Disciplinarum Scientia. Série: Naturais e Tecnológicas, Santa Maria, v. 21, n. 3, p. 139-155, 2020.
Recebido em: 15.10.2020. Aprovado em: 10.12.2020.
ISSN 2176-462X
DOI: 10.37779/nt.v21i3.3559

RECENT ADVANCES IN POLYPHENOLS NANOCARRIERS AGAINST BREAST CANCER THERAPY FOCUS ON IN VITRO STUDIES: LITERATURE REVIEW[1]

AVANÇOS RECENTES EM NANOCARREADORES DE POLIFENÓIS CONTRA TERAPIA DO CÂNCER DE MAMA FOCO EM ESTUDOS IN VITRO: REVISÃO DE LITERATURA

Mariana Fernandes Ribeiro[2], Francine Carla Cadoná[3] e Patrícia Gomes[4]

ABSTRACT

Cancer is considered a severe public health problem worldwide. Among the most incident cases, breast cancer, which affects many women in the entire world, can be mentioned. Currently, there are well-established protocols for the treatment of this type of cancer. However, cancer treatment presents collateral effects that can compromise the patient's quality of life. Therefore, studies have suggested that plants and fruits rich in polyphenols have antitumor activity, decrease chemotherapy resistance, and reduce side effects caused by chemotherapy. However, most of these compounds have low bioavailability making their potential pharmacological challenging. Therefore, the search for carriers that can efficiently protect and transport these bioatives to tumor cells is of great interest. In this sense, nanostructured systems can be included as the delivery of bioactive molecules and drugs. Thus, this study aimed to report the current studies using nanocarriers containing phenolic compounds to evaluate their antitumor effect against breast cancer cells. Data collection included the virtual databases Science Direct and Web of Science using the descriptors: nanoparticles and polyphenols and breast cancer, for experimental articles published from 2015 to September 15, 2020. The search resulted in a total of 1346 articles, of 37 met the inclusion criteria. The studies have demonstrated the efficiency of nanostructures containing polyphenols against cancer cells, suggesting excellent perspectives in the use of nanotechnology combined with bioactive compounds in the treatment of breast cancer.

Keywords: Anticancer activity, Nanotechnology, Phenolic compounds.

RESUMO

O câncer é considerado um grave problema de saúde pública em todo o mundo. Entre os casos mais incidentes, pode-se citar o câncer de mama, que atinge muitas mulheres em todo o mundo. Atualmente, existem protocolos bem estabelecidos para o tratamento desse tipo de câncer. No entanto, o tratamento do câncer apresenta efeitos colaterais que podem comprometer a qualidade de vida do paciente. Portanto, estudos têm sugerido que plantas e frutas ricas em polifenóis têm atividade antitumoral, diminuem a resistência à quimioterapia e reduzem os efeitos colaterais causados pela quimioterapia. No entanto, a maioria desses compostos tem baixa biodisponibilidade, tornando seu potencial desafio farmacológico. Portanto, a busca por carreadores que possam proteger e transportar de forma eficiente esses bioativos para as células tumorais é de grande interesse. Nesse sentido, os sistemas nanoestruturados podem ser incluídos como a entrega de moléculas bioativas e fármacos. Assim, este trabalho teve como objetivo relatar os estudos atuais utilizando nanocarreadores contendo compostos fenólicos para avaliar seu efeito antitumoral contra células de câncer

[1] Study performed at Nanosciences Posgraduate Program.

[2] Student of the Nanosciences Posgraduate Program - Universidade Franciscana. E-mail: mariana.ribeiro@ufn.edu.br
[3] Teacher of the Health and life sciences Posgraduate Program - Universidade Franciscana. E-mail: f.cadona@ufn.edu.br
[4] Teacher of the Nanosciences Posgraduate Program -Universidade Franciscana. E-mail: patriciagomes@ufn.edu.br

de mama. A coleta de dados incluiu as bases de dados virtuais Science Direct e Web of Science utilizando os descritores: nanopartículas e polifenóis e câncer de mama, para artigos experimentais publicados de 2015 a 15 de setembro de 2020. A busca resultou em um total de 1.346 artigos, dos quais 37 atenderam à inclusão critério. Os estudos demonstraram a eficiência de nanoestruturas contendo polifenóis contra células cancerosas, sugerindo excelentes perspectivas no uso da nanotecnologia combinada com compostos bioativos no tratamento do câncer de mama.

Palavras-chave: *Atividade anticâncer, Nanotecnologia, Compostos fenólicos.*

INTRODUCTION

Breast cancer is the most commonly diagnosed neoplasm worldwide, being the leading cause of cancer death in women. According to estimates by the National Cancer Institute (INCA) the estimated number of incident breast cancer cases in Brazil, for 2020, was 66,280 for each year of the 2020-2022 triennium. The incidence of this pathology comes persistently due to several genetic and environmental factors such as eating habits, physical inactivity, radiation exposure, hormonal therapy, alcohol consumption, cases of cancer in the family, among others (KOLAK *et al*., 2017). Currently, treatment for breast cancer can be classified as systemic, radical, or conservative. Among the protocols used in treatments includes hormonal or cytotoxic chemotherapy, immunotherapy, surgery, and radiotherapy. However, one of the main problems associated with cancer treatment is the toxic side effect. Most chemotherapeutic agents used cannot differentiate between normal and tumor cells and induce cell death in all cells that present a rapid proliferation (RAMLJAK *et al*., 2005).

In search of compounds that can be efficient with low or no adverse effects, the pharmaceutical industry is continuously investigating natural products to prevent and treat cancer (SILVA *et al*., 2019). Polyphenols are one of the most numerous and widely distributed groups of natural products. Research on polyphenols in the diet has shown positive results by reducing several chronic diseases, including cancer. Some studies reported antioxidant, anti-inflammatory, and antimicrobial effects (KHAN *et al*., 2019). Different mechanisms have been suggested to explain the anticancer effects of phenolic compounds, such as, for example, acting as suppressive agents that inhibit the formation and growth of tumors, inhibiting proliferation offering better preventive and therapeutic options.

