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Review Article

# Nanoparticles with Antitumoral Activity: An Integrative Literature Review

**Nicolete R[1], Ferreira VPG[2], de Alencar Santos Júnior JG[3] and Rodrigues JPV[4]**

*[1]Graduate Program in Development and Technological Innovation in Medicines, Federal University of Ceará, Fortaleza, CE, Brazil; [2]Graduate Program in Pharmaceutical Sciences, Federal University of Ceará, Fortaleza, CE, Brazil; [3]Oswaldo Cruz Foundation (Fiocruz Ceará), Eusébio, CE, Brazil; [4]Research and Medicine Development Center (NPDM), Federal University of Ceará, Fortaleza, CE, Brazil*

## ABSTRACT

Nanotechnology is used to describe materials, devices and systems with structures and components, exhibiting new and/or significantly improving physical, chemical and biological properties. In the biomedical area, these materials have unique nanoscale properties of 1 nanometers to 100 nanometers. Thus, the objective was to evidence the available scientific knowledge in the literature on some advances related to the use of nanoparticles with antitumor activity. The present study uses as an integrative literature review method, allowing to search, evaluate and synthesize the available evidence to contribute to the development of the discussion about the theme. Crossing the descriptors "nanoparticles" and "antitumoral", 62 studies were found, of which one was repeated in more than one place. Thus, of the 61 publications listed, 26 addressed the main theme proposed with emphasis on the use of nanoparticles/nanoemulsion against tumor cells, in this way were selected to compose this study. Nanotechnology can be considered a new technology in the oncology area. The major challenges are to gather information about the properties and risks of these nanomaterials, the in vivo application as well as specific clinical trials.

**Keywords:** Nanoscience; Nanoparticles; Cancer biotechnology; Antitumoral

## INTRODUCTION

Nanotechnology is aimed at the characterization, manufacture, manipulation and application of biological and non-biological structures at the nanoscale. The prefix "nano" is related to a measurement scale in which a nanometer represents one billionth of the meter or one millionth of a millimeter. These structures have unique functional properties not found on the macro scale [1]. Scientifically, nanotechnology is used to describe materials, devices and systems with structures and components, exhibiting new and/or significantly improving physical, chemical and biological properties. In the biomedical area, these materials have unique nanoscale properties of 1 nanometers to 100 nanometers (nm). Changes in properties are due to increased surface area and dominance of quantum effects associated with extremely small sizes. The principles involving biological systems in nature can be mimicked by nanostructures, for example, biomolecules such as proteins, peptides, DNA, lipids and carbohydrates can function as nanomodels, using their chemical forms and properties to produce inorganic substances, such as metals at the nanoscale. The history of nanotechnology is not new, for in 1959 at the California Institute of Technology, physicist Richard Feynman addressed in a speech these physical properties of materials and the potentialities that could come from this knowledge. There are basically two approaches to the synthesis of nanostructures, regardless of the field of application: the bottom-up approach, involving the manipulation of atoms and molecules for nanostructures and the top-down, in which techniques of miniaturization of existing materials are employed. Nanotechnology applications focus on three main areas: nanomaterials, nanoelectronics and nanobiotechnology, branching into sub-areas of materials, electronics, environment, metrology, energy, safety, robotics, health care, information technology, biomimetics, products pharmaceuticals, artifacts in general, agriculture, construction, transportation, food processing, among others [2].

Regarding the challenges of nanotechnology to favor the delivery or addressing of drugs in a selective and efficient manner, problems such as low bioavailability of molecules, their chemical instability, solubility, intestinal absorption, among others, constitute a great obstacle to therapeutic efficacy, leading to the appearance of often adverse or adverse effects and fluctuations in plasma drug levels (below the therapeutic range or above, generating toxic levels). In this context, for example, polymeric and liposomal nanostructured

***Correspondence to:** Nicolete R, Chief Research and Medicine Development Center (NPDM), Federal University of Ceará, Fortaleza, CE, Brazil, Tel: 85999609650; E-mail: jpedroviana@alu.ufc.br

