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# NANOMEDICATIONS IN THE TREATMENT OF MELANOMA - A REVIEW[1]

## *NANOMEDICAMENTOS NO TRATAMENTO DO MELANOMA - UMA REVISÃO*

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**ABSTRACT**

Cutaneous melanoma is a type of cancer that arises from melanocytes, cells responsible for melanin production, formed during embryonic development from the neural crest. This cancer originates in the skin and can be superficial, extensive, nodular, malignant, and acral lentiginous. In this article, we present a literature review on nanomedicines as a possible treatment for this type of cancer. Our search for articles took place on the Web of Science platform over the last 5 years. It was possible to verify that advances in nanoscience led to more modern and effective treatments, with fewer side effects and adverse effects, allowing more safety and quality of life for the patient undergoing treatment.

**Keywords:** Skin Cancer, Clinical Protocol, Nanoscience, Nanomedicines.

***RESUMO***

*O melanoma cutâneo é um tipo de câncer que surge a partir dos melanócitos, células responsáveis pela produção de melanina, formadas durante o desenvolvimento embrionário a partir da crista neural. Esse câncer tem origem na pele e pode ser superficial, extenso, nodular, maligno e lentiginoso acral. Neste artigo, apresentamos uma revisão da literatura sobre os nanomedicamentos como possível tratamento para este tipo de câncer. Nossa busca por artigos ocorreu na plataforma Web of Science nos últimos 5 anos. Foi possível verificar que os avanços da nanociência levaram a tratamentos mais modernos e eficazes, com menos efeitos colaterais e adversos, possibilitando mais segurança e qualidade de vida ao paciente em tratamento.*

***Palavras-chave:*** *Câncer de Pele, Protocolo Clínico, Nanociência, Nanomedicamentos.*

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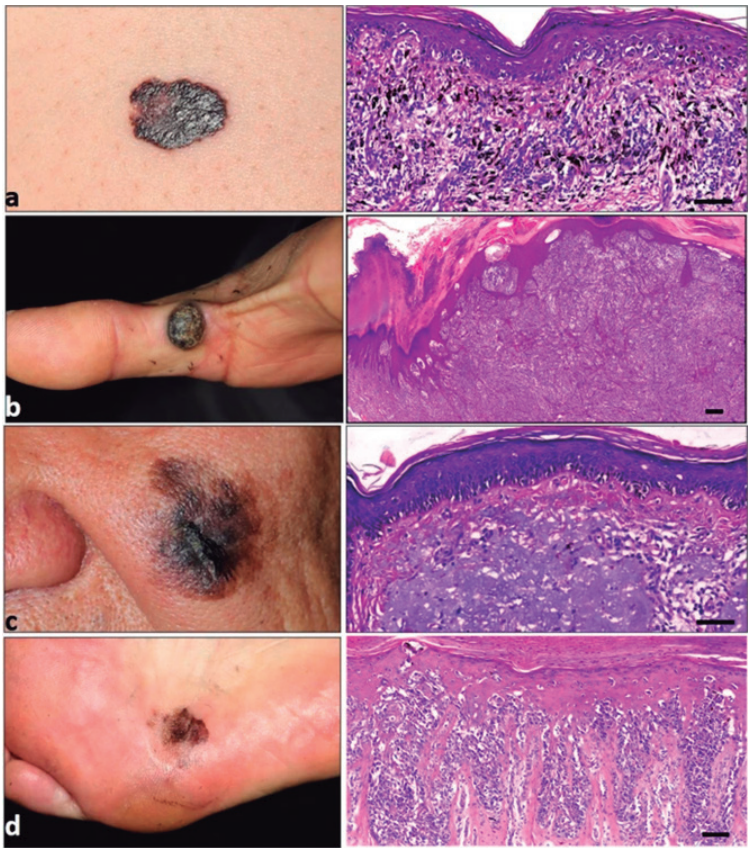
## INTRODUCTION

*Cancer* can be defined as cells that grow in a disordered manner, divide rapidly, and can be aggressive and uncontrollable. These cells form tumors that invade organs and tissues and spread to other body regions (INCA, 2019). Cutaneous melanoma is the 12th most frequent type of cancer in the world, located predominantly in the skin but also found in eyes, ears, and oral and genital mucous membranes (Swetter *et al*., 2019). It is one of the diseases that most lead to death for Brazilians of different ages. According to the National Cancer Institute (INCA, 2022), 704 thousand new cancer cases are estimated in Brazil for each year of the 2023-2025 triennium, emphasizing the South and Southeast regions, which concentrate about 70% of the incidence.