However, the low solubility, rapid metabolism, and low gastrointestinal absorption of polyphenols used in the diet are significant obstacles to their pharmacological potential (KHAN *et al*., 2019). To overcome the polyphenols bioavailability problem and improve the pharmacokinetics, several methodologies have been proposed for the encapsulation of these compounds, generating more stable forms of delivery. Nanostructures are one of the main options for being a delivery system for bioactive compounds, offering advantages such as protection against degradation, interaction with the biological environment, better absorption, retention time, controlled delivery, among other

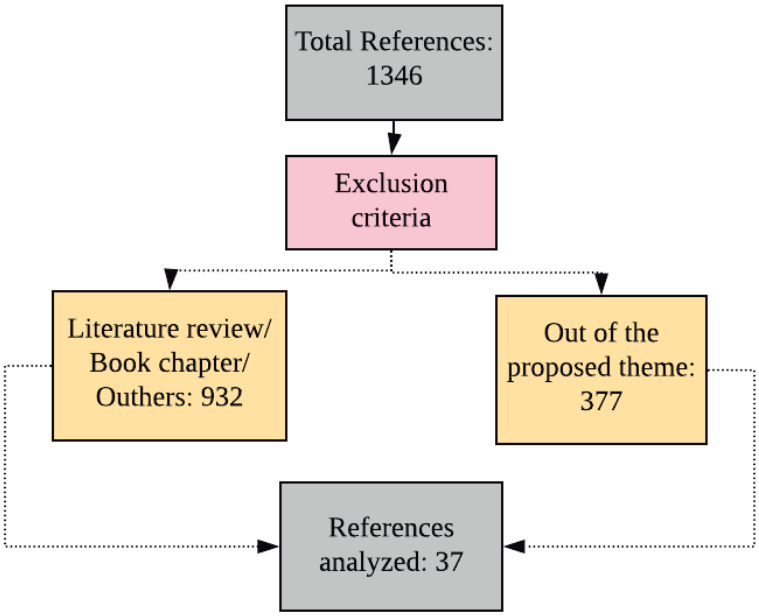
benefits (SANTOS *et al.*, 2019). Through the targeted administration of drugs through nanoformulations, better administration of the tumor site, and better therapeutic responses can reduce side effects. Besides, there is an increase in cell selectivity reducing the adverse effects caused by conventional chemotherapy, showing that nanotechnology may be able to overcome the limitations of polyphenols, causing promising results in the treatment of cancer (DAVATGARAN-TAGHIPOUR *et al.*, 2017; PEREZ -RUIZ *et al.*, 2018). This study aims to review available data on nanoformulations containing natural polyphenols as chemopreventive and chemotherapeutic agents and discuss anticancer action mechanisms in recent years.

MATERIALS AND METHODS

This study is a systematic literature review. The search for work publications happened from January to September 2020 through the electronic databases: Science Direct and Web of Science. The descriptors used for this review were: *nanoparticles and polyphenols, and breast cancer*, with articles published from 2015 to September 15, 2020. The inclusion criteria used to select the items were: article-type publications with texts in the English language. The exclusion criteria were publications whose central theme did not match the research, literature review studies, book chapters, and other works that did not correspond to experimental studies.

The search in the databases resulted in 1346 articles, of which 37 met the proposed criteria. Figure 1 shows the flowchart for the selection of items in the databases.

Figure 1 - Flowchart representing the search for articles in the databases according to the established criteria.

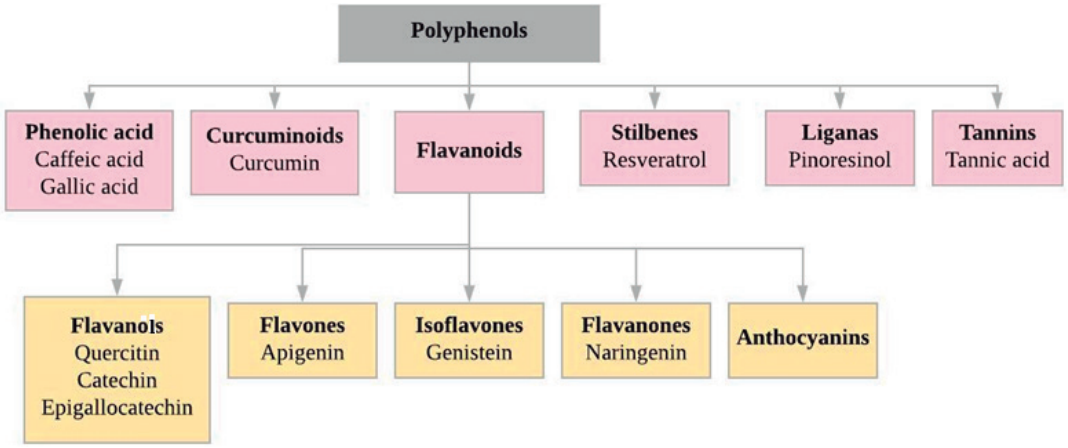


Source: Author's construction.

RESULTS AND DISCUSSIONS

According to the chemical structure, polyphenols are classified into flavonoids, phenolic acids, stilbenes, lignans, curcuminoids, and tannins, as illustrated by some examples in the figure below (MOJZER *et al.*, 2016) (Figure 2). Many of these compounds have been found in the literature as a primary or adjuvant asset with chemotherapy drugs evaluating their cytotoxic potential *in vitro* studies against different lines of breast cancer cells (AVTANSKI, PORETSKY, 2018).

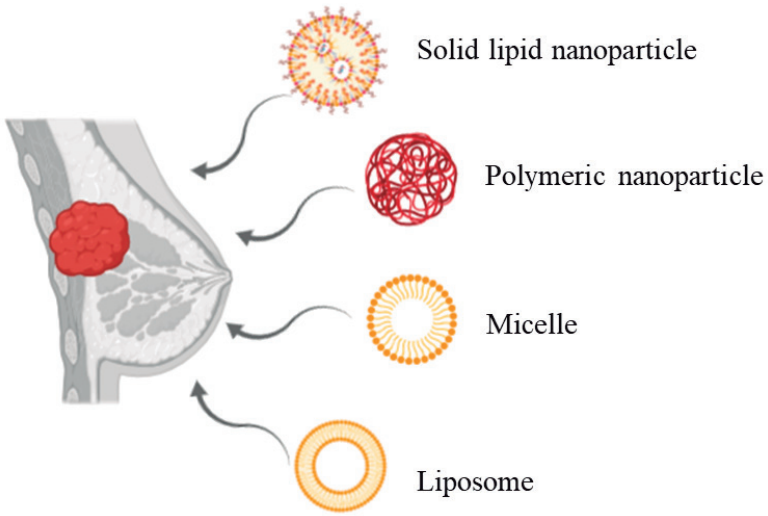
Figure 2 - Flowchart representing the main classes of polyphenols.



