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Melanin and Melanin-like Nanoparticles: A Versatile Platform for Synergistic Cancer Photothermal and Immunotherapy

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Abstract: Melanin, a ubiquitous natural pigment, possesses diverse physicochemical properties that extend beyond its conventional photoprotective role, making it a compelling agent in oncology. This review synthesizes current knowledge on melanin, with a particular focus on nanoformulations (MNPs), and critically examines their potential as multifaceted platforms for cancer therapy. We highlight the distinctive capabilities of MNPs, including their efficient photothermal conversion for tumor ablation and an innate propensity for lymphatic accumulation, whichpositions them as a highly promising vehicle for synergizing photothermal therapy with immunotherapy. While the broader biomedical potential of MNPs is acknowledged, this article concentrates on the challenges of standardization and long-term biocompatibility that must beaddressed through multidisciplinary collaboration. The objective of this work is to catalyze further research aimed at translating these innovative discoveries into next-generation cancertherapeutics.

Keywords: Cancer, nanoparticles, melanin, vaccines, antigens immunotherapy, photo-thermal therapy

1. INTRODUCTION

Cancer remains a leading cause of global morbidity and mortality, underscoring the persistent need for more effective and less toxic therapeutic strategies. While conventional treatments like surgery, chemotherapy, and radiotherapy form the current standard of care, their efficacy is often hampered by severe systemic side effects, non-specific targeting, and the development of resistance (Zafar et al., 2025). The most prevalent illnesses worldwide. According to estimates from the global burden of disease, cancer accounts for one in six deaths worldwide (Ferlay et al., 2024) (Cuzzubbo, Carpentier, et al., 2021). The estimated top five cancer sites are detailed in Figures 1.1 and 1.2. For males, the leading sites were lung (10.6%), mouth (8.4%), prostate (6.1%), tongue (5.9%), and stomach (4.8%). For females, breast cancer was predominant (28.8%), followed by cervical (10.6%), ovarian (6.2%), corpus uteri (3.7%), and lung (3.7%) cancers (Sathishkumar et al., 2022). Conventional modalities such as surgery, radiation therapy, and chemotherapy have significantly reduced cancer incidence. However, their efficacy is often limited by substantial systemic toxicity and the emergence of multidrug resistance, driving the need for alternative therapeutic strategies (Yue & Zhao, 2021a).

Notwithstanding the enormous progress that has been made in treatment and prognosis over the past few decades, cancer cells have a unique ability to evade apoptosis, enable angiogenesis, and induce invasion and metastasis (Marcovici et al., 2022). Adjuvant chemotherapy, surgery,

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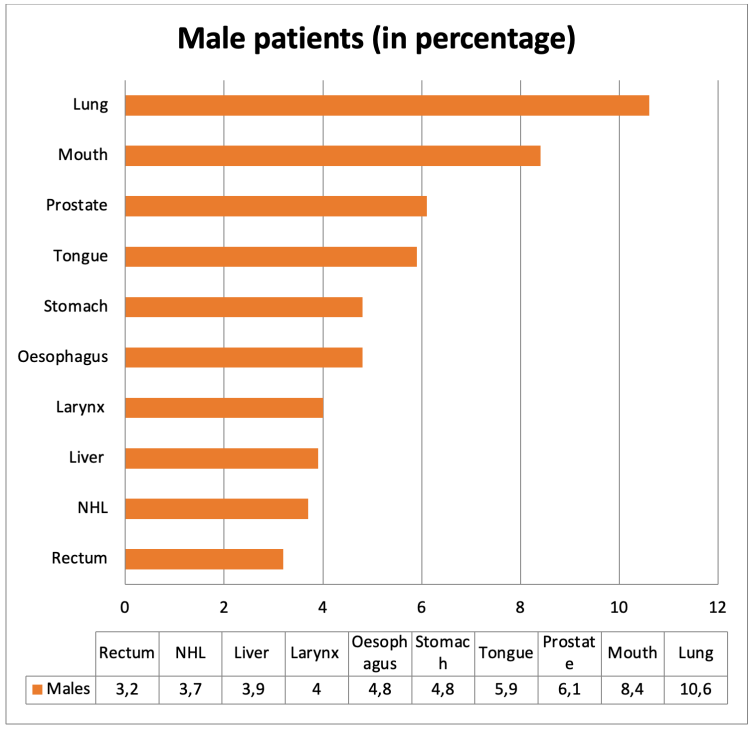
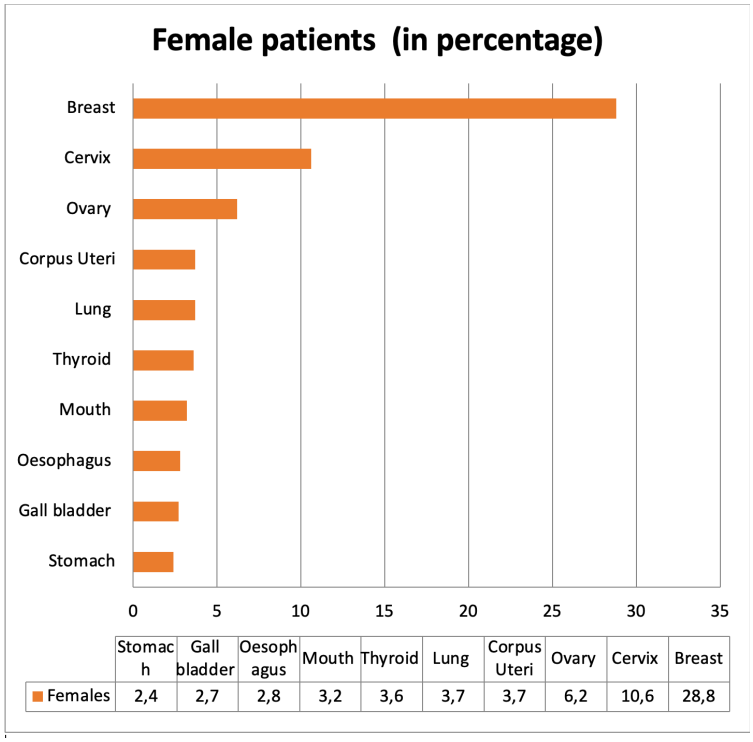


	Rectum	NHL	Liver	Larynx	Oesophagus	Stomach	Tongue	Prostate	Mouth	Lung
Males	3,2	3,7	3,9	4	4,8	4,8	5,9	6,1	8,4	10,6

Figure 1.1. Leading sites of cancer among males. It's clear from the graph that lung cancer in males is high (Ferlay et al., 2021)



	Stomach	Gall bladder	Oesophagus	Mouth	Thyroid	Lung	Corpus Uteri	Ovary	Cervix	Breast
Females	2,4	2,7	2,8	3,2	3,6	3,7	3,7	6,2	10,6	28,8

Figure 1.2. Leading sites of cancer among females. It's clear from the graph that breast cancer in female is high (Ferlay et al., 2021)

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biotherapy, concurrent chemotherapy and radiation therapy, sequential neoadjuvant chemotherapy, and medication combinations are among the contemporary cancer therapies (Dailah et al., 2024) (Figure 1.3). Immunotherapy has emerged as a prominent modality in cancer treatment. Although conventional therapies can control the primary tumor, they are often ineffective against disseminated tumor cells responsible for metastatic relapse. Consequently, a critical objective in oncology is the eradication of these circulating and dormant cells to prevent distant metastases. Immunotherapy addresses this need by targeting the metastatic cascade and improving patient survival and quality of life (Schuster et al., 2006). The immune response that immunotherapy produces in the host is what drives the tumors' long-term removal (Dailah et al., 2024). And for immunotherapy to achieve, we need to trigger our immune system. Cancer vaccines are generally categorized according to their uses and purposes, such as cancer preventive vaccines and therapeutic vaccines. In contrast to preventive vaccinations that target viruses, the therapeutic cancer vaccine works by stimulating the immune system to launch an assault on cancerous cells or tissues within the body (Li et al., 2023). In recent years, vaccines against cancer have been administered using nanotechnology, which has produced durable and potent immune responses. Cancer vaccines administrated via tagging it with nanomaterials can be tailored to specific immune profiles, making them more effective than standard vaccinations many antigen-derived cancer vaccines have been developed in response to the identification and characterisation of numerous tumor antigens; however, many of these vaccinations are not clinically effective due to their low immunogenicity. Therefore, adjuvants are added to vaccination formulations in order to elicit potent and sustained immune responses (Cuzzubbo, Mangsbo, et al., 2021).

Since most cancer antigens are not very immunogenic, several adjuvants have been added to vaccination formulations to increase their effectiveness. Lately, the swift advancement in nanomedicine presents a chance to provide a novel and accurate cancer diagnosis or treatment, enabling enhanced clinical outcomes with fewer unfavorable side effects (Caldas et al., 2020). Because they serve as antigen transporters, nanoparticle (NPs) systems are potentially useful technologies (Cuzzubbo, Carpentier, et al., 2021). While there is ongoing debate and investigation into the precise mechanism of action and uptake of NPs, the majority of experts concur that one of the main concerns regarding the utilization of NPs is their potential toxicity. Therefore, there is a need for the development of bioresorbable, biodegradable, biocompatible and effective versatile nanoplatforms for nanomedicine. The reticuloendothelial system has been observed to accumulate a significant number of inorganic NPs, which can lead to long term toxicity and low passive targeting specificity (Kurowiak et al., 2023).