This cancer is a neoplasm that forms from the transformation of melanocytes, which are melanin-producing cells originating embryologically from the neural crest, as shown in Figure 1. It develops due to multiple changes in cellular DNA, which can be caused by mutations or deletions of tumor suppressor genes, structural alteration of the chromosome, or activation of proto-oncogenes (Smith *et al*., 2018). Some recognized risk factors for melanoma include heredity, exposure to ultraviolet (UV) radiation, and skin phenotype (Gandini *et al.,* 2005).

**Figure 1 -** Caption: Corresponding clinical and histopathological images of melanomas.




Generally, melanomas are classified into four main types according to histopathologic features, namely superficial extensive melanoma (a), nodular melanoma (b), lentigo malignant melanoma (c), and acral lentiginous melanoma (d). The corresponding histopathologic image from the same patient is shown on the right. Scale bar = 100 μm.
Source: Guo; Wang; Li (2021).

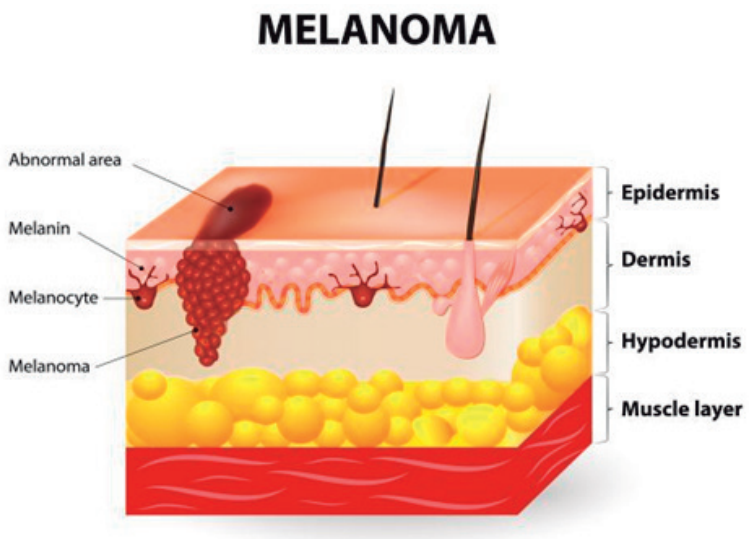
Chronic exposure to ultraviolet (UV) radiation is the primary cause of skin carcinomas. This exposure can cause errors in the DNA strand, forming pyrimidine dimers (Rstom *et al*., 2014). The most direct repair form involves enzymes that reverse the chemical modification that caused the defect, namely photolyase. Photolyase binds to cyclobutane-pyrimidine dimers (CPDs), and exposure of the photolyase-dimers complex to radiation converts the dimerized pyrimidines to their original structure, combating this process of carcinogenesis (Sancar, 2008).

Traditional cancer therapies, immunotherapy, surgery, chemotherapy, and radiotherapy have represented a breakthrough in treating this disease, helping to reverse the deadly trends of several types of cancer (Vagia; Mahalingam; Cristofanilli, 2020). Some current treatments are limited in one way or another by several factors, such as drug resistance, adverse side effects, low therapeutic indices, low bioavailability, and lack of specificity, among other limitations (Hare *et al*., 2017). For this reason, there are great efforts and research to try alternative therapeutic approaches (Vagia; Mahalingam; Cristofanilli, 2020).

Melanoma is the most aggressive form of skin cancer, with a high rate of brain metastases in about 50% of cases. Of the cases of skin cancer, 2% are melanomas, and they are responsible for 80% of the causes of death of cancer patients (De Moura *et al.,* 2021). Several treatments have been investigated to treat this disease, but drug resistance remains an important factor in the failure of conventional therapy and the high rates of relapse (Yang *et al*., 2020; De Moura *et al*., 2021).

