Nanoparticles in Cancer Treatment: General Aspects, Antineoplastic Mechanisms of Action and Tumor Applications

doi: https://doi.org/10.32635/2176-9745.RBC.2019v65n4.400

Utilização de Nanopartículas no Tratamento do Câncer: Aspectos Gerais, Mecanismos de Ação Antineoplásicos e Aplicabilidades Tumorais

Nanopartículas en el Tratamiento del Cáncer: Aspectos Generales, Mecanismos de Acción Antineoplásicos y Aplicaciones Tumorales

Juliana Carvalho Lopes[1]; Maria Lúcia Pereira Torres[2]

Abstract

Introduction: Technological advances in recent decades have led to the development of therapeutic approaches in medicine on a new scale of nanometric molecular applications, allowing the establishment of new therapies such as nanotherapy. The use of nanoparticles entails numerous opportunities as well as major challenges for human application where use requires a thorough understanding of the biocompatibility and pharmacodynamics of molecules. In cancer, nanoparticles act mainly in the active forms that are characterized by the use of ligands or antibodies on their surfaces where they bind to certain cells, and in the passive form, where particles accumulate in tumor tissues due to the large fractions of tumor endothelium. **Objective**: To address the main properties of protein, metal, polymer and lipid nanoparticles, their structures and uses against specific cancer cells and the advantages and disadvantages of their use. **Method**: Selection of articles with studies on nanoparticles from 2010 to 2018 in the PubMed and SciELO databases through narrative review of the literature. **Results:** Nanoparticles have different mechanisms of action and may obtain more favorable results according to their chemical structure. **Conclusion**: Based in this review, it was concluded that certain nanoparticles have functionalities that enhance the anticancer effects of antineoplastic drugs and emerge as a new approach for cancer treatments.

Key words: Nanoparticles/administration & dosage; Nanoparticles/therapeutic use; Neoplasms; Antineoplastic Agents.

Resumo

Introdução: Os avanços tecnológicos das últimas décadas levaram ao desenvolvimento de abordagens terapêuticas na medicina em uma nova escala de aplicações moleculares nanométricas, permitindo o estabelecimento de novas terapias como a nanoterapia. O uso de nanopartículas implica inúmeras oportunidades e também grandes desafios para a aplicação humana, esse uso requer uma compreensão minuciosa da biocompatibilidade e da farmacodinâmica das moléculas. No câncer, as nanopartículas atuam principalmente na forma ativa, que se caracteriza pela utilização de ligantes ou anticorpos em suas superfícies onde se ligam a determinadas células, e, na passiva, onde as partículas se acumulam nos tecidos tumorais em razão das largas frenestrações dos endotélios tumorais. **Objetivo**: Abordar as principais propriedades das nanopartículas de proteína, metal, polímero e lipídio, suas estruturas e utilizações contra células cancerígenas específicas e as vantagens e desvantagens do seu uso. **Método**: Selecionar artigos com estudos sobre nanopartículas entre os anos de 2010 a 2018 nos bancos de dados PubMed e SciELO por meio de revisão integrativa da literatura. **Resultados:** As nanopartículas apresentam diferentes mecanismos de ação e podem obter resultados mais favoráveis de acordo com sua estrutura química. **Conclusão**: Concluiu-se com esta revisão que determinadas nanopartículas apresentam funcionalidades que potencializam os efeitos anticancerígenos dos fármacos antineoplásicos e surgem como uma nova abordagem para tratamentos contra o câncer.

Palavras-chave: Nanopartículas/administração & dosagem; Nanopartículas/uso terapêutico; Neoplasias; Antineoplásicos.

Resumen

Introducción: Los avances tecnológicos en las últimas décadas han llevado al desarrollo de enfoques terapéuticos en medicina en una nueva escala de aplicaciones moleculares nanométricas, lo que permite el establecimiento de nuevas terapias como la nanoterapia. El uso de nanopartículas conlleva numerosas oportunidades, así como desafíos importantes para la aplicación en humanos, este uso requiere un conocimiento profundo de la biocompatibilidad y farmacodinámica de las moléculas. En el cáncer, las nanopartículas actúan principalmente en las formas activas que se caracterizan por el uso de ligandos o anticuerpos en sus superficies donde se unen a ciertas células, y el pasivo, donde las partículas se acumulan en los tejidos tumorales debido a las grandes fracciones del endotelio tumoral. **Objetivo**: Abordar las principales propiedades de las nanopartículas de proteínas, metales, polímeros y lípidos, sus estructuras y usos contra células cancerosas específicas y las ventajas y desventajas de su uso. **Método**: Seleccionar artículos con estudios sobre nanopartículas de 2010 a 2018 en las bases de datos PubMed y SciELO, a través de revisión de la literatura integrativa. **Resultados**: Las nanopartículas tienen diferentes mecanismos de acción y pueden obtener resultados más favorables según su estructura química. **Conclusión**: Concluido con esta revisión que ciertas nanopartículas tienen funcionalidades que mejoran los efectos anticancerígenos de los fármacos antineoplásicos y emergen como un nuevo enfoque para los tratamientos contra el cáncer.

Palabras clave: Nanopartículas/administración & dosificación; Nanopartículas/uso terapéutico; Neoplasias; Antineoplásicos.

[1] Biomedicine Course, University Center Christus. Fortaleza, (CE), Brazil. Orcid iD: https://orcid.org/0000-0003-4523-8461
[2] Biomedicine Course, University Center Christus. Fortaleza, (CE), Brazil. Orcid iD: https://orcid.org/0000-0003-0153-7558
Address for correspondence: Juliana Carvalho Lopes. Rua Padre Mororó, 795 - Casa 14 – Centro. Fortaleza (CE), Brazil. CEP 60015-220. E-mail: julianacarvalho.l21@hotmail.com

INTRODUCTION

Nanotechnology studies the production of particles in nanometric scale from 1 to 100 nm that can be applied in various areas as in technology industry or in medicine and calls the attention of the scientists for its good performance in trials either *in vivo* as *in vitro*[1]. The physics Richard Feynman was the first to quote nanotechnology as an optimized tool, demonstrating some methods that helped the development of extremely small molecules to the size that was necessary[2].

The nanoparticles can be produced from many materials and in various sizes, which depending on their forms, are encountered in 0D, 1D, 2D or 3D[3]. Through the possibility of molding its size and form, these particles are extremely useful in the treatment of infirmities by the capacity of carrying drugs, for being a tumor flag and yet, helping the diagnosis of diseases and configure themselves as a new therapy targeted to the use of nanoparticles (NP) in the medical mean, the nanotherapy[4].