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systems (submicron and nanoscale scale) can overcome such challenges, leading to the generation of encapsulated and protected drugs within a polymeric or lipid matrix. After specific mechanisms of physical and chemical degradation (erosion, diffusion, hydrolysis, etc.), these systems can release the encapsulated content in a given biological microenvironment, avoiding or minimizing undesired enzymatic metabolisms and promoting specific cellular events via binding to cell, for example. Nanostructures that escape the cellular mechanisms of endocytosis or phagocytosis and promote release of a drug in a more sustained form can also be produced. By manipulating the characteristics of the polymers, this release kinetics can be controlled to achieve the desired therapeutic concentration and duration of treatment. Nanostructures may be conjugated to moieties for cell targeting, for example, favoring the binding between the polymer-active substance and the target receptor. Binding can be achieved by the incorporation of amino acids, peptides, lipids or small chains as molecular spacers. In cancer chemotherapy, a drug delivery system can target only the malignant tumor, thereby minimizing the death of neighboring healthy tissue.

The use of polymer nanoparticles is a noninvasive approach to penetration into the blood brain barrier in the case of neurodegenerative, cerebrovascular and inflammatory disorders. New drug delivery methods using nanotechnology allow pharmaceutical companies to reshape existing drugs on the market, expanding their therapeutic applications, improving clinical efficacy, safety and acceptability by the patient [3].

Cancer is the name given to a collection of genetic diseases. Genetic changes that lead to cancer can stem both from the inheritance of the parent and from a person's lifetime through errors in cell division or damage to DNA by environmental factors [4,5]. Metastasis is the spread of cancer cells of a tumor to sow secondary tumors in distant locations, is one of the biggest challenges in treating cancer today. For many patients when cancer is detected, metastasis has already occurred in more than 80% of diagnosed patients. Few patients with metastatic cancer are cured by surgical intervention, and other treatment modalities are limited. In all types of cancer, only one in five patients diagnosed with metastatic cancer will survive more than 5 years [6].

Conventional drugs used in the treatment of cancer are distributed non- specifically by the body, reaching both cancer cells and healthy cells, which imposes a limit on their dosage because of their cytotoxicity. Such a limit, in turn, causes the treatment of the disease to produce effects beyond what would be desirable. Modified drug release systems are pharmaceutical preparations with strong avant-garde appeal in the frontier area of knowledge and with great potential for modification of the pharmacological properties of drugs and other compounds for therapeutic purposes [7].

Thus, the objective was to evidence the scientific knowledge available in the literature on some advances related to the use of nanoparticles with antitumor activity.

## METHODOLOGY

The present study uses as an integrative literature review, allowing to search, evaluate and synthesize the available evidence to contribute to the development of the discussion on the subject. For the elaboration of the present integrative revision the following steps were covered: definition of the guiding question - problem, and objectives of the research; establishment of inclusion criteria and exclusion of publications (sample selection); search in literature; analysis and categorization of studies, presentation and discussion of results [8].

To guide the research, the following question was formulated: what has been produced in the literature on nanoparticles with an emphasis on antitumor activity? The search for publications indexed in the last five years was carried out in June 2017 in the following databases: National Library of Medicine, National Institutes of Health (PubMed), and Latin American and Caribbean Literature in Health Sciences (LILACS) and the Electronic Electronic Library Online (SciELO) electronic library. We chose these databases and library because they understand that they reach the literature published in Latin American and Caribbean countries, as well as Brazilian technical-scientific references and include periodicals from the health area.

Crossing the descriptor "nanoparticles" with "antitumor" was used. The inclusion criteria were research that addressed the use of nanoparticles against tumor cells, published in English, Portuguese or Spanish; in the form of articles, dissertations and theses. As exclusion criteria: papers that did not present full abstracts in the searched databases and library.

The abstracts were evaluated, and the productions that met the previously established criteria were selected for this study and read in full. An instrument was used to collect the information, in order to answer the guiding question of this review, composed of the following items: title, authors, profession of authors, method, periodical, year of publication, place of origin of the research, objective of study and main results.

