

## Nanoparticles in the Use of Natural Products for the Treatment of Lung Cancer

### Nanopartículas en el empleo de productos naturales para el tratamiento del cáncer de pulmón

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#### ABSTRACT

**Objective:** Carry out a bibliographical survey about the use of nanoparticles in the delivery of natural products for the treatment of lung cancer.

**Methods:** A bibliographic review was made using the descriptors “Nanoparticles”, “Biological Products” and “Lung Neoplasms”, through the databases ScienceDirect, PubMed and SciELO, in the period from 2009 to 2018.

**Results:** After analyzing the articles according to the inclusion criteria, we obtained 31 articles, of which 25.81% refer to natural products in the treatment of lung cancer, 29.03% to nanoparticles in the treatment of lung cancer and 45.16% to nanoparticles as carriers of natural products for the treatment of lung cancer.

**Conclusion:** The use of nanoparticles allows the delivery of natural products, increasing their therapeutic properties against lung cancer cells, and decreasing the side effects of these highly toxic agents.

**Key words:** Nanoparticles; Biological Products; Lung Neoplasms.

#### RESUMEN

**Objetivo:** Realizar un estudio bibliográfico sobre el uso de nanopartículas en el transporte de productos naturales para el tratamiento del cáncer de pulmón.

**Métodos:** Se realizó una revisión bibliográfica utilizando los descriptores “Nanoparticles”, “Biological Products” y “Lung Neoplasms”, a través de las bases de datos ScienceDirect, PubMed y SciELO, en el período comprendido entre 2009 y 2018.

**Resultados:** Después del análisis de los artículos de acuerdo con los criterios de inclusión, obtuvimos 31 artículos, de los cuales 25.81% hacían referencia a productos naturales en el tratamiento del cáncer de pulmón, el 29.03% a nanopartículas en el tratamiento del cáncer de pulmón y un 45.16% a nanopartículas como agentes transportadores de productos naturales para el tratamiento del cáncer de pulmón.

**Conclusión:** El uso de nanopartículas permite el transporte de productos naturales, aumentando sus propiedades terapéuticas contra las células de cáncer de pulmón, además de disminuir los efectos secundarios de estos agentes altamente tóxicos.

**Palabras clave:** Nanopartículas; Productos Biológicos; Neoplasias pulmonares.

## INTRODUCTION

Lung cancer accounts for about 2 million new cases of cancer worldwide, considered to be one of the most common malignancies. Responsible for more than 1.7-1.8 million cases of death, it is classified by the *Global Burden of Disease Study* (2015) as the main cause of cancer mortality. According to the National Cancer Institute (INCA), estimated 634,880 new cases of cancer in 2018 in Brazil, of these 31,270 (14.9%) are referring to new cases of lung cancer<sup>(1-3)</sup>. As in other countries, in Brazil, lung cancer is the leading cause of cancer death, with a 5-year survival rate, similar to the overall rates of 10% to 20%<sup>(4)</sup>.

The therapeutic modalities for lung cancer are surgery, radiotherapy and chemotherapy. Tumors in stages I and II are indicated for removal of the tumor, often associated with postoperative chemotherapy. Preoperative chemotherapy may be indicated at stage III, and is complemented post-operatively. In more advanced cases, stage IV, the surgical approach may be used associated with the use of chemotherapy and/or radiotherapy. Brazil is significantly behind in the incorporation of systemic therapies and technologies for the treatment of lung cancer. Many of the drugs used have several side effects compromising the quality of life of the patient<sup>(5-6)</sup>.

Natural products represent an important source of biologically active compounds that play an important role in the treatment of cancer. Currently, about 60% of the drugs found on the market originate from natural products. Among these are vinorelbine, vinblastine, vincristine, paclitaxel, cisplatin and etoposide. Despite many findings, natural sources are still available in abundance and offer better possibilities in the search for substances of therapeutic interest, because despite the arsenal of drugs, several solid tumors still do not have suitable treatment, such as lung cancer that presents modest responses to all available therapeutic regimens<sup>(7-8)</sup>.

It is known that many of the natural products have pharmaceutical deficiencies associated with low solubility and bioavailability. New therapeutic approaches have emerged with the intention of improving these characteristics<sup>(9)</sup>. Nanotechnology brings alternatives in the development of systems of controlled release of drugs in the treatment of various diseases, acting at the target site and enabling the potentiation of the therapeutic effects and decrease of the side effects of the drugs, being this one of the main concerns of the oncological treatment. There are currently several nanosystems that can be classified according to the nature of their composition, such as inorganic, lipid or polymeric making it possible to reformulate and improve

existing drugs for the treatment of cancer<sup>(10)</sup>. Therefore, this review aimed to carry out a bibliographical survey of the use of nanoparticles of natural products for the treatment of lung cancer.

