act as an instrument to optimize the times and dosages levels for each patient, also assess the result of the approach of an early-stage therapy, where it is able to allow appropriate and individualized changes in the therapeutic protocols of affected patients with cancer. Many authors agree with the potential of using nanoparticles in the theranostic approach, as metallic as organic origin, because each one has a characteristic that correlates with a need, whether for greater specificity, biocompatibility, less toxicity with greater efficacy and fewer side effects.

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