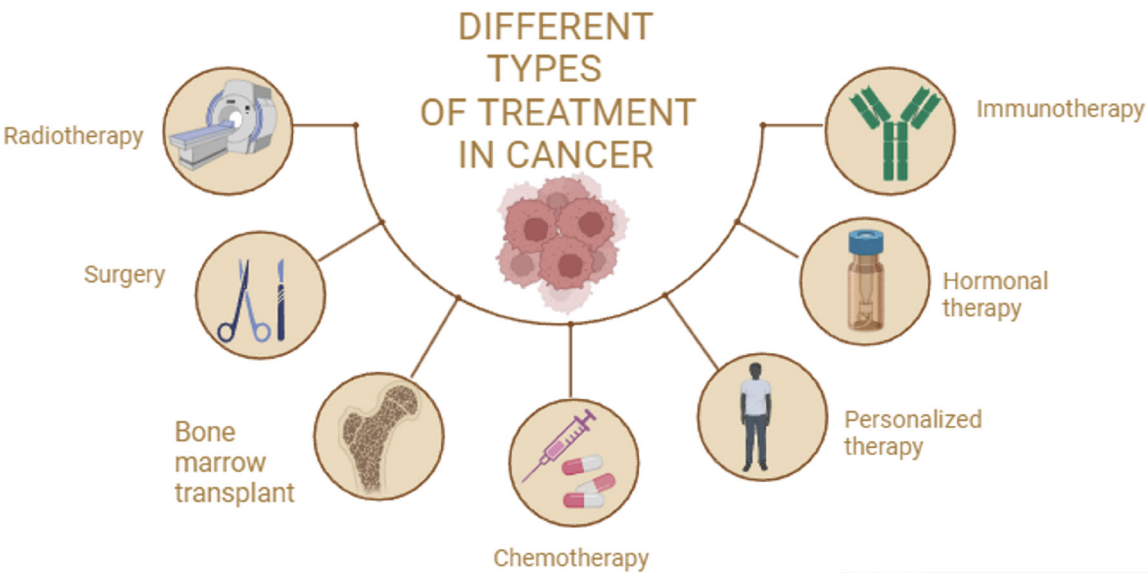

Figure 1.3. Different types of treatment in cancer. In this radiotherapy and chemotherapy are mostly used worldwide

These findings may likely hinder the development of nanomaterials intended for clinical studies. On the other hand, in this context, biomolecules derived from living things, are receiving increasing attention because of their inherent biocompatibility and biodegradability as well as the multifunctional and also because they play diverse physiological roles (Mavridi-Printezi et al., 2020). The scientific community has been looking more and more for green biomaterials, which are conveniently sourced from nature (Caldas et al., 2020). One such organic and green biopolymer is melanin. Biopolymer melanin, which is present in both plants and living animals, has demonstrated great promise in a variety of scientific fields, including biomedicine, dermo-cosmetics, nanotechnology, and bioengineering. Its biodegradability and biocompatibility play a significant role in the development of biomaterials because they must be free of cytotoxicity and adverse consequences. In actuality, antigenic reaction is one of the primary issues with the biomaterials that are now in use, along with their inability to remain stable under physiological settings. The lack of particular enzymes in the human body that can break down melanin and display other beneficial properties of biostability solves this issue in the case of melanin. Nevertheless, melanin is a type of NPs can be eliminated by kidney and liver, which lowers the likelihood of a long-term buildup in organs, typically linked to harmful consequences (Caldas et al., 2020).

It has recently been revealed that melanin-based NPs effectively locate into lymphoid tissues that are draining leading to eliciting the immunological responses against antigens that are loaded (Cuzzubbo, Carpentier, et al., 2021). Melanin's unique properties make it an ideal biomaterial for a variety of biomedical applications, including bioengineering, bioelectronics, controlled medication release, and imaging. This biomaterial also exhibits broad UV-visible radiation absorption, metal chelation, free radical scavenging, electrical conductivity, antioxidant activity, and the capacity to form bonds with various target molecules. As a result of these inherent qualities, melanin nanoparticles (MNPs) are crucial in the fabrication of novel controlled delivery systems and the pursuit of novel therapeutics based on the modification of internal or external circumstances (Caldas et al., 2020). There are currently therapeutic vaccines available for cancer in the market, however preventive vaccines are still going through clinical trials. The pigment melanin helps in making and effective working of preventive cancer vaccine is a question Provence®, a vaccination recommended for patients with prostate cancer, is the only one that has received approval so far (Cuzzubbo, Carpentier, et al., 2021). The U.S. Food and Drug Administration (FDA) authorized autologous cellular immunotherapy, known as PROVENGE (sipuleucel-T; Dendreon), in April 2010 for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC) who are asymptomatic or hardly symptomatic (Cheever & Higano, 2011).

The utility of melanin-like nanoparticles (MNPs) extends beyond targeted drug delivery and immunotherapy. As biocompatible and functional green biopolymers, they are uniquely suited for theranostic applications, integrating imaging capabilities with therapeutic modalities such as photothermal therapy. An ideal theranostic agent for cancer treatment that not only enables targeted delivery of different therapeutic agents, such as antitumor drugs, photothermal agents, photosensitizers, immunoadjuvants, and so forth, but also accurately assesses detailed tumor characteristics (e.g., location, size, and shape) through a variety of imaging modalities (Xue et al., 2021). Massive theranostic nanoplatforms, such as those based on metal, carbon, calcium, silica, conjugated polymers, and nano-complexes containing small molecule organic dyes, have recently been investigated for imaging-guided disease therapy. Few of them, meanwhile, have been used in clinical trials due to their possibility of long-term harm. Natural endogenous biomaterials derived from organisms have attracted a lot of interest because of their capacity to be metabolized and broken down in the body with minimal side effects, in contrast to exogenous nanomaterials. This ability is crucial for ensuring the biosafety of the materials in vivo. A well-known biopolymer, melanin is found in nearly all living things, including humans, animals, plants, and microbes. It is also found in human skin, hair, and eyes. Therefore, due to their several uses, melanin and MNPs have drawn more interest recently in the design and development of multifunctional nanoplatforms for medicinal applications (J. Sun et al., 2023)

This review comprehensively examines the diverse applications of melanin, with a primary focus on its role in cancer therapy. We will discuss its fundamental properties, synthesis, and sources to establish a foundational understanding. Therapeutically, the review will concentrate on melanin's applications

in photothermal therapy and immunotherapy, critically evaluating recent advancements and future prospects.

2. MATERIALS AND METHODS

2. Search Strategy

To ensure a comprehensive and reproducible analysis of the literature on melanin and melanin-like nanoparticles for cancer therapy, a systematic search strategy was employed.

2.1. Databases

Primary literature searches were conducted across three major interdisciplinary databases:

- PubMed / MEDLINE
- Scopus
- Web of Science Core Collection.

2.2. Keywords and Search Strings

A combination of controlled vocabulary (e.g., MeSH terms in PubMed) and free-text keywords was used. The core concepts were combined using Boolean operators (AND, OR) to create focused search strings.

Concept 1 (Material): "melanin nanoparticle" OR "melanin-like nanoparticle" OR "polydopamine nanoparticle*" OR "eumelanin" OR "synthetic melanin"

Concept 2 (Application): "photothermal therapy" OR "photothermal ablation" OR "PTT" OR "hyperthermia"

Concept 3 (Application): "immunotherapy" OR "cancer vaccine" OR "immune checkpoint inhibitor" OR "antigen presentation" OR "adjuvant"

Concept 4 (Disease): "cancer" OR "neoplasm*" OR "tumor" OR "oncology"

The retrieved records were first de-duplicated. Titles and abstracts were screened against the inclusion/exclusion criteria. The full texts of potentially relevant articles were then obtained and assessed for final inclusion. Reference lists of key reviews were also manually searched to identify additional seminal works. This structured approach ensures the methodological rigor and transparency of the literature synthesis presented in this review.

3. RESULTS

1.1. Cancer

Cancer is a multifaceted disease classically characterized by the uncontrolled proliferation and survival of cells. This proliferation is a consequence of acquired capabilities, including sustained proliferative signaling and evasion of growth suppressors. (Hassanpour & Dehghani, 2017). Carcinogenic chemicals found in the environment can affect a cell's cytoplasm and nucleus directly or indirectly, which can result in genetic abnormalities and gene mutations (Poon et al., 2014). Chemicals clearly play a vital role in the development of cancer cells and gene alterations. Furthermore, smoking contains a number of chemical components that cause cancer, including lung cancer (Aizawa et al., 2016). Other carcinogenic causes include radiation, bacteria, and viruses, which together account for 7% of all cancer cases (Parkin, 2006). Critical genes generally malfunction as a result of cancer's disruption of cellular relationships. Anomalous proliferation results from this disruption of the cell cycle (Seto et al., 2010). Hence an unhealthy lifestyle that includes things like smoking, drinking tobacco, eating an unbalanced food, experiencing stress, and not exercising has a significant impact estimating the risk of cancer (Figure 1.4) (Wu et al., 2018).

The advent of immunotherapy has transformed the oncology landscape by harnessing the body's own immune system to combat tumors. Immune checkpoint blockade (ICB) and cancer vaccines represent significant breakthroughs, yet their success is not universal. Key challenges, particularly for cancer vaccines, include poor immunogenicity of antigens and the immunosuppressive nature of the tumor microenvironment, which hinder robust and durable anti-tumor immune responses. It has been difficult to determine how much of proto-oncogene mutations, tumor suppressor gene expression patterns, and DNA repair-related genes are involved. Merely 5–10% of cancer cases have a hereditary component (Anand et al., 2008). Categories of cancer include; Carcinoma, Sarcoma, Lymphoma, Leukemia and Myeloma (Figure 1.5) (Rajput, 2023). In that there are different types, some of the commonly occurring are Lung cancer, Liver cancer, Anal cancer, Appendix cancer, Adrenal cancer, Bone cancer, Oral cancer (Kumar et al., n.d.).