## RESULTS AND DISCUSSION

Crossing the descriptors "nanoparticles" and "antitumor", 62 studies were found, of which one was repeated in more than one place. Thus, of the 61 publications listed, 26 addressed the main theme proposed with emphasis on the use of nanoparticles or nanoemulsion against tumor cells, in this way were selected to compose this study.The following is an overview of publications.

When analyzing the types of publications selected, 6 were in Portuguese, 5 in Spanish and 16 in English, as to the type of production was found 24 articles, 1 dissertation and 2 theses. Regarding the journals of the selected publications, 4 were identified, with emphasis on Nanomedicine, responsible for 14.8% of the productions on the subject analyzed.

As for the publication period, it was found that the years that presented the greatest number of articles published were in 2016 with eight publications. The years 2013, 2014 and 2017 have four studies each, in 2015 were found 6 and the largest number of publications was in the year 2016 with 9, which represents 33.3% of the selected publications.

In relation to the research design, we identified 9 (33.3%) of the literature review type with a qualitative approach and 18 (66.7%) of the experimental type with a qualitative and quantitative approach. Of these six (22.2%) in Portuguese, five (18.5%) Spanish and 16 (59.2%) in English.

Tables 1-3 shows the distribution of the selected publications by location, where it is seen the highlight of Spain with 8 (29.6%) of the publications, and Brazil with 6 (22.2%) publications. As far as the authors' profession is concerned, 65 authors participated in this study, of which 3 were teachers, 6 researchers, 23 pharmacists, 9 chemists, 2 biomedical scientists, 3 biologists, 3 dentists, 2

**Table 1:** Distribution of the selected publications in the databases and electronic library, 2017.

| Database and Electronic Library | Antitumoral nanoparticles | Selected publications |
|---|---|---|
| LILACS | 3 | 2 |
| PubMed | 58 | 24 |
| SciELO | 1 | 1 |
| **Total** | 62 | 27 |

Source: Prepared by the author

**Table 2:** Distribution of articles according to the periodicals.

| Periodical | Selected Articles |
|---|---|
| Applied Materials e Interfaces | 1 |
| Biblioteca Virtual USP | 1 |
| Biomed Research International | 2 |
| Current Drug Targets | 1 |
| Current Pharmaceutical Design | 2 |
| Current Topics in Medical Chemistry | 1 |
| Diagnostic (Perú) | 1 |
| Einstein | 1 |
| Elsevier | 2 |
| Expert Opinion on Drug Delivery | 1 |
| Frontier in Pharmacology | 1 |
| International Journal of Pharmaceutics | 2 |
| Invest New Drugs | 1 |
| Molecular Pharmacology | 1 |
| Nanomedicine | 4 |
| Pharmaceutical Research | 1 |
| PLOS ONE | 1 |
| Revista Quimíca Agricola e Alimentar | 1 |
| Acta A Mol Biomol Spectrosc | 2 |
| **Total** | **27** |

Source: Prepared by the author

**Table 3:** Distribution of selected publications by location.

| Location | Quantity |
|---|---|
| Brazil | 6 |
| Peru | 2 |
| France | 2 |
| Singapore | 1 |
| Canada | 1 |
| Spain | 8 |
| India | 1 |
| USA | 1 |
| China | 4 |
| Not found | 1 |
| **Total** | 27 |

Source: Prepared by the author

veterinary doctors, 3 chemical engineers and 8 their profession.

The analysis of the data made it possible to analyze that the emergence of nanotechnology had a profound impact in several areas of health, since this science is providing tools for nanomedicine in scientific research, especially in the treatment of cancer and the production of new antitumor drugs associated with nanoparticles [9].

