

## THE USE OF NANOCARRIERS IN THE TREATMENT OF COLON CANCER: A LITERATURE REVIEW<sup>1</sup>

### *O USO DE NANOCARREADORES NO TRATAMENTO DE CÂNCER DE CÓLON: UMA REVISÃO DE LITERATURA*

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#### ABSTRACT

Colon cancer is one of the most prevalent diseases with a high morbidity and mortality rates and is considered the 4th most common cause of cancer-related death. Nanocarriers are multifunctional platforms capable of delivering therapeutic agents to a specific tissue/cell and may enhance the therapeutic effect of the drug with the combination of magnetic hyperthermia or phototherapy. From that, this study aims to review the literature on the use of nanocarriers in the treatment of colon cancer and discuss the main found results. By analyzing the researched articles, we can conclude that the nanocarriers co-charged with drugs and genes have improved antitumor effects and an excellent efficiency in the delivery of drugs to the tumor site and are promising for the treatment of colorectal cancer.

**Keywords:** colorectal cancer, nanocarriers, nanotechnology.

#### RESUMO

*O câncer de cólon é uma das doenças mais prevalentes com alta taxa de morbidade e mortalidade, sendo considerada a 4ª causa mais comum de morte relacionada ao câncer. Os nanocarreadores são plataformas multifuncionais capazes de distribuir agentes terapêuticos a um tecido/célula específica e podem aumentar o efeito terapêutico do medicamento com a associação de hipertermia magnética ou fototerapia. A partir disso, esse estudo objetivou fazer uma revisão de literatura sobre o uso de nanocarreadores no tratamento de câncer de cólon e discutir os principais resultados encontrados. Analisando os artigos encontrados, concluiu-se que os nanocarreadores co-carregados com fármacos e genes possuem efeitos antitumorais melhorados e uma excelente eficiência na entrega de medicamentos ao local do tumor, sendo promissoras para o tratamento de câncer colorretal.*

**Palavras-chave:** câncer colorretal, nanocarreadores, nanotecnologia.

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## INTRODUCTION

Cancer is the name given to a set of more than 200 diseases that have in common the rapid multiplication of abnormal cells that grow beyond their usual limits and which can, through the blood or lymphatic circulation, invade adjacent parts of the body and spread to other organs. Cancer is one of the leading causes of mortality in the world. In Brazil the fact that cancer is a public health problem is undeniable. The Ministry of Health estimates about 21.4 million new cases of cancer and 13.2 million deaths related to the disease in 2030, since it led to the elaboration of Cancer Control and Prevention Programs in the country (COSTA; SILVA, 2017).

Colorectal cancer (CRC) refers to a slow-developing cancer that occurs from the accumulation of genetic and epigenetic changes of epithelial cells of the rectum or colon, leading to tissue growth in the inner lining of the rectum or colon. If this abnormal growth, known as a polyp, eventually becomes cancerous, it may form a tumor in the wall of the rectum or colon, and subsequently progress to an invasive and metastatic adenocarcinoma (MARLEY; NAN, 2016). Colon cancer is a neoplasm of epithelial origin that contributes significantly to the mortality and morbidity of people by cancer in the world. This neoplasm is known as a silent disease, since many patients only present symptoms when the disease is already at an advanced stage (FRAGOSO, 2017).

Risk factors related to the development of colon cancer include obesity, sedentary behavior and a diet rich in fiber and fats, dietary intake rich in red and / or processed meat, refined sugar and excessive consumption of alcohol and cigarettes. In addition, genetic predisposition, family history, diabetes and chronic bowel inflammation are also among the risk factors for the development of colon cancer (MARLEY; NAN, 2016).

The most common types of treatment for colon cancer include chemotherapy, surgery, radiation and a combination of any of these treatments. However, there are challenges associated with traditional treatments - non-specificity, toxicity, etc. The current challenge of drug therapy is the optimization of the pharmacological action of the drug and the minimization of its toxic side effect. The local concentration of the drug in the cancerous sites needs to be high, while in other tissues low, to avoid any negative reaction. The application of nanotechnology in the treatment of cancer has the potential to help in these limitations. Designing nanoparticles loaded with multifunctional drugs and functionalizing their surfaces with recognition proteins may target specific cancer cells (HO et al., 2017).