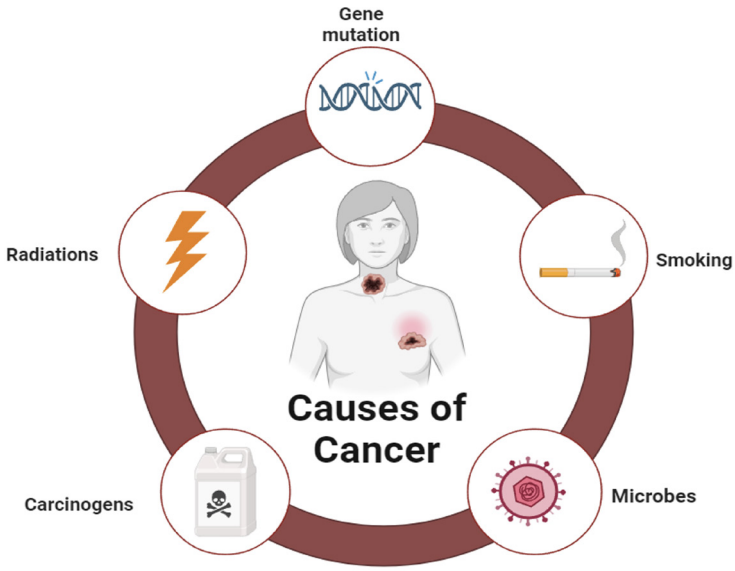

Figure 1.4. The pathogenesis of cancer is multifactorial, arising from a complex interplay of genetic, environmental, and lifestyle factors

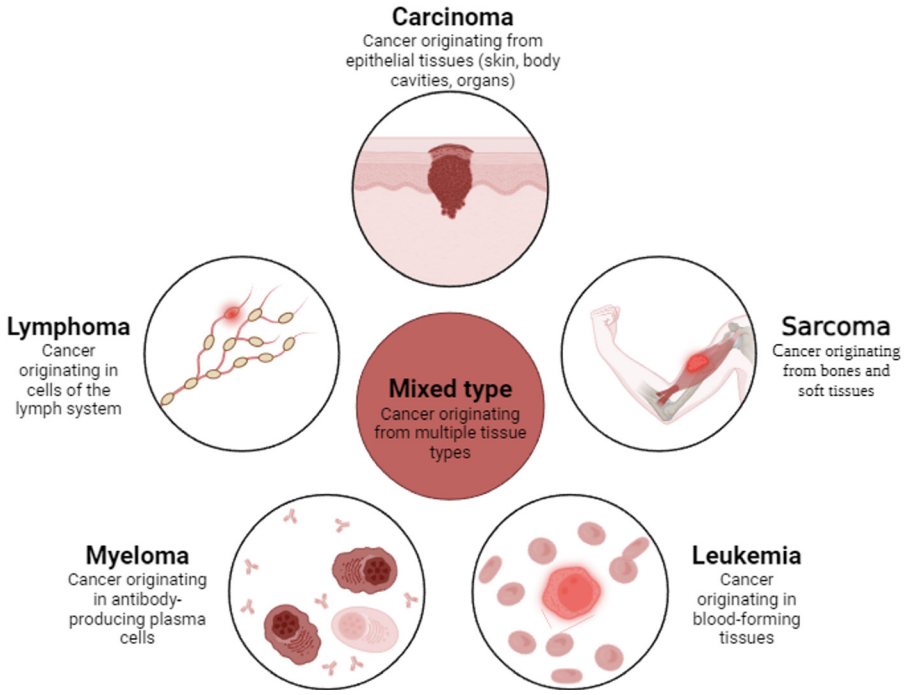

Figure 1.5. Classes of cancer and in it comes lung cancer, liver cancer pancreatic cancer etc.

1.2. Difficulty in Targeting Cancer Antigen

Cancer cells exhibit DNA and RNA that are similar, but not identical, to the cells of the organism from whence they came. This inherent property explains their low immunogenicity and ability to evade immune surveillance, a phenomenon that is exacerbated in immunocompromised hosts (Sharma et al., n.d.). Immunogenicity of cancer antigens is often low (Cuzzubo, Carpentier, et al., 2021). Modern vaccinations frequently elicit antibody responses, however these responses are ineffective in cases when intracellular antigens are present,

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as is typically the case with cancer. Cytotoxic T-lymphocytes are primarily responsible for mediating immunity in malignancy. CTLs identify eight to ten amino acid residues, or short peptide epitopes, that are mostly produced by intracellular proteins that have been broken down. These epitopes are displayed on the surfaces of target cells, also known as antigen-presenting cells (APCs), by MHC class I molecules. Nevertheless, inducing cytotoxic T lymphocyte (CTL) responses in humans is more challenging than eliciting antibody responses. This is because CTL activation requires exogenous antigens to be diverted from the MHC class II pathway to the MHC class I pathway through cross-presentation (Figure 1.6) (Carpentier et al., 2017). Since the process of producing a CD8+ T cell response depends on the cross-presentation of foreign antigen on MHC class-I is an essential design factor in the development of T cell (Balloon & Wilson, 2022). Consequently, tumor-associated macrophages (TAMs) have been identified as suitable targets for cancer immunotherapy. TAMs, the predominant leukocytes in the tumor microenvironment, have an M2-like phenotype and are responsible for the maintenance and growth of tumours. (Deng et al., 2019) Many cancers contain large numbers of tumor-associated macrophages (TAMs), which mostly have an immunosuppressive M2-like activity that encourages tumor growth and malignant dissemination (Rung et al., 2019).

2. Nano-particles

Nanotechnology offers a promising solution to these delivery and efficacy challenges. By engineering nanocarriers, researchers can protect therapeutic cargo, enhance tumor accumulation through the enhanced permeability and retention (EPR) effect, and enable precise, controlled release. However, many inorganic nanoparticles raise concerns regarding long-term toxicity and biocompatibility, limiting their clinical translation (Nandhini Chitikela & Chaitanya B, 2025). Nanoparticles are particulate dispersions or solid particles with a size in the range of 10-100 nm. A nanoparticle matrix is used to dissolve, entrap, encapsulate, or bind the drug. One can obtain nanoparticles, nanospheres, or nano-capsules depending on the preparation technique used (Mohanraj & Chen, 2006). The effectiveness of cancer therapy is frequently hindered by the need for frequent and high drug dosing. This is because, even with significant advancements in cancer research and the wide range of potent drugs currently available, the lack of pharmaco-selectivity to diseased cells, indiscriminate drug toxicities, and poor patient compliance remain major obstacles. Therefore, novel pharmaceutical solutions are required to effectively deliver the cytotoxic drugs to the tumor site while minimizing systemic exposure to frequent and high drug doses (Karra & Benita, 2012). These days, there are numerous scientific fields where NPs find use. NPs have been frequently mentioned as having a big part in modern medicine in recent years. They have been examined for several

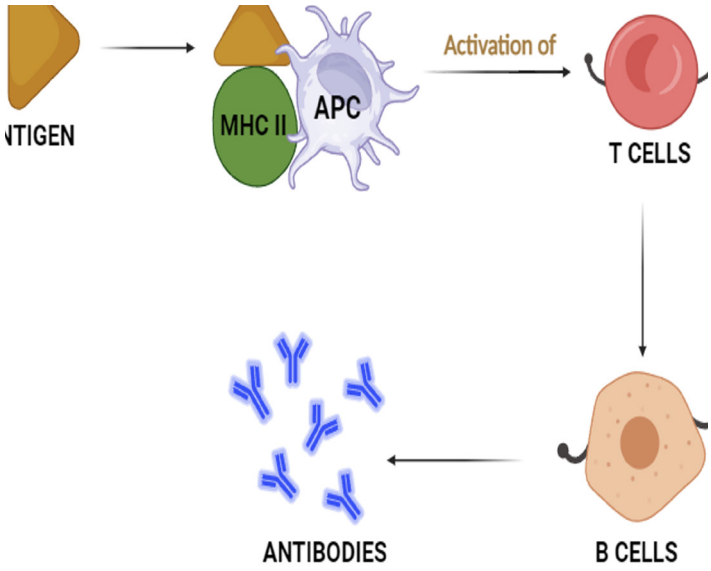

Figure 1.6. Working of immune system. Antigen presentation is a big task for immune cells to get activated and this is done by any MHC molecule

clinical uses, including as contrast agents in imaging, drug transporters, and gene transfer to malignancies (Aghebati-Maleki et al., 2020). By exhibiting good pharmacokinetics, accurate targeting, decreased side effects, and drug resistance, nanoparticle-based drug delivery systems have demonstrated benefits in cancer treatment and management (Dadwal et al., 2018). The unique tumor and tumor environment properties are used in the nanoparticle drug delivery method. In addition to addressing the shortcomings of traditional cancer treatment, nanoparticles also defeat multidrug resistance (Gavas et al., 2021). These NPs are appealing for medical applications due to their significant and distinctive characteristics, which include

a) Their capacity to adsorb and transport other compounds,
b) Their quantum properties,
c) And a surface to mass ratio that is significantly higher than that of other particles
d) NPs can bind, adsorb, and transport other substances including medications, probes, and proteins thanks to their comparatively broad (functional) surface
e) Increased safety and biocompatibility,
f) More targeted drug administration,
g) Decreased toxicity while preserving therapeutic effects,
h) And quicker creation of novel, safe medications

A significant obstacle in drug delivery is getting the medication where it is required in the body without perhaps harming healthy organs. This is particularly difficult when treating cancer since the tumor may have different metastases in different organs. Thus, the whole therapeutic potential of chemotherapy is limited by its unrestricted (cyto)toxicity. Increased local drug concentrations are the outcome of local drug delivery or drug targeting, which also offers approaches for more targeted therapy. Certain particles in NPs act as tools to make these tactics possible (De Jong & Borm, 2008). Furthermore, nanoparticles (NPs) can be administered via various routes, including oral, nasal, rectal, and parenteral methods. (Mohanraj & Chen, 2006b). As a result, NPs actively contribute to the delivery of medications to the intended cell and form a drug delivery system (Hu et al., 2019). Solid lipid NPs, aptammers, emulsions, liposomes, dendrimers, carbon nanotubes, nanobodies, and other polymers are some of the organic drug carriers in drug delivery system (Figure 1.7) (Senapati et al., 2018)(Aghebati-Maleki et al., 2020) (Din et al., 2017). In addition to these drug delivery system, a magnetic NPs that can be attracted to a specific area of the body when exposed to a magnetic field can be a highly effective drug delivery method (Asmatulu et al., 2005).