Because of the heterogeneity of cancer, new strategies of approaching the processes of neoplastic death are being evaluated[5], opening space for the utilization of NP that alleviate the disseminated side effects of chemotherapies[6] because of its specificity targeted to the tumor tissue and of its higher absorption[7,8]. The NP are molded to be able to deposit themselves in inflammation or tumor sites because of the distance of the endothelial cells, characteristic of the neoplastic tissue[9]. The overall objective of this article is to evaluate the principal properties of protein, metal, polymer and lipid NP, its structures, utilizations and advantages against carcinogenic cells.

METHOD

To elaborate this integrative review of the literature, the current databases PubMed and SciELO were searched between 2010 and 2018 because of the increasing evolution of the studies about nanotherapy during these years. It were used the descriptors nanoparticle; cancer, anticancer to refine the searches, without the utilization of the Boolean descriptors (AND, OR, AND NOT). Among the criteria of literature selection, were articles in English and Portuguese, articles that presented experiments *in vivo* and *in vitro* with NP, articles that addressed protein, metallic, lipidic and polymeric NP encountered currently in trials and articles involving nanoparticles carriers or not of drugs. For the selection of the main metallic NP, the most frequent NP were filtered in the database where bibliographic search was conducted. Upon reading the articles encountered, only the metallic zinc, platin and silver NP were selected to elaborate this review in the category of metal.

It were encountered 1,219 articles involving the descriptors utilized for the search in the two databases, of which, only 261 complied with the inclusion criteria. Non-specific studies involving neoplastic cells were excluded and the following exclusion criteria were applied: productions involving only articles with experiments of production of NP, articles that used NP as tumor marker indirectly, articles that presented only trials of cellular cytotoxicity without using experiment with malignant neoplastic cells and articles that failed to inform the time of execution of the experiment performed. After thorough reading and application of the exclusion criteria, 65 articles were selected to form the bibliographic review. For better approach of this review, five complementary literature with journals and books involving physiology of cancer and fabrication of NP were added to the bibliographic compilation.

RESULTS AND DISCUSSION

NP can be produced from several materials. Metals, lipids, proteins, liposomes or polymers are some of the NP found today in the main lines of research of cancer treatment[6].

The normal vascular endothelium has nearly 5 to 10 m of distance between its fenestrations (openings among the cells), while the new vessels, that appear because of the tumor angiogenesis[10] and of the high necessity of nutrition[11], have sizes ranging from 100 to 780 nm[10]. This type of utilization of NP is known as Enhanced Permeability and Retention (EPR) or passive vectorization targeted to the accumulation of these NP in the neoplastic endothelium[9].

In addition to the mechanism of accumulation, there is another technique involving the administration of NP, the active vectorization. In this process, ligands designed in the surface of the NP will interact specifically with cancer cells and its receptors. These ligands can be monoclonal antibodies, aptamers or peptides[10]. After NP is absorbed by the cell, through the formation of micropinosome and endosome[12], the endosome is fused with the lysosome, which will be responsible for degrading the particle absorbed[13]. Many drugs utilize the endosomal pathway to reach the cytosol and initiate its mechanisms of action[14].

The quantity of metals utilized in the pharmaceutical industry as antimicrobial[15] and antineoplastic agent is vast[16]. Metals as silver, gold, platinum and iron form the list of the principal metals used in experiments in cancer therapy[17], whose importance of metallic agents for nanomedicine is attractive for investigators. Being able to be molded in various sizes and variate forms the metallic particles present pharmacodynamic and pharmacokinetics

aspects that favor the induction of the cancer cells to death[18].

Overall, the mechanism metals use to generate cell death is mainly the induction of apoptosis or necrosis by the generation of reactive oxygen species (ROS). The ROS are the main molecules responsible for damaging the structure of the cellular membrane through peroxidation and protein denaturation occasionally leading the cell to death[17]. Cell death caused by generation of ROS is specific of the metals NP. The excess of production of ROS can be damaging for the cell, being responsible also for damages to double-band DNA[19].

Cell death by apoptosis is a natural process positively regulated by tumor suppressor genes as p53, which induces other pro-apoptotic genes as receptors of the cellular death and genes of the family BCL-2 that release apoptotic cells for cytosol, accelerating the process of cellular death[20]. The principal producing source of ROS inside the cell is the mitochondria because of its chemical processes of generation of energy. When ROS are in excess or escape from mitochondria, these molecules invade the cytosol, succeeding in destroying larger molecular structures as DNA or cause oxidative stress by lesion of the plasmatic membrane[16], making ROS an important mechanism against neoplastic cells[19]. After the genetic lesion, the pro-apoptotic genes are activated, inducing the cell to death by apoptotic pathways or by autophagy[16].

Zinc is a metal encountered in several industry segments, as cosmetics, dental products, plastics, etc. Recently, with the advance of nanomedicine, it became an important component utilized to produce NP. The efficacy of the zinc molecules against hepatocellular carcinoma cells (HepG2), prostate cancer and ovary cancer has been reported in several experimental studies[21].

Zinc is a metal acknowledged as safe by the Food and Drug Administration (FDA) and presents low levels of toxicity in relation to its size, aspect that needs attention to not become a dangerous and unstable carrier with low biocompatibility[22]. The zinc molecule induces the cancer cell to death from the oxidative stress caused by ROS, provoking rupture of the genetic material and successively cellular death. Pro-inflammatory molecules as Interferon C, interleukin 2 (IL-2) or tumor necrosis alpha factor are observed in high levels when zinc NP is utilized[16].

Studies utilizing zinc NP report high selectivity for cancer cells in comparison with other anticancer therapies[16]. In the study presented by Chung et al.[23], for instance, the zinc NP are utilized to treat cells of HepG2 in different doses and concentrations that alternate between 50 mg and 500 mg (Table 1).

At higher doses of 500 mg, it was observed a rate of cellular death of approximately 86% in cells HepG2 in the first 24 hours, concluding that cellular death is mainly dose-dependent. In this study, it were also measured the levels of caspases present in the culture, in different concentrations of zinc NP, indicating the progressive increase along the dosage, which contrasts with cellular death of HepG2.

Another study that can substantiate the effectiveness of zinc NP is the experiment conducted by Bai et al.[16]. In this study, the zinc dioxide NP (ZnO) were utilized to treat ovary cancer cells in concentrations of up to 30 μg/ml during 12 and 24 hours. After 24 hours, Bai et al.[16] observed that there was a reduction of almost 70% of cancer cells when these were exposed to 30 μg/ml of ZnO NP (Table 1).