Nanotechnology is associated with the manipulation of matter at the nanoscale (corresponding to one billionth of a meter). In this scale, the atoms reveal peculiar characteristics that can present/display tolerance to the temperature, color, chemical reactivity, electrical conductivity, or even show force of extraordinary intensity, being thus advantageous for the constitution of nanoparticles (also called nanocarriers or nanosystems) methods of diagnosis and treatment of cancer (COSTA; SILVA, 2017).

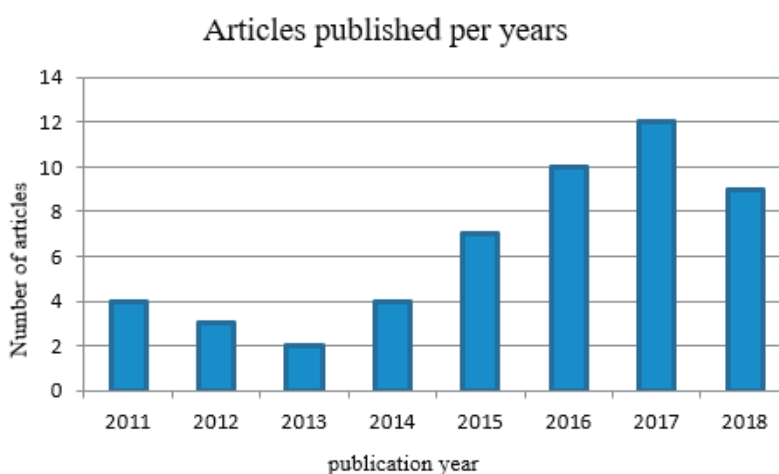
An area of application of nanoscience and nanotechnology that deserves to be highlighted is biomedicine, which has received massive and increasing investments over the last years. The fact that nanoparticles have sizes comparable to biological entities, such as cells, viruses, molecules, proteins and even genes, makes them suitable for biomedical applications. In addition, the large relative surface of the nanoparticles can be suitably modified, or functionalized, to receive biological agents, organic molecules, vitamins, antibiotics, peptides or polymeric coating for the purpose of altering their properties or scheduling them to accumulate specifically in cells “Target” (FALLEIROS et al., 2011).

In view of the above, the objective of this study was to review the available literature on the studies involving the use of nanocarriers for the treatment of colon cancer and to compare the results among the articles already published.

## MATERIALS AND METHOD

This study is based on a literature review, conducted between August and December 2018, in which a query was made in the *PubMed* database. The search in the database was performed without limitation of year using the descriptors “*nanocarriers and colon cancer*”. We found 52 articles using the descriptors, as shown in the graph of figure 1. Of the 52 articles found, 17 were used to carry out the review article and the rest were excluded because they were chapters of books or review articles, or because they did not address specifically the subjects highlighted in this study.

**Figure 1** - Files in the *PubMed* Platform using the descriptors “nanocarriers and colon cancer”.



Source: *PubMed*

## RESULTS AND DISCUSSIONS

Painting 1 shows a summary of the articles found and selected in the *PubMed* database for the review.