Moreover, the ability of NPs systems to act as carriers of various antigens to the lymph nodes,

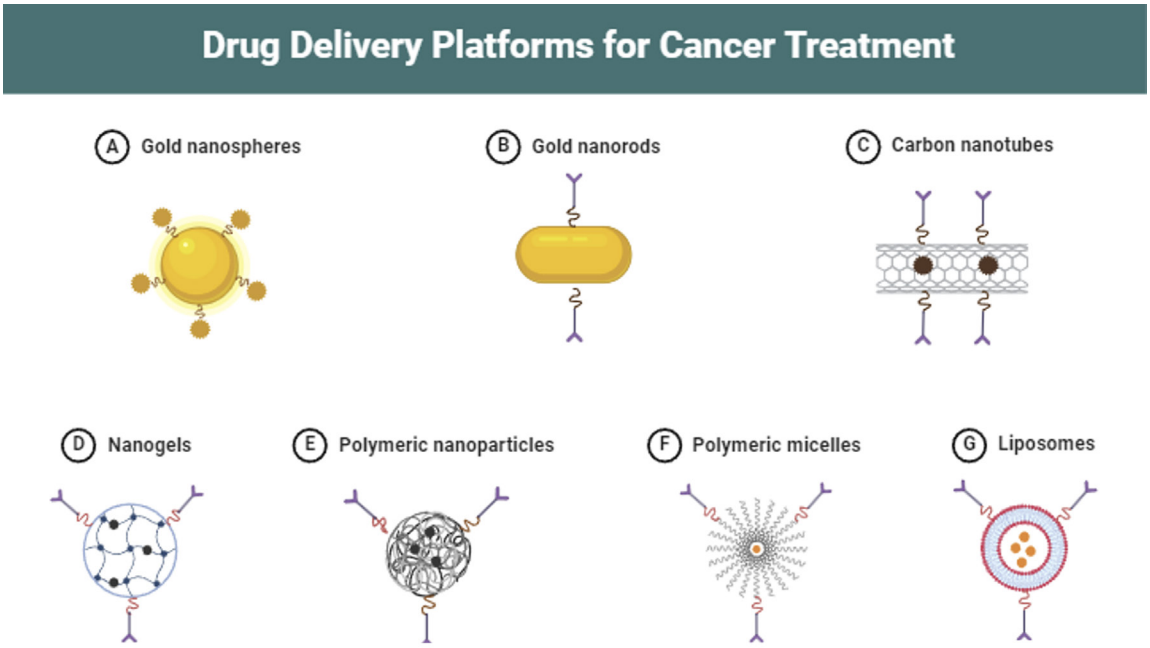

Figure 1.7. Different types of drug delivery systems for cancer treatment

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thereby particularly targeting antigen-presenting cells, has garnered significant interest in the field of cancer vaccines. Furthermore, NPs have certain immunostimulatory characteristics. In that field, bioinspired nanomaterials are particularly interesting due to their biocompatibility. In many cancer vaccine formulations, MNPs effectively localize into draining lymphoid tissues and demonstrate immunostimulatory properties (Cuzzubbo, Carpentier, et al., 2021).

3. Melanin

Melanin is the general term for the most mysterious, common, and diverse bio pigments found in nature. It comes from the Greek word "means," which means "dark." (Marcovici et al., 2022). Animals, plants, and microbes all contain the heterogeneous, multifunctional oligomeric pigments known as melanins, which range in color from dark brown to black (El-Obeid eal., 2020). It is a common natural pigment found in fungi, bacteria, plants, and animals (Yang et 2023).

3.1. Type and Sources of Melanin

Natural biological pigments come in a variety of forms, from monomeric (carotenoids, luciferin, flavonoids) to polymeric (melanins, tannins, and humic compounds) and heme porphyrin-based (chlorophylls, bilirubin, hemoglobin, hemocyanin). Conjugated moieties, or aromatic rings, are present in all pigments and enable electronic resonances as well as mediate energy transfer events within cells. Among them, melanin is a special class (Cordero & Casadevall, 2017).

There are four different types of melanins—eumelanins, pheomelanins, neuromelanins, and allomelanins and all of them have different origins, colors, structures, and physiological characteristics from one another (Figure 1.8). Tyrosine is the amino acid that produces the pigments black eumelanin and yellow-reddish pheomelanin in humans and animals. A distinct kind of melanin found in mammals, neuromelanin is a blend of pheomelanin and eumelanin, which is developed inside catecholaminergic neurons through dopamine oxidation rather than by melanocytes. Allomelanins are colored molecules without nitrogen that originate from plants, microorganisms, and fungi. Their precursor is often 1,3,6,8-tetrahydroxynaphthalene. (Marcovici et al., 2022).

Melanin is found in specialised organelles called melanosomes in certain organisms (animals), widely deposited in seed coats in other organisms (plants), deposited in cell walls in organisms such as fungi, and secreted extracellularly in bacteria (Figure 1.9) (Yang et al., 2023). Melanin can be broadly classified into four categories based on the precursors from which it originates. These comprise the most prevalent form of melanin in humans, called eumelanin; pheomelanin, which is found in large quantities in both human and bird feathers; neuromelanin, which is found in the human brain; and heterogeneous allo-melanins, which include pyomelanin in bacteria, DHN melanin in fungi, catechol melanin in plants, etc (Kurian, 2022). Eumelanin can be found in the tissues of silky fowl (Tu et al., 2009a), cuttlefish ink, and sturgeon spawn(Yang et al., 2023). *Streptomyces* spp. (Yang et al., 2023), *Bacillus subtilis* (Ghadge et al., 2020), *Sporisorium reilianum* (Fu et al., 2022),

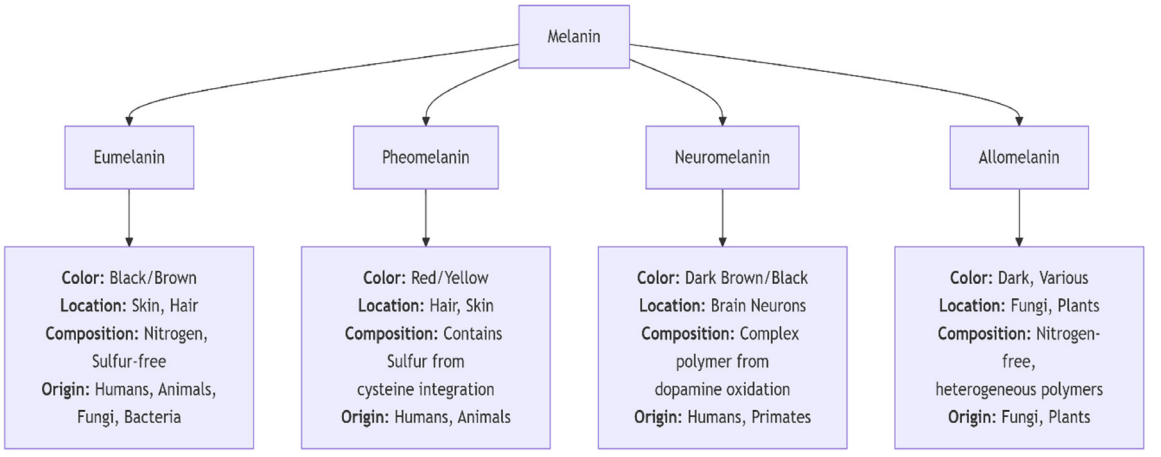

Figure 1.8. Types of melanin. Allomelanin, pheomelanin, neuromelanin, eumelanin are described above

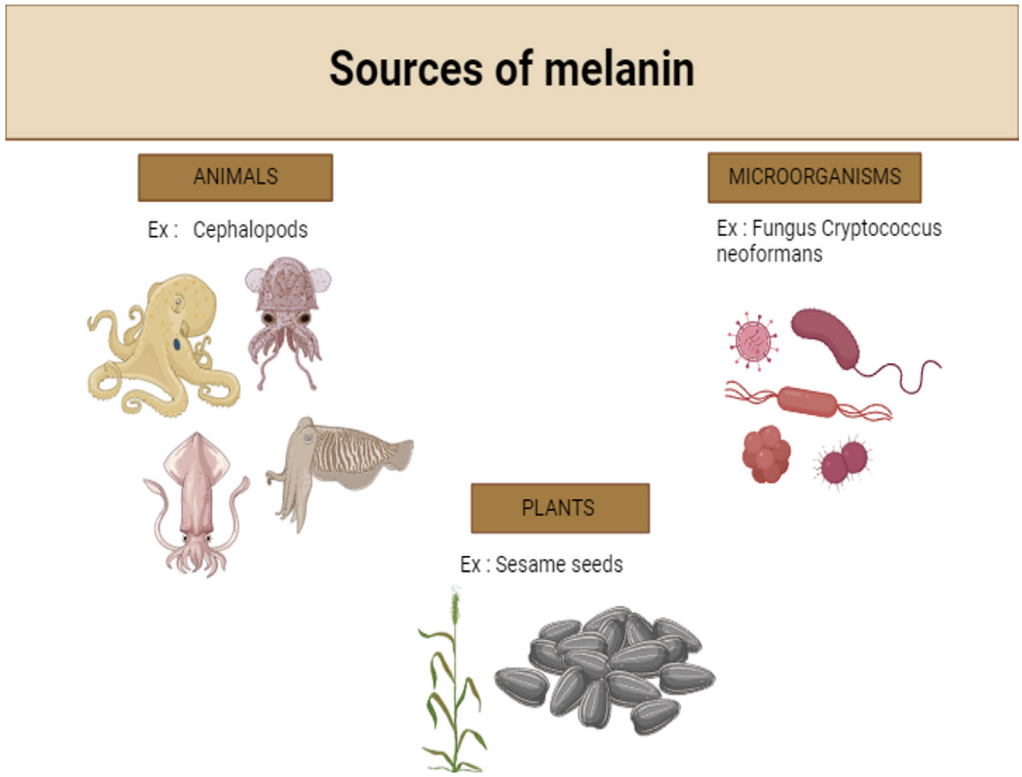

Figure 1.9. Sources of melanin: Melanin from bacteria and fungus are widely used for extraction purposes