Silver is largely commercialized and is present in many products as industrial machinery, prosthetics and surgical instruments[24]. For a long time, silver NP were used in electronics and energy, but recently has been drawing the attention for its apoptotic properties[25].

Silver ions can induce cellular cytotoxicity through increasing the instability of sodium and potassium in

Table 1. Experiments involving base-metal nanoparticles

	Author/year	*In vivo/in vitro*	Type of tumor cell	Cell line	Concentration	Reduction of viability (%) after 24 h
Zinc	Wang et al., 2014	*In vitro*	Oral	CAL-27	100 ug/ml	*>80%
	Bai et al., 2017	*In vitro*	Ovary	SKOV3	30 mg/ml	*>70%
	Arooj et al., 2015	*In vitro*	Melanoma	Ht144	100 ug/ml	*>80%
Silver	Choi et al., 2016	*In vitro*	Ovary	2780	1,000 ug/ml	60 %
	Han et al., 2017	*In vitro*	Germina tiva	F9	50 ug/ml	60 %
	Baharara et al., 2018	*In vitro*	Cervical	HeLa	60 ug/ml	80%

Caption: *> = cellular death bigger or above.

the ionic channels of the cellular membrane, which destabilizes the mitochondria and releases ROS, leading the cell to death[19]. Despite its efficacy in generating ROS and tumor death, in the study of Bhanumathi et al.[26], mild cytotoxic effects were observed in healthy tissues of mice that would have been exposed to silver NP in the heart, kidneys, brain and lung.

Studies show that human epithelial alveolar tumor cells (A549), neuroendocrine cells and ovary cells have been encountered in experiments with silver[19], in addition of having been proven its effectiveness against myeloid leukemia cells and breast cancer[27]. In Table 1, some experiments involving silver NP and its respective rates of tumor depletion are presented.

In the studies of Bahahara et al.[28] and He et al.[29], silver NP were produced from natural extracts of plants and fruits, utilizing the alternative principle of Green Technology or Environmental Technology, an option that utilizes only natural components[9]. In the study of He et al.[29], the extract of *Dimocarpus longan*, a traditional Chinese fruit, was utilized as a compound that reduces silver, because of its phenolic composition. He et al.[29] observed that, when exposed to lung cancer cells, silver NP produced from *Dimocarpus longan* succeeded in inhibiting until 90% of the percent of tumor growth. In the study of Bahahara et al.[28] (Table 1), silver NP were not only reduced with the extract of *Zataria multiflora*, but have also received oxidative compounds of this plant, which potentialized the toxic effect already present in the silver NP, showing its apoptotic effect in tumor cells.

In only 24 hours, silver NP was able to reduce in up to 80% the growth of cervical cancer cells in a concentration of 60 μg/ml, demonstrating oxidative and apoptotic efficacy of natural extracts also encountered in the study of He et al.[29] .

Choi et al.[20] have also utilized Green Technology to produce silver NP from cultures of *E. coli.* In 24 hours, the cellular viability was reduced in 50% and the levels of lactate dehydrogenase prominin-1 and other markers of cellular lesion by immunofluorescence were also quantified.

In contrast with the natural reducers utilized in the studies of Bahahara et al.[28] and He et al.[29], the experiment presented by Bhanumathi et al.[26] utilizes the chemical compound sodium borohydride ($NaBH_4$) as reducer agent of silver NP. In the study of Bhanumathi et al.[26], the silver NPs carried folic acid and berberine in its interior causing a reduction of more than 80% of the cellular viability of breast cancer cells. Another important data is demonstrated in the study of Bhanumathi et al.[26], who exposed silver NPs conjugated with folic acid and berberine to healthy breast cells, being observed that the toxic effect of the cellular viability in relation to these cells was of nearly 20% in 48 hours, concluding that normal breast cells would not be severely affected when exposed to silver NPs conjugated.

Metal-based NP, mainly zinc, present significant generating effects of autophagia that facilitate and potentialize the effects caused by ROS and, consequently, induce more easily the death of cancer cells, also caused by the flexibility of zinc molecules, which also makes them optimal molecules carriers[21,30,31].

In nanotherapy, platinum presents various chemical and conjugated forms. The drugs cisplatin and carboplatin are two examples of platinum-based variations in studies[32]. These drugs are applied to treat head and neck, ovary and lung cancer[33].

Cisplatin or cis-diamminedichloroplatinum[34] is an antineoplastic drug utilized to treat ovary, testicles cancers and cells of the human peripheral cells[35]. The mechanism of action of cisplatin is related to the rupture of the DNA. The drug can annihilate the biological processes of transition and translation, leading the cell to death by genetic lesion[36]. However, cisplatin finds many biological barriers as fast elimination, drug-resistance, severe toxic effects in kidneys, brain, liver and mainly, in bone marrow cells[34].

Despite the toxic aspects of cisplatin, some studies did not find elevated cytotoxicity in determined cells. In the experiment conducted by Bendale et al.[37], the platinum NPs did not show cytotoxic effects in mononuclear cells of the peripheral blood. However, when in contact with lung, pancreas and ovary cancer cells, the NPs managed to induce them to cellular death, proving their cytotoxic specific effect for tumor cells, mainly in phase G1 of the cellular cycle.

Carboplatin, formed by cis-diammine platinum (1,1-cyclobutanodicarboxilate), was developed to replace cisplatin[33] mainly for its capacity of being administered in elevated doses[38], becoming more recommended than cisplatin and presenting less toxicity and higher compatibility. Regardless of its non-toxic peculiarities, carboplatin presents low tumor uptake, which makes it a drug with reduced efficacy[33]. This drug was ineffective against neck cancer cells, testicular germinative cells and squamous carcinoma cells[38].

Protein NPs demonstrate biodegradability as one of its great advantages, an important characteristic that is not present in the metals due to environmental technology[9]. Protein NPs are biocompatible, easily degraded by the organism and have facility to mold themselves and add ligands in their surfaces[39].

The protein NP have better compatibility with the human body because they are produced from an existing

protein as gelatin or albumin[9]. Albumin NP or NAB, as is also known, is produced from a drug encapsulated inside the albumin molecule, having great importance for nanotechnology because of its power of tumor retention in the vessels that irrigate the cancer tissue[40]. The main application of protein NPs in anticancer treatment is its drug carrier capacity that circumvent the immune system making the drug carried by protein NP to remain in the blood flow for more time[39].