## Painting 1 - List of articles used in the study.

Year	Title	Autor
2011	Anticancer effectiveness of polymeric drug nanocarriers on colorectal cancer cells.	WANG and PENG, 2011.
2012	Novel alginate-enclosed chitosan-calcium phosphate-loaded iron-saturated bovine lactoferrin nanocarriers for oral delivery in colon cancer therapy.	KANWAR et al., 2012.
2013	Drug delivery by polymeric micelles: an in vitro and in vivo study to deliver lipophilic substances to colonocytes and selectively target inflamed colon.	VALERII et al., 2013.
	Fabrication and Intracellular Delivery of Doxorubicin/Carbonate Apatite Nanocomposites: Effect on Growth Retardation of Established Colon Tumor.	HOSSAIN et al., 2013.
2015	Functional-segregated coumarin-containing telodendrimer nanocarriers for efficient delivery of SN-38 for colon cancer treatment.	XU et al., 2015.
	Poly(butylcyanoacrylate) and Poly( $\epsilon$ -caprolactone) Nanoparticles Loaded with 5-Fluorouracil Increase the Cytotoxic Effect of the Drug in Experimental Colon Cancer.	ORTIZ et al., 2015.
2016	Enhanced Efficacy of Artemisinin Loaded in Transferrin- Conjugated Liposomes versus Stealth Liposomes against HCT-8 Colon Cancer Cells.	LETO et al., 2016.
2017	Poly (HydroxyButyrate-co- HydroxyValerate) (PHBHV) Nanocarriers for Silymarin Release as Adjuvant Therapy in Colo-rectal Cancer.	RADU et al., 2017.
	Mesoporous Silica Nanoparticles (MSNs)-Based Organic/Inorganic Hybrid Nanocarriers Loading 5-Fluorouracil for the Treatment of Colon Cancer with Improved Anticancer Efficacy.	PAN et al., 2017.
	Chitosan-coated cinnamon/oregano -loaded solid lipid nanoparticles to augment 5-Fluorouracil cytotoxicity for colorectal cancer: extracts standardization, nanoparticles optimization and cytotoxicity evaluation.	KAMEL et al., 2017.
	Multifunctional nanospheres for co-delivery of methotrexate and mild hyperthermia to colon cancer cells.	LIMA et al., 2017.
2018	Newly Designed Silica-Containing Redox Nanoparticles for Oral Delivery of Novel TOP2 Catalytic Inhibitor for Treating Colon Cancer.	VONG et al., 2017.
	Hyaluronidase Enzyme-responsive Targeted Nanoparticles for Effective Delivery of 5-Fluorouracil in Colon Cancer.	JIANG et al., 2018.
	Hypoxia-inducible bidirectional shRNA expression vector delivery using PEI/chitosan-TBA copolymers for colorectal Cancer gene therapy.	JAVAN et al., 2018.
	In Vivo Evaluation of Magnetic Targeting in Mice Colon Tumors with Ultra-Magnetic Liposomes Monitored by MRI.	THÉBAULT et al., 2018.
	Colorectal cancer combination therapy using drug and gene co-delivered, targeted poly(ethylene glycol)- $\epsilon$ -poly(caprolactone) nanocarriers.	WANG et al., 2018.

Source: Authors' construction.

Wang and Peng (2011) studied the anticancer efficacy of nanocarriers of polymeric drugs in colorectal cancer cells. Doxifluridine, a prodrug of 5-fluorouracil (5-FU), was used as the initiator directly in  $\epsilon$ -caprolactone ring-opening polymerization to form doxifluridine-polyhydrophobic ( $\epsilon$ -caprolactone) (doxifluridine-PCL) which was subsequently grafted with hydrophilic chitosan to synthesize doxyphluridine-PCL-chitosan amphiphilic copolymer. This amphiphilic copolymer was self-aggregated into micellar nanoparticles. After the HT-29 colon cancer cells were treated with the polymeric drug nanocarrier, prodrug doxifluridine was converted to 5-fluorouracil by the endogenous thymidine phosphorylase (TP) and thereby resulting in cell death. The chemotherapeutic drug 7-ethyl-10-hydroxy camptothecin (SN-38) was further encapsulated in the hydrophobic core of the nanocarriers of the polymeric drug and treated with HT-29 cells. The anticancer effectiveness of the polymeric drug nanocarriers was extensively enhanced by synergistic anticancer activity of slowly released