and *Streptomyces hyderabadensis* (Yang et al., 2023)are among the fungus and bacteria that contain eumelanin. Mammals' (Manning et al., 2019) and birds' (Rodríguez-Martínez et al., 2023) skin and hair contain pheomelanin. Oyster mushrooms (Yang et al., 2023)and Auricularia auricula(Hou et al., 2019) both contain pheomelanin. The brain's catecholaminergic neurons contain neuromelanin (Fedorow et al., 2005) Black garlic, grape peel (Yang et al., 2023) date palm fruits (Alam et al., 2022), and lichen are examples of plants that contain allomelanin (Yang et al., 2023).

Compared to melanin from animals and plants, melanin derived from microorganisms offers several benefits. Since microorganisms adapt to the medium and conditions they are given, they are chosen arsenals and do not cause the problems associated with seasonal variations (Tarangini & Mishra, 2014). Melanin can be isolated from bacteria more easily than from any other cell or tissue. Melanin is secreted extracellularly by bacteria, which facilitates its precipitation from culture medium (Kurian, 2022). However, marine cephalopods are the biggest producers; this is the melanin that has been studied the most to far, and Sepia releases it as a defense mechanism against their enemies (Mbonyiryivuze et al., 2015).

3.2 Properties of Melanin

Oxidative polymerization of phenolic and/or indolic chemicals forms melanins, which are high molecular weight, negatively charged, hydrophobic pigments. In both organic and aqueous solutions, they are insoluble (Arturo Casadevall, n.d.). Melanin-based nanomaterials resemble inorganic semiconductor material more than organic chromophore due to their broad-band monotone absorption spectra. Moreover, melanin-based nanomaterials are naturally occurring theranostic reagents for cancer because of their capacity for photothermal conversion (Hong et al., 2020).

Melanins are superior to traditional pharmaceuticals in several ways, including their broad spectrum of action and low toxicity. It was also mentioned that melanin has a paramagnetic quality, which could influence how it interacts with medications and metal ions (Marcovici et al., 2022). In additiona, melanin has the ability to efficiently absorb light energy and transform it into heat, making it a

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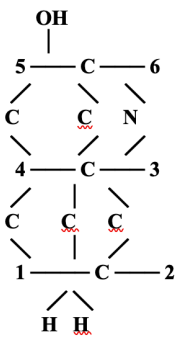
photosensitizer (Cuzzubbo, Carpentier, et al., 2021). Melanin-like nanoparticles' superior optical qualities come from their effective conversion of absorbed light energy into heat (Yue & Zhao, 2021b). This allows for the selective heating of melanin within tissues, which is then applied in photothermal treatment (PTT) (Cuzzubbo, Carpentier, et al., 2021). Melanin's unique properties make it an ideal biomaterial for a variety of biomedical applications, including bioengineering, bioelectronics, controlled medication release, and imaging. Additionally, this biomaterial exhibits broad UV-visible radiation absorption, metal chelation and free radical scavenging capabilities, electrical conductivity, antioxidant activity, and the capacity to form bonds with various target molecules (Caldas et al., 2020). One noteworthy intrinsic property of melanin-based polymers is their strong adherence to a wide range of materials, independent of their complex shapes. To increase the selectivity for malignancies, functional groups such as amines or imines that are exposed on the surface of melanin-based nanomaterials might covalently link molecules that target cancer biomarkers, like aptamers and antibodies (Table 1) (Hong et al., 2020).

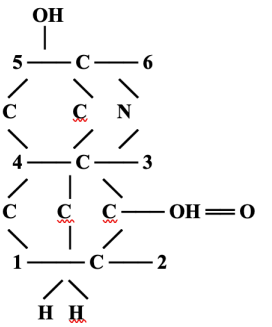
3.3 Structure of Melanin

a) 1. 5,6-Dihydroxyindole



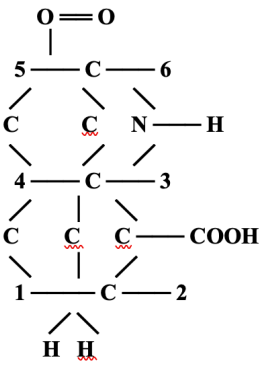
IUPAC Name: 5,6-Dihydroxy-1H-indole

b) 2. 5,6-Dihydroxyindole-2-carboxylic acid



IUPAC Name: 5,6-Dihydroxy-1H-indole-2-carboxylic acid

c) DOPAquinone



IUPAC Name: (2S)-2-Amino-3-(3,4-dioxocyclohexa-1,5-dien-1-yl)propanoic acid

Despite its biological ubiquity, the precise structural architecture of melanin remains an enigma, largely due to its heterogeneous, amorphous, and insoluble nature (Cordero & Casadevall, 2017). In the last fifty years, melanin structural research has gained scholarly attention and grown in importance within the field of natural pigments. However, due to melanin poor solubility in water and most organic solvents, its precise structure is still unknown..(S. Sun et al., 2016).

Table 1. Properties of melanin

Charge	Negative	(Tarangini & Mishra, 2014)
Nature	Hydrophobic	(Arturo Casadevall, n.d.)
Solubility	Insoluble in Aqueous and Organic Solvents	(Arturo Casadevall, n.d.)
Molecular Formula	C18H10N2O4	(Marcovici et al., 2022)
Molecular Mass	318.288 g.mol−1	(Marcovici et al., 2022)

These complex polymers are amorphous in nature and are formed from polymerized phenolic and/or indolic chemicals. According to one model of melanin structure, indolic and/or phenolic monomers polymerize into a variety of ordered planar arrangements of stacked layers with regular interspacing, resembling graphite, which can then cross-link into more disordered and heterogeneous macromolecular structures. The melanin granules, which are disordered particles with spherical dimensions, are formed by the aggregation of hydrogen and ionic bonded nanostructures of uncertain dimensions, together with p-stacking. This process is referred to as the local-ordereglobal-disorder model of melanin (Cordero & Casadevall, 2017). The structural foundations of eumelanin and pheomelanin are comparatively well-established, in contrast to the more obscure structure of allomelanin. Eumelanin is primarily composed of 5,6-dihydroxyindole (DHI) and 5,6-dihydroxyindole-2-carboxylic acid (DHICA) units, whereas pheomelanin is characterized by sulfur-containing benzothiazine and benzothiazole monomers (S. Sun et al., 2016).

3.4. Synthesis of Melanin

Melanin is found in several regions and forms complexes with various other biomolecules in a range of organisms, including bacteria and mammals. This results in differences in the process of extracting melanin from plant, animal, and microbial tissues (Kurian, 2022). Chemical synthesis or biological extraction are two methods for producing MNPs (Figure 1.10). The first technique involves physically isolating and purifying melanin nanoparticles from various natural sources, such as hair, black sesame, and cuttlefish ink, and then processing these materials to develop MNPs that are soluble in water (Cuzzubbo, Carpentier, et al., 2021). A prominent example of a synthetic melanin is polydopamine (PDA), a material produced by the oxidative polymerization of dopamine, mimicking the natural process of eumelanin formation (Marcovici et al., 2022).

Artificially synthesized melanin-like NPs are more controllably produced than those native melanin-like NPs derived from living things. A primary example of synthetic melanin-like nanoparticles is polydopamine (PDA), produced through the oxidative polymerization of its dopamine monomer. While several methods exist for fabricating PDA nanoparticles, the solution oxidation technique remains the most prevalent due to its procedural simplicity and effectiveness (Yue & Zhao, 2021a). The majority of fungal melanins are produced through the polymerization of 1,8-dihydroxynaphthalene (DHN); however, other pigment precursors, including tyrosine, homogentisic acid, gamma-glutaminyl-4-hydroxybenzene (GHB), catechol, and (þ)-scytalone, can also be utilized by fungal species. The phenolic precursors go through several stages of oxidation and reduction throughout the manufacture of melanin. These reactions can happen passively by spontaneous polymerizations or enzymatically. Indeed, even in the absence of enzymes, a transparent

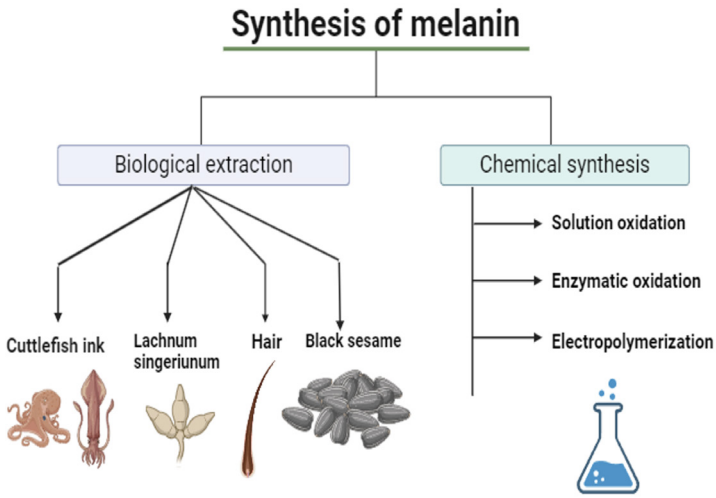


Figure 1.10. Methods of synthesizing melanin. Biological extraction and chemical synthesis are the 2 methods by which melanin can be synthesized

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L-Dopa water solution will eventually precipitate into melanin particles at ambient temperature. Polyphenoloxidases, such as tyrosinase, laccase, and catechol oxidase, are important enzymes that perform the rate-limiting first oxidations of phenolic melanin precursors, which are a necessary part of the formation of melanin (Cordero & Casadevall, 2017).