Protein NP can also be utilized with other NP of different chemical compositions as in the study presented by Azizi et al.[41]. In this experiment, the albumin NP were utilized to carry silver NP. The rate of breast cancer cells dead by this complex reached nearly 70% with NP of size 100 μM. The albumin NP are commonly studied and are already in the pharmaceutical market as an albumin NP that carries the antineoplastic placlitaxel in its interior[9]. In the study of Lee et al.[42], placlitaxel was internalized in an albumin NP coated with polyethylenoglycol (PEG) to treat a xenographic tumor of breast cells. Lee et al.[42] observed that, in a concentration of 100 nm, the tumor cellular viability was reduced in more than 50% in only 24 hours.

Regardless of albumin being the main protein utilized as nanocarrier, it is not the only one. Some studies utilize other NP as proteins of camel milk[43] gelatin, elastin and even soy proteins[39].

The lipid NP, which encompasses the liposomal and micellar forms, are atoxic and biocompatible inside the human body[10]. Some studies report the facility of lipid NP of being molded in solid forms and, therefore, become more susceptible to encapsulation of drugs in its interior[44]. The lipid NP have the most efficient delivery of the drug in the sites of action in the treatment against cancer, because of its hydrophilic structure with only one layer of phospholipid[10].

The liposomal form of lipid NP is one category of chemotherapic drug carrier. Currently, liposomal NP present two drugs in study, cytarabine and irinotecan[45]. With its phospholipid structure, the liposomes enable the carrying of hydrophilic and lipophilic drugs at the same time, in addition of presenting more fluidity compared to lipid NP[10]. The micelles also are part of the lipid NP. These NP present layers of amphiphilic copolymers that are disposed around a hydrophobic nuclear structure, where are incorporated the drugs with low solubility in water that will be encapsulated[45].

Despite its benefits, some important obstacles are faced by lipid NP. The easy degradation by the stomach PH and by the enzymes of the intestine, for example, reduce the capabilities of storage of these particles. Other frequent problems are the instability in lipid mean and the toxicity of compounds utilized in the fabrication of these NP[46]. In Chart 1, the main advantages and disadvantages of biodegradable NP (proteins, polymers and lipids) and of metals are shown.

The attribution of polymers as NP appeared from the necessity of new forms of fabrication of NP that were not toxic to the environment. These synthetic-based polymers molecules are biocompatible, have optimal tissue uptake and are not toxic for the organism, which makes this category one of the subtypes of NP utilized in the most recent trials with delivery of drugs[47].

There are several types of synthetic formulations of polymers that differ according to the therapeutic finality it is planned to be obtained. The most used polymers

Chart1.Advantages and disadvantages of the categories of metals nanoparticles and biocompatible

	Metallic	Polymeric, lipid and proteic
Advantages	- Can generate oxygen reactive species - Are easily molded and produced - Can be produced by Green Technology	- Normally, they don't use toxic reagent for the environment - Can carry two drugs at the same time in its structure (lipids) - Polymers can circumvent the formation of protein corona, in addition to preventing non-specific phagocytosis - Less expensive and biocompatible
Disadvantages	- Can cause cellular cytotoxicity - Normally present neurotoxic or nephrotoxic effects - In its production, some toxic components to the environment are used	- Lipids can suffer enzymatic action earlier and not being absorbed by the tumor cell

as drug carriers are polyacid lactic (PLA) and PEG[48]. PLA is a polymer formed from copolymerization of two monomers, the glycolic acid and the lactic acid, that are easily degraded by the human metabolism by the cycle of Krebs[49]. PLA is present in plastic bags, packages or even cosmetics[47].

PLA has effective tumor retention from the passive vectorization in systems *in vivo* and is much associated to other polymers as PEG, in the combined form of MPEG-PLA[50].

PEG is another biodegradable polymer with properties that favor its utilization as a good carrier. Many times, PEG is manipulated associated to other molecules or simply as coating polymer of NP[51]. Its main function is to make NP coated by it non perceptible to the immune system and to the cells of the reticulo-endothelial system (RES)[52], for blocking the insertion of the corona protein in its surfaces[49], prolonging the systemic circulation of the NP in the organism[53]. PEG and PLA (PEG-PLA) are commonly encountered as excellent carriers of molecules. Its conformation is amphipathic, can be administered in aqueous or lipid mean after intravenous administration[50].

In the study presented by Xiang et al.[54], PEG NP in association were utilized to carry doxorubicin against cells of hepatocarcinoma. The authors observed that, in the first 24 hours, the cancer cellular viability reduced in 40%, compared with the culture control in different concentrations of this conjugation.

PLA and PEG can also be used as carriers of molecules, as miRNA, as demonstrated in the experiment of Devulapally et al.[55]. Chart 2 shows the summary of the main NP addressed and its general utilizations that encapsulated miRNA suppressor of protein and the drugs gentamicin against hepatocarcinoma cells in PLA NP.

They observed that the cellular viability of the tumor was reduced in 30% insofar as the size of the NP increased[55]. Cosco et al.[56] also utilized PLA together with chitosan to carry RNA of interference against myeloma cells. The two cell lines utilized in this study[56] had their viability reduced in until 30% in 24 hours. After 48 hours, the cellular viability diminished in 50% with a concentration of 100 nm of chitosan NP (Table 2).

Quitosana or chitosan (N-acetyl glucosamine) is a biodegradable polymerized polysaccharide, of low immunogenicity and nontoxic, which is also utilized as drug carrier[57]. It can be encountered in association both with PLA and PEG, carrying known antineoplastic as cisplatin or doxorubicin[58]. However, chitosan also presents challenges as low solubility of its material, characteristic of natural compounds[57,59].

In the studies of Xiang et al.[54] and Devulapally et al.[55], both involving hepatic tumor cell lines HepG2, it can be observed discrepancies through the molecules carried and the concentrations involved in the study. In the experiment of Xiang et al.[54], the reduction of 70% of the quantity of tumor cells was observed in the first 24 hours, while in the study of Devulapally et al.[55], only after 48 hours the rate of reduction reached 60% indicating that the conjugated presented by Xiang et al.[54] is more effective against cells of HepG2.