cytotoxic drugs (i.e., 5-FU and SN-38). In addition, HT-29 cells transfected with TP-encoding plasmids were selected by G418 antibiotic to obtain HT-29 / TP cells. These TP enzyme-overexpressed cells were challenged with doxifluridine-PCL-chitosan polymer prodrug micelles. The viability of HT-29 / TP cells dropped significantly after 72 hours of treatment. Besides that, Valerii et al. (2013) synthesized core-shell polymeric micelles obtained by self-assembly of block copolymers to provide high efficiency of anti-inflammatory and anticancer compounds to colon and colon mucosa. Highly lipophilic substances, such as Nile Red and Retinoic Acid, were loaded quantitatively into core-shell polymeric micelles. When loading with prednisone and doxorubicin, which are slightly soluble in water, the drug loaded into the micelles decreased after dialysis. Prednisone ( $EE \geq 60\%$ ) was quantified by HPLC after disassembly of the core-shell micelles with acetonitrile. BPMs are not toxic and leave cell viability unaffected in a wide range of eukaryotic cells.

Considering their size, these nanoparticles are reasonably internalized by an endocytic mechanism and disassemble into their constituting polymeric chains (unimers) when the decreased pH reduce the thermodynamic stabilization given by the anionic corona, delivering their content into the cytosol. This report demonstrated that BPMs are able to deliver different lipophilic drugs to colonocytes. Interestingly, BPMs efficiently overcome the multidrug resistance that may become characteristic of transformed colon cells. As a result of the study, the authors obtained efficient intracellular delivery of these hydrophobic compounds (prednisone, retinoic acid and doxorubicin) to cultured colonocytes without cell toxicity. The effectiveness of retinoic acid and doxorubicin administered was significantly increased using nanometric vehicles. In addition, polymeric micelles have been found to bypass the multidrug resistance efflux mechanism by effectively distributing doxorubicin to multidrug resistant colon cancer cells. These nanocarriers are also suitable for selective *in vivo* release of lipophilic drugs by administering enema to the inflamed colon tissue specifically targeting the inflamed mucosa.

Vong et al. (2017) developed in their study a newly designed redox silica-based nanoparticle (siRNP) capable of eliminating reactive oxygen species (ROS) as an ideal oral nanocarrier for a new hydrophobic antineoplastic compound BNS-22 to treat cancer-associated colitis. Crosslinking of silica portions significantly increased stability under acidic conditions and improved the BNS-22 siRNP loading capacity compared to conventional redox nanoparticle. Following oral administration to mice, BNS-22 loaded siRNP (BNS-22 & siRNP) markedly improved the bioavailability and distribution of the BNS-22 colon tumor. As a result, BNS-22 loaded siRNPs significantly inhibited tumor progression in colitis-associated colon cancer mice compared to other control treatments, in addition, orally administered BNS-22 @ siRNP suppressed the adverse effects of colitis. BNS-22 due to its ROS clearance capability and no other noticeable toxicity was observed in mice treated with BNS-22 @ siRNP although siRNP is located in the gastrointestinal tract.