## METHODS

In this study an integrative review of the literature was carried out, whose purpose is to gather and summarize the scientific knowledge already produced related to the topic nanoparticles in the use of natural products in the treatment of lung cancer. The preparation of the integrative review was carried out from the following stages: definition of the problem and objectives of the research, establishment of inclusion criteria and exclusion of publications, search in scientific literature, analysis and categorization of studies, presentation and discussion of results<sup>(11)</sup>.

In order to carry out the study, the period from 2009 to 2018 was considered. Data collection was done through a bibliographic survey in the ScienceDirect, PubMed and SciELO databases using the descriptors "Nanoparticles", "Biological Products" and "Pulmonary Neoplasms" in its English versions.

Inclusion criteria were adopted complete articles published in the period established for the research (2009 to 2018), which dealt with the use of nanoparticles in improving the therapeutic effects of natural products, demonstrating the activity of natural products against lung cancer cells and which showed the benefits of nanoparticles for the treatment of lung cancer, excluding articles available only in summary, articles that although they addressed the therapeutic effects of natural products did not refer to lung cancer, which demonstrated the benefits of using nanoparticles in natural products but did not correlate with lung cancer and papers that although they talked about the treatment of lung cancer did not refer to the use of natural products.

After reading the selected articles, we continued with the analysis and organization of the themes: Natural products in the treatment of lung cancer; Nanoparticles in the treatment of lung cancer; Benefits of using nanoparticles as carriers of natural products.

## RESULTS AND DISCUSSION

A total of 1442 articles were published in the databases proposed in the methodology, in which 1239 were excluded because they did not fit the established inclusion criteria, 153 were repeated and 19 were available only in summary, and only 31 articles were selected for this review. In this study, it was observed that the Journal of Materials Science and Engineering: C is what the most publish on this subject,

with 19.35% of publications and 2018 was the year with the most publications related to the subject analyzed, 32.26% of publications, followed by 2015 (16.13% of publications) and 2011 (9.68% of publications). Table 1 shows a survey of all journals and their respective years of publications on the subject.

Table 1 shows a survey of all journals and their respective years of publications on the subject. (n) Number of articles published and (%) refers to the percentage of the number of articles published by journal.

Journal	Selected articles		Year of Publication
	(n)	(%)	
Acta Biomaterialia	02	6.45	2016, 2015
Biochemical Pharmacology	01	3.22	2010
Biomaterials	01	3.22	2014
Biomedicine & Pharmacotherapy	04	12.90	2018, 2014, 2012
Biosensors and Bioelectronics	01	3.22	2015
Cancer Letters	01	3.22	2011
Colloids and Surfaces B: Biointerfaces	01	3.22	2013
Egyptian Journal of Basic and Applied Sciences	01	3.22	2018
Food and Chemical Toxicology	01	3.22	2011
Human Pathology	01	3.22	2009
International Journal of Biological Macromolecules	03	9.68	2018, 2014
International Journal of Pharmaceutics	02	6.45	2018, 2015
Journal of Controlled Release	02	6.45	2018, 2011
Journal of Thoracic Oncology	01	3.22	2015
Materials Science and Engineering: C	06	19.35	2018, 2017, 2013
Nanomedicine: Nanotechnology, Biology and Medicine	01	3.22	2016
PharmaNutrition	01	3.22	2015
The Lancet Oncology	01	3.22	2012
Total	31	99.92	

Source: Research Data

When we evaluated according to the type of publications, it was observed that 96.77% of the published articles were original articles and 3.22% were articles of revision. Data analysis enabled the classification of publications in three thematic categories, in which the first refers to the use of natural products in the treatment of lung cancer, representing 25.81% of the publications inserted in this integrative review.

Due to the great difficulty of obtaining drugs with great therapeutic potentials, the natural products have been explored in order to supply this need and obtain drugs with less toxicity. Paclitaxel and docetaxel are derived from the plant *Taxus brevifolia* and widely used in the treatment of several tumors, including non-small cell lung carcinoma<sup>(12)</sup>.

Another plant derivative is *Atractylenolide III* (ATL-III), which is the main bioactive component of the *Atractylodes rhizome* which is related to inhibition of the production of tumor necrosis factor alpha (TNF- $\alpha$ ) and lipopolysaccharide-induced nitric oxide in macrophages. Kang et al.<sup>(13)</sup> evidence the benefits of ATL-III in the treatment of lung cancer by inducing apoptosis in A549 cells of lung carcinoma lineage.