There are many reasons for melanoma treatment failures, including cancer cells' ability to develop mechanisms to escape apoptosis, which results in continued cell proliferation (Rigon *et al*., 2015). Other factors include poor drug bioavailability and inefficient delivery to target cells. In common with other solid tumors, the malignancy of melanoma depends on the stage at diagnosis. Loco-regional metastasis to the lymph nodes is often followed by colonization of other organs, distant metastasis, and associated acquired mutations, making treatment less effective. Standard treatment procedures involve cytoreduction surgery (removal of the primary tumor), chemotherapy, radiotherapy, targeted therapy, and immunotherapy (Mattia *et al*., 2018). Figure 2 shows the most common form of melanoma in the human body.

**Figure 2 -** Melanoma.




Source: Staff (2018).

Over the years, Nanotechnology has gained space in the health area, bringing innovations in the pharmaceutical industry and contributing to new techniques for diagnosing, preventing, and treating diseases, including cutaneous melanoma (Cassano *et al*., 2021). The application of nanotechnology to different types of medications can optimize the most desirable properties of a formulation, facilitate the sustained release of bioactive compounds, reduce the required quantities (doses), minimize side effects, and increase their therapeutic potential (Mamillapalli, 2016).

Nanotechnology presents some options for treating cutaneous melanoma, including photothermal therapy, a technique using photosensitizer (PS) compound and light at an appropriate wavelength for its activation. Thus, the destruction of tumor cells occurs through selective heating (Martinelli *et al*., 2023). In addition, drug-carrying nanoparticles can be designed to carry specific drugs to cancer cells, allowing a controlled release of the drug at the tumor site, thus increasing the effectiveness of the treatment (Refaat *et al*., 2019).

However, the importance of designing strategies for preventing, diagnosing, and treating neoplasms is evident, considering that the social and economic damages caused by these pathologies are inestimable (Campos; Praça; Kavicz, 2022). Thus, this study aims to conduct a literature review of the main treatments available using nanotechnology to treat cutaneous melanoma.

## METHODOLOGY

This article reviews the literature to synthesize knowledge and answer the research question, referring to what is most current in treating Melanoma involving Nanotechnology. This work is an integrative literature review that seeks significant studies of information needed to be applied in practice (Souza; Silva; Carvalho, 2010).

After defining the research question, the second step was to search for articles in the Web of Science database. The descriptors used were selected from the vocabularies found in the Health Sciences Descriptors (DeCS) and Medical Subject Heading Terms (MeSH). The descriptors used were "Nanotechnology", "Melanoma", and "Treatment", separated by the Boolean operator AND.

The search included Portuguese, English, and Spanish studies, with temporal selection of the last 5 years (2018-2023), without restriction of location. Those repeated in the databases, only in abstract format, studies not available in full, points of view, literature reviews, or those that did not answer the research question were excluded.