The clinical use of 5-fluorouracil, one of the drugs of choice in colon cancer therapy, is limited by a nonuniform oral absorption, a short plasma half-life, and by the development of drug resistances by malignant cells. The hypothesized is that the formulation of biodegradable nanocarriers for the efficient delivery of this antitumor drug may improve its therapeutic effect against advanced or recurrent colon cancer. Hence, Ortiz et al. (2015) have designed two nanoparticulate systems loaded with fluorouracil based on the biodegradable polymers poly (butylcyanoacrylate) and poly ( $\epsilon$ -caprolactone). Synthesis methodologies of 5-FU-loaded PBCA NPs and 5-FU-loaded PCL NPs were based on the emulsion polymerization of the butylcyanoacrylate monomer in an aqueous solution and on the interfacial polymer disposition, respectively. Both methods generated biodegradable 5-FU-loaded particles with an average size  $\leq 100$  nm, which could be deemed appropriate to facilitate their cellular uptake thus resulting in a considerable accumulation of drug molecules within malignant cells. In fact, particle diameters ranging from 100 to 200 nm have been associated with cell internalization by endocytosis, while larger particles can be internalized by phagocytosis. The incorporation of drugs into the nanosystems was accomplished by entrapment (encapsulation / dispersion) within the polymer network during the synthesis of nanoparticles. The association of 5-FU molecules with nanocarriers has yielded diverse results against colon cancer cell lines. Nanocarriers based on copolymers such as poly( $\gamma$ -benzyl-L-glutamate) and poly(ethylene glycol) can increase the plasma half-life of 5-FU, thus inducing a greater growth inhibition of colon cancer cells. The reduction in the percentage of relative proliferation (RP %) caused by the 5-FU-loaded PBCA and PCL NPs could be the consequence of a faster (and more intense) 5-FU internalization by malignant cells, therefore facilitating greater drug concentrations within the cancer cells. Furthermore, NP internalization within cancer cells depends not only on their hydrophilic/hydrophobic character and physical chemistry (*i.e.*, size and surface charge) but also on the endocytosis processes involved which can be considered to be more important in tumor cells. Both types of nanocarriers significantly increased the antiproliferative effect of the encapsulated drug. In addition, both nanoformulations produced in vivo an intense inhibition of tumor growth and increased the survival rate of the mice used in the tests, the greatest reduction in tumor volume being obtained when using the poly ( $\epsilon$ -caprolactone) based formulation. The results suggested that these nanocarriers may enhance the antitumor activity of fluorouracil and may be used against advanced or recurrent colon cancer.

In collaboration with the study by Ortiz et al. (2015), Pan et al. (2017) developed a new type of inorganic / organic hybrid nanoparticles based on mesoporous silica nanoparticles (MSNs) covalently linked to poly (oligo (ethylene glycol) monomethyl ether methacrylate) (POEGMA) for better stabilization and target peptide (RGD) for targeted delivery to improve the antineoplastic performance of 5-Fluorouracil (5-FU). Briefly, MSN was synthesized by the base-catalyzed hydrolysis of tetraethyl orthosilicate using N-cetyltrimethylammonium bromide as the template. The obtained MSN was modified with 3-aminopropyltriethoxysilane, leading to the formation of amine-functionalized MSN, MSN-NH<sub>2</sub>.

MSN-Br was then prepared by the reaction of amino groups of MSN-NH<sub>2</sub> with 2-bromo-2-methylpropionyl bromide. A typical TEM image obtained by drying the aqueous solution of MSN-Br revealed the presence of spherical nanoparticles with a diameter of ~110 nm. In the study, it was shown that 5-FU can be effectively loaded on MSN-based nanoparticle mesopores. 5-FU @ MSN can effectively improve cell death in vitro and reduce tumor growth in vivo than free 5-FU. The improved anticancer performance of 5-FU@MSN might be explained as follows. It is known that a single MSN contains more than one 5-FU molecule due to its large surface area and many meso-pores. So, with the internalization of one nanoparticle many 5-FU molecules enter into cells simultaneously. The improved 5-FU amount in cells ultimately led to more cell death. Moreover, the cell viability further declined when 5-FU@MSN-RGD was used. At a 5-FU concentration of ~50 mg/mL, the cell viability decreased to ~40.8% and the IC<sub>50</sub> further dropped to as low as ~25.86 mg/mL. This result reveals that attaching RGD onto the nanoparticle might exert a crucial role in enhancing the anticancer performance. But serious side effect was observed. The introduction of RGD halves into nanomedicines (5-FU @ MSN-RGD) gave it better internalization in colon cancer cells in vitro, improved in vitro cell death, increased accumulation in tumor tissues, reduced tumor proliferation and reduced side effects than 5-FU @ MSN and free 5-FU.