Czerwonka et al.<sup>(14)</sup> tested the aqueous extract of *Spirulina*, which is a dietary supplement derived from algae *Arthrospira platensis*, against non-small cell lung carcinoma A549 cells, showing in its study anticancer activity and chemopreventive properties of *Spirulina*.

One of the effective alternatives to increase the cytotoxicity of drugs is to associate drugs with different mechanisms of action and to be able to destroy a large amount of neoplastic cells. Gorzalczany et al.<sup>(15)</sup> combined a tyrosine kinase inhibitor with autophagy-inducing drugs to combat non-small cell lung cells expressing epidermal growth factor receptor (EGFR), showing benefits in the association of these agents with the cells of strain A549. Karthik et al.<sup>(16)</sup> associated the drugs romidepsin and bortezomib, noting that when associated they potentiate their cytotoxic activity on lung cancer cells by inducing synergistically apoptosis in lung cancer cells.

Another benefit of the analysis of natural products is the possibility of identifying specific markers of a type of cancer. Luu et al.<sup>(17)</sup> proposed the analysis of asparaginyl- $\beta$ -hydroxylase (ABH), which are protein products, showing that ABH overexpression is probably related to a potential increase in tumor invasion and metastatic spread.

Curcumin is well studied because it has a potential anti-neoplastic effect, many studies are aimed at improving the activity of curcumin *in vivo*. Imaizumi<sup>(18)</sup> developed a highly bioavailable curcumin called Theracurmin, with a therapeutic effect 27 times greater than that of commercially available curcumin.

The second thematic category deals with nanoparticles in the treatment of lung cancer, representing 29.03% of the publications of this integrative review.

With the advancement of molecular biology research, it was possible to decipher the complexity of the underlying biology of lung cancer, offering valuable information, in the demonstration of molecularly diverse groups of neoplastic processes, leading rapidly to development, clinical evaluation and approval of new targeted drugs specifically for the treatment of lung cancer, having as example the potent and highly specific tyrosine kinase inhibitors targeting molecular changes and thereby providing a prolonged control of the disease<sup>(19-20)</sup>.

Due to the high toxicity of the chemotherapeutic agents, the molecular biology findings allowed to identify specific pathophysiological characteristics of some types of tumors, leading to the development of therapeutic agents directed to the specific markers of each tumor aiming to reduce the toxicity due to the systemic of the treatment<sup>(21)</sup>.

As many drugs currently obtained are of vegetable origin, they present some biopharmaceutical problems that confer low solubility and low bioavailability<sup>(18)</sup>. With the advancement of nanotechnology, it has become possible to develop therapeutic formulations based on nanoparticles. Accord-

ing to the *European Technological Observatory*, in 2006 more than 150 pharmaceutical companies were developing nanoscale therapies in which the idea of controlled drug delivery has been shown to improve their therapeutic index, increased concentration in specific tissues, organs or cells, which led to a decrease in side effects and potentiation of the therapeutic effect of the drugs. Because of these advantages, efforts are made to include the chemotherapeutic agents, many of which are plant-derived or semisynthetic, in nanosystems to improve cancer therapy<sup>(22)</sup>. Figure 1 shows the main nanotechnological systems for the treatment of lung cancer.

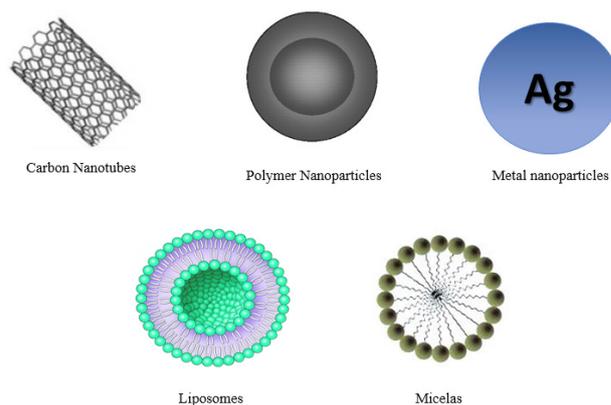


Figure 1. Main nanosystems tested for the treatment of lung cancer

Source: Adapted from Cho et al.<sup>(23)</sup>; Mohanta et al.<sup>(24)</sup>; Pinho & Figueiras<sup>(25)</sup>; Zaborski<sup>(26)</sup>; Sharma et al.<sup>(27)</sup>