Fasehee et al.[60] verified a drop of 80% in the tumor viability when encapsulating disulfiram, an inhibitor of aldehyde dehydrogenase (ALDH) with molecules of *Poly(lactic-co-glycolic) acid* (PLGA). In this study, it were observed disulfiram free and disulfiram encapsulated. In the study of Fasehee et al.[60], the maximum inhibition was obtained after 48 hours and the effect of cytotoxicity doubled in relation to the first 24 hours. However, in the study of Wang et al.[61], it were not observed great cytotoxic effects within 48 hours in relation to the first 24 hours, even utilizing different cancer line cells for comparison.

There was no drop of visible viability between 24 and 48 hours, demonstrating that in the study of Wang et al.[61], the main limiting factor was not the encapsulation in PGLA, but the carried molecules utilized in the tumor cells lines.

Normally, the most utilized process of production of NP is the chemical method, where a specific reducing solution of ions as $NaBH_4$ or sodium nitrate is used to reduce a certain compound that contains the material wanted.

Chart 2. Principal types of nanoparticles and its general functionalities

Types of nanoparticles	Principal nanoparticles molecules represented	General Utilization
Metallic	Platinum, iron and silver	Potentialization of tumor death through generation of reactive oxygen species; drug carrier
Polymeric	Polyethylene glycol and lactic polyacid	Nanoparticles coating; drug carrier
Proteic	Albumin	Drug carrier
Lipid	Micellar, liposomal and lipid	Drug carrier

Table 2. Experiments involving polymer nanoparticles

Author/year	Polymer utilized	Molecule carried	*In vivo/ in vitro*	Type of tumor cell	Cell line	Concentration µg/mL	Reduction of viability (%) after 48 h
Fesehee et al., 2017	PLGA	Disulfiram	*In vitro*	Breast	MCF-7	500*	80%
Xiang et al., 2013	PEG-PDLLA	Doxorubicin and *monomethyl ether* Hematoporphyrin	*In vitro*	Liver	HepG2	2	70%**
Cao et al., 2016	PLGA	*Docetaxel e LHRH*	*In vitro*	Prostate	LNCaP	10	80%
Devula-pally et al., 2016	PLGA-PEG	*Gemcitambine e miRNA*	*In vitro*	Liver	HepG2	5*	60%
Cosco et al., 2015	PLGA	*miR-34a*	*In vitro*	Multiple myeloma	SKMM1	*100**	*50%*
Wang et al., 2015	PLGA	Paclitaxel and Etoposide	*In vitro*	Bone	Saos-2	10	70%

Captions: *The concentration is expressed in nanometer (nm); **The rate of reduction presents in the first 24 hours.

There are other methods of fabrication as the radiolytic, photochemicals or biogenic[62]. In the entire process, the administration of reagents needs to be very careful, because any error caused by the differences of concentrations can disturb the formation of nanomolecules[63].

The problem of utilization of the many chemical compounds involved in this process of fabrication is the high rate of toxicity that restrains the application of these solutions, in addition to being quite expensive. Recently, because of this obstacle, a new alternative for the production of NP is being addressed in nanotechnology, the Green Technology[64] or environmental technology focused in the non-utilization of chemical compounds in industry. This new tool, in addition of not using toxic substances for the environment, is less expensive and can use plants, bacteria or proteic compounds as inputs[9,65].

Extracts from plants and fruits are used to substitute the oxidation reduction of chemical compounds and can be stabilizers or even promote, depending on the extract utilized, biological activity without causing damages to the organism[66]. The golden NP, as demonstrated in the experiment of Bahahara et al.[28], were constructed from an India-origin plant, the *Zataria multiflora,* utilized as metal reducer. Despite the benefits of the Green Technology, its utilization in the scientific laboratories is still farther ahead because of the lack of knowledge and training in this technique[65].

In addition to the Green Technology, other applications are appearing along the years involving NP in the treatment of cancer, for example, phototherapy and photothermal therapy. Phototherapy is a direct combination with chemotherapics, where photosensitizers are activated from a source of irradiation, becoming an option of safer and specific application, since NP will be activated in the region of the body where the light is concentrated[67].

In photothermal therapy, NP are activated from a heat source, normally, infrared, where waves of small or great length are applied. After activation through heat, the NP already absorbed is disintegrated by heat, causing necrosis to the tumor cell. Normally, carbon-based NP are used in this procedure[68].

Another type of recent application with NP is the genic therapy. In this therapy, small molecules that can interfere or change of DNA structure are incorporated in the interior of the NP, as plasmids of DNA, miRNA or RNA of interference[67], as shown in the studies of Devulapally et al.[55] and Xiang et al.[54] Therapies that use interfering genes and chemotherapy are favorable for the eradication of tumors, but face challenges as reduced structure of its materials, failing to reach considerable effects[67]. The viruses are also been studied as new drugs carriers because they have biocompatible characteristics with the human body, facility of mold in several sizes and forms, can be conjugated with PEG to prolong its time in the blood flow.

Some treatments already known as radiotherapy and chemoradiotherapy are adopting the use of NP. In the study of Au et al.[69], the wortmannin was conjugated with docetaxel in PEG-PLA NP, presenting tumor size below 10% in a period of 120 days. Inorganic compounds also present optimal uptake of radiation and are good materials to be used in radiotherapy[70].

CONCLUSION

The discovery of nanotechnology in medicine granted the utilization of anticancer therapies that earlier would have high toxicity rate for the human body because of the possibility of reduction of cytotoxic adverse events caused by the non-specificity of conventional therapy. As time went by, the techniques involving fabrication and application of NP evolved, offering improved efficiency in delivering drugs and site-specific orientation. In addition to metallic NP already known by the scientific community, other molecules have gained space because they pursued the use of cleaner production methods and non-toxicity as polymer, proteins and lipid-based NP that occupy the center of the new chemotherapy scenario with NP, being responsible for introducing important drugs in the tumor fight.

With its diversified chemical properties and its mechanisms of generation of ROS, some NP have toxic effects against different tumor cells, despite carrying or not any drug and can present more effective antitumor effect in certain tumor cell lines that indicate cellular susceptibility for that type of NP or drug carried. Despite the good results involving NP and antineoplastic, obstacles as nonspecific phagocytosis and adverse effects caused by toxicity of fabrication need to be well discussed and studied.

CONTRIBUTIONS

Both authors contributed equally for the study conception and planning, gathering, analysis and interpretation of the data and wording and/or critical review and final approval of the version published.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

FUNDING SOURCES

None.