The study by Jiang et al. (2018) also demonstrates that a new delivery strategy for one of the major antineoplastic drugs, 5-Fluorouracil (5-FU), could have enormous potential for colon cancer segmentation. In the study, mesoporous silica nanoparticles conjugated with 5-fluorouracil (5-FU) loaded hyaluronic acid (HA) were added to increase anticancer effectiveness in colon cancers. Mesoporous silica nanoparticles (MSN) were prepared by base-catalyzed sol-gel method wherein TeOS was used as a silica source, CTAB as a structural agent and NaOH as a base catalyst. The CTAB, surfactant was removed by calcination process. The HA was conjugated on the MSN surface using reaction between amino group of MSN and carboxylic group of HA by EDC/NHS chemistry. The average particle size of FMSN was ~120 nm with a uniform dispersity index. The particle size of MSN increased to ~190 nm after the surface conjugation of HA. The increase in the particle was mainly attributed to the high molecular weight of HA on the MSN surface. The HA modification on the MSN surface increased the stability and dispersion of particles. The presence of HA on the surface of nanoparticles targeted the overexpressed CD44 receptors in colon cancer cells. In vitro cell viability and the apoptosis assay clearly showed the superior anticancer effect of 5-FU-loaded mesoporous silica nanoparticles conjugated with hyaluronic acid (HA / FMSN) in HT colon cancer cells. This could be attributed to the better accumulation in the tumor tissues by virtue of enhanced permeation and retention effect. As expected, HA/ FMSN exhibited a significant reduction in the tumor burden compared to that of any group. HA/FMSN was 3-fold more effective than free drug and 2-fold more effective than FMSN. HA / FMSN exhibited 43% of remarkably higher cells in the early apoptosis phase and 55% of cells in the late apoptosis phase, indicating the superior anticancer effect of HA / FMSN. HA / FMSN exhibited a significant reduction in tumor burden compared to that of any group.

Kamel et al. (2017) synthesized solid chitosan-loaded lipid nanoparticles coated with chitosan in order to increase the cytotoxicity of 5-Fluorouracil for colorectal cancer. In the current study, SLNs coated with chitosan were prepared and optimized using hot melt emulsification homogenization/ultrasonication method using a mixture of lipid with different melting point. Extract-loaded SLN-Cs was prepared using optimum levels of experimental variables. The developed experimental-model suggested optimum formulation with 2% lipid, 2.3% surfactant and 0.4% chitosan to achieve particle-size of 254.77nm, polydispersity-index of 0.28, zeta-potential of +15.26, and entrapment-efficiency % of 77.3% and 69.1% for cinnamon and oregano, respectively. Both extracts inhibited HCT 116 cells, which confirmed their cytotoxic activity against colon cancer, showed high percentage of cell inhibition, high percentage of apoptotic cells, high activation of caspases and high suppression of mitochondrial membrane potential confirming the success of suggested combination with one of the standard drugs (5-FU) to treat human colon carcinoma, also decreasing the side effects of the free drug.

In agreement with the study, Javan et al. (2018) built a hypoxia/colorectal dual-specific bidirectional short hairpin RNA (shRNA) expression vector and to transfect it into the colon cancer cell line HT-29 with PEI/ chitosan-TBA nanoparticles for the simultaneous knock down of  $\beta$ -catenin and Bcl-2 under hypoxia. The double targeting vector was delivered to colon cells using the copolymer, PEI/chitosan-TBA. The PEI/chitosan-TBA blend system provided effective transfection with low cytotoxicity. An in vitro transfection assay demonstrated that the combination of the HRE of the VEGF gene and the CEA promoter specifically knocked down both gene expression under hypoxia in colon cancer cells. Moreover, pRNAT-bipHRE-CEAsh (Bcl2- $\beta$ -catenin) could induce cell cycle arrest and increase colorectal cell apoptosis under hypoxic conditions. Therefore, designed vector may have potential therapeutic utility in human colon cancer. Additionally, PEI/chitosan-TBA copolymer with high gene transfection efficiency and low cytotoxicity might be a promising gene carrier for use in gene transfer in vivo.