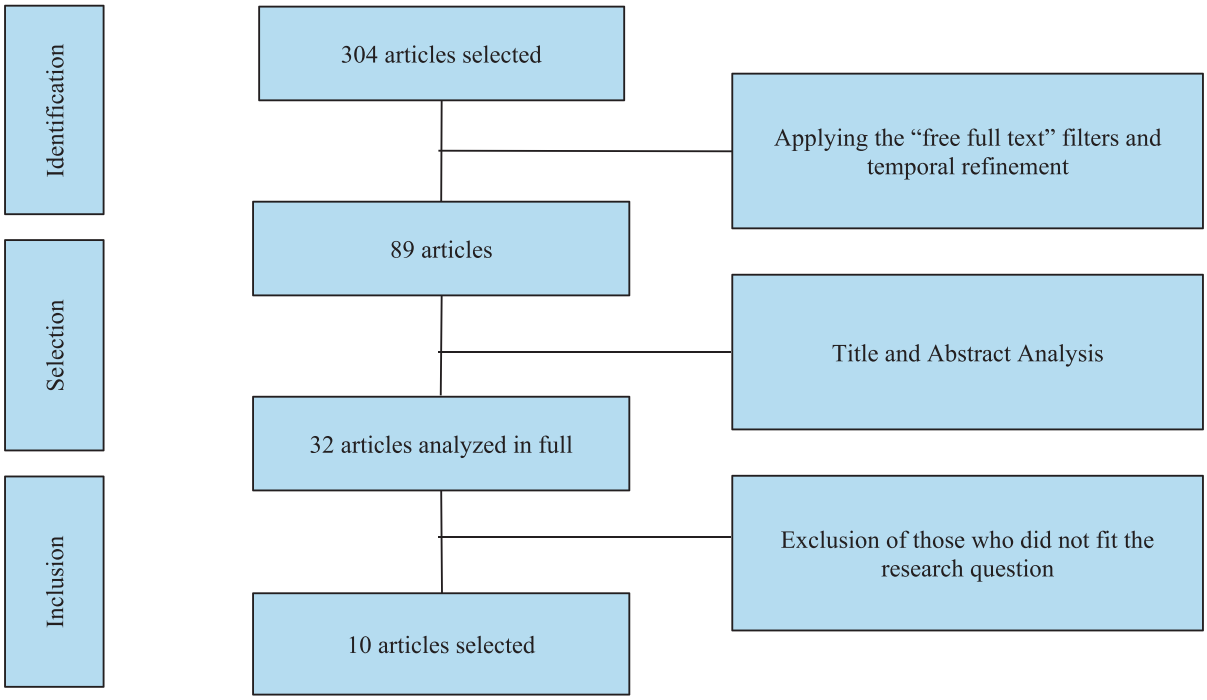
The third methodological step consisted of data collection based on the abovementioned criteria. Initially, all the titles and respective abstracts of the articles identified by the search strategy were analyzed, and those abstracts with insufficient information or outside the expected context were excluded. The abstracts that met the eligibility criteria were thoroughly assessed.

In the fourth phase, those that fit the research criteria were carefully analyzed. To assist in the choice of articles, we sought works with a high level of scientific evidence, prioritizing randomized clinical trials since combining several methodologies can contribute to the need for more research rigor. Data and relevant information were extracted in the fifth and final phase, and the results were analyzed and discussed. The selected articles were inserted into a spreadsheet prepared by the researchers in the Excel® Program, organizing the information clearly and objectively.

## RESULTS OF THE COLLECTION OF ARTICLES

A total of 304 articles were found in the Web of Science database, where after refining the search by time criteria, 184 papers remained. When excluding articles unavailable, 89 results remained to be evaluated by title and abstract. A total of 32 articles were analyzed in full, where only 10 fit the research question, according to Figure 3.

**Figure 3 -** Flowchart with the selection of the articles used.




Source: author's construction.

After selecting the articles for the research, the main data were extracted and organized according to Table 1.

**Table 1 -** Research Table on the Use of Nanomedications in the Treatment of Melanoma.

| Author(s)/ year | Title, Journal | Aim | Conclusion |
|---|---|---|---|
| Dianzani *et al*., 2020 | Nanoemulsions as Delivery Systems for Poly-Chemotherapy Aiming at Melanoma Treatment | To investigate a new polychemotherapy based on nanotechnology, which employs temozolomide (TMZ), rapamycin (RAP) and bevacizumab (BVZ) co-loaded in injectable nanoemulsions, for the treatment of advanced-stage melanoma, through in vitro and *in vivo* through rodents. | The proposed polychemotherapy increases efficacy against melanoma in both *in vitro* and *in vivo* models. |
| Garcia-Hevia *et al*., 2022 | Magnetic lipid nanovehicles synergize the controlled thermal release of chemotherapeutics with magnetic ablation while enabling non-invasive monitoring by MRI for melanoma theranostics | A biocompatible magnetic lipid nanocomposite carrier was developed through an efficient, green and simple method to simultaneously incorporate magnetic nanoparticles and an anticancer drug (doxorubicin) into a natural nanomatrix, it is approved by the FDA for its application in humans. | Chemotherapy with magnetic lipid nanocomposites (mLNVs-DOX) combined with alternating magnetic field-induced hyperthermia exhibited a strong cytotoxic effect on malignant melanoma cells, both in vitro and in vivo, even at relatively low doses of DOX. |