REFERENCES

1. Bea DB, Tejeda AP, Pardo AA, et al. Nanomedicine: general aspects of a promissory future. Rev Habanera Cienc Méd. 2011;10(3):410-21.
2. Disner GR, Cestari MM. Nanociência e nanotecnologia. Evidência. 2016;16(1):71-6. doi: https://doi.org/10.18593/eba.v16i1.10660
3. Khan I, Saeed K, Khan I. Nanoparticles: properties, applications and toxicities. Arabian J Chemistry. 2019. 12(7):908-31. doi: https://doi.org/10.1016/j.arabjc.2017.05.011
4. Zhang P, Wang P, Yan L, et al. Synthesis of gold nanoparticles with *Solanum xanthocarpum* extract and their in vitro anticancer potential on nasopharyngeal carcinoma cells. Int J Nanomedicine. 2018;13:7047-59. doi: https://doi.org/10.2147/IJN.S180138
5. Fang RH, Kroll AV, Zhang L. Nanoparticle-based manipulation of antigen-presenting cells for cancer immunotherapy. Small. 2015;11(41):5483-96. doi: https://doi.org/10.1002/smll.201501284
6. Asai T. Nanoparticle-mediated delivery of anticancer agents to tumor angiogenic vessels. Biol Pharm Bull. 2012;35(1):11:1855-61. doi: https://doi.org/10.1248/bpb.b212013
7. Tang L, Yang X, Yin Q, et al. Investigating the optimal size of anticancer nanomedicine. PNAS. 2014;111(43):15344-9. doi: https://doi.org/10.1073/pnas.1411499111
8. Din FU, Aman W, Ullah I, et al. Effective use of nanocarriers as drug delivery systems for the treatment of selected tumors. Int J Nanomedicine. 2017;12:7291-7309. doi: https://doi.org/10.2147/IJN.S146315
9. Vieira DB, Gamarra LF. Avanços na utilização de nanocarreadores no tratamento e no diagnóstico de câncer. Einstein. 2016; 14(1):99-103. doi: https://doi.org/10.1590/S1679-45082016RB3475
10. Oliveira LC, Taveira EJF, Souza LG, et al. Aplicações das nanopartículas lipídicas no tratamento de tumores sólidos: revisão de literatura. Rev Bras Cancerol. 2012;58(4):695-701. doi: https://doi.org/10.32635/2176-9745.RBC.2012v58n4.581
11. Golan DE. Princípios de farmacologia antimicrobiana e antineoplásica. In: Golan DE, Tashjian AH, Armstrong EJ, et al. Princípios de farmacologia: a base fisiopatológica da farmacologia. 3. ed. Rio de Janeiro: Guanabara Koogan; 2009. Cap. 32, p. 572.
12. Zhang S, Gao H, Bao G. Physical principles of nanoparticle cellular endocytosis. ACS Nano. 2015;9(9):8655-71. doi: https://doi.org/10.1021/acsnano.5b03184
13. Vilar-Alvarez E, Cambón A, Pardo A, et al. Gold nanorod-based nanohybrids for combinatorial therapeutics. ACS Omega. 2018;3:12633-47. doi: https://doi.org/10.1021/acsomega.8b01591
14. Jurj A, Braicu C, Pop LA, et al. The new era of nanotechnology, an alternative to change cancer treatment. Drug Des Devel Ther. 2017;11:2871-90. doi: https://doi.org/10.2147/DDDT.S142337
15. Khan M, Khan M, Al-Marrari AH, et al. Apoptosis inducing ability of silver decorated highly reduced graphene oxide nanocomposites in A549 lung cancer. Int J Nanomedicine. 2016:11:873-83. doi: https://doi.org/10.2147/IJN.S100903
16. Bai DP, Zhang XF, Zhang, GL, et al. Zinc oxide nanoparticles induce apoptosis and autophagy in human

ovarian cancer cells. Int J Nanomedicine. 2017:12:6521-35. doi: https://doi.org/10.2147/IJN.S140071