Source: Adapted from Mojzer *et al.* (2016).

Despite its numerous advantages, most phenolic compounds have limitations on bioavailability. Therefore different systems have been proposed as carriers of drugs and bioactive compounds, including, for example, polymeric nanoparticles, solid lipid nanoparticles, liposomes, nanogels, nanoemulsions, among others (FANTINI *et al.*, 2015; CONTE *et al.*, 2016) (Figure 3). Nanostructures have declared excellent performance as medication delivery vehicles, as in the studies covered in this review.

Figure 3 - Use of different nanostructures in the treatment of breast cancer.



Source: Author's construction.

Punica granatum, contains many phenolic compounds with high antioxidant and free radical scavenging activity, including flavonoids and tannins. Given its excellent antioxidant, anti-inflammatory, and antitumor potential, the fruit has been widely explored in the treatment of several diseases, including breast câncer (ROCHA *et al*., 2012; SHIRODE *et al*., 2015) (Table 1).

Table 1 - Studies were showing nanocarriers containing polyphenols present in pomegranate in the treatment of breast cancer *in vitro* tests.

Nanocarrier	Compounds	Cell line	References
PLGA - PEG Nanoparticles	Pomegranate extract, punicalagin and ellagic acid.	MCF-7 and Hs578T	Shirode *et al.*, 2015
Solid lipid nanoparticles	Pomegranate extract	MCF-7	Badawi *et al.*, 2018
Silver nanoparticles	Black-skinned pomegranate polyphenols.	MCF-7	Khorrami; Zarepour; Zarrabi, 2019
Schizophyllan and chitin nanoparticles	Ellagic acid	MCF-7	Pirzadeh-Naeeni *et al.*, 2020

Source: Author's construction.

Shirode *et al.* (2015) produced PLGA/PEG nanoparticles containing pomegranate extract, punicalagin, and ellagic acid to evaluate their activity in MCF-7 and Hs578T breast ifere cell lines. This study showed particles of approximately 150 nm. To assess the uptake of nanoparticles *in vitro*, cells were incubated for 5 minutes, 2 hours, 6 hours, and 24 hours and in the cell growth evaluation, it was observed that all pomegranate nanoparticles inhibited the growth of ifere cells in a significantly higher than the free extract in both cell lines. This corroborates the studies by Khorrami, Zarepour, Zarrabi (2019) and Badawi *et al.* (2018). They produced nanoparticles loaded with pomegranate extract showing more significant cell proliferation inhibition when compared to the free form, in addition to acting selectively against breast ifere cells.

Pirzadeh-Naeeni *et al.* (2020) used ellagic acid, the main antitumor compound of pomegranate loaded in schizophyllan and chitin nanoparticles, to investigate its effectiveness in the treatment of MCF-7 cells. The iferentete activity indicated that during the first three hours, the actions of eliminating free ellagic acid and nanoparticles containing ellagic acid increased the iferentete activity to 77% and 70%, respectively. Cell viability assessment showed significant antiproliferation effects on MCF-7 cells, which improved at higher concentrations. These studies may suggest that nanoparticles using polyphenols iferent in pomegranate represent a method of choice for further investigations regarding breast ifere treatment using nanocarriers.

One of the most commonly found polyphenols in the literature in the treatment of breast ifere is curcumin. Extracted from the rhizome of *Curcuma longa*, it has been widely used in medicine due to its antitumor, iferentete, anti-inflammatory, healing, and antibacterial benefits (BANIK *et al*., 2017). Despite many advantages in the medical field, curcumin has low bioavailability when administered freely. This is one of the main reasons this bioactive compound needs a carrier capable of protecting and

delivering it effectively, as is the case with nanostructures. Because it has a hydrophobic characteristic, curcumin is nanoencapsulated mainly in lipid nanoparticles and liposomes (FENG *et al.*, 2017) (Table 2).

Table 2 - Studies were showing nanocarriers containing curcumin in the treatment of breast ifere *in vitro* trials.

Nanocarrier	Compounds	Cell line	References
Miristic acid-chitosan nanogels	Curcumin	MDA-MB231	Khosropanah *et al.*, 2016
Liposomes	Curcumin	MCF-7 and MDA-MB-468	Kangarlou *et al.*, 2017
Tocotrienol nanoemulsion	Curcumin	MCF-7	Steuber *et al.*, 2016
Nanoparticles PLGA/PEG	Curcumin	MCF-7	Mirakabad *et al.*, 2016
Nanoparticles PLGA/PEG	Metformin and curcumin	T47D	Farajzadeh *et al.*, 2018
Nanocapsules	Curcumin and quercetin	MCF-7	Ghayour *et al.*, 2019
Nanostructures of zinc oxide-βcyclodextrin	3-Mercaptopropionic acid and curumin	MCF-7	Ghaffari *et al.*, 2019
Dextran nanoparticles	Methotrexate and curcumin	MCF-7	Curcio *et al.*, 2020
Apoferritin nanoparticles	Curcumin and quercetin	MCF-7	Mansourizadeh *et al.*, 2020

Source: Author's construction

In the studies presented by Kangarlou *et al.* (2017) curcumin-loaded liposomes linked to homing peptides were produced for targeting integrin and neuropilin-1-mediated internalization in MCF-7 and MDA-MB-468 breast ifere lines. The particles were evaluated for cell viability using free curcumin and liposomes in both cell lines 24 hours. Liposomes showed a significant reduction in IC50 concerning free curcumin. They were indicating significant advantages of liposomes conjugated to peptides in the iferentete drugs to ifere cells.