| | | | |
|---|---|---|---|
| De Moura *et al*., 2021 | Docetaxel and Lidocaine Co-Loaded (NLC-in-Hydrogel) Hybrid System Designed for the Treatment of Melanoma | To evaluate a hybrid hydrogel with a nanostructured lipid carrier (CLN) containing docetaxel (DTX) on murine fibroblasts (NIH/3T3), melanoma cells (B16-F10), human keratinocytes (HaCaT). | In vivo tests indicated that the hybrid hydrogel was able to inhibit tumor growth equivalently to conventional treatment (free DTX). Furthermore, treatment with the hybrid hydrogel showed no adverse effects as revealed by physical, biochemical, and histopathological parameters. |
| Liu C, *et al*., 2018 | A targeted therapy for melanoma by graphene oxide composite with microRNA carrier | Graphene oxide (GO) is a new nanomedicine carrier. Acting as a nanocarrier of antineoplastics. | Cell transfection results show that the microsphere materials prepared in this study can be taken up by cells and accumulate in the cytoplasm. |
| Clemente *et al*., 2021 | Verteporfin-Loaded Mesoporous Silica Nanoparticles' Topical Applications Inhibit Mouse Melanoma Lymphangiogenesis and Micrometastasis In Vivo | To evaluate in vivo (rodents) efficacy of mesoporous silica nanoparticles (MSNs) conjugated with verteporfin (Ver-MSNs) administered transcutaneously to mice to treat lymphangiogenesis and micrometastasis in cutaneous melanoma. | To evaluate the efficacy of mesoporous silica nanoparticles (MSNs) conjugated with verteporfin (Ver-MSNs) administered transcutaneously to mice to treat lymphoangiogenesis and micrometastasis in cutaneous melanoma. |
| Naeem *et al*., 2023 | Anticarcinogenic impact of extracellular vesicles (exosomes) from cord blood stem cells in malignant melanoma: A potential biological treatment | To evaluate DNA damage in melanoma (CHL-1) and lymphocytes from melanoma patients and healthy individuals after treatment with varying concentrations of exosomes derived from umbilical cord blood stem cells (CBSC). | It was conclued that exosomes derived from umbilical cord blood have the ability to prevent the induction of tumors by displaying certain MicroRNAs that may be beneficial in reducing tumorigenicity and growth of cancer cells. |
| Wang; Xuan; Pan, 2022 | Photothermal ablation of murine melanomas by $Fe_3O_4$ nanoparticle clusters | Examine the morphology of clusters of superparamagnetic $Fe_3O_4$ nanoparticles and test their ability to convert light into heat. Then, evaluate its effectiveness as photothermal therapy in melanoma cells. | In vitro experiments using light field microscopy and cell viability assay showed that $Fe_3O_4$ in conjunction with near-infrared irradiation effectively killed A375 melanoma cells by inducing open apoptosis. |
| Lees *et al*., 2021 | Multi-sample measurement of hyperpolarized pyruvate-to-lactate flux in melanoma cells | Develop na experimental protocol to enable measurement of metabolic flux in multiple mass-limited cell suspension samples, thereby increasing experimental efficiency and providing greater control of the methodological variability associated with HP experiments. This new method explores the use of deuterated dissolution buffer in combination with a microcoil design conducive to rapid sample turnover. | A multi-sample protocol, with as few dissolutions as possible. For measuring the flux of pyruvate to lactate in melanoma cells for the evaluation of treatment BRAFi demonstrated a significant reduction of k PL after 24 and 48 hours of treatment in BRAF V600E cells and no significant effect in BRAF WT cells. |

| | | | |
|---|---|---|---|
| Murray *et al*., 2018 | In Situ Vaccination with Cowpea vs Tobacco Mosaic Virus against Melanoma | Seek to understand how structural differences between CPMV- and TMV-based in situ vaccine formulations can enhance or impede effective immune activation, leading to a TME conducive to an antitumor response. | A scenario of dermal melanoma in mice has been discovered: tobacco mosaic virus (TMV) used as an in situ vaccine provokes a weak antitumor immune response againts melanoma, showing a tendency to reduce tumor burden and prolong survival - however, the effectiveness of CPMV could not be matched; there were no apparent differences comparing the efficacy of native TMV measuring 300 × 18 nm vs short TMV measuring ~50 × 18 nm or spherical TMV, SNP; however, free CPs did not elicit an antitumor response or immunostimulation (as measured by cytokine/chemokine levels). |
| Zatta *et al*., 2018 | An Inhalable Powder Formulation Based on Micro- and Nanoparticles Containing 5-Fluorouracil for the Treatment of Metastatic Melanoma | Develop new formulations for the treatment of advanced metastatic melanoma based on 5FU micro- and nanoparticles for pulmonar delivery. | Both formulations exhibited adequate aerodynamic properties and dose uniformity for efficient pulmonary delivery. The formulations were tested for their cytotoxic action on melanoma cancer cells (A2058 and A375) and both showed a cytotoxic effect of 4.3 and 1.7 times greater than the pure 5FU drug. The resulsts showed that the 5FU-MS and 5FU-NS formulations have favorable complementary properties for pulmonary delivery. If combined into a single therapeutic system, the powders, with different particle sizes, could be administered through a dry powder inhaler with satisfactory distribution of the drug throughout the respiratory tract. |