17. Bisht G, Rayamajhi S. ZnO nanoparticles: a promising anticancer agent. Nanobiomedicine (Rij). 2016;3:9:1-11. doi: https://doi.org/10.5772/63437
18. M JF, P L. Apoptotic efficacy of biogenic silver nanoparticles on human breast cancer MCF-7 cell lines. Prog Biomarter. 2015;4:113-21. doi: https://doi.org/10.1007/s40204-015-0042-2
19. Han JW, Gurunathan S, Choi YJ, et al. Dual functions of silver nanoparticles in F9 teratocarcinoma stem cells, a suitable model for evaluating cytotoxicity- and differentiation-mediated cancer therapy. Int J Nanomedicine. 2017;12:7529-49. doi: https://doi.org/10.2147/IJN.S145147
20. Choi YJ, Park JH, Han JW, et al. Differential cytotoxic potential of silver nanoparticles in human ovarian cancer cells and ovarian cancer stem cells. Int J Mol Sci. 2016;17(12):2077. doi: https://doi.org/10.3390/ijms17122077
21. Wang J, Gao S, Wang S, et al. Zinc oxide nanoparticles induce toxicity in CAL 27 oral cancer cell lines by activating PINK1/Parkin-mediated mitophagy. Int J Nanomedicine. 2018:13:3441-50. doi: https://doi.org/10.2147/IJN.S165699
22. Rasmussen JW, Martinez E, Louka P, et al Zinc oxide nanoparticles for selective destruction of tumor cells and potential for drug delivery applications. Expert Opin Drug Deliv. 2010;7(9):1063-77. doi: https://doi.org/10.1517/17425247.2010.502560
23. Chung M, Rahuman AA, Marimuthu S, et al. An investigation of the cytotoxicity and caspase-mediated apoptotic effect of green synthesized zinc oxide nanoparticles using *Eclipta prostrata* on human liver carcinoma Cells. Nanomaterials. 2015;5(3):1317-30. doi: https://doi.org/10.3390/nano5031317
24. Chakraborty B, Pal R, Ali M, et al. Immunomodulatory properties of silver nanoparticles contribute to anticancer strategy for murine fibrosarcoma. Cell Mol Immunol. 2016;13(2):191-205. doi: https://doi.org/10.1038/cmi.2015.05
25. Gurunathan S, Park JH, Han JW, et al. Comparative assessment of the apoptotic potential of silver nanoparticles synthesized by Bacillus tequilensis and Calocybe indica in MDA-MB-231 human breast cancer cells: targeting p53 for anticancer therapy. Int J Nanomedicine. 2015;10:4203-23. doi: https://doi.org/10.2147/IJN.S83953
26. Bhanumathi R, Manivannan M, Thangaraj R, et al. Drug-carrying capacity and anticancer effect of the folic acid- and berberine-loaded silver nanomaterial to regulate the akt-erk pathway in breast cancer. ACS omega 2018;3(7):8317-28. doi: https://doi.org/10.1021/acsomega.7b01347
27. Lee MJ, Lee SJ, Yun SJ, et al. Silver nanoparticles affect glucose metabolism in hepatoma cells through production of reactive oxygen species. Int J Nanomedicine. 2016;11:55-68. doi: https://doi.org/10.2147/IJN.S94907
28. Bahahara J, Ramezani T, Hosseini N, et al. Silver nanoparticles synthesized coating with zataria multiflora leaves extract induced apoptosis in HeLa cells through p53 activation. Iran J Pharm Res. 2018;17(2):627-39. doi: https://doi.org/10.22037/IJPR.2018.2191
29. He Y, Du Z, Ma S, et al. Effects of green-synthesized silver nanoparticles on lung cancer cells in vitro and grown as xenograft tumors in vivo. Int J Nanomedicine. 2016;11:1879-87. doi: https://doi.org/10.2147/IJN.S103695
30. Wang T, Yang S, Mei LA, et al. Paclitaxel-loaded PEG-PE-based micellar nanopreparations targeted with tumor-specific landscape phage fusion protein enhance apoptosis and efficiently reduce tumors. Mol Cancer Ther. 2014;13(12):2864-75. doi: https://doi.org/10.1158/1535-7163.MCT-14-0052
31. Arooj A, Nazir S, Nadhman A, et al. Novel ZnO:Ag nanocomposites induce significant oxidative stress in human fibroblast malignant melanoma (Ht144) cells. Beilstein J Nanotechnol. 2015;6:570-82. doi: https://doi.org/10.3762/bjnano.6.59
32. Rokade SS, Joshi KA, Mahajan K, et al. Gloriosa superba mediated synthesis of platinum and palladium nanoparticles for induction of apoptosis in breast cancer. Bioinorg Chem Appl. 2018;2018: 4924186. doi: https://doi.org/10.1155/2018/4924186
33. Sadhukha T, Prabha S. Encapsulation in nanoparticles improves anti-cancer efficacy of carboplatin. AAPS PharmSciTech. 2014;15(4):1029-38. doi: https://doi.org/10.1208/s12249-014-0139-2
34. Leite EA, Souza CM, Carvalho-Junior AD, et al. Encapsulation of cisplatin in long-circulating and pH-sensitive liposomes improves its antitumor effect and reduces acute toxicity. Int J Nanomedicine. 2012;7:5259-69. doi: https://doi.org/10.2147/IJN.S34652
35. Haririan I, Alavidjeh MS, Khorramizadeh MR, et al. Anionic linear-globular dendrimer-cis-platinum (II) conjugates promote cytotoxicity in vitro against different cancer cell lines. Int J Nanomedicine. 2010;5:63-75. doi: https://doi.org/10.2147/IJN.S8595
36. Guven A, Rusakova IA, Lewis MT, et al. Cisplatin@us-tube carbon nanocapsules for enhanced chemotherapeutic delivery. Biomaterials. 2012;33(5):1455-61. doi: https://doi.org/10.1016/j.biomaterials.2011.10.060
37. Bendale Y, Bendale V, Paul S. Evaluation of cytotoxic activity of platinum nanoparticles against normal and cancer cells and its anticancer potential through induction of apoptosis. Integr Med Res. 2017;6(2):141-8. doi: https://doi.org/10.1016/j.imr.2017.01.006

38. Oberoi HS, Nukolova NV, Kabanov AV, et al. Nanocarriers for delivery of platinum anticancer drugs. Adv Drug Deliv Rev. 2013;65(13-14):1667-85. doi: https://doi.org/10.1016/j.addr.2013.09.014

39. Lohcharoenkal W, Wang L, Chen YC, et al. Protein nanoparticles as drug delivery carriers for cancer therapy. Biomed Res Int. 2014:180549. doi: https://doi.org/10.1155/2014/180549

40. Noorani L, Stenzel M, Liang R, et al. Albumin nanoparticles increase the anticancer efficacy of albendazole in ovarian câncer xenograft model. J Nanobiotechnology. 2015;13:25. doi: https://doi.org/10.1186/s12951-015-0082-8

41. Azizi M, Ghourchian H, Yazdian F, et al. Anti-cancerous effect of albumin coated silver nanoparticles on MDA-MB 231 human breast cancer cell line. Scientific Reports. 2017;7:5178. doi: https://doi.org/10.1038/s41598-017-05461-3

42. Lee JE, Kim MG, Jang YL, et al. Self-assembled PEGylated albumin nanoparticles (SPAN) as a platform for cancer chemotherapy and imaging. Drug Deliv. 2018;25(1):1570-78. doi: https://doi.org/10.1080/10717544.2018.1489430

43. Badawy AA, El-Magd MA, AlSadrah SA. Therapeutic effect of camel milk and its exosomes on MCF7 cells in vitro and in vivo. Integr Cancer Ther. 2018;17(14):1235-46. doi: https://doi.org/10.1177/1534735418786000

44. Huang R, Li J, Kebebe D, et al. Cell penetrating peptides functionalized gambogic acid-nanostructured lipid carrier for cancer treatment. Drug Deliv. 2018;25(1):757-65. doi: https://doi.org/10.1080/10717544.2018.1446474

45. Cho H, Lai TC, Tomoda K, et al. Polymeric micelles for multi-drug delivery in cancer. AAPS PharmSciTech. 2015;16(1):10-20. doi: https://doi.org/10.1208/s12249-014-0251-3

46. Selvamuthukumar S, Velmurugan R. Nanostructured lipid carriers: a potential drug carrier for cancer chemotherapy. Lipids Health Dis. 2012;11:159. doi: https://doi.org/10.1186/1476-511X-11-159

47. Silva MC, Oliveira SV, Araújo EM. Propriedades mecânicas e térmicas de sistemas de PLA e PBAT/PLA. Revista Eletrônica de Materiais e Processos. 2014;9(2):112-117.