Steuber *et al.* (2016) produced tocotrienol nanoemulsion to incorporate curcumin, evaluating the increased iferente efficacy against breast and ovarian carcinomas. The formulations exhibited a particle size of around 260 nm, which remained unchanged for at least eight weeks. The nanoemulsion demonstrated the cytotoxic profile of MCF-7 cells in almost all concentrations tested, reaching a maximum cell death (> 90%) at <30 μM curcumin, notably suppressing the constitutive activation of the NF-κB antibody and induced effector caspases, mediating ifere apoptosis.

Farajzadeh *et al.* (2018) assessed the level of hTERT iferentet in the T47D breast cell line, combining metformin and curcumin in ifere-sized PLGA/PEG nanoparticles of 202 nm. In the analysis of cell cytotoxicity, curcumin and metformin were tested synergistically and separately for 72 hours and the metformin-curcumin nanoparticles. The non-encapsulated compounds showed a concentration-dependent cytotoxic effect, and the nanoparticles significantly interrupted the growth of ifere cells compared to free assets. The PCR assay showed that the nanoparticles suppressed the hTERT gene's iferentet more efficiently than the delivery of metformin and curcumin in the same concentrations, indicating a synergistic effect.

In iferen studies, Ghaffari *et al.* (2019) produced zinc oxide-βcyclodextrin (βCD) nanostructures functionalized by folic acid as a system for delivering curcumin. Cell viability assessment was carried out for 48 hours against breast ifere cells MDA-MB-231. The curcumin-loaded formulation exhibited a higher toxicity activity against the MDA-MB-231 cell line, with no effect on normal cells

and better absorption of curcumin. Finally, it was observed that the structures conjugated with synthesized folic acid suppressed better size stability and high curcumin uptake for the cells.

To effectively deliver the chemotherapy methotrexate to breast ifere cells, Curcio *et al.* (2020) designed a nanocarrier system for the self-assembly of dextran and curcumin (DC). Nanoparticles with na average diameter of 290 nm were observed. In the cell viability test, MCF-7 breast ifere cells were used, which after 48 h of incubation with DC nanoparticles, cell viability was reduced by up to 47%, suggesting the possibility of significantly reducing the dose of methotrexate for a treatment effective iferente with the combination of dextran-curcumin in nanocarriers.

Mansourizadeh *et al.* (2020) used apoferritin as a carrier in nanoparticles loaded with quercetin and curcumin, two phenolic compounds with antitumor activity, to evaluate their effect breast ifere cells. In the evaluation of cell apoptosis, the results showed that the nanoparticles produced more significant synergistic inhibition of the viability of MCF-7 cells than the administration of the same concentration of the free combination. Besides, apoferritin significantly reduced the cytotoxic effect on MCF10A breast iferente cells. Corroborating with studies carried out by Ghayour *et al.* (2018). They synthesized nanocapsules containing the polyphenols quercetin and curcumin in casein-based delivery systems to determine the cytotoxicity effect on human breast ifere cell line MCF-7. The nanoparticles showed a dose-dependent cell viability assessment. Even so, the nanoparticles containing the polyphenols showed more significant cell cytotoxicity than the free compounds.

Another natural product widely explored in research is green tea, with a chemical matrix full of polyphenols, especially catechins (YIANNAKOPOULOU, 2014). The literature discusses the role of green tea (*Camellia sinensis*) in preventing neoplasms by containing in its chemical matrix a variety of catechins responsible for its protective effect on DNA and in the induction of apoptosis in tumor cells (RAFIEIAN-KOPAEI; MOVAHEDI, 2017). Like other polyphenols, nanotechnology is used to efficiently protect and deliver assets, as shown in the following studies (MUKHERJEE *et al.*, 2015) (Table 3).

Table 3 - Studies were showing nanocarriers containing green tea polyphenols *in vitro* experiments with breast ifere cells.

Nanocarrier	Compounds	Cell line	References
Liposomes	Epigallocatechin gallate (EGCG) and Paclitaxel	MDA-MB-231	Ramadass *et al.*, 2015
PLGA-casein nanoparticles	Epigallocatechin gallate (EGCG) and Paclitaxel	MDA-MB-231	Narayanan *et al.*, 2015
Gold nanoparticles	Epigallocatechin-3-gallate	MCF-7	Mukherjee *et al.*, 2015
Human ifer albumin nanoparticles	Morina and Epicatechin	MDA-MB-231	Gosh *et al.*, 2016
Solid lipid nanoparticles	Tea green extract	MCF-7	Kulandaivelu, Mandal, 2016
Nanoparticles of lecithin-chitosan	Epicatechin	MCF-7, MDA-MB-231, MDA-MB-436 and SK-Br3	Perez-Ruiz *et al.*, 2018
Nanogels	Epigallocatechin and siRNA	MDA-MB-231	Ding *et al.*, 2018
Chitosan nanoparticles	Epigallocatechin-3-gallate	MCF-7	Liu *et al.*, 2018
PLGA nanoparticles	Epigallocatechin-3-gallate (EGCG) decorated with folate	MDA-MB-231	Kazi *et al.*, 2020

Source: Author's construction.

Ramadass *et al.* (2015) produced liposomes as co-delivery of epigallocatechin gallate and paclitaxel, a chemotherapeutic ifere used in breast ifere treatment ifere to inhibit target metalloproteinases. It has already been shown that MMP-2 and MMP-9 metalloproteinases are entirely expressed in cancerous tissues, and this has drawn a ifere attention due to their implications for tumor invasion and metastasis. Therefore, there are reports that epigallocatechin 3-gallate (EGCG) reduces the iferentet of MMP-2 and MMP-9. The cell viability showed high inhibition of metalloproteinases in the treatment with liposomes, with the activity of MMP-2 and MMP-9 being reduced by about 80% compared to the control. This study corroborates with that carried out by Narayanan *et al.* (2015). They also investigated EGCG and Paclitaxel's combination as na inhibitor of multiple signaling, focusing on the NF-kB pathway. It was encapsulated in a PLGA-casein nanoparticle targeted at breast ifere cell line MDA-MB-231 that sensitized paclitaxel-resistant breast ifere cells, inducing their apoptosis and inhibiting the activation of NF-κB by regulating the genes associated with angiogenesis and tumor metastasis.