Source: adapted by the author based on the articles mentioned above.

## DISCUSSION

Treatment for melanoma depends on several factors, including the disease's stage, the tumor's location, the presence of metastases, and the patient's individual characteristics (Tagliaferri *et al.*, 2022). Melanoma treatment is highly personalized and should be discussed with a specialized multiprofessional team, who can assess the most appropriate options for each patient based on their specific case. In addition, advances in cancer treatment are constantly occurring, so new therapies and approaches may become available over the years (Namikawa; Yamazaki, 2019).

Surgery is usually the main treatment for melanoma. It involves surgically removing the tumor and a margin of normal skin around it. In advanced cases, it may be necessary to remove nearby lymph nodes (Morton *et al.,* 2014). Radiotherapy may be used after surgery to kill remaining cancer cells or to relieve symptoms in advance using high-energy radiation (Tagliaferri *et al.,* 2022).

Immunotherapy is a treatment that stimulates the patient's immune system to fight cancer, so immune checkpoint inhibitors, such as pembrolizumab and nivolumab, have been effective in treating advanced melanoma (Namikawa; Yamazaki, 2019). Traditional chemotherapy has a limited role in the treatment of melanoma but can still be used in advanced cases or when other treatments are not available (Yang; Chapman, 2009).

Nanoscience and nanotechnology represent an expanding area of research, which involves structures, devices, and systems with new properties and functions due to the arrangement of their atoms on the scale of 1-100 nm (Ahmed; Gultekinoglu; Edirisinghe, 2020). Nanotechnology has been repeatedly proposed as a critical player in the next generation of antitumor drugs, particularly in drug delivery, where some examples have already impacted the clinic (Hare *et al.,* 2017). Some treatment options for melanoma involving nanotechnology include targeting an injectable chemotherapeutic drug and radiation-controlled release into the tumor cell environment, reducing unwanted side effects and significantly increasing treatment efficacy (Won *et al.,* 2021).

Drug delivery systems represent an effective strategy for the release of antineoplastic agents since they reconfigure the biodistribution of drugs, providing (i) longer circulation time with high stability, (ii) better bioavailability, (iii) controlled release of the drug, (iv) reduced dosage and (v) minimal toxic effects (Mainardes *et al.,* 2006).

Brazilian researchers such as Zatta and collaborators (2018) concluded in their research a new means of applying 5-Fluorouracil (5-FU), an antineoplastic widely used in the treatment of solid cancers and melanoma. The application takes place by inhaling nano and microparticles containing 5-FU, presenting increased cytotoxic effects referenced to the traditional method, which is 5-FU via the systemic route. These particles were designed to be easily inhaled and deposited in the lungs to treat melanoma lung metastases. Through *in vitro* and *in vivo* studies, the diagnosis that the powder formulation could release 5-FU in a controlled and sustained manner resulted in a higher therapeutic efficacy against melanoma cells. In addition, administration by inhalation allowed direct delivery of the drug to lung metastases, increasing its concentration at the site of action and generating systemic adverse effects.

Dianzani *et al.* (2020) bring in their research on using nanoemulsions to deliver multidrug therapy in treating melanoma. Polychemotherapy involves using multiple antineoplastic drugs in combination, targeting different signaling pathways involved in the growth and spread of melanoma. This approach seeks to maximize therapeutic efficacy and minimize the development of drug resistance. The article highlights in vitro and in vivo studies that have shown promising results,

including tumor growth progression, reduction of metastasis, and increased survival in animal models (Dianzani *et al.,* 2020).