Nanocarriers have the potential to modify the properties of drugs by increasing their efficacy, stability and solubility, as well as reducing their toxicity and sustaining their release<sup>(18,22)</sup>. The first drug inserted in nanoparticles and approved by the US *Food and Drug Administration* (FDA) was DOXIL (Figure 2), which is doxorubicin encapsulated in a lipid nanoparticle. Research clearly shows that the delivery of nanoparticles specifically to cancer cells can increase the release of chemotherapeutics into tumors while reducing the accumulation of drugs in healthy cells. There are few studies that are concerned with studying the use of nanoparticles as carriers of drugs for the treatment of lung cancer, targeting only incident cancers such as breast cancer<sup>(28)</sup>. Several authors show benefits of using nanoparticles in lung cancer, Masood et al.<sup>(29)</sup> reports in his study that the development of poly (3-hydroxybutyrate-co-3-hydroxyvalerate) based nanoparticles as ellipticine carriers show an inhibition of A549 lung cancer cells twice as high as ellipticin alone.

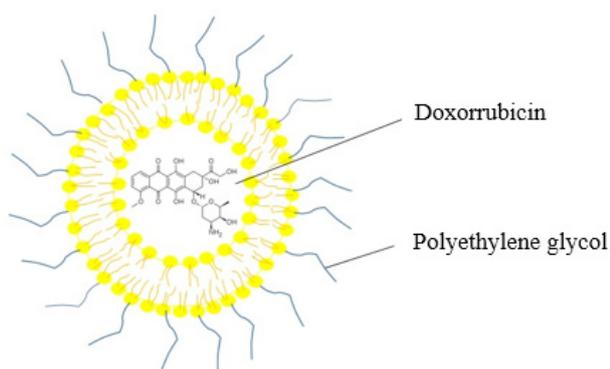


Figure 2. Liposomes loaded with doxorubicin

Studies also indicate that nanoparticles may enhance the activity of drugs widely used in clinical practice. Kumar et al.<sup>(30)</sup> developed vincristine loaded folic acid-chitosan nanoparticles (Figure 3) and tested on cancer cells from non-small cell lung cancer NCI-H460 showing from the cell viability assay a higher cytotoxicity of vincristine in lung cancer cells when inserted into the nanoparticles.

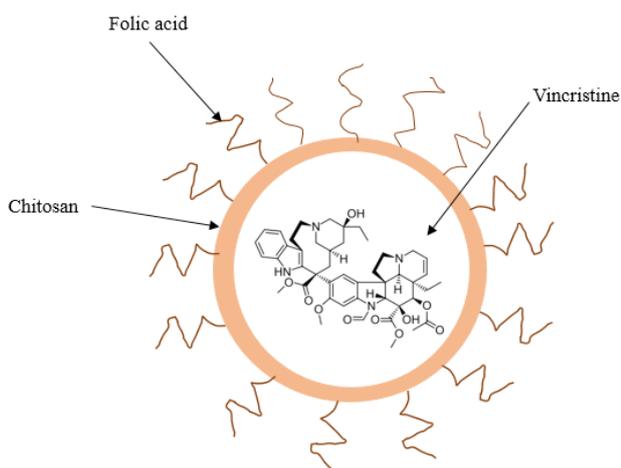


Figure 3. Nanoparticle of chitosan conjugated to folic acid loaded with vincristine

Rychahou et al.<sup>(28)</sup> evidence that it is possible to make use of polymer nanoparticles as potential drug carriers at the pulmonary level for treatment of lung metastases, due to the accumulation of polymeric nanoparticles in lung tissue, showed a high affinity of polymer nanoparticles for lung cells.

Not only focused on improving lung cancer therapy, nanotechnology also allows the detection of lung cancer cells, thereby facilitating their diagnosis. Mir et al.<sup>(31)</sup> used in their study, gold nanoparticles for the development of an amperometric nanobiosensor for the detection of lung cancer cells (A549), showing high affinity of the biosensor for lung cancer cells compared to control cells, including prostate

cancer cells (PC3), normal lung cells (MRC-5) and liver tumor cells (HepG2).

The third thematic category includes articles that consider the benefits of using nanoparticles as carriers of natural products for the treatment of lung cancer, representing 45.16% of publications.

The use of the nanoparticles allows to deliver the drugs to their target sites, generating a specificity, without causing many side effects. Docetaxel is a chemotherapeutic agent widely used in the treatment of lung cancer, showed effectiveness in prolonging the life span of many patients, being that some patients suffering from allergy, fluid retention, leukocyte reduction, alopecia, weakness, among other reactions caused by this drug. With the use of nanoparticles these effects can be reduced and the efficacy of the treatment can be increased<sup>(32)</sup>. The study by Liang et al.<sup>(32)</sup> developed nanoparticles of docetaxel with the polylactic acid (PLA) polymer in order to reduce tumor growth and liver metastases from small cell lung cancer, obtaining positive results both *in vitro* and *in vivo*.