In another study, Mukherjee *et al.* (2015) produced gold nanoparticles conjugated to EGCG and nanoparticles with green ifere assess toxicity against MCF-7 breast ifere cells. The nanoparticles showed toxic effects on MCF-7 cells, while they did not show any cytotoxic effects on the mice's hepatocytes used as controls. Besides, they limited the activation of NFr-B by almost 50% and triggered the onset of apoptosis. It also iferente significant cell uptake and good results in iferentete activity *in vitro.*

Ghosh *et al.* (2016) solubility enhancement of morin and epicatechin through encapsulation in an albumin based nanoparticulate system and their anticancer activity against the MDA-MB-468 breast cancer cell line. In *in vitro* toxicity assays, NPs-HSA-Mor and NPs-HSA-EC were able to destroy breast ifere cells by 42% and 26%, respectively, compared to morine and epicatechin alone had more significant results ifere cells are highly toxic.

Perez-Ruiz *et al.* (2018) prepared lecithin-chitosan nanoparticles loaded with epicatechin (NPs-EC-LCT) by molecular self-assembly and to assess their cytotoxic potential against breast ifere cells. To compare the iferente activity of (-) - epicatechin and nanoparticles containing epicatechin, their cytotoxicity was evaluated in iferente breast ifere cell lines and non-cancer cells used as controls. It was observed that (-) - epicatechin showed no effect during 72 h of incubation. In contrast, NPs-EC-CLT generated the most significant inhibition of cell proliferation in all breast ifere cell lines and did not show cytotoxic effects to healthy cells, demonstrating that these nanoparticles have na inhibitory effect on human breast ifere cell line, in addition to presenting cell selectivity.

Resveratrol is a polyphenol that is iferen the class of stybenes. This compound has attracted attention due to its potential health benefits. It is widely found in plants such as grapes, plums, and peanuts (WANG *et al.*, 2017; SUN *et al.*, 2019). Its iferente, anti-inflammatory, iferentete, anti-aging, blood-sugar-lowering, and beneficial cardiovascular effects have been reported in many *in vitro* studies. Resveratrol iferent demonstrated its antiproliferative activity against tumor cells of various ifere types

with resistance to multiple drugs (KO *et al.*, 2017). Due to its low bioavailability, many studies have associated resveratrol with several nanocarriers as a iferen transport and delivery (WANG *et al.*, 2017) (Table 4).

Table 4 - Studies were showing nanocarriers containing resveratrol in breast ifere cell assays.

Nanocarrier	Compounds	Cell line	References
Liposomes	Paclitaxel and resveratrol:	MCF-7	Meng *et al.*, 2016
Solid lipid nanoparticles	Resveratrol	MDA-MB231	Wang *et al.*, 2017
Nano-sponge based on cyclodextrin	Resveratrol and curcumin	MCF-7	Pushpalatha; Selvamuthukumar; Kilimozhi, 2019
Gold nanoparticles	Resveratrol	MDA-MB-231	Thipe *et al.*, 2019
Oxidized mesoporous iferen nanoparticles	Resveratrol	MDA-MB-231	Fan *et al.*, 2019
Mimetic lipoprotein nanoparticles	Resveratrol folate receptor	MCF-7	Poonia *et al.*, 2020
Nanoespheres	Resveratrol	MDA-MB-231	Cassano *et al.*, 2020

Source: Author's construction.

Meng *et al.* (2016) co-encapsulated a PEGylated Paclitaxel liposome combined with resveratrol as therapy for breast ifere treatment, using the MCF-7 line for *in vitro* studies. The average size of the liposomes, as observed by microscopy, was approximately 50 nm. In assessing antitumor efficacy in MCF-7 cells, the free compounds showed less cytotoxicity. In contrast, the liposomes composed of resveratrol and paclitaxel showed significant cytotoxicity concerning the liposomes with the isolated compounds. Thus, indicating that the combined therapy potentially had a wide range of applications in ifere treatment.

Thipe *et al.* (2019) developed gold nanoparticles conjugated with biocompatible resveratrol (NPs-Res-Au) to explore the pro-apoptotic properties inherent in gold nanoparticles (NPs-Au) through synergistic antitumor characteristics of resveratrol in three types of ifere cells, including breast ifere. The particle size was in the range of 200nm, allowing na iferente penetration of NPs-Au through tumor cells. Thus, the cell viability test showed promising results from this combination, where a double antitumor effect was observed due to the composition of resveratrol and gold nanoparticles.

Pushpalatha, Selvamuthukumar, Kilimozhi (2019) aimed to design the transdermal co-delivery of curcumin and resveratrol using a nano-sponge-based cyclodextrin hydrogel. The nano-sponges containing curcumin had na average particle size of 490 nm and a load of 47.5%. The nano-sponges with resveratrol had a size of 532 nm and loading of 48.8%. The nanostructures showed a synergistic effect against MCF-7 cells in evaluating cytotoxicity *in vitro* showing high toxicity to the cells compared to the assessed assets in isolation and suggesting that this nanocarrier is na effective alternative against breast ifere cells.

Other phenolic compounds with antitumor effects are also associated with nanotechnology in breast ifere (Table 5).

Table 5 - Studies were associating nanotechnology with iferente phenolic compounds *in vitro* experiments with breast ifere cells.

Nanocarrier	Compounds	Cell line	References
Gold nanoplaticles	Kaempferol	MCF-7	Raghavan *et al.*, 2015
Silver nanoparticles	Longan extract.	MCF-7	Khan *et al.*, 2018
Mesoporous ifere nanoparticles	Folic acid and quercitin	MDA-MB231 and MCF-7	Sarkar *et al.*, 2016
Solid lipid nanoparticle	Tannic acid and paclitaxel	MDA-MB-231	Chowdhury *et al.*, 2018
Nanopartícles	Quercitin	MCF-7	Aghapour *et al.*, 2018
PLGA Nanopartícles	*Callistemon citrinus* extract	MCF-7, MCF-10ª and MDA-MB 231	Ahmed *et al.*, 2019
Zinc oxide nanoparticles	Quercitin	MCF-7	Sadhukhan *et al.*, 2019
Silver nanoparticles	*Vitis vinífera* tannin	MCF-7	Hashim *et al.*, 2020

Source: Author's construction

Sarkar *et al.* (2016) synthesized mesoporous ifere nanoparticles labeled with folic acid and loaded with quercetin with na average 200 nm size. In the evaluation of cell uptake, nanoparticles labeled with folic acid showed greater uptake in MDA-MB-231 cells than unmarked nanoparticles. In the test to evaluate cell viability, nanoparticles containing quercetin and folic acid showed a reduction in cell viability by 50%. In comparison, nanoparticles containing only quercitin had a 30% reduction, proving to be na effective therapeutic option against ifere cells breast.