Garcia-Hevia *et al.,* (2022) address the development of a new strategy for the treatment of melanoma through nanotechnology, which combines the controlled release of chemotherapeutics through magnetic lipid nano vehicles with magnetic ablation and non-invasive monitoring by magnetic resonance imaging (MRI). One of the advantages of this approach is the ability to monitor the treatment non-invasively using magnetic resonance imaging (MRI). The presence of magnetic nanovehicles in the tumor cells makes it possible to detect and accurately visualize the tumor throughout treatment. This procedure enables doctors to assess the effectiveness of the treatment, adjust the dose of chemotherapy drugs, and monitor the tumor's response to combination therapies. Researchers observed a significant reduction in tumor size and a higher remission rate than conventional approaches (Garcia-Hevia *et al.,* 2022).

An *in vivo* trial brings a hybrid system for melanoma treatment, which consists of the co-loading of docetaxel and gives together with lidocaine in a nanostructured lipid system (NLC) embedded in a hydrogel. Docetaxel is an effective chemotherapeutic in the treatment of melanoma, and lidocaine is a local anesthetic that can help relieve pain associated with treatment. The results of the pathogenetic study showed that the hybrid system could inhibit the growth of melanoma cells *in vitro* more effectively than either docetaxel or lidocaine alone. In addition, the system was shown to reduce the pain associated with melanoma treatment, providing significant relief for patients (De Moura *et al.,* 2021).

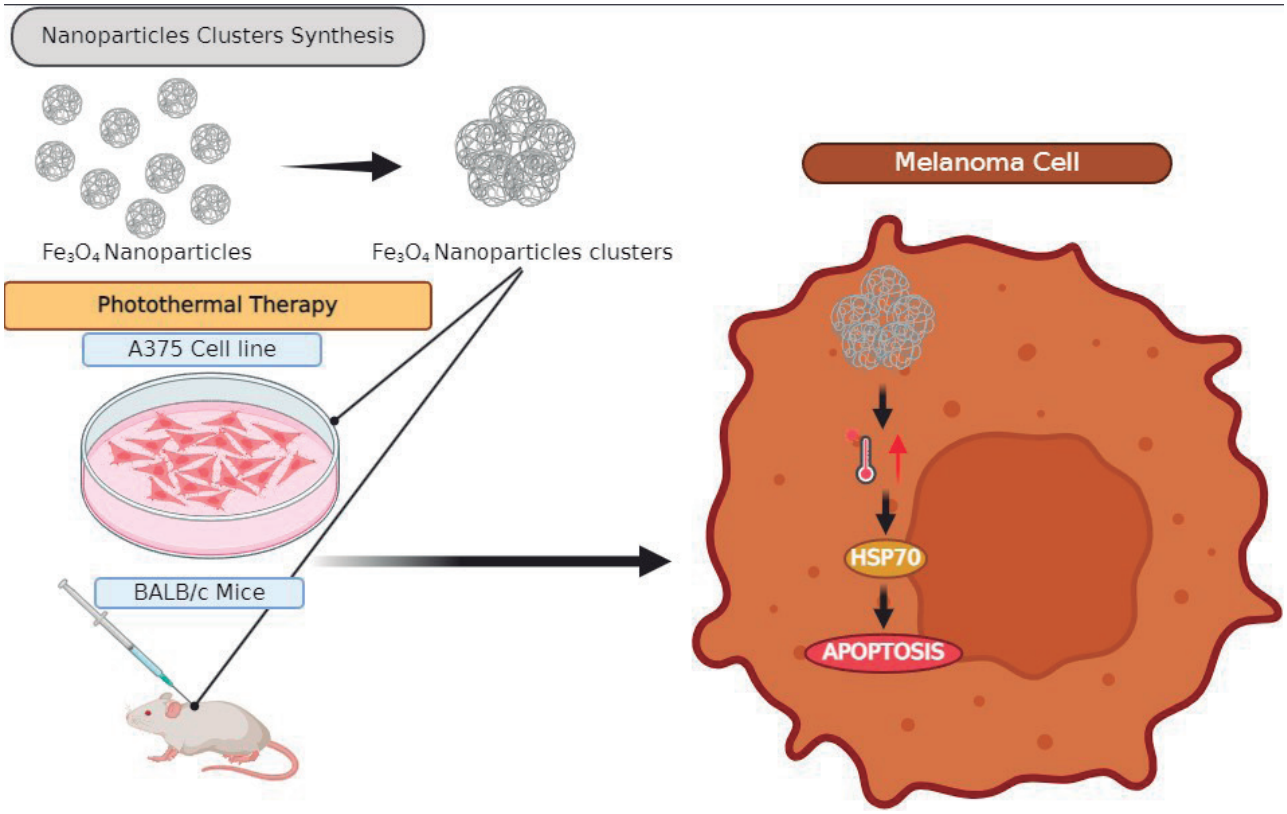
Obtaining the structural characteristics of the materials generally uses techniques such as infrared spectroscopy and Raman spectroscopy to investigate the actual structure of the prepared nanopharmaceutical carrier material. Liu *et al.,* (2018) proposed using graphene oxide, a two-dimensional material with unique properties, to transport microRNA to melanoma tumor cells. MicroRNA is an RNA molecule that is important in regulating gene expression. Graphene oxide was functionalized and loaded with the desired microRNAs, allowing for their stabilization and specific targeting of melanoma cells. Once internalized by the tumor cells, the graphene oxide composite released the microRNAs, which then performed their role in gene regulation. The study's results demonstrated that the composite had a significant efficacy in adhering to the growth of melanoma cells in vitro (Liu *et al.,* 2018).