A possible strategy in the treatment of tumors is to improve the therapeutic efficacy of chemotherapeutics and to reduce their adverse effects, is the use of nanoparticulate colloidal systems. Since these drugs are encapsulated within nanoparticles of 50 to 800 nm, they are not able to cross the vessel wall of healthy regions of the body (the space between these cells is only 15 to 30 nm), unlike occurs in inflamed regions or even those where tumors are found, in which endothelial cells are less attached to each other than those in healthy regions, resulting in an accumulation of nanoparticles in tumor tissue adjacent to the blood vessel [10].

Several applications of nanotechnology have been seen, including the use of solid lipid nanoparticles (NLS), nanoemulsions, nanocapsules and the use of nanocomposites for food packaging. Solid lipid nanoparticles are colloidal transport systems, which can be produced by: homogenizing under high pressure hot or cold; microemulsion dilution; preparation of multiple emulsion; emulsification/solvent evaporation, or solvent diffusion [11].

Nanoemulsions are true emulsions, with a dispersed and a continuous phase, generally between 50 nm and 1000 nm in diameter; are transparent or translucent and have stability against sedimentation [12].

Nanocapsules are composed of a polymer envelope wrapped around a core in which the active compound is found, which will be protected against adverse environmental factors, or will be gradually released [13]. The use of nanocomposites for food packaging protects, life and is considered an environmentally correct alternative because it reduces the requirement of using plastics as packaging materials [14].

The appropriate preparation with surface coating, magnetic NPs can be dispersed in suitable solvents, forming homogeneous suspensions, called magnetic fluids. Thus, there is opportunity for various biomedical applications, making viable their use as magnetic resonance contrast agents, such as magnetic field guided drug carriers treatment of tumors via hyperthermia; biomolecular separation and for diagnosis [15].

Among those analyzed a large part underscores the promise of nanotechnology due to already have nanoparticulate in the market, such as the liposomes that were the first nanocarreadores approved by the regulatory agencies to carry a series of chemotherapeutics. The first liposomal formulation to be marketed was Doxil®, in 1995, for the treatment of AIDS-associated Kaposi's sarcoma. Other liposomal formulations for cancer treatment are also on the market, such as DaunoXome® [16].

Liposomes are the most common and well investigated nanocarriers for targeted drug delivery. They have been presented as an improvement to a set of biomedical applications by stabilizing therapeutic compounds, overcoming obstacles to tissue and cellular uptake, and improving the biodistribution of compounds to target sites in vivo [17-18]. Liposomes are defined as phospholipid vesicles consisting of one or more concentric lipid bilayers enclosing discrete aqueous spaces. The unique ability of liposomal systems to trap lipophilic and hydrophilic compounds allows a diverse group of drugs to be encapsulated by these vesicles. The hydrophobic

molecules are inserted into the lipid bilayer, and the hydrophilic molecules can be trapped in the aqueous center [17-20].

In this way, it is observed many efforts with a focus on nanocarrings, choosing the most appropriate is not obvious, because several factors can affect in its biodistribution and its target. Combination chemotherapy strategies can be tailored to optimize tumor treatment and should rely on specific combinations of nanocarriers and target molecules, contributing to improved therapeutic outcomes and cancer diagnosis.

## CONCLUSION

Under the light of the nanotechnology market, there are currently more than 300 products using bactericidal or antifungal nanoparticles, with application in coatings, refrigerators, washing machines, hair dryers, wipes, wall coverings, fabrics, etc. Recent data from the Organization for Economic Cooperation and Development (OECD) and consulting firms indicate that the market for nanotechnology products moves about $350 billion and by 2020 it is estimated that this figure will exceed $3 trillion. The interdisciplinary nature of nanotechnology allows diversification and development in order to improve the quality of life. Scientists in diverse fields such as engineering, materials science, food, biomedical sciences, environmental sciences, agriculture, energy and information technology should be able to use this frontier technology of knowledge to advance research and development.

Nanotechnology can be considered a new technology in the oncology area. The major challenges are to gather information on the properties and risks of these nanomaterials, the in vivo application as well as specific clinical trials. However, all research will enable the development of better quality, safer and more efficient nanotechnology products.

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