Chowdhury *et al.* (2018) used tannic acid, a polyphenol belonging to the tannin class, together with the chemotherapeutic paclitaxel. With this, they developed nanoparticles of tannic acid-paclitaxel (NP-TAPs) to increase iferente effects in breast ifere cells MDA-MB-231, presenting nanoparticles of average size around 100 nm. Cell uptake results were quite iferente with NP-TAPs compared to paclitaxel used alone. In the MTT test, the nanoparticles exhibited dose-dependent toxic effects against the MDA-MB-231 and MCF-7 strains. After 48 hours of treatment, there was a significant reduction in IC50 in NP-TAPs compared to chemotherapy used alone. From the results presented in this study, the authors suggest that tannic acid has na iferente iferente potential combined with chemotherapy drugs to treat breast ifere.

Ahmed *et al.* (2019) developed PLGA nanoparticles loaded with Callistemon citrinus, a plant known as Bottle Brush and rich in phenolic compounds, to assess its effects on the growth and proliferation of three types of breast ifere cell lines: MCF-7, MCF-10ª, and MDA-MB 231. The nanoparticles had na average size of 250.7 nm with a storage period of 28 days at 4°C at 0.1 mg/mL-1, a mixture of nanoformulation and C. berberine citrinus induced the most iferen inhibition (33%) of MDA-MB 231 cells. In contrast, the same concentration in the unformulated form induced only about 12% growth inhibition, suggesting that encapsulation resulted in na almost three-fold increase in nano-formed treatments' effectiveness.

Khan *et al.* (2016) used the fruits of Longan (*Euphoria longana Lam*.) Grown in Asia and which contain gallic acid, ellagic acid, and corilagin as main constituents. In this study, Longan's aqueous extract was associated with silver nanoparticles as na iferente ifere used in breast ifere cells.

The cell viability test demonstrated a cytotoxic effect against MCF-7 cells of 88% at 100 µg/mL-1 just as the iferentete evaluation by the DPPH method proved to be quite iferente, suggesting a useful alternative as a future treatment.

Aghapour *et al.* (2018) prepared quercetin nanoparticles to evaluate their effect on the MCF-7 strain cells. The nanoparticles had na average size of 84 nm. When performing the MTT test with iferente formulation concentrations, a higher inhibition (87%) was observed in the 72h period in a dose-dependent manner. Besides, the nano-quercetin inhibitor's antiproliferative effect measured the progression of the cell cycle from phase G1 to phase S and apoptotic cell death in MCF-7 cells.

Finally, it can be observed that several phenolic compounds present in different fruits and plants cytotoxicity against breast cancer cells in the in vitro treatments performed, showing greater effectiveness when nanostructured in comparison with free compounds, resulting in the nanoencapsulated compounds having greater protection when exposed to external factors of degradation. In addition, some studies reported here brought results in which they point out that the nanostructures had an action on the modulation of gene and protein expression, suggesting a better targeting of the nanostructures in the treatment of cancer. However, it is necessary to carry out further studies using different experimental models that can ensure their effectiveness.

CONCLUSION

The present study reported the current research carried out regarding nanocarriers' production containing polyphenols in isolation or association with drugs for the treatment and prevention of breast cancer. Most of the polyphenols found in the studies have limitations in their bioavailability to the organism when included in the diet. In recent years, nanotechnology has gained significant prominence for developing carriers that can safely forward drugs and bioactive compounds, maintaining their chemical properties. We brought here different nanostructures for this purpose. Those that present significant results focus on liposomes and lipid nanoparticles associated with chemotherapy drugs and phenolic compounds to treat breast cancer cells *in vitro* studies. As well, curcumin and catechins were the most evident polyphenols in the studies, presenting satisfactory results. The studies, including nanotechnology for breast cancer treatment reported here, are of great interest to complement future research.

REFERENCES

AGHAPOUR, Fahimeh *et al.* Quercetin conjugated to silica nanoparticles inhibits tumor growth in MCF-7 breast cancer cell lines. **Communications of Biochemical and Biophysical Research**, v. 500, n. 4, p. 860-865, 2018.

AHMED, Rashid *et al.* Poly (lactic-co-glycolic acid) Nanoparticles Loaded with Callistemon citrinus Phenolics Exhibited Anticancer Properties against Three Breast Cancer Cell Lines. **Journal of Food Quality**, v. 2019, 2019.

AVTANSKI, Dimiter; PORETSKY, Leonid. Phyto-polyphenols as potential inhibitors of breast cancer metastasis. **Molecular Medicine**, v. 24, n. 1, p. 29, 2018.

BADAWI, Noha M. *et al.* Pomegranate extract-loaded solid lipid nanoparticles: design, optimization, and in vitro cytotoxicity study. **International journal of nanomedicine**, v. 13, p. 1313, 2018.

BANIK, Urmila *et al.* Curcumin: the spicy modulator of breast carcinogenesis. **Journal of Experimental & Clinical Cancer Research**, v. 36, n. 1, p. 98, 2017.

CASSANO, Roberta *et al.* Preparation, characterization and in vitro evaluation of resveratrol-loaded nanospheres potentially useful for human breast carcinoma. **Journal of Drug Delivery Science and Technology**, v. 57, p. 101748, 2020.

CHOWDHURY, Pallabita *et al.* Nanoparticles of paclitaxel inspired by tannic acid for intensified anticancer effects in breast cancer cells. **Journal of Colloid and Interface Science,** v. 535, p. 133-148, 2019.

CONTE, R. *et al.* Polyphenols nanoencapsulation for therapeutic applications. **Journal. Biomolecular Research Therapeutics**, v. 5, n. 2, p. 139, 2016.