In order for the nanoparticle to exhibit selectivity for the lung, it is necessary to obtain small nanoparticles, smaller than 10 nm, and the composition of the nanoparticle also becomes important to obtain stable nanosystems that do not present toxicity when administered in the body<sup>(33-34)</sup>. The use of chitosan is well explored to obtain several nanoparticles due to its high potential in the treatment of lung cancer, because it is a natural polysaccharide with non-toxic, biocompatible and biodegradable properties. Samadi et al.<sup>(34)</sup> developed nanofibrous systems with the use of chitosan for the sustained delivery of doxorubicin in the treatment of lung cancer, achieving an effective delivery system in inhibiting the proliferation of A549 lineage lung cancer cells.

Maya et al.<sup>(35)</sup> developed chitosan nanoparticles for the delivery of docetaxel associated with the monoclonal antibody Cetuximab, as driving agents the expression of the EGFR gene for the treatment of non-small cell lung cancer, showing that nanosystems can be obtained with the association of drugs used in the clinic, potentiating the effect of the drugs due to their targeting on cancer cells.

Another nanotechnology developed as promising for the delivery of chemotherapeutic agents is the chitosan folate-conjugated carbon nanotubes, developed by Singh et al.<sup>(36)</sup> for the sustained release of docetaxel, showing a high cytotoxicity of this system and a low toxicity when compared with docetaxel free. Another important factor is that nanocarriers can carry an association of drugs that are compatible with each other and that improve the characteristics

of the chemotherapeutic agent, is the case of the development of vitamin E TGPS nanoparticles with the objective of improving the solubilization of paclitaxel, besides helping in its mechanism of action, because of the power of such a system to retain the drug in the microenvironment, with increased permeability at the tumor target site, thereby leading to a reduction of the free drug within the bloodstream, resulting in improved tolerability and increased efficacy of the chemotherapeutic agent<sup>(37)</sup>.

Hydroxyapatite is an inorganic bone component widely used in bone tissue reconstruction, and more recent studies have found that hydroxyapatite nanoparticles have selective anticancer activity for lung cancer cells. Ignjatovic et al.<sup>(38)</sup> demonstrate that it is possible to develop hydroxyapatite nanoparticle with chitosan and poly-lactic-co-glycolic (PLGA) to make them more selective for the A549 lung cancer cell line than for healthy cells. Chen et al.<sup>(39)</sup> also makes use of nanoparticles of hydroxyapatite in the delivery of ionizing radiation for the treatment of lung cancer, obtaining positive results and proposing a new alternative for the treatment of lung cancer.

New therapeutic approaches were developed from the properties of nanosystems, such as the development of chitosan micelles with cholesterol for the combined administration of small fragments of RNA and curcumin with cytotoxic activity on lung cancer cells, a promising system for the delivery of small fragments of RNA and chemotherapeutic agent with low solubility for cancer cells<sup>(40)</sup>. Curcumin has promising anticancer properties, however it has poor solubility in aqueous medium and low bioavailability, Ibrahim et al.<sup>(41)</sup> encapsulated curcumin in liposomes coated with lipids of marine origin (Marinosomas) in order to develop potential anticancer therapy from low-cost and readily available nutraceuticals, showing a favorable system of *in vitro* drug delivery in the fight against lung cancer.

Biological products in addition to presenting cytotoxic effects to cancer cells may also aid in the development of the nanoparticle, being tested as possible ecologically correct nanofactors for the development of silver nanoparticles, being active against lung cancer cells. Gengan et al.<sup>(42)</sup> obtained biosynthesized silver nanoparticles using the leaf of *Albizia adianthifolia*, which is an abundant plant on the east coast of southern Africa, and presents a range of biological and pharmacological activities. Dadashpour et al.<sup>(43)</sup> also managed to obtain silver nanoparticles, using the extract of the *Matricaria chamomilla* plant with positive results against the A549 line of lung cells.

## CONCLUSIONS

The use of nanoparticles has been widely used as potentiators of the activity of various agents obtained from natural products with the aim of improving their pharmaceutical properties, decrease their toxicity, and allow the delivery of associated agents that minimize the toxicity of drugs widely used in clinical practice.

Many techniques are being developed to improve the therapy of lung cancer, which is currently the main cause of death from cancer. The nanoparticles have a great potential, due to their properties that confer selectivity and specificity to lung cancer cells, with promising drug delivery systems that enable the use of natural products for the treatment of lung cancer.

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