3.5. Application of Melanin

Melanins have a diverse number of functions in the biosystem, such as photo-protection, antioxidation, thermoregulation, metal chelation, and some involvement in nerve systems and so forth (Huang et al., 2018). One of the major natural pigments, melanin is widely and traditionally utilized in a variety of industrial domains, such as food, cosmetics, pharmaceuticals, medications, and other industries. The most intriguing aspect is that melanin can be added to food as a supplement to stop bacteria-induced rancidity by blocking bacterial quorum sensing (S. Sun et al., 2016). In materials science and green technology, melanin has lately made waves as a useful coating or addition that can significantly boost the performance of traditional materials for a variety of applications (Tran-Ly, Reyes, et al., 2020). Heavy metals in the environment that may be harmful to cells can be bound by melanins (Nosanchuk & Casadevall, 2003), this property of chelation acquired by melanin has many applications in industries and can also contribute in green chemistry for example, a review by Tran-Ly et al; demonstrated that fungus-derived melanin from Armillaria cepistipes (Empa 655) is a potentially useful biosorbent for eliminating hazardous heavy metals from water. In single-component solutions, 90% of the heavy metals could be eliminated by fungus-derived melanin. The melanized membranes' ability to preserve the raw melanin's adsorption capacity was further demonstrated by the metal adsorption profiles. As a result, the removal of heavy metals from water can be accomplished effectively using these innovative membranes as filtration membranes. Therefore, using fungal melanin for biosorption is economical and prevents the production of harmful byproducts (Tran-Ly, Ribera, et al., 2020). Melanins play a fundamental role in biological defense across diverse organisms. In humans and other animals, incorporated melanin functions as a photoprotective agent, scavenging reactive oxygen species (ROS) and dissipating ultraviolet radiation as heat, thereby acting as a natural sunscreen. It also serves in camouflage and visual communication. In fungi, melanin is a critical component of the cell wall that enhances survival under extreme environmental stress, conferring resistance against high-energy radiation, desiccation, temperature shifts, and nutrient scarcity. Similarly, in plants, melanin deposition is frequently associated with enhanced resistance to microbial and viral pathogens, often forming a physical-chemical barrier at infection sites (Huang et al., 2018). A naturally occurring nanocomponent with several active components is melanin.

Melanin is a naturally occurring nanocomponent that contains multiple active components. To begin with, a) melanin is a pigment that is safe to use as a natural colorant in cosmetics b) melanin's anti-radiation and antioxidant properties can be used as a photoprotective agent in cosmetics to delay their aging process (Liberti et al., 2020) Moreover, it functions as an anti-aging agent and has a somewhat opsonizing impact on the skin, much like vitamins C and E (Guo et al., 2023). Additionally, Melanin acts as neuroprotectant by facilitating chemical transfer, which accelerates nerve impulses (Petrosyan, 2015). The biopolymer of melanin may have a role in the formation of silver and gold nanostructures as a reducing and stabilizing mediator. The L-DOPA-melanin pigment transformed silver nitrate and chloroauric acid, respectively, into silver and gold nanostructures. The study demonstrated that silver nanoparticles exhibited potent antifungal properties and could function effectively as paint additives (Apte et al., 2013) Melanin has demonstrated significant potential as a functional polymeric material due to its unique physicochemical characteristics and structural complexity (Mostert, 2021). Melanin also offers significant benefits in agricultural practices. As reviewed by Sansinenea E, melanin provides effective photoprotection for Bacillus thuringiensis (B.t.) formulations. The insecticidal activity of B.t. is often unstable and rapidly degrades under solar ultraviolet (UV) radiation in field conditions. Since melanin acts as a broad-spectrum radiation absorbent, its co-formulation with B.t. insecticides can shield the microbial active ingredient, thereby enhancing its persistence and efficacy (Sansinenea & Ortiz, 2015). The valorization of plant residues and food industry waste streams presents a viable pathway for obtaining biodegradable materials and achieving zero-waste objectives. For instance, melanin extracted from watermelon seeds has been

successfully employed as a functional modifier to develop bioactive biopolymer films. These films demonstrate significant potential for applications in food packaging and biomedicine, highlighting the broader utility of melanin as a beneficial component for the food industry (Łopusiewicz et al., 2020).

Additionally, MNPs have demonstrated defense against oxidative stress and ionizing radiation-induced DNA damage. Current evidence indicates that melanin-like nanoparticles (MNPs) do not induce tissue damage and can be regarded as safe antioxidant and antiradical agents with immunomodulatory properties, MNP therapy following radiation therapy may be helpful in avoiding adverse effects on tissues surrounding tumors brought on by oxidative stress and long-lived radicals during cancer radiation therapy (Rageh & El-Gebaly, 2018). A study revealed that *A. auricula* melanin may be a useful treatment for alcohol-induced liver damage, suggesting that melanin may also have some protective properties against alcohol-induced liver damage (Rageh & El-Gebaly, 2018).

Melanin/MNPs can be used to develop a novel multifunctional nanoplatforms for imaging-guided disease therapy on a single nanoplatform, maximizing the theranostic performance (J. Sun et al., 2023). Both manufactured and natural polydopamine nanoparticles exhibit strong photothermal conversion efficiency and have a good light absorption impact when converting near-infrared light into heat energy (Guo et al., 2023) (Figure 1.11, Table 2).

3.6. Role of Melanin in Treating Cancer

The initiation of an anti-tumor immune response requires antigen-presenting cells (APCs) to present tumor-associated antigens effectively to T cells (Cuzzubbo, Carpentier, et al., 2021). The direct interaction between naive T-cells in the T-cell zone of lymph nodes and dendritic cells, a kind of antigen-presenting cell, is necessary for the induction of antigen-specific immunity (Mohagheghpour et al., 2000). Synthetic melanin's surface area determines its ability to adsorb drugs, therefore both the loading efficiency and the drug's release can be regulated (Cuzzubbo, Carpentier, et al., 2021). After injection, melanin forms a local depot that lasts for a few weeks, enabling local release. Melanin can be utilized as a carrier for a molecule to enter the lymphatic system because it is also partly driven to the draining lymph nodes (Carpentier et al., 2017). Peptides are frequently employed as antigen sources due to their direct loading onto MHC molecules as T-cell epitopes, minimal toxicity, and low cost. However, when administered via subcutaneous injection, free peptides rapidly enter the systemic circulation, and antigen-presenting cells (APCs) capture only a small fraction of the injected dose. To initiate an anti-tumor immune response, APC must effectively convey antigen to T cells. Only when antigens and MHC (major histocompatibility complex) class I molecules are given, combined with the concurrent expression of costimulatory molecules by APCs, can cytotoxic T cells be effectively activated.

Furthermore, the ability of some nanoparticulated formulations to both enhance antigen presentation

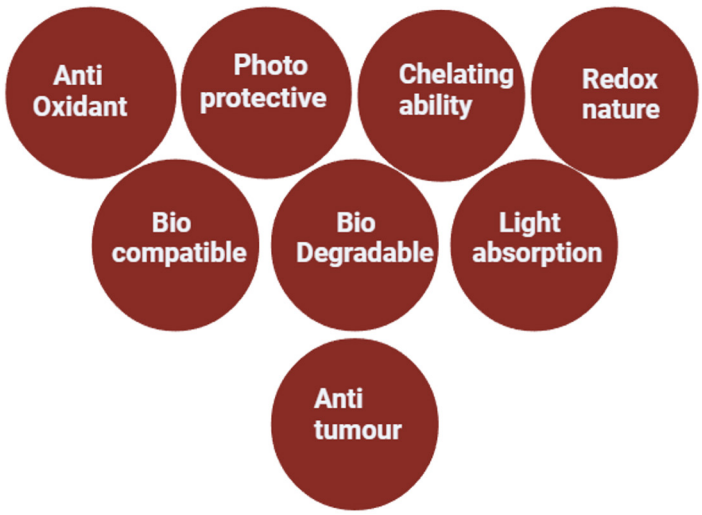

Figure 1.11. Features of melanin

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Table 2. Effect of different sources of melanin

Source	Action	Reference
Bacterial melanin from Pseudomonas maltophilia AT18	Photoprotective	(Geng et al., 2008)
Bacterial melanin from Pseudomonas otitidis DDB2	Photoprotective	(Seelam et al., 2021)
Bacterial melanin from Streptomyces glaucescens NEAE-H	Antioxidant, anticancer, anti-hemolytic	(El-Naggar & El-Ewasy, 2017)
Melanin from the muscles of Gallus domesticus Brisso	Antioxidant	(Tu et al., 2009b)
Fungal melanin from Aspergillus nidulans	Antioxidant	(De Cássia et al., 2005)
Herbal melanin from Nigella sativa seed coats	Immunomodulatory Anticancer	(El-Obeid et al., 2006) (Marcovici et al., 2022)
B16F10 melanoma tumor lysates containing melanin (microneedle patch)	Anticancer	(Marcovici et al., 2022)
Synthetic melanin	Immunomodulatory	(Carpentier et al., 2017)

and incite inflammatory responses in dendritic cells has piqued curiosity. The size of nanoparticles is a critical determinant of their trafficking to lymph nodes. Studies indicate that particles ranging from 20 to 200 nm in diameter efficiently drain through lymphatic capillaries, reach the lymph nodes, and are subsequently phagocytosed by resident macrophages and dendritic cells. Consequently, numerous nanoparticulate carriers within this size range are being developed for peptide vaccines. Melanin-like nanoparticles (MNPs) offer a significant advantage in this context due to their inherent biocompatibility, low toxicity, and biomimetic properties.