In the study by Wang and co-workers (2022), $Fe_3O_4$ nanoparticle clusters of uniform spherical shape were fabricated, with high absorption in the near-infrared wavelength of 808 nm, superparamagnetism, and strong photothermal conversion ability. Both *in vitro* studies using an immortalized A375 melanoma cell line and *in vivo* research using the BALB/c xenografted mice model confirmed that these nanoclusters, under NIR irradiation, led to overt cell apoptosis and stopped the growth of implanted tumor xenografts at concentrations that did not elicit cytotoxicity when administered alone. Mechanistically, the heat shock protein HSP70 was discovered as a plausible explanation for the therapeutic benefits observed due to hyperthermia. The results of the current study accentuate

the potential application of $Fe_3O_4$ nanoparticle clusters in melanoma treatment, as shown in Figure 4 (Wang *et al.,* 2022).

So far, only a few melanoma-specific therapies have been approved by the FDA (Food and Drug Administration), e.g., dacarbazine, which has high efficacy against melanoma and the development of drug resistance therapeutics remains a problem associated with low survival rates (Mattia *et al.,* 2018). In this context, targeted therapeutic approaches offer an opportunity to increase the efficacy of treatments against melanoma.

**Figure 4 -** Schematic representation of $Fe_3O_4$ NPC-mediated photothermal therapy in melanoma.




Fonte: author's construction.

## CONCLUSION

Melanoma is a common cancer in the Western world with an increasing incidence. Sun exposure is still considered the leading risk factor for melanoma. The prognosis of patients with malignant melanoma (advanced stage) differs widely between countries, but public campaigns advocating early detection have led to significant reductions in mortality rates.

Brazil is one of the leading countries in tumor incidence in the world. Initial staging is based on the search for signs and symptoms that may indicate metastatic disease. Treatments have been changing significantly, and this work aims to present a review emphasizing the new treatments proposed by nanoscience. Studies show a continuous evolution of treatment options in recent times.

Nanotechnology in health is one of this sector's most significant scientific advances. With nanotechnology, it is possible to facilitate and optimize treatments, diagnostics, and research. The advantages related to nanotechnology, particularly nanoparticulate systems for controlled drug release, are influenced by the carrier system.

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Some advantages of nanopharmaceuticals are improved biocompatibility, controlled release of the drug, ability to increase the concentration at the target, improved stability, avoidance degradation of the drug, selectivity towards the biological target, a lower amount of the active ingredient of the drug, reduced side effects, protection of fragile drugs/proteins from harsh biological environments, faster, safer and more accurate diagnosis of the disease, no vessel obstruction and no impairment of circulation, drug molecules can be endocytosed/phagocytosed by the target cell, and drugs can cross some biological barriers.

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