CURCIO, Manuela *et al.* Dextran-Curcumin Nanoparticles as a Methotrexate Delivery Vehicle: A Step Forward in Breast Cancer Combination Therapy. **Pharmaceuticals**, v. 13, n. 1, p. 2, 2020.

DAVATGARAN-TAGHIPOUR, Yasamin *et al.* Polyphenol nanoformulations for cancer therapy: experimental evidence and clinical perspective**. International Journal of Nanomedicine**, v. 12, p. 2689, 2017.

DING, Jie *et al.* "Stealth and Fully-Laden" Drug Carriers: Self-Assembled Nanogels Encapsulated with Epigallocatechin Gallate and siRNA for Drug-Resistant Breast Cancer Therapy. **ACS Applied Materials & Interfaces**, v. 10, n. 12, p. 9938-9948, 2018.

FAN, Conghui *et al.* Resveratrol loaded oxidized mesoporous carbon nanoparticles: A promising tool to treat triple negative breast cancer. **Biochemical and Biophysical Research Communications**, v. 519, n. 2, p. 378-384, 2019.

FANTINI, Massimo *et al.* Efeitos antitumorais in vitro e in vivo de combinações de polifenóis, ou polifenóis e drogas anticâncer: perspectivas no tratamento do câncer. **Jornal Internacional de Ciências Moleculares** , v. 16, n. 5, p. 9236-9282, 2015.

FARAJZADEH, Raana *et al.* Nano-encapsulated metformin-curcumin in PLGA/PEG inhibits synergistically growth and hTERT gene expression in human breast cancer cells. **Artificial Cells, Nanomedicine and Biotechnology**, v. 46, n. 5, p. 917-925, 2018.

FENG, Ting *et al.* Liposomal curcumin and its application in cancer. **International journal of nanomedicine**, v. 12, p. 6027-6044, 2017.

GHAFFARI, Seyed-Behnam *et al.* Flower-like curcumin-loaded folic acid-conjugated ZnO-MPA-β-cyclodextrin nanostructures enhanced anticancer activity and cellular uptake of curcumin in breast cancer cells. **Materials Science and Engineering: C**, v. 103, p. 109827, 2019.

GHAYOUR, Nazanin *et al.* Nanoencapsulation of quercetin and curcumin in casein-based delivery systems. **Food hydrocolloids**, v. 87, p. 394-403, 2019.

GHOSH, Pooja *et al.* Solubility enhancement of morin and epicatechin through encapsulation in an albumin based nanoparticulate system and their anticancer activity against the MDA-MB-468 breast cancer cell line. **RSC Advances**, v. 6, n. 103, p. 101415-101429, 2016.

HASHIM, Nornisrina *et al.* Green mode synthesis of silver nanoparticles using Vitis vinifera's tannin and screening its antimicrobial activity/apoptotic potential versus cancer cells. **Materials Today Communications**, v. 25, p. 101511, 2020.

INCA - José Alencar Gomes da Silva National Cancer Institute. The situation of breast cancer in Brazil: synthesis of data from information systems. José Alencar Gomes da Silva **National Cancer Institute**. - Rio de Janeiro. Accessed in: November/2020.

KANGARLOU, Sogol *et al.* Curcumin-loaded nanoliposomes linked to homing peptides for integrin targeting and neuropilin-1-mediated internalization. **Pharmaceutical Biology**, v. 55, n. 1, p. 277-285, 2017.

KAZI, Julekha *et al.* Folate decorated epigallocatechin-3-gallate (EGCG) loaded PLGA nanoparticles; in-vitro and in-vivo targeting efficacy against MDA-MB-231 tumor xenograft. **International Journal of Pharmaceutics**, v. 585, p. 119449, 2020.

KHAN, Arif Ullah *et al.* An eco-benign synthesis of AgNPs using aqueous extract of Longan fruit peel: Antiproliferative response against human breast cancer cell line MCF-7, antioxidant and photocatalytic deprivation of methylene blue. **Journal of Photochemistry and Photobiology B: Biology**, v. 183, p. 367-373, 2018.

KHAN, Haoon *et al.* Flavonoid nanoparticles in cancer: treatment, prevention and clinical perspectives. **In: Seminars on Cancer Biology**. Academic press, 2019.

KHORRAMI, Sadegh; ZAREPOUR, Atefeh; ZARRABI, Ali. Green synthesis of silver nanoparticles at a low temperature at an accelerated rate, with exclusive elimination of DPPH radicals and selective cytotoxicity against the MCF-7 and BT-20 tumor cell lines. **Biotechnology Reports**, v. 24, p. e00393, 2019.

KHOSROPANAH, Mohammad Hossein *et al.* Analysis of the antiproliferative effects of curcumin and nanocurcumin in MDA-MB231 as a breast cancer cell line. **Iranian Journal of Pharmaceutical Research: IJPR**, v. 15, n. 1, p. 231, 2016.

KO, Jeong-Hyeon *et al.* The role of resveratrol in cancer therapy. **International Journal of Molecular Sciences**, v. 18, n. 12, p. 2589, 2017.

KOLAK, Agnieszka *et al.* Prevenção primária e secundária do câncer de mama. **Ann Agric Environ Med** , v. 24, n. 4, p. 549-553, 2017.

KULANDAIVELU, Karikalan; MANDAL, Abul. Positive regulation of biochemical parameters by solid lipid nanoparticles encapsulated with tea polyphenol under in vitro and in vivo conditions. **IET Nanobiotechnology**, v. 10, n. 6, p. 419-424, 2016.

LIU, Yingyi *et al.* Preparation of chitosan-Epigallocatechin-3-O-gallate nanoparticles and their inhibitory effect on the growth of breast cancer cells. **Journal of Innovative Optical Health Sciences**, v. 11, n. 04, p. 1850018, 2018.

MANSOURIZADEH, Fariba *et al.* Efficient synergistic combination effect of Quercetin with Curcumin on breast cancer cell apoptosis through their loading into Apo ferritin cavity. **Colloids and Surfaces B: Biointerfaces**, v. 191, p. 110982, 2020.