While the toxicity of certain NPs remains a worry, other NPs, such cationic polymers and carbon nanotubes, have demonstrated their effectiveness in inducing an immune response and delivering antigens.

A research utilizing a vaccine formulation built on artificial L-DOPA melanin that has been injected with artificial peptides were performed. Melanin-peptide complexes enter the sinusal and paracortical zones of the draining lymph nodes in mice following subcutaneous injection. Since these regions are T-cell zones, the highly effective antigen presentation to T-cells (both CD4 and CD8 + T-lymphocytes) may be explained by this spontaneous targeting (Cuzzubbo, Carpentier, et al., 2021). The cultivation of bone marrow-derived dendritic cells (BMDCs) with L-DOPA melanin did not significantly activate these cells, suggesting that L-DOPA melanin primarily functions as an antigen transporter with little immunostimulant effect (Cuzzubbo, Carpentier, et al., 2021).

Because of their many uses, melanin and melanin-like nanoparticles have drawn more attention in recent years when designing and building multifunctional nanoplatforms for medicinal applications (J. Sun et al., 2023). MNPs have been used in positron emission tomography and magnetic resonance imaging to precisely reflect tumor tissue function and metabolism data due to their potent metal chelation capabilities (Yue & Zhao, 2021a). Conventional cancer therapies involve radiation therapy, chemotherapy, and surgery, either separately or in combination. Cancer has not yet been fully beaten, despite numerous treatments. Cancer treatment calls for innovative therapeutic approaches. Recently, PTT has been suggested as a substitute for conventional cancer treatment (Kim et al., 2020). Photothermal therapy is a method of killing cancer cells by accumulating a substance that absorbs light and converts it into heat when irradiated with a laser. At 39–40 °C, cancer cells get damaged, and at 42–45 °C, they get necrotize. Based on the fact that cancer cells are more vulnerable to heat than normal cells, PTT is being actively pursued (Kim et al., 2020). In recent years, PTT has shown promise

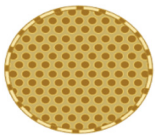
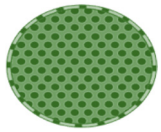
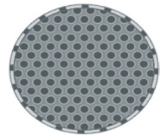
as a noninvasive cancer therapy method. But there are still obstacles in the way of creating biomaterials that are safe, biodegradable, and have a high photothermal efficiency in vivo (Jiang et al., 2017). The mechanism of PTT is that photothermal agents strongly absorb and convert near infrared (NIR) light into thermal energy after their adequate accumulation within tumors. Currently, various materials have been explored as effective photothermal agents, including inorganic nanomaterials (e.g. gold-, carbon-, palladium-, and magnetic nanoparticles), NIR dye (indocyanine green, IR825), polymer nanoparticles (e.g. polydopamine, polyaniline, polypyrrole, poly(ethylenedioxythiophene) (PEDOT)) and other nanomaterials (e.g. porphysomes, Prussian blue). The long-term safety of these artificial nanoparticles in vivo may still restrict their further clinical applicability in cancer treatment, despite their remarkable photothermal impact. For instance, metallic nanoparticles, especially those non-degradable metallic nanoparticles, would retain in the biological system for a very long time and cause metal-related cytotoxicity, while carbon-based nanomaterials have been extensively documented to cause major side effects following administration, including oxidative stress and pulmonary inflammation. been extensively documented to cause major side effects following administration, including oxidative stress and pulmonary inflammation. Therefore, the development of biocompatible and biodegradable photothermal nanomaterials with high photothermal conversion efficiency is of significant clinical value for advancing in vivo cancer photothermal therapy (PTT) (Jiang et al., 2017). Melanin-like NPs have shown great promise in the field of biomedicine in recent years, particularly in the area of photothermal anti-tumor therapy (Yue & Zhao, 2021a). Melanin-derived nanomaterials possess the following characteristics that make them promising as biocontrast agents: (1) MNPs can be used directly for in vivo PAI due to their extensive optical absorption.; (2) by adsorbing Fe2+, Fe3+, Mn2+, Gd3+, etc., melanin-based nanomaterials can be used for MRI; (3) by adsorbing radionuclides such as 64Cu, melanin-based nanomaterials can be used for PET; (4) nanomaterials based on PDA can be used for PET; (4) by the integration of different imaging modalities into a single nanoplatform, multifunctional melanin-based biological probes can be constructed and used for multimodal molecular imaging (Tian et al., 2022). For a variety of biomedical applications, cell membrane coating has become an exciting biomimetic technique to give nanomaterials the characteristics and activities of parent cells. In their review, Qin Jiang,et al ; coated hybrid membrane of different types of cells onto nanoparticle surface to achieve additional functions. Here, they created an erythrocyte-cancer (RBC-M) hybrid membrane-camouflaged melanin nanoparticle (Melanin@ RBC-M) platform to improve the therapeutic efficacy of photothermal therapy (PTT) by fusing red blood cell (RBC) membrane with MCF-7 cell membrane. (Jiang et al., 2019). Similarly, Min Ah Kim, et al ; in their research article showed how melanin-PEG (polyethyleneglycol) nanoparticles have great potential as photothermal agents for cancer therapy. When they injected melanin-PEG nanoparticles into tail vein of 4T1-bearing mouse followed by exposure to 808 nm NIR laser at a power density of 1.5 W/cm^2, temperature of the tumor region was increased to 48°C and tumor growth was less than 50 % compared to that of the control group(Song et al., 2024). Thus, excellent suppression of tumor growth under NIR laser irradiation was seen following intravenous injection of melanin-PEG nanoparticles. The breadth of melanin's biological applications can be expanded by conjugating PEG to melanin (Kim et al., 2020).

4. Comparison Between Variety of Nanoparticles

Despite the advantages of reproducible synthesis and high stability, gold nanoparticles can demonstrate cytotoxic effects, as summarized in Table 3 (Singh et al., 2018). Chitosan has good bioavailaibility but gives unstable product (Dang & Guan, 2020). Liposomes has complex synthesis, high cost of production and unstable product (Schwendener, 2014). On the other hand melanin like nanoparticles provide high loading rate, versatility, gives reproducibility in synthesis, provides good biocompatibility and also has low cost of production unlike gold nanoparticle and liposomes.

In this context, bioinspired organic materials have emerged as ideal candidates. Among them, melanin a natural pigment renowned for its photothermal conversion efficiency, inherent biocompatibility, and versatile surface chemistry stands out. Melanin and its synthetic analogues, melanin-like nanoparticles (MLNPs), offer a unique multifunctional platform. They can act as potent photothermal agents for localized tumor ablation while simultaneously serving as nanocarriers for immunotherapeutic

Table 3. Differentiation of different nano-particles. Melanin like nano-particles show a promising result when it comes to biocompatibility, biodegradability, reproducibility and cost of production

GOLD NANOPARTICLE	LIPOSOMES	CHITOSAN	MELANIN NANOPARTICLES
			
High loading ratio	High and versatile drug loading: DNA, mRNA, proteins, peptides, immunostimulating agents	Low loading ratio Unstable product Low cost of production Good Biocompatibility	High loading rate Versatility: chemotherapeutics, tumor lysate, proteins, peptides
Reproducible synthesis, stable product	Complex synthesis Unstable product	Easy synthesis Unstable product	Reproducible synthesis, stable product
High cost of production	High cost of production	Low cost of production	Low cost of production
Cytotoxicity has been reported depending on the size and charge of gold nanoparticle	Good biocompatibility, but improvement of the bio-distribution in vivo is needed	Good biocompatibility	Good biocompatibility
Controllable size, shape, and surface charges • Ability to combine photo-thermal therapy (PPT) with delivery system activity	Versatility: targeted design with the desired size, charge, and distribution	Biocompatibility	• Biocompatibility • Reproducibility • Versatility due to controllable size, shape, and surface charges • Applications in cancer vaccine • Ability to combine PPT with delivery system activity

agents, creating a powerful synergy that can overcome the limitations of monotherapies.

This review aims to provide a comprehensive analysis of melanin and MLNPs as a next-generation platform for combined cancer therapy. First, we will outline the fundamental properties, natural sources, and synthesis methods of these materials. We will then critically evaluate their primary applications, with a dedicated focus on their dual role as photothermal converters and immunomodulatory delivery vehicles. Finally, we will discuss the current challenges, future perspectives, and the translational potential of this versatile nanoplatform in achieving synergistic photothermal-immunotherapy.