Kanwar et al. (2012) developed nanoparticles of iron saturated iron-saturated lactoferrin (Fe-bLf) containing chitosan and calcium phosphate for oral administration in colon cancer therapy. Fe-BLF or paclitaxel (Taxol) were adsorbed on calcium phosphate nanocarriers (NCs), closed in biodegradable polymers chitosan and alginate. Fe-bLf or Taxol-loaded NCs indicated as NCs AEC-CP-Fe-bLf or AEC-CP-Taxol, respectively, were made by combining ionic gelling and nanoprecipitation. The size distribution, morphology, internalization and release profiles of the NCs were studied together with the evaluation of anticancer activities in vitro and in vivo and compared with paclitaxel. The AEC-CP-Fe-bLf NCs were highly effective when given orally as a pre-treatment 1 week prior to Caco-2 cell injections. None of the NC-fed AEC-CP-Fe-bLf mice developed tumors or showed any signs of toxicity, while mice fed the AIN 93G control diet showed normal tumor growth. Fe-bLf or Taxol, when given orally in a diet as nanoformulations after tumor development, showed a significant regression in tumor size with complete inhibition of tumor growth later, while



intratumoral injection of Taxol only delayed the growth of tumors. Pharmacokinetic and bioavailability studies indicated that nanoformed Fe-bLf was predominantly present in tumor cells compared to non-nanoformed Fe-bLf. It has also been found that NCs loaded with Fe-bLf aid in the absorption of iron and therefore may have utility in increasing iron absorption during iron deficiency without interfering with calcium absorption.

Also following the biodegradable line, Radu et al. (2017) designed and constructed biocompatible poly (hydroxybutyrate-co-hydroxy valerate) nanocarriers for the release and targeting of silymarin as adjuvant therapy in HT-29 colon cancer cells. The researchers' great challenge was to address one of the main problems of today's nanomedicine era: the bioavailability of poorly water-soluble drugs such as silymarin. The silymarin-loaded PHBHV nanoparticles were prepared by the nanoprecipitation method using a PVA solution as a stabilizer for the polyester solution, a diameter of about 80-100 nm was determined for the nanoparticles. It was observed that the nanoparticles did not influence cell viability nor exert any cytotoxic effects, in addition, silymarin-loaded PHBHV nanocarriers significantly decreased the viability of HT-29 cells after 6 and 24 h of treatment. PHBHV nanocarriers showed satisfactory ability to penetrate three-dimensional structures and administer the drug.

Already a study developed by Xu and coworkers (2015) synthesized coumarin-containing nanodencils selected for the targeted release of 7-ethyl-10-hydroxycamptothecin (SN-38), a prominent and effective anticancer agent for the treatment of colon cancer. The encapsulation of the nanoparticles significantly increased the solubility of SN-38 in aqueous solution. Dynamic light scattering (DLS) showed that the size of these SN-38 nanoparticles is about 50 nm, and rod-shaped micelles were observed using transmission electron microscopy (TEM). The formulations were demonstrated as non-cytotoxic and non-hemolytic and could release the drug gradually over several days in vitro. Through near-infrared fluorescent optical imaging (NIRF), it was possible to monitor tumor-targeted delivery of SN-38 / NPs by co-loading a NIRF dye. These NPs have been shown to accumulate preferentially in tumors when compared to healthy tissue, which is a major challenge when it comes to current cancer treatment options. The study revealed promising new therapeutic agents for the treatment of colorectal cancer SN-38 loaded nanoformulations exhibit superior antitumor efficacy compared to Irinotecan at an equivalent dose of SN-38 in HT-29 human colon cancer xenograft models.