MENG, Jie *et al.* Combination therapy using co-encapsulated resveratrol and paclitaxel in liposomes for drug resistance reversal in breast cancer cells in vivo. **Scientific Reports**, v. 6, p. 22390, 2016.

MIRAKABAD, Fatemeh Sadat *et al.* A comparison between the cytotoxic effects of pure curcumin and PLGA-PEG nanoparticles loaded with curcumin in the MCF-7 human breast cancer cell line. Artificial Cells, **Nanomedicine and Biotechnology**, v. 44, n. 1, p. 423-430, 2016.

MOJZER, Eva *et al.* Polyphenols: Extraction methods, antioxidative action, bioavailability and anticarcinogenic effects. **Molecules**, v. 21, n. 7, p. 901, 2016.

MUKHERJEE, Sudeshna *et al.* Gold-conjugated green tea nanoparticles for enhanced anti-tumor activities and hepatoprotection-Synthesis, characterization and in vitro evaluation. **The Journal of Nutritional Biochemistry**, v. 26, n. 11, p. 1283-1297, 2015.

NARAYANAN, Sreeja *et al.* Sequential release of epigallocatechin gallate and paclitaxel from PLGA-casein core/shell nanoparticles sensitizes drug-resistant breast cancer cells. **Nanomedicine: Nanotechnology, Biology and Medicine**, v. 11, n. 6, p. 1399-1406, 2015.

PEREZ-RUIZ, Adriana Guadalupe *et al.* Lecithin-chitosan-TPGS nanoparticles as nanocarriers of (−)-epicatechin enhanced its anticancer activity in breast cancer cells. **RSC Advances**, v. 8, n. 61, p. 34773-34782, 2018.

PIRZADEH-NAEENI, Shirin *et al.* A comparative study on schizophyllan and chitin nanoparticles for ellagic acid delivery in treating breast cancer. **International Journal of Biological Macromolecules**, v. 144, p. 380-388, 2020.

POONIA, Neelam *et al.* Resveratrol-loaded folate targeted lipoprotein-mimetic nanoparticles with improved cytotoxicity, antioxidant activity and pharmacokinetic profile. **Materials Science and Engineering: C**, v. 144, p. 111016, 2020.

PUSHPALATHA, R.; SELVAMUTHUKUMAR, S.; KILIMOZHI, D. Cyclodextrin nanosponge based hydrogel for the transdermal co-delivery of curcumin and resveratrol: Development, optimization, in vitro and ex vivo evaluation. **Journal of Drug Delivery Science and Technology**, v. 52, p. 55-64, 2019.

RAFIEIAN-KOPAEI, Mahmoud; MOVAHEDI, Mino. Breast cancer chemopreventive and chemotherapeutic effects of Camellia Sinensis (green tea): an updated review. **Electronic Physician**, v. 9, n. 2, p. 3838, 2017.

RAGHAVAN, Bhuvanasree *et al.* Kaempferol mediated synthesis of gold nanoparticles and their cytotoxic effects on MCF-7 cancer cell line. **Process Biochemistry**, v. 50, n. 11, p. 1966-1976, 2015.

RAMADASS, Satiesh Kumar *et al.* Paclitaxel/epigallocatechin gallate coloaded liposome: a synergistic delivery to control the invasiveness of MDA-MB-231 breast cancer cells. **Colloids and Surfaces B: Biointerfaces**, v. 125, p. 65-72, 2015.

RAMLJAK, D. *et al.* Pentameric procyanidin from Theobroma cacao selectively inhibits growth of human breast cancer cells. **Molecular Cancer Therapeutics**, v. 4, n. 4, p. 537-546, 2005.

ROCHA, Ana *et al.* Pomegranate juice and specific components inhibit cell and molecular processes critical for metastasis of breast cancer. **Breast Cancer Research and Treatment**, v. 136, n. 3, p. 647-658, 2012.

SADHUKHAN, Pritam *et al.* Targeted distribution of quercetin via pH-responsive zinc oxide nanoparticles for breast cancer therapy. **Materials Science and Engineering**, v. 100, p. 129-140, 2019.

SANTOS, Ana Cláudia *et al.* Nanotechnology-based formulations for resveratrol delivery: Effects on resveratrol in vivo bioavailability and bioactivity. **Colloids and Surfaces B: Biointerfaces**, v. 180, p. 127-140, 2019.

SARKAR, Abhijit *et al.* Targeted delivery of quercetin loaded mesoporous silica nanoparticles to the breast cancer cells. **Biochimica et Biophysica Acta (BBA)-General Subjects**, v. 1860, n. 10, p. 2065-2075, 2016.

SHIRODE, Amit B. *et al.* Nanoencapsulation of pomegranate bioactive compounds for breast cancer chemoprevention. **International Journal of Nanomedicine**, v. 10, p. 475-484, 2015.

SILVA, Claudia *et al.* Selective pro-apoptotic and antimigratory effects of polyphenol complex catechin: lysine 1: 2 in breast, pancreatic and colorectal cancer cell lines. **European Journal of Pharmacology**, v. 859, p. 172533, 2019.

STEUBER, Nelson *et al.* Tocotrienol nanoemulsion platform of curcumin elicit elevated apoptosis and augmentation of anticancer efficacy against breast and ovarian carcinomas. **International Journal of Molecular Sciences**, v. 17, n. 11, p. 1792, 2016.

SUN, Yang *et al.* O resveratrol inibe a migração e metástase do câncer de mama humano MDA--MB-231 ao reverter a transição epitelial-mesenquimal induzida por TGF-β1. **Molecules** , v. 24, n. 6, p. 1131, 2019.

THIPE, Velaphi *et al.* Development of resveratrol-conjugated gold nanoparticles: Interrelationship of increased resveratrol corona on anti-tumor efficacy against breast, pancreatic and prostate cancers. **International Journal of Nanomedicine**, v. 14, p. 4413, 2019.

WANG, Wenrui *et al.* Anticancer effects of resveratrol-loaded solid lipid nanoparticles on human breast cancer cells. **Molecules**, v. 22, n. 11, p. 1814, 2017.

YIANNAKOPOULOU, Eugenia C. Interaction of green tea catechins with breast cancer endocrine treatment: a systematic review. **Pharmacology**, v. 94, n. 5-6, p. 245-248, 2014.