48. Bao W, Liu R, Wang Y, et al. PLGA-PLL-PEG-Tf-based targeted nanoparticles drug delivery system enhance antitumor efficacy via intrinsic apoptosis pathway. Int J Nanomedicine. 2015;10:557-66. doi: https://doi.org/10.2147/IJN.S75090

49. Mirakabad FST, Nejati-Koshki K, Akbarzadeh A, et al. PLGA-based nanoparticles as cancer drug delivery systems. Asian Pac J Cancer Prev. 2014;15(2):517-35. doi: https://doi.org/10.7314/APJCP.2014.15.2.517

50. Zheng W, Li M, Lin Y, et al. Encapsulation of verapamil and doxorubicin by MPEG-PLA to reverse drug resistance in ovarian cancer. Biomed Pharmacother. 2018;108:565-73. doi: https://doi.org/10.1016/j.biopha.2018.09.039

51. Zheng S, Li X, Zhang Y, et al. PEG-nanolized ultrasmall selenium nanoparticles overcome drug resistance in hepatocellular carcinoma HepG2 cells through induction of mitochondria dysfunction. Int J Nanomedicine. 2012;7:3939-49. doi: https://doi.org/10.2147/IJN.S30940

52. Cao LB; Zeng S, Zhao W. Highly Stable PEGylated Poly(lactic-co-glycolic acid) (PLGA) nanoparticles for the effective delivery of docetaxel in prostate cancers. Nanoscale Res Lett. 2016;11(1):305. doi: https://doi.org/10.1186/s11671-016-1509-3

53. Udofot O, Affram K, Smith T, et al. Pharmacokinetic, biodistribution and therapeutic efficacy of 5-fluorouracil-loaded pH-sensitive PEGylated liposomal nanoparticles in HCT-116 tumor bearing mouse. J Nat Sci. 2016;2(1):e171.

54. Xiang GH, Hong G, Wang Y, et al. Effect of PEG-PDLLA polymeric nanovesicles loaded with doxorubicin and hematoporphyrin monomethyl ether on human hepatocellular carcinoma HepG2 cells in vitro. Int J Nanomedicine. 2013;8(1):4613-22. doi: https://doi.org/10.2147/IJN.S54142

55. Devulapally R, Foygel K, Sekar TV, et al. Gemcitabine and antisense-microRNA co-encapsulated PLGA-PEG polymer nanoparticles for hepatocellular carcinoma therapy. ACS Appl Mater Interfaces. 2016;8(49):33412-22. doi: https://doi.org/10.1021/acsami.6b08153

56. Cosco D, Cilurzo F, Maiuolo J, et al. Delivery of miR-34a by chitosan/PLGA nanoplexes for the anticancer treatment of multiple myeloma. Sci Rep. 2015;5:17579. doi: https://doi.org/10.1038/srep17579

57. Wei X, Liao J, Davoudi Z, et al. Folate receptor-targeted and GSH-responsive carboxymethyl chitosan nanoparticles containing covalently entrapped 6-mercaptopurine for enhanced intracellular drug delivery in leukemia. Mar Drugs. 2018;16(11):439. doi: https://doi.org/10.3390/md16110439

58. Xu Q, Leong J, Chua QY, et al. Combined modality doxorubicin-based chemotherapy and chitosan-mediated p53 gene therapy using double-walled microspheres for treatment of human hepatocellular carcinoma. Biomaterials. 2013;34(21):5149-62. doi: https://doi.org/10.1016/j.biomaterials.2013.03.044

59. Andima M, Costabile G, Isert L, et al. Evaluation of β-sitosterol loaded PLGA and PEG-PLA nanoparticles for effective treatment of breast cancer: preparation, physicochemical characterization, and antitumor activity. Pharmaceutics. 2018;10(4):232. doi: https://doi.org/10.3390/pharmaceutics10040232

60. Fasehee H, Ghavamzadeh A, Alimoghaddam K, et al. A comparative cytotoxic evaluation of disulfiram

encapsulated PLGA nanoparticles on MCF-7 cells. Int J Hematol Oncol Stem Cell Res. 2017;11(2):102-7.

61. Wang B, Yu XC, Xu SF, et al. Paclitaxel and etoposide co-loaded polymeric nanoparticles for the effective combination therapy against human osteosarcoma. J Nanobiotechnology. 2015;13:22. doi: https://doi.org/10.1186/s12951-015-0086-4
62. Souto EB, Severino P, Santana MHA. Preparação de nanopartículas poliméricas a partir de polímeros pré-formados: parte II. Polímeros. 2012;22(1):101-6. doi: https://doi.org/10.1590/S0104-14282012005000005
63. Junior MAM, Santos LSS, Gonçalves MC, Nogueira AF. Preparação de nanopartículas de prata e ouro: um método simples para a introdução da nanociência em laboratório de ensino. Quim Nova. 2012;35(9):1872-78. doi: https://doi.org/10.1590/S0100-40422012000900003
64. Lalitha A, Subbaiya R, Ponmurugan P. Green synthesis of silver nanoparticles from leaf extract Azhadirachta indica and to study its anti-bacterial and antioxidant property. Int J Curr Microbiol App Sci [Internet]. 2013 [cited 2018 July 13];2(6):228-35. Available from: https://pdfs.semanticscholar.org/d811/bdb6b1ff1f9c98a63249408fee6ac36d6baf.pdf
65. Rani K, Sridevi V. An overview on role of nanotechnology in green and clean technology. Austin Environ Sci. 2017;2(3):1026. doi: https://doi.org/10.26420/austinenvironsci.2017.1026
66. Ivashchenko O, Przysiecka L, Poplinska B, et al. Gel with silver and ultrasmall iron oxide nanoparticles produced with Amanita muscaria extract: physicochemical characterization, microstructure analysis and anticancer properties. Scientific Reports. 2018;8:13260. doi: https://doi.org/10.1038/s41598-018-31686-x
67. Meng F, Han N, Yeo Y. Organic nanoparticle systems for spatiotemporal control of multimodal chemotherapy. Expert Opin Drug Deliv. 2017;14(13):427-46. doi: https://doi.org/10.1080/17425247.2016.1218464
68. Machado IRL, Mendes HMF, Alves GES, et al. Nanotubos de carbono: potencial de uso em medicina veterinária. Cienc Rural. 2014;44(10):1823-29. doi: https://doi.org/10.1590/0103-8478cr20140003
69. Au KM, Min Y, Tian X, et al. Improving cancer chemoradiotherapy treatment by dual controlled release of wortmannin and docetaxel in polymeric nanoparticles. ACS Nano. 2015;9(9):8976-96. doi: https://doi.org/10.1021/acsnano.5b02913
70. Casals E, Gusta MF, Siles MC, et al. Cancer resistance to treatment and antiresistance tools offered by multimodal multifunctional nanoparticles. Cancer Nanotechnol. 2017;8(1):7. doi: https://doi.org/10.1186/s12645-017-0030-4

Recebido em 15/8/2019
Aprovado em 2/12/2019