Another group of successful drug targeting and delivery researchers was led by Wang and co-workers (2018): active targeted nanocarriers (NCs) with drugs and co-loaded genes have improved antitumor effects and excellent gene delivery efficiency at the tumor site. In the present research, poly (ethylene glycol) -  $\epsilon$ -poly (caprolactone) block copolymer was used for the co-loading of 5-fluorouracil (5-FU) and gene. Physico-chemical, in vitro and in vivo anticancer characteristics, and efficiency of gene transfection were tested in colon cancer cells and tumor-bearing mice. The 5-FU and co-loaded gene nanocarriers had a size of 145 nm. It can be seen that the tumor volume of the nanocarried groups on day 21 was about 320 mm<sup>3</sup>, which is significantly smaller compared

to the free 5-FU group (852 mm<sup>3</sup>) and the control group (1,059 mm<sup>3</sup>); may be considered promising for colorectal cancer therapy.

Hossain et al (2013) developed pH-sensitive nanosystems to achieve a slightly acidic extracellular pH environment of solid tumors. When nanosystems are combined with release mechanisms triggered at endosomal or lysosomal acid pH along with the endosomotic capacity, nanocarriers have been shown to overcome the multidrug resistance of several tumors. Thus, Hossain and colleagues successfully fabricated a nano-size release device for the anticancer drug Doxorubicin (DOX) in tumor cells using the inorganic apatite carbonate crystals with nano-scale characteristics and rapid release of DOX in response to low pH, resulting in increased cell uptake and significantly increased the tumor-inhibiting effects of the drug, even with a very low dose of antineoplastic drug. The extraordinary inhibitory effect of proliferation on tumor cell lines was achieved by virtue of their sensitivity to pH, resulting in the rapid release of the vehicle's drugs, thus achieving significant antitumor activity in the mouse colorectal model. Therefore, using carbonate apatite and a chemotherapeutic agent, they propose a new therapeutic strategy of nano-based pH targeting against human malignancies.

Leaving for the nanospheres, Lima et al. (2017) studied synthesis and multifunctionality for co-delivery of Methotrexate and mild hyperthermia to colon cancer cells. They synthesized polyethylene glycol-poly(lactic acid) (PEG-PLA) nanospheres loaded with iron oxide superparamagnetic nanoparticles (SPIONs) for targeted delivery of methotrexate (MTX) to colon cancer therapy. Multifunctional nanospheres were able to increase MTX cytotoxicity relative to Caco-2 and SW-480 colon cancer cells compared to free drug. By an emulsion-evaporation method, the nanospheres were produced and then characterized by size distribution, zeta potential, in vitro drug release profile and cell studies. Co-delivery of MTX and SPIONs into PEG-PLA nanospheres resulted in nanocarriers with a size of 160 nm in diameter, a polydispersity index below 0.2, and a potential zeta of ca. -18 mV. In addition, nanospheres allowed embedded MTX to induce greater cell cycle arrest and apoptotic effects than free MTX.

Leto and colleagues (2016) developed a new nanocarrier for the delivery and activation of Artemisinin (ART) in cancerous tissues. ART is considered a promising candidate for antitumor drug but its solubility in water is not satisfactory, has low bioavailability and its half-life is short so the drug was loaded onto transferrin-conjugated liposomes (ART-L-Tf) because transferrin liposomes are widely expressed in cancer cells and the iron content is higher than in normal cells. Further information on nanocarrier characteristics have not been reported but it is noted a better distribution in cancer target cells, as well as a significant decrease in cytotoxicity as a result of the presence of iron ions, resulting in synergism derived from increased transferrin receptor expression on the surface of tumor cells and attracting increasing interest in their antitumor properties in a variety of cancer cells.

## CONCLUSION

The development and application of functionalized nanoparticles with biomarkers and cell recognition molecules have not only allowed the early diagnosis and the localization of tumor cells, but have also contributed to optimize the targeting of the active agent in the tumor, enhancing the efficacy of treatment because of peculiar pharmacokinetic characteristics such as increased agent time in the blood circulation, absorption, volume of distribution and half-life. The study shows that nano-carriers co-loaded with drugs and genes have improved antitumor effects and excellent drug delivery efficiency at the tumor site. Therefore, nanocarriers can be used as a promising nanomedicine for the delivery of antitumor drugs and may contribute significantly to colorectal cancer therapy.

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