4. DISCUSSION

This review synthesizes compelling evidence that melanin and melanin-like nanoparticles (MLNPs)

Table 4. Current clinical trials on cancer treatment taken from the https://clinicaltrials.gov/. In this table the different cancer conditions, its treatment and no. of phases the drug has undergone, is given

Sr. No.	Condition / Indication	Patented/Proprietary Intervention	Highest Trial Phase
1	Cervical Intraepithelial Neoplasia (CIN)	Proprietary HPV (Types 16, 18) Vaccine, Adsorbed	Phase 4 (Post-Marketing)
2	Cervical Intraepithelial Neoplasia (CIN)	V3-P Vaccine (Proprietary Formulation)	Phase 2
3	Diffuse Intrinsic Pontine Glioma (DIPG)	H3.3-K27M Neoantigen-Specific Vaccine (Novel Antigen Target)	Phase 1
4	Cholangiocarcinoma	Oral V3-X Therapeutic Vaccine (Proprietary Platform)	Phase 2
5	Metastatic Neoplasms	Personalized Cellular Vaccine (Autologous Platform)	Phase 1
6	Lung Carcinoma	Synthetic MUC1 Peptide-Poly-ICLC Adjuvant Vaccine (Defined Antigen/ Adjuvant Combo)	Phase 1

constitute a versatile and powerful nanoplatform for advancing cancer therapy. Their unique convergence of inherent properties—biocompatibility, potent photothermal conversion, and a natural tropism for lymphatic tissues—positions them as ideal candidates for synergistic photothermal-immunotherapy. This discussion critically analyzes the mechanisms underlying their efficacy, the rationale for their synergy, their comparative advantages, and the challenges that must be surmounted for clinical translation.

4.1. Mechanisms of Action: Innate Properties Driving Efficacy

The effectiveness of MLNPs is not serendipitous but is fundamentally rooted in their intrinsic physicochemical and biological characteristics.

- Lymphatic Targeting and Antigen Presentation: The size range of optimally engineered MLNPs (20-200 nm) is perfectly suited for passive drainage via interstitial flow into initial lymphatic capillaries, bypassing direct entry into the systemic bloodstream. This innate lymphatic targeting ensures direct delivery to the antigen-presenting cells (APCs), primarily dendritic cells (DCs), resident in the draining lymph nodes—the command centers of the adaptive immune response. Once within the lymph nodes, the negatively charged, hydrophobic surface of melanin facilitates adsorption and stable presentation of peptide antigens or adjuvants. This creates a sustained local antigen depot, promoting prolonged exposure and efficient cross-presentation on Major Histocompatibility Complex (MHC) class I molecules, which is essential for activating cytotoxic CD8+ T-lymphocytes. As reviewed, studies with synthetic L-DOPA melanin confirm its accumulation in the paracortical T-cell zones of lymph nodes, leading to robust antigen-specific T-cell activation without significant intrinsic DC activation, highlighting its primary role as an efficient "antigen ferry."
- Photothermal Conversion for Ablation: The broad, monotonic absorption spectrum of melanin, spanning UV to near-infrared (NIR) regions, allows for deep tissue penetration when using NIR light. Melanin's exceptional efficiency in converting absorbed photon energy into thermal energy (heat) is the cornerstone of photothermal therapy (PTT). This property enables localized, hyperthermic ablation of tumor cells upon laser irradiation, with minimal off-target effects due to the spatial precision of the light source.

4.2. Synergistic Photothermal-immunotherapy: Creating an in situ Vaccine

The true transformative potential of MLNPs lies in their ability to integrate these two distinct mechanisms into a single, synergistic therapeutic regimen. This creates a powerful self-reinforcing cycle, often termed an *in-situ* vaccination effect.

1. Induction of Immunogenic Cell Death (ICD): MNP-mediated PTT, when calibrated appropriately, does not merely kill cancer cells through necrosis. It can be tuned to induce ICD—a functionally unique form of cell death characterized by the release of tumor-associated antigens (TAAs), damage-associated molecular patterns (DAMPs) like calreticulin, ATP, and HMGB1. These signals act as "danger" flags for the immune system.
2. Antigen Capture and Immune Activation: The same MLNPs present at the tumor site, or a secondary dose administered post-PTT, can now serve a dual purpose. They can actively adsorb the newly released TAAs and DAMPs from the ablated tumor milieu. Subsequently, leveraging their inherent lymphatic trafficking capability, these antigen-loaded MLNPs migrate to the draining lymph nodes.
3. Amplified Anti-Tumor Immunity: In the lymph nodes, the MLNPs efficiently deliver this "antigen package" to DCs. The immunogenic context provided by DAMPs promotes DC maturation and the potent cross-presentation of tumor antigens to T cells. This process primes a systemic, tumor-specific cytotoxic T-cell response capable of attacking both the primary tumor and, crucially, distant metastases. This synergy addresses a key limitation of standalone PTT, which often fails to elicit a durable systemic immune memory, and of standalone immunotherapy, which can be hindered by poor antigen immunogenicity and delivery.

4.3. Critical Analysis of Melanin's Comparative Advantages

The comparative analysis in Table 3 highlights why MLNPs hold significant promise over other prominent nanocarriers like gold nanoparticles (AuNPs), liposomes, and chitosan in a clinical translation context:

- Biocompatibility vs. Toxicity Concerns: Unlike AuNPs, which can exhibit cytotoxicity dependent on size, shape, and surface chemistry, and some inorganic particles that accumulate in the reticuloendothelial system, melanin is a natural human biopolymer with a long evolutionary history in the body. This inherent biocompatibility and biodegradability (with clearance via liver and kidneys) significantly mitigate long-term toxicity risks, a paramount concern for regulatory approval.
- Reproducibility and Cost: While liposomes offer high versatility, their synthesis can be complex, and product stability can be a challenge, impacting reproducibility and cost. In contrast, synthetic melanin-like NPs, particularly polydopamine (PDA), can be produced via simple, scalable oxidative polymerization in aqueous solutions, leading to highly reproducible and stable nanoparticles at a relatively low cost.
- Multifunctionality: MLNPs uniquely combine high drug/antigen loading (via adsorption and covalent conjugation), excellent photothermal properties, and metal-chelation ability for imaging (e.g., MRI, PET) in a single platform. This multifunctionality for theranostics (therapy + diagnosis) is harder to achieve with comparable simplicity in other single-material systems.

4.4. Current Limitations and Future Challenges

Despite the promising outlook, several key challenges must be rigorously addressed to pave the way for clinical application:

1. Standardization and Source Variability: Natural melanin extracted from different biological sources (sepia ink, fungi) can exhibit batch-to-batch heterogeneity in molecular weight, structure, and impurity profile. Synthetic melanin (e.g., PDA), while more reproducible, itself has a complex and heterogeneous structure that requires precise control over polymerization conditions to ensure consistent pharmaceutical properties.
2. Long-Term In Vivo Fate and Metabolism: While biocompatible, the detailed pharmacokinetic profile, long-term degradation pathways, and ultimate metabolic fate of synthetic MLNPs,

especially after repeated doses, require comprehensive toxicological studies. The potential for oxidative degradation products needs characterization.

3. Optimization of PTT Parameters: In clinical PTT, avoiding off-target heating of healthy tissue is critical. The laser power density, irradiation time, and tumor accumulation of MNPs must be optimized to maximize therapeutic efficacy while minimizing collateral damage. Strategies like active targeting (using antibodies/aptamers conjugated to MNPs) or external triggers can enhance specificity.
4. Scalable Good Manufacturing Practice (GMP): Translating laboratory-scale synthesis to GMP-compliant, large-scale production of sterile and pyrogen-free MNP formulations is a non-trivial but essential step.

The future of MLNP-based cancer therapy lies in a multidisciplinary approach. Collaborative efforts between materials scientists, immunologists, and clinicians are needed to engineer next-generation MLNPs with enhanced targeting, controlled drug release, and optimized immunostimulatory profiles. By systematically overcoming the existing challenges, this versatile bioinspired platform holds immense potential to evolve from a promising preclinical concept into a mainstream paradigm for synergistic and personalized cancer treatment.

5. CONCLUSION

Melanin and melanin-like nanoparticles (MNPs) represent a distinctive and versatile class of bioinspired nanoplatforms with immense potential for advancing cancer theranostics. This review has highlighted how the unique intrinsic properties of melanin—its innate biocompatibility, potent photothermal conversion efficiency, and natural propensity for lymphatic accumulation—coalesce to create a multifunctional system ideally suited for synergistic cancer therapy. Rather than functioning as a direct cytotoxic agent, melanin primarily serves as an intelligent carrier and transducer, capable of delivering therapeutic payloads to key immune hubs while simultaneously converting external energy into localized tumor ablation.

The core innovation of this platform lies in its ability to seamlessly integrate photothermal therapy (PTT) with immunotherapy. MNPs can mediate localized tumor destruction via hyperthermia, a process that can induce immunogenic cell death and release a spectrum of tumor antigens. The same nanoplatform can then act as a vehicle, capturing and delivering these antigens to antigen-presenting cells in the draining lymph nodes, thereby potentiating a robust and systemic anti-tumor immune response. This synergistic mechanism effectively transforms a localized thermal treatment into a systemic *in-situ* vaccine, addressing the limitations of both monotherapies.

Comparative analysis underscores the potential advantages of MNPs over many inorganic and other organic nanocarriers, particularly in terms of biocompatibility, biodegradability, and multifunctional simplicity. However, the pathway to clinical translation is not without significant challenges. Key hurdles include the standardization of MNP synthesis, comprehensive evaluation of long-term *in vivo* fate and safety, and the optimization of treatment parameters for clinical PTT. The resolution of these issues demands rigorous, systematic investigation.

In conclusion, while melanin-based nanoparticles possess transformative potential as next-generation theranostic agents, their full clinical promise remains to be unlocked. Successfully navigating the translational pathway will require a concerted, multidisciplinary effort from materials scientists, immunologists, and clinicians. Unlocking the full clinical potential of MNPs will thus require a concerted, multidisciplinary effort to translate these innovative concepts into safe and effective oncological interventions, ultimately paving the way for a new class of theranostic agents.

HIGHLIGHTS

- Gave a brief about why is targeting cancer antigens so difficult.
- Enlisted and explained the sources of melanin and from where it can be synthesized and how it can be synthesized.
- Elaborated the mechanism of melanin and how is it useful in carrying the cancer antigen to draining lymph nodes targeting the T cells to make